Electrophysiological properties of the human atrium in atrial fibrillation

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Abstract

It has been reported that ectopic foci from the pulmonary veins can initiate atrial fibrillation (AF) and can also act as drivers for maintaining AF. However, not all patients with atrial arrhythmias initiate AF. A substrate for atrial propensity to AF is required for AF initiation and maintenance. Thus, we reviewed and discussed mainly the electrophysiological properties observed in AF. Abnormal atrial electrograms during sinus rhythm and abnormal responses of the atrium elicited by programmed stimulation have been observed more frequently in patients with paroxysmal AF than in those without. A shorter atrial effective refractory period, greater dispersion of the atrial refractoriness and atrial conduction delay are also of electrophysiologic significance in the genesis of AF. Electrical remodeling is likely to be a final common pathway that ultimately supervenes. Even if atrial electrical remodeling facilitates AF initiation and AF perpetuation, the initiation of AF requires a trigger. Further investigation into the electrophysiological properties in AF will be needed in order to contribute to the future development of an appropriate treatment.

Keywords: Antiarrhythmic agents; Arrhythmia (mechanisms); Mapping; Supraventr. arrhythmia

1. Introduction

Since the beginning of this century, the debate on ectopic foci versus reentry as the mechanism underlying atrial fibrillation (AF) in humans has continued. Recently, the mechanism of atrial fibrillation (AF) is considered to be a spiral wave with a continuously changing pattern of the activation wave front [1,2], that is, a random multiple reentry [3,4] of independent wavelets wandering in the atria around arcs of refractory tissue [5,6] or the accentuation of focal activity originating mainly from the pulmonary veins (PVs) [7–10] or the superior vena cava [11], ligament of Marshall [12,13].

Although a reentrant activation sequence of multiple wavelets has been demonstrated in human AF by epicardial mapping just before the surgical treatment of this arrhythmia [5,14], the method is not suitable or feasible for diagnostic or investigational purposes in the clinical electrophysiologic laboratory. In addition, once AF is induced in the laboratory, pharmacologic or electrical cardioversion is required to restore sinus rhythm. However, these interventions make it impossible to repeat the baseline study for the mechanism of AF. Therefore, clinical electrophysiologic studies have become focused mainly on the electrophysiologic properties of the substrates in the atrial muscle during sinus rhythm and on the atrial electrical responses elicited by the premature stimulation method. However, many fundamental aspects of this arrhythmia have been poorly understood until quite recently.

In recent years, a wealth of new information has been published on the genesis of AF, especially arrhythmogenic PVs as the triggers of AF [7–10], and on electrical remodeling [15–21] of the electrophysiologic properties in the atrial muscle as modifying factors of AF. Furthermore, a possible genetic basis of AF has been suggested in some cases [22], although little is known about its electrophysiology. Approaches to the surgical management have improved and have provided information about the...
clinical determinants of AF [6,23,24]. Information has been obtained about post-operative AF [25] and the response to implanted devices, such as both atrial pacemakers [26–32] and atrial defibrillators [33,34].

Generally, arrhythmias are generated by the presence of substrates, triggers, or modifying factors for arrhythmias. Therefore, this review was designed to investigate the electrophysiologic properties of the substrates and triggers, and modifying factors of the electrophysiologic properties of AF and the electrophysiologic properties during AF.

2. The electrophysiological properties of the substrate in AF

The investigation was based on the recordings of local abnormal atrial electrograms during sinus rhythm and their characteristic distribution, and on several abnormal responses elicited by premature atrial stimulation

2.1. Atrial endocardial mapping during sinus rhythm

At the time of atrial endocardial mapping during sinus rhythm, an abnormally prolonged and fractionated right atrial electrogram may reflect slow and anisotropic conduction through the diseased atrial muscle [35]. The first attempt to define the quantitative characteristics of the normal atrial endocardial electrograms was made by Tanigawa et al. [36]. The atrial mapping technique was performed with a bipolar catheter electrode array with a 10-mm interelectrode distance, and the atrial endocardial electrograms were filtered from 50 to 1000 Hz. They recorded atrial electrograms from the anterior, lateral, posterior and medial aspects of the high, middle and low RA (Fig. 1). The duration of the atrial electrogram was defined as the time from the beginning of the earliest electrical activity that deviated from the stable baseline to the last point of the atrial electrogram that crossed the baseline. The number of fragmented deflections was measured by counting the number of downward deflections [36] (Fig. 2). In subjects with normal sinus node function and without paroxysmal AF, the mean duration and mean number of fragmented deflections were 74±11 ms and 3.9±1.3 (mean±S.D.), respectively. Atrial electrograms with values >2 times the S.D. of the mean values were considered abnormal. Therefore that number would be the mean plus 2 times the S.D. for the number of deflections, i.e. 3.9+2×1.3=6.5. Tanigawa et al. defined the atrial electrogram as abnormal when either the duration was >100 ms, there were eight or more fragmented deflections, or both.

There are certain limitations to the catheter mapping technique of the RA during sinus rhythm. The 12 sites used may not be enough to detect abnormal atrial electrograms. The interelectrode distance of bipolar catheters, filter-frequency settings [37], high-gain recordings and motion at the electrode–tissue interface with the cardiac movement [38] may affect the recording of the atrial endocardial electrograms and might generate certain features of the fractionated electrogram. Catheters with a 10-mm interelectrode distance can record more distant electrical activity. No method can discriminate with certainty the local activation from the electrotonic activity or far-field effects. The filter setting is known to influence the amplitude of the electrogram. They have not measured their amplitude of the electrogram. In addition, one of the major problems in determining the number of deflections is the noise level. What should be considered as a real deflection (2× or 10× the noise level)? Finally, since left atrial catheter mapping was not performed, further investigation is needed to shed light on this issue.

2.2. Abnormal atrial electrograms

2.2.1. Distribution

Centurion et al. [39] quantitatively measured 1195 atrial endocardial electrograms in 101 patients to determine the sites in the RA where the electrical activity is likely to be abnormal. They then correlated the distribution of abnormal atrial electrograms with the likelihood of paroxysmal
AF developing in patients with sick sinus syndrome. Of the 130 abnormal atrial electrograms recorded, 84 (65%) were found in the high RA, 30 (23%) in the middle RA, and 16 (12%) in the low RA (Fig. 3). Furthermore, 88% of the abnormal atrial electrograms were recorded in the posterolateral high RA. They concluded that the greater the extent of the compromised atrial muscle, the greater the likelihood that paroxysmal AF would develop.

Pathologic studies have demonstrated that patients with sinoatrial block without PAF had lesions localized to the sinus node and its vicinity. On the other hand, patients with bradycardia–tachycardia syndrome have been found to have more diffuse lesions of the atrium [40]. Electrophysiologic studies conducted in this investigation were found to be in accordance with earlier histologic findings [39]. The electrophysiologic observations reported in patients with partial atrial standstill [41–43] however, have been of particular interest. Ezaki et al. [41] observed that neither electrical activity nor electrical activation by electrical stimulation of \( \pm 10 \) V was present in the RA of their patients, except for the low RA. Zipes and Dejoseph [42] reported a patient in whom no right atrial activity could be recorded, and atrial pacing was accomplished only from the low atrial septum. Effendy et al. [43] reported a patient whose atrial standstill was present only in the high RA. Therefore, it appears that the high RA may be more diseased than the lower regions of the RA in these patients with partial atrial standstill. Irrespective of the presence or absence of paroxysmal AF in the patients [39], a significantly greater number of abnormal atrial electrograms have been recorded in the high RA. It is difficult to provide a simple explanation for the characteristic distribution of the abnormal atrial electrograms.

From birth, the basic structure of a small amount of connective tissue beneath the endothelial lining of both
atria is altered by proliferation of smooth muscle cells and elastic and collagen fibers. This process, called endocardial hypertrophy by Bharati and Lev [44], is more diffuse in the left atrium and more focally distributed in the RA. By maturity, there is an increase in elastic and collagenous fibers in the atrial subendocardium. At all times, the endocardial hypertrophy is more marked in the posterior wall of the atria [44]. Anderson et al. [45] have shown that during the development of the internodal atrial myocardium, the sinoatrial ring and the sinus venous are positioned in the posterior atrial wall. These findings may partially support the electrophysiologic findings of this study. Another important factor to be considered is the mechanical force of the blood entering the RA. Miyatake et al. [46] observed, by using a real-time two-dimensional Doppler flow imaging technique, that the blood flow pathway into the RA lies mainly along the posterior right atrial wall. This may account in part for the significantly higher number of abnormal atrial electrograms observed in the high RA.

2.2.2. Mechanism

During conduction of a propagating impulse, axial current flows from one myocardial cell to the adjacent cell through the gap junctions of the disks, which normally have a relatively low resistance [47]. Conduction perpendicular to the long axis of atrial muscle fibers can be delayed due to the higher effective axial resistance in the direction perpendicular to the fiber orientation [48]. This higher axial resistance results in part from fewer and shorter intercalated disks in a side-to-side direction than in an end-to-end direction. When atrial myocardial fiber bundles are separated by connective tissue, the conduction properties may be altered because of the effects on axial resistance, leading to anisotropic discontinuous propagation [49].

Spach et al. [50] reported that depressed conduction velocity reduced the amplitude and broadened the duration of the extracellular electrogram in the canine Purkinje system. In a computer model of electrogram generation, it was demonstrated that decreased conduction velocity was responsible for increased electrogram width, while increased intracellular resistance was responsible for the fractionated nature of the electrogram [51]. It was suggested that the occurrence of reentry in a given region of the atrium depends on both spatial differences in membrane properties and anatomic complexities such as a nonuniform anisotropic atrium, in which the connective tissue separates the muscle bundles [49]. Histologic studies in patients with paroxysmal AF have shown fibrodegenerative changes in the atrial muscle, muscle loss in the internodal tracts, and fibrous thickening of the pericardium [52]. In addition, detailed pathologic quantification in patients with both AF and sick sinus syndrome has disclosed an extensive fibrosis of the atrial muscle in the approaches to the sinus node and internodal tracts [53].

Fibrosis may indeed play a crucial role in AF, especially in elderly people. Furthermore, Polontchouk et al. have shown that there are also changes in the gap junction expression and distribution [54].

Therefore, an abnormally prolonged and fractionated atrial electrogram recorded in patients undergoing endocardial catheter mapping during sinus rhythm may reflect inhomogeneous local electrical activity related to a delayed and nonuniform anisotropic conduction through diseased atrial muscle [36].

2.3. Electrophysiologic findings by programmed atrial stimulation

The programmed atrial stimulation method has been most widely performed in studies with paroxysmal AF. The atrial refractory period (A-ERP) and the extent of its dispersion can be determined through use of the programmed atrial stimulation method. This method also allows eliciting of several abnormal responses of the atrial muscle, such as repetitive atrial firing, fragmented atrial activity, and intra-atrial conduction delay. The interval between the longest and shortest coupling interval that elicited one of these indicators of atrial vulnerability is often referred to as the zone of each indicator [55,56]. Patients with paroxysmal AF not only have been found to have a higher incidence of, but also to have significantly wider zones of, repetitive atrial firing, fragmented atrial activity and conduction delay than the control subjects [55–57].

2.3.1. Repetitive atrial firing

Several clinical studies have demonstrated that repetitive atrial firing is a common finding in patients with paroxysmal AF [58,59]. According to Wyndham et al. [60], repetitive atrial firing is defined as the occurrence of two or more successive atrial complexes with a return cycle of <250 ms and a subsequent cycle length of <300 ms (Fig. 4). The occurrence of repetitive atrial firing requires the presence of a short refractory period at the pacing site and prolongation of the maximum conduction delay [59,61]. The mechanism of repetitive atrial firing appears to be a local reentry around the point of stimulation in a double circuit ‘figure-of-eight’ pattern, as has been shown in experimental studies that have used a rabbit atrium and an open-chest dog [62]. Other mechanisms, such as triggered activity or enhanced automaticity, also have been described as possible mechanisms [63].

Because repetitive atrial firing can be induced in patients with paroxysmal AF or flutter, as well as in controls, some investigators have stated that this is not a specific phenomenon [56,60,64]. Nevertheless, patients with AF demonstrated a higher incidence of repetitive atrial firing and a significantly wider repetitive atrial firing zone than did the control subjects, suggesting the existence of a common
electrophysiologic mechanism in both paroxysmal AF and repetitive atrial firing [57].

Repetitive atrial firing often precedes atrial flutter or degenerates to AF [59,64–66]. Recently, Saksena et al. [66] performed simultaneous catheter mapping of right and left atrial regions at the onset and during sustenance of spontaneous AF and found that spontaneous AF was initiated by atrial premature contractions (APCs) arising from different right or left atrial regions in patients with structural heart disease. They further found that the initial region of atrial activation in AF was in proximity to the region of the APC origin. Organized and repetitive electrical activation is frequently observed in both the right and left atria at the AF onset. Although electrically-induced AF may have different activation patterns than spontaneous AF at the onset in many patients, both types of AF demonstrate organization and the earliest atrial activation in the proximity of the initiating APC.

2.3.2. Fragmented atrial activity

A single atrial extrastimulus often results in widening of the local atrial electrogram. It has been demonstrated that fragmentation and slowing of conduction in response to premature stimulation are related to paroxysmal AF [55,56,67]. Presumably, the mechanism of fragmented atrial activity is similar to that of the abnormal atrial electrogram, as previously described [36,47–54].

Ohe et al. [55] defined fragmented atrial activity elicited by atrial extrastimuli as the occurrence of disorganized atrial activity ≥150% of the duration of the local atrial electrogram of the basic beat recorded in the RA (Fig. 4). The duration of the local atrial electrogram and the induction zone of fragmented atrial activity are greater in patients with PAF than in controls [55,56]. Electrophysiologic studies performed in patients with chronic sustained lone AF after electric cardioversion also have shown a wider fragmented atrial activity zone than that in controls [57].

2.3.3. Conduction delay

The slowing of intra-atrial conduction is considered to be one of the most important requirements for the initiation of reentry and, thus, for AF or atrial flutter to develop [56,64]. A significantly wider zone of the intra-atrial conduction delay was observed in patients with paroxysmal AF than in the controls [56,67].

Recently, biatrial pacing has been developed as a technique for simultaneous activation of the RA and left atrium to reduce the intra-atrial conduction delay [26,27]. This has been reported to prevent the recurrence of AF in paced patients with a marked intra-atrial conduction delay [68]. Thus, these facts indicate that the intra-atrial conduction delay can play an important role in the onset of AF.

2.4. Abnormal atrial electrograms and atrial vulnerability with programmed atrial pacing

To evaluate the relationship among abnormal atrial electrograms recorded during sinus rhythm, repetitive atrial firing and fragmented atrial activity elicited by atrial premature stimuli [69], the patients were divided either by the presence of sick sinus syndrome and paroxysmal AF or on the basis of the presence or absence of abnormal atrial electrograms. A significantly greater vulnerability of the atrial muscle to AF was demonstrated in patients who had abnormal atrial electrograms than in those who did not have them [69]. Abnormal atrial electrograms showed
specificity and positive predictive accuracy for the inducibility of AF.

2.5. The atrial refractory period and dispersion of atrial refractoriness

It is generally believed that patients with paroxysmal AF have relatively shorter A-ERPs and a relatively wider dispersion of atrial refractoriness [70]. Simpson et al. [71] found no association between ERP and a history of paroxysmal AF or the ability of an early cycle premature beat to induce AF. Some researchers have found shorter A-ERPs in patients with paroxysmal AF [64], whereas others have not [70,72]. By determining the refractory periods at four different atrial sites, the dispersion of refractoriness was studied and no significant difference was found between patients with and without paroxysmal AF [61]. The same results were shown in patients with sinus node dysfunction and paroxysmal AF by Luck and Engel [70]. On the other hand, Michelucci et al. [73] found a wider dispersion of atrial refractoriness in idiopathic AF. These discrepancies may be partly related to the different underlying cardiac disease in patients studied, yet they also suggested that simple comparison of the refractory period or the dispersion of refractoriness might not be enough.

The A-ERPs were significantly shorter at pacing sites where repetitive atrial firing was induced than at sites where it was not induced [61]. Attuel et al. [74] stated that an increase in the vulnerability of the atrium to develop fibrillation was found to be linked to an absence, or near absence, of the physiologic adaptation of the refractory period to increasing pacing rates. Ramdat Misier et al. [75] studied AF intervals at multiple sites in the RA of patients undergoing antiarrhythmic surgery. They found that both a shorter refractory period and a larger dispersion in refractoriness are responsible for the recurrence of AF. The increase in the dispersion of refractoriness has been nicely determined in patients with idiopathic AF, using decapolar catheters [76]. Gaita et al. [77] also reported that electrical activity during AF showed a significant spatial inhomogeneity, which was more evident in patients with paroxysmal AF. Nonhomogeneous recovery of excitability has been observed at the cellular level, studied by microelectrode technique, in isolated human atrial specimens from patients with AF [78].

2.6. Site-dependent differences in electrophysiological properties

It has been observed that atrial extrastimuli are more likely to induce AF when delivered from the high RA than from the coronary sinus [79]. The repetitive atrial firing zone has been shown to be greater when the extrastimulus is delivered from the high RA than from the coronary sinus [61]. The mechanism of this phenomenon is not fully understood. It may be related to site-dependent differences in how the impulse propagates within the atrial myocardium and activates sites critical for the initiation of AF or repetitive atrial firing [80]. The presence of site-specific conduction delay can be explained on the basis of non-uniform atrial anisotropy. In addition, site-dependent dispersion of refractoriness also appears to be an important factor in the electrophysiological properties of AF [80].

2.7. Limitation of the programmed atrial stimulation method

Electrophysiologic study of the atrial muscle by using programmed stimulation has several limitations. The catheter electrode contact with the atrial endocardium seems to be one of the major problems due to the movement of the catheter with cardiac motion causing recording artifacts on the atrial electrogram and affecting the stimulation strength used for measuring the effective and functional refractory periods of the atrial muscle. Atrial vulnerability to repetitive atrial firing, AF, or both is supposed to be present also in the left atrium, but few data on this issue have been collected. The vulnerability of the other parts of the left atrium remains to be investigated. The recording of fragmented atrial activity was performed only at the high RA. Because the recording of the high RA covers a limited area of the high lateral atrium, it is possible that the electrical abnormality of the atrial area is overlooked. The sensitivity, specificity, positive and negative predictive values of the repetitive atrial firing and the fragmented atrial activity for the spontaneous episode of AF remain controversial in spite of numerous studies. The exact mode of initiation and progression of the AF wavelets remain to be defined, due to the limitations of the current recording techniques of the endocardial atrial electrogram.

3. The electrophysiological properties of triggers in AF

Research on the mechanisms and management of AF has exploded over the past 5 years, with much important work having been done in man. Especially, the work of Jais and Haissaguerre has opened the new era of electrophysiologic studies and therapies for AF to us [7,8].

Surgical therapy has been applied to the treatment of AF for almost two decades. At present, the most commonly used approach is the maze operation developed by Cox [6,23]. In this operation, critically located incisional lines prevent AF. Currently, these lines also are drawn during operations using radiofrequency current [81–84]. Thus, Haissaguerre et al. [84] investigated a staged anatomical approach using radiofrequency catheter ablation lines to prevent paroxysmal AF and they noticed that successful radiofrequency catheter ablation of paroxysmal AF was
feasible using linear atrial lesions complemented by focal ablation targeted at arrhythmogenic foci.

From previous studies, a focal mechanism was considered to be very unlikely [5,6,85]. Jais et al. and Hais-saguerre et al. [7,8] first documented that paroxysmal AF could be initiated by ectopic beats from the PVs. Chen et al. [9] more deeply investigated the electrophysiologic characteristics of both the ectopic beats originating from the PVs and the atrium and found that the electrophysiologic characteristics of the PVs were different from those in the atria. The major source of ectopic beats initiating paroxysmal AF is from PVs. However, Chen’s group reported one subgroup of focal AF is a right atrial focal AF that they observed in 4.7–6.2% of patients who had clinically documented attacks of paroxysmal AF [11,86]. The ligament of Marshall may be the origin of focal AF in some patients [13,87].

There is the possibility that ectopic foci from the PVs can also act as drivers for maintaining AF according to the electrophysiologic findings from the surgical [25] or catheter ablation [88–90] of the PV orifices in patients with chronic AF. PV isolation may be curative for chronic AF, suggesting that AF-induced atrial electrical remodeling might be reversible after the elimination of the focal source or modification of the anatomical substrate.

4. Modifying factors of the electrophysiologic properties of the atrium

It has been shown that the initiation, maintenance, and termination of AF were affected by many modifying factors of the electrophysiologic properties at the atrium (e.g. aging, AF itself, underlying heart disease, drugs, autonomic nerve system, etc.).

4.1. Aging

The increase in prevalence of AF in elderly persons has been reported to be associated with degeneration of the atrial muscle in pathologic studies [91]. Spach and Dolber [92] found evidence in the human atrial muscle of an age-related electrical uncoupling of the side-to-side connections between bundles, related to the proliferation of extensive collagenous tissue septa in intercellular spaces [92]. The zone of repetitive atrial firing, of fragmented atrial activity, and of intra-atrial conduction delay did not significantly change with aging [93]. Though this would mean that the refractory period increased, which would reduce vulnerability for AF, the longest coupling interval giving rise to these indicators of atrial vulnerability was prolonged significantly in correlation with age. Therefore a premature atrial beat, even with a long coupling interval, could induce AF, suggesting that the atrial muscle is more prone to develop AF with advancing age.

4.2. AF itself (electrical remodeling)

Developments in our understanding of AF over the last several years have led to the recognition that AF itself modifies the atrial properties (AF begets AF) [15] in a way that promotes the occurrence and maintenance of the arrhythmia. This process has been termed ‘atrial electrical remodeling’ [15]. Thus, once initiated, AF causes alterations in atrial electrical properties, including both rapid functional change and slower alternation in the ionic channel gene expression [19,20]. Electrical remodeling decreases the A-ERP in a heterogenous way, thus decreasing the size and stability of the functional atrial reentry waves and promoting multiple-circuit reentry. Whatever the initial cause of AF, electrical remodeling is likely a final common pathway that ultimately supervenes [94]. In the regional change in the atrial electrophysiologic properties related to AF, the electrophysiologic changes observed in the patients with paroxysmal AF appear to behave as if in transition from the control state to chronic AF, suggesting progressive changes in the atrial electrophysiologic properties [95]. The electrical changes were reversed within 24 h after conversion [16]. However, no return to normal atrial electrophysiology was demonstrated after long episodes of sinus rhythm in patients who previously had sustained AF [17].

AF is predominantly accompanied by decreased protein contents of the L-type Ca$^{2+}$ channel [19], sarcoplasmic reticular Ca$^{2+}$-ATPase gene [20] and several potassium channels. Reductions in the L-type Ca$^{2+}$ channels correlate with the A-ERP and rate adaptation [19]. Alterations in the gene expression of proteins involved in the calcium homeostasis occur only in patients with long-term persistent AF. In the absence of underlying heart disease, the changes are rather secondary than primary to AF [96]. Altered gene expression is an important component of the electrical remodeling process and may contribute to repolarization abnormalities in AF [97]. In patients with paroxysmal AF these reductions were observed predominantly at the protein level and not at the mRNA level, suggesting a post-transcriptional regulation [98].

In general, the expression of connexins is related to the construction of the gap junctions. The major connexins expressed in mammalian myocardium are connexin40 (Cx40) and connexin45 (Cx45) in atrium and conduction system [54,99]. As Cx40 is known to influence the conduction properties of atrial tissue and the vulnerability for AF, attenuated gap junctional remodeling with conduction slowing might be another factor in the tachycardia-induced increase in the stability of AF [54,99]. The change in expression and distribution of Cx40, results in microscopic changes in conduction properties with the generation of small areas of conduction blocks and dispersion of conduction, which stabilizes AF. The above data support the notion that conduction through the atria may be slowed while the intrinsic conduction velocity is normal [18].
4.3. Underlying heart disease

4.3.1. Wolff–Parkinson–White syndrome

AF assumes a great clinical importance in the setting of Wolff–Parkinson–White (WPW) syndrome because of the potential risk for ventricular fibrillation, circulatory collapse, and sudden death. However, the pathogenesis of AF in WPW syndrome remains unclear. Electrophysiologic evidence has been reported suggesting that AF can occur as a result of atrioventricular reciprocating tachycardia [100]. Atrial vulnerability has been found to be enhanced at short cycle lengths [100]. Therefore, abolishing atrioventricular reciprocating tachycardia should reduce the incidence of AF in patients with WPW syndrome. In addition, it has been suggested that the accessory atrioventricular pathways may participate directly in the induction of AF [101].

On the other hand, Fujimura et al. [102] reported longer intra-atrial conduction times and shorter atrial functional refractory periods in the patients with WPW syndrome associated with paroxysmal AF than in those without paroxysmal AF. Konoe et al. [103] demonstrated a significantly longer duration and greater number of fragmented deflections of atrial electrograms in patients with AF associated with WPW syndrome than in those with WPW syndrome alone. These findings suggest that the intrinsic electrical abnormalities of the atrial muscle may play an important role in the occurrence of paroxysmal AF in patients with WPW syndrome. Jackmann et al. [101] suggested, by using accessory pathway potential recordings, that the accessory connection site to the atrium functions as a network of fibers where AF originates. However, since clinical AF did not occur in patients without organic heart disease after surgical ablation of the accessory pathway [100], one should be cautious in concluding that intrinsic abnormality of the atrial muscle is the definitive factor for the development of AF. In addition, so far there is no information that the triggers (or short bursts of reentry) of AF cannot occur any longer after the ablation of the accessory pathway.

4.3.2. Other underlying heart diseases

The other arrhythmic mechanisms (e.g. atrial flutter, AV node reentry, atrial tachycardia) and all the other cardiac conditions (e.g. hypertension, valve disease, thyrotoxicosis, congestive heart failure (CHF), etc.) are also important modifying factors for the electrophysiologic properties of the atrial muscle. However, there has been little information on the relationship between the electrophysiologic substrate and underlying cardiac diseases. AF was induced in 11% of patients with hypertrophic cardiomyopathy during electrophysiologic study [104]. Patients with hypertrophic cardiomyopathy are prone to develop AF due to worsening diastolic dysfunction and left atrial dilatation rather than as a primary electrical phenomenon [105]. Li et al. [106] demonstrated a unique study to test the hypothesis that AF maintained by different substrates responds differently to antiarrhythmic-drug therapy. In this study, dofetilide was highly effective in inducting AF by atrial burst pacing in dogs with CHF but was totally ineffective in dogs with RAP. Epicardial mapping showed that CHF-related AF was often due to macroreentry, with dofetilide terminating AF by causing block in the reentry circuit. These results indicate that electrophysiologic properties of AF are different for the different types of underlying disease in AF.

4.4. Effects of drugs on the atrial electrophysiologic properties

The class I antiarrhythmic drugs have been studied most extensively regarding their effects on the electrophysiologic properties of the atrium. Intravenous administration of disopyramide (2 mg/kg) suppressed completely the induction of repetitive atrial firing in 56–59% [107,108] of patients with paroxysmal AF. The zones of repetitive atrial firing and fragmented atrial activity have been shown to be significantly decreased by disopyