ATRIAL FIBRILLATION

REVIEW ARTICLE

Recent Insights into the Mechanisms Underlying Persistent Atrial Fibrillation

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KEYWORDS. atrial fibrillation, pulmonary vein.

Introduction

Atrial fibrillation (AF) is a gradually progressive atrial disease process manifesting as the most common heart rhythm disorder. Early in its clinical course, the arrhythmia may be frequently triggered by rapid firing of impulses from focal sources. Almost all cases of true paroxysmal AF are caused by ectopic signals that originate in the thoracic veins, especially the pulmonary veins, allowing catheter-mediated elimination of sources, with clinical success rates of 70–85%.1 By contrast, atrial tissue that has widespread electrostructural alterations resulting from oxidative stress, inflammation, and atrial fibrosis is largely the source of persistent forms of AF wherein the clinical outcome of drug therapy and/or ablation is variably low.

In addition to focal sources, widely spread, biatrial substrate plays a large role in initiating and sustaining persistent AF. The improvement in the outcomes of therapy for persistent AF needs better understanding of the underlying complex mechanisms. Below, we present recently developed insights into the mechanisms of persistent AF from invasive and non-invasive mapping techniques.

Classification of atrial fibrillation

The American College of Cardiology, the American Heart Association, and the European Society of Cardiology have provided guidelines that classify AF as paroxysmal, persistent, or permanent to direct the management of this disorder.2 However, these divisions are not mutually exclusive. A patient is said to have recurrent AF if they have experienced two or more episodes. If the arrhythmia is intermittent, the AF is designated paroxysmal. When episodes are sustained for longer than 7 days, AF is classified as persistent. Persistent AF also includes cases of long-standing AF (>1 year), which usually leads to permanent AF where cardioversion has failed or has not been attempted.2

Progression of atrial fibrillation

Progression of paroxysmal AF to more sustained forms is frequently seen. However, not all patients progress to persistent AF, and not all persistent AF patients commence the arrhythmia as paroxysmal AF.

In the Euro Heart Survey of 1,219 paroxysmal AF patients, those who experienced AF progression after 1 year of follow-up were identified.3 Progression of AF occurred in 178 (15%) patients. Multivariate analysis showed that heart failure, age, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, and hypertension were the only independent predictors of AF progression. Using the regression coefficient as a benchmark, the HATCH score was calculated. Nearly 50% of the patients with a HATCH score 5 progressed to persistent AF compared with only 6% of patients with a HATCH score of 0, allowing the HATCH score to identify the patients who are likely to progress to sustained forms of AF in the near future. During follow-up, patients with AF progression were
Mechanisms Underlying Persistent AF

Pathophysiology of persistent atrial fibrillation

AF is a progressive disorder, and basic research has led to the hypothesis that “AF begets AF,” meaning that the changes in the atrial substrate caused by AF lead to persistence of AF. However, before AF sets in, specific stressors impact the atriovenous substrate such that a spectrum of pathophysiological changes initiate in the atria in a time-dependent manner in order to maintain homeostasis against these stressors. The most common “stressors” of atrial myocytes include high atrial depolarization rates (as seen in AF), and volume/pressure overload such as in heart failure syndromes. The adaptive and/or maladaptive changes these stressors induce in the atrial structure and function constitute remodeling.

Substrate remodeling (electrical)

Remodeling involving the atrial electrical properties are of particular interest from the standpoint of persistent AF. Whereas atrial dilatation is the hallmark of structural remodeling, atrial arrhythmias, especially AF, are the most common manifestations of left atrial electrical remodeling from any cause. Conversely, once AF sets in, it potentiates the process of atrial electrical remodeling. The remodeling mediated by atrial high rates is characterized by shortening of the effective refractory period and reduction in the action potential duration. AF is thereby promoted through formation of multiple wavelets, which favor re-entry. The remodeling mediated by heart failure differs from the atrial high rates model because heart failure does not shorten the effective refractory period or action potential duration. The proposed mechanisms by which AF is sustained in this situation include triggered activity and delayed after depolarization. The differences in electrophysiological properties between atrial tachycardia and heart failure remodeling are attributed to a marked reduction of L-type calcium channels in the former but not so in the latter. Aside from ionic channel alterations, cellular and extracellular modifications also contributed to electrophysiological changes during the remodeling process. Left atrial dilatation increases electrical instability with shortening of the effective refractory period. Atrial ischemia slows atrial conduction. A dilated left atrium provides circuits for re-entry, besides rendering atrial myocytes vulnerable to depolarization.

Electrophysiological mechanisms, focal triggers, and multiple wavelets

The multiple-wavelet hypothesis as the mechanism of re-entrant AF was advanced by Moe and Abildskov, who proposed that fractionation of wavefronts propagating through the atria results in self-perpetuating “daughter wavelets.” In this model, the number of wavelets at any time depends on the refractory period, mass, and conduction velocity in different parts of the atria. A large atrial mass with a short refractory period and delayed conduction increases the number of wavelets, favoring sustained AF. The multiple-wavelet hypothesis was the dominant theory explaining the mechanism of AF for several decades, and experimental models which demonstrated drug- and pacing-induced focal triggering of AF received minimal attention until the recently made important observation that a focal source for AF identified in humans was supported by elimination of AF after focal ablation of the source. While pulmonary veins are the most frequent sources of these rapid atrial impulses, foci have also been found in the superior vena cava, ligament of Marshall, left posterior free wall, crista terminalis, and coronary sinus.

Whether AF is a focally triggered or a multiple-re-entrant wavelet-mediated arrhythmia, the existence of triggers for AF does not negate the role of substrate in persistent AF. In some patients with persistent AF, disruption of the muscular connections between the pulmonary veins and the left atrium may terminate the arrhythmia. In others, AF persists following isolation of the supposed trigger. Thus, in some patients with abnormal triggers, sustained AF may depend on an appropriate anatomical substrate.

The electrophysiological studies in humans have implicated atrial vulnerability in the pathogenesis of AF. In patients with idiopathic paroxysmal AF, widespread distribution of abnormal electrograms in the right atrium predicted development of persistent AF, suggesting an abnormal substrate. In patients with persistent AF who had undergone conversion to sinus rhythm, there was significant prolongation of intra-atrial conduction compared with a control group, especially among those who developed recurrent AF after cardioversion. Non-uniform alterations of refractoriness and conduction throughout the atria may provide a milieu for the maintenance of AF. However, the degree to which changes in the atrial architecture contribute to the initiation and maintenance of AF is not known.

Autonomic nervous system

Among several other factors potentially involved in the induction or maintenance of AF, autonomic nervous system activity is one of the foremost. Increased sympathetic or parasympathetic tone has been implicated in the initiation of AF. Autonomic ganglia containing parasympathetic and sympathetic fibers are present on the epicardial surface of both the atria, clustered on the posterior wall near the ostia of the pulmonary veins,
superior vena cava, and coronary sinus. In animal models, parasympathetic stimulation shortens atrial and venous refractory periods, potentiating initiation and maintenance of AF, and vagal denervation of the atria prevents induction of AF.28

Renin–angiotensin–aldosterone system

Atrial stretch is a potent stimulus for several molecular pathways including the renin–angiotensin–aldosterone system (RAAS). Both angiotensin II and transforming growth factor-β1 are upregulated in response to stretch, and these molecules induce production of connective tissue growth factor, thereby promoting interstitial fibrosis and atrial dilatation.29 This system acts at the microvascular and cellular levels to promote remodeling of the substrate by increasing the deposition of fibrous tissue.

Atrial tissue from patients with persistent AF undergoing open-heart surgery demonstrated increased amounts of extracellular signal-regulated kinase mRNA and expression of angiotensin-converting enzyme was increased threefold during persistent AF.30 A study of 250 patients with AF and an equal number of controls demonstrated the association of RAAS gene polymorphisms with this type of AF.15

Genetic predisposition

Familial AF is rare and genetically more heterogeneous than other familial monogenic cardiac disorders such as hypertrophic cardiomyopathy and long-QT and Brugada syndromes. In 1997, Brugada and colleagues described the first genetic locus for AF; however, the causative gene at the locus remains elusive. In 2003, Chen and colleagues described the first mutation in a Chinese family with early-onset AF. The causative mutation resulted in a gain of function in KCNQ1 (the a-subunit of IKs). In subsequent years, multiple mutations have resulted in a gain of function in KCNQ1 (the a-subunit of IKs). In subsequent years, multiple mutations have been identified in potassium and sodium channels, gap junction proteins and signaling molecules. It has recently been appreciated that parental history of AF and history of early-onset familial AF put the offspring at high to very high risk of AF.

Familial forms of AF are of interest mainly to progress our understanding of the pathophysiological mechanisms of this illness. The identification of the genes of these variants could represent predisposing factors to AF.

Novel insights from high-density invasive mapping

Atrial fibrillation-driving rotors

Krummen et al hypothesized that AF may emanate from the sites of high rate and regularity with fibrillatory conduction to adjacent areas. To find evidence for such potential AF drivers, simultaneous, high-density mapping was undertaken in 24 patients including 12 with persistent AF using 32 left atrial bipolar electrode catheters in addition to pulmonary veins, coronary sinus, and right atrial electrodes. AF cycle length by Fourier transform and electrogram regularity at each electrode were determined. Evidence for potential AF drivers was found in 11 patients (five persistent). While in paroxysmal AF six of nine sites were observed at the pulmonary veins; these sites lie at the coronary sinus and left atrial roof but not at the pulmonary veins in persistent AF (p<0.05). During ablation, a subset of patients experienced AF cycle length prolongation or termination with a focal lesion; in each case this lesion mapped to potential driver sites on blinded analysis. However, sequential mapping failed to reveal these sites, possibly due to fluctuations in the dominant frequency at driver locations in the context of migratory AF. Future work should determine if real-time ablation of AF-maintaining regions defined in this fashion eliminates AF.

Complex fractionation in atrial fibrillation

Jadidi et al mapped the sites with complex fractionated atrial electrograms (CFE) using a 20-pole, spiral, high-density catheter aided by a three-dimensional (3D) electroanatomic system. The impact of activation direction (rhythm) and rate on electrogram fractionation was evaluated in serial high-density left atrial maps (≥400 points/map) in 18 patients (nine persistent AF) just prior to ablation. Mapping was done during AF, sinus rhythm (SR), and CS-paced (CSp) rhythm. In SR and CSp, fractionation was defined as an electrogram with four or more deflections, although, in AF, a CFE mean <80 ms was considered as continuous CFE. The anatomic distribution of CFE sites was assessed, quantified, and correlated between rhythms. Mechanisms underlying fractionation were investigated by analysis of voltage, activation, and propagation maps. A minority of continuous CFE sites displayed electrogram fractionation in SR (15±4%) and CSp (12±8%). Fractionation did not match between SR and CSp at 70±10% sites. Activation maps in SR and CSp showed that wave collision (71%) and regional slow conduction (24%) caused fractionation. Electrogram voltage during AF (0.59±0.58 mV) was lower than during SR and CSp (>1.0 mV) at all sites. During AF, the electrogram voltage was higher at continuous CFE sites than at non-CFE sites (0.53 mV (Q1, Q3: 0.33–0.83) versus 0.30 mV (Q1, Q3: 0.18–0.515), p<0.00001). Global left atrial voltage in AF was lower in patients with persistent AF versus patients with paroxysmal AF (0.6±0.59 mV versus 1.12±1.32 mV, p<0.01).

The investigators concluded that the distribution of fractionation is highly variable, depending on the direction (rhythm) and rate of activation (SR versus CSp versus AF). Fractionation in SR and CSp rhythms mostly resulted from wave collision. All sites with continuous fractionation in AF displayed normal voltage in SR, suggesting absence of structural scar. Thus, many
fractionated electrograms are functional in nature, and their sites dynamic.

**Slowing of intra-atrial conduction prior to atrial fibrillation onset**

High-density invasive mapping was also used to identify functional determinants of AF initiation by a group of investigators who hypothesized that since conduction slowing is required for re-entry, AF might initiate at sites exhibiting rate-dependent slowing in conduction velocity or local slowing evidenced by reduced amplitude and prolonged duration of signals (i.e. fractionation), immediately before its onset.\(^{49}\)

Bialtrial conduction time and electrogram fractionation were measured at 64 or 128 electrodes with baskets in the left or both atria during superior pulmonary vein pacing at cycle lengths accelerating from 500 ms to AF onset in 28 patients with established AF and three control subjects without AF. AF was initiated in 19 of 28 AF patients and there were no control subjects. During pacing rate acceleration, conduction slowed in 23 of 28 AF patients (versus no control subjects, \(p=0.01\)) at the site of AF initiation (15 of 19) or latest activated site (20 of 28). The conduction time lengthened from 79 ± 23 ms to 107 ± 39 ms (\(p<0.001\)) on acceleration, in a spectrum from persistent AF (greatest slowing) to control subjects (least slowing \(p<0.05\)). Three patterns of prolongation in conduction times were observed: 1) gradual prolongation, 37% patients; 2) abrupt prolongation at CL 266 ± 62 ms, 42% patients; and 3) no prolongation, 21% AF patients and all control subjects. The AF initiation was more prevalent in patients with the prolongation of conduction times than in those without (17 of 23 versus 2 of 8; \(p=0.03\)). Patients with gradual prolongation had larger atria (\(p=0.03\)) and were more likely to have persistent AF (\(p=0.04\)). Notably, neither amplitude nor duration (fractionation) of the local atrial signal at the AF initiation site were rate dependent (both \(p=NS\)). The authors concluded that acceleration-dependent slowing of atrial conduction velocity precedes AF initiation, whereas absence of prolongation identifies inability to induce AF. Also, the conduction slowing but not fractionated electrograms may track the functional milieu enabling AF initiation.

**Complex fractionation in atrial fibrillation**

Complex fractionation detected during substrate mapping for persistent AF may arise due to rapid localized activity, disorganized wave collisions, or they could represent far-field electrograms. MAP recordings were used in an attempt to comprehend the precise nature of complex fractionated electrograms.\(^{51}\) Besides monophasic action potentials to map local refractoriness in AF, multipolar catheters were used to map activation sequence in 18 patients prior to persistent AF ablation (age 57 ± 13 years, left atrial diameter 45 ± 8 mm). AF cycle length, bipolar voltage, and spectral dominant frequency were measured to characterize types of complex fractionated electrograms. Fractionated electrograms were observed at 91 sites, most of which (83%) showed discrete MAPs. Fractionation associated with discrete MAP recordings were mostly due to non-local (far-field) signals (67%). Pansystolic local activity (8%) and fractionation associated with AF acceleration, often with MAP alternans (8%), were responsible for the remaining minority. Fractionation associated with discrete MAPs and pansystolic activation (consistent with rapid localized AF sites) had shorter cycle length (\(p<0.05\)) and lower voltage (\(p<0.05\)) and tended to have higher dominant frequency than other sites. In conclusion, the majority of fractionation reflects far-field signals, AF acceleration, or disorganization. In a majority of cases, it indicates rapid local activity.

**Novel insights from monophasic action potential recordings**

**Action potential duration and atrial fibrillation onset**

To understand the differences in the vulnerability to AF in subjects with established AF (paroxysmal or persistent) and control subjects without AF, Narayan et al\(^{50}\) analyzed beat-to-beat oscillations in action potential duration (APD) derived from monophasic action potential (MAP) recordings obtained during atrial pacing. Patients in AF were electrically cardioverted to sinus rhythm and studied after 15 min. Action potentials were recorded from the distal poles of the MAP catheter while pacing from the proximal poles or a nearby stable position. Pacing was delivered for 74 beats starting at a cycle length of 600 ms or 500 ms, followed by that at 450 ms, 400 ms, 350 ms, and 300 ms and then in 10-ms steps to AF or capture failure, whichever came first. APD was measured in the antra of the right or left superior pulmonary vein and the high right atrium. APD alternans was observed preceding all AF episodes but never when AF did not initiate. APD alternans was established at progressively slower pacing rates in patients with persistent AF, in patients with paroxysmal AF, and controls (cycle length 411 ± 94 versus 372 ± 72 versus 218 ± 33 ms; \(p<0.01\)). In AF patients, APD alternans occurred at rates as slow as 100–120 bpm. At fast rates, APD alternans disorganized to complex oscillations en route to AF. Complex oscillations also arose at progressively slower pacing rates for persistent AF, paroxysmal AF, and controls (cycle length 316 ± 99 versus 266 ± 19 versus 177 ± 16 ms; \(p=0.02\)). In controls, APD alternans arose only at very fast rates (cycle length < 250 ms; \(p<0.001\) versus AF groups) just preceding AF. In four AF patients in whom rapid pacing did not initiate AF, APD alternans arose transiently and then extinguished. The authors concluded that the atrial APD alternans reveals dynamic substrates for AF, arising most readily in persistent AF then paroxysmal AF, and least readily in controls.
Insights from novel body surface mapping techniques

Non-invasive 3D atrial fibrillation mapping

Cucculich et al. non-invasively mapped biatrial epicardial activation sequences of human AF using a novel multilead electrocardiographic imaging system. The study was divided into two phases. In the testing phase, the system’s accuracy was evaluated by comparing its maps with coregistered CARTO images during atrial pacing in six patients. Spatial accuracy for determining initiation sites from pacing was 6 mm. Additionally, correlative observations from catheter mapping and ablation were compared with the system’s maps in three patients. In the study phase, the maps during AF in 26 patients were analyzed for mechanisms and complexity. The system could non-invasively image the low-amplitude signals of AF in a wide range of patients (97% procedural success) and showed diverse patterns of atrial activation, as follows.

- Multiple wavelets: For most patients (24/26; 92%), at least two simultaneous wavelets (range 1–5) were visible. Individually, each patient had a consistent number of wavelets over the course of imaging. Rarely (2/26; 8%), the predominant mechanism was a single-wave macro-re-entry, involving both atria.
- Rotors: Rotor pattern was less common (4/26; 15%) and was observed in the posterior left atrium, often near pulmonary vein ostia and occasionally in the anterolateral right atrium. Rotors rarely sustained one full rotation before breaking into less organized wavelets. Although the rotors seemed short-lived, in the four patients with rotor patterns, the location of the rotor was reproducible over several hours. Interestingly, rotors were only seen in patients with non-paroxysmal AF.
- Focal sites: Radial epicardial activation from a focus frequently occurred near the pulmonary veins (18/26; 69%) during AF. Non-pulmonary vein focal sites were also common (16/26; 62%) and were predominateley seen in the left atrial posterior wall, coronary sinus, lateral right atrium, or vena cavae. These focal sites were seen in addition to simultaneous activation wavelets during AF.

AF clinical type and complexity of non-invasive maps: Among 26 patients imaged during AF, there were significant differences in complexity (number of wavelets and focal sites) between the clinical groups (paroxysmal, persistent, longstanding persistent). Patients with paroxysmal AF had fewer wavelets (1.1 ± 0.2 wavelets) than patients with persistent AF (2.2 ± 0.9 wavelets; p = 0.017) or longstanding persistent AF (2.6 ± 0.5 wavelets; p = 0.005). Similarly, patients with paroxysmal AF had fewer focal sites (1.0 ± 0.7 focal sites) than patients with persistent (2.3 ± 1.1 focal sites; p = 0.034) or longstanding persistent AF (3.2 ± 1.8 focal sites; p = 0.034). Within the paroxysmal AF group, there was relative homogeneity and simplicity in the number of wavelets (1–2 wavelets) and focal sites (0–2 focal sites). In contrast, patients with persistent AF demonstrated considerable heterogeneity. Patients in this group had one to four simultaneous wavelets and one to four focal sites visible during AF. The patients with longstanding persistent AF had the most complex AF patterns. Although patients who have had prior surgical or catheter ablation represent a clinically important type of AF, the effect of previous intervention may introduce artificial complexity to the AF patterns. The validation of AF activation patterns with correlative invasive data was not available for the majority (23/26) of these cases. The investigators concluded that the novel non-invasive 3D mapping system could image AF in a wide range of patients. It revealed a variety of coexisting AF mechanisms with more complex mechanisms in patients with long duration of non-paroxysmal AF. These mechanisms were observed to remain stable in each individual over the period of mapping lasting up to a few hours.

Whether this system can help selection of patients for ablation and devise individualized ablation strategy need to be seen in future. Similarly, its non-invasive nature could be suited for follow-up mapping and periodic assessment of the ablation outcome.

Perspective

The aim of mapping persistent AF, a complex arrhythmia, using novel techniques/tools has been to simplify the mechanisms underlying its onset and sustenance. The ultimate aim is to define limited targets for substrate ablation and improve acute and long-term arrhythmia-free survival. The sites with complex fractionation of local electrograms have been important targets of ablation but as elucidated recently and discussed above, this characteristic of persistent AF is functional and largely represents passive sites or far-field electrical activity. It has been recently found that besides deciphering the active versus passive fractionation sites, there could also be a limited number of sites wherefrom the stable rotors drive the arrhythmia in the rest of the atrial chamber. Although there may be more than one mechanism driving the arrhythmia in any given patient and combinations may vary from one to another, it seems that for a given individual, the causative mechanism(s) remains steady over time possibly paving the way for individually tailored therapy in the future.

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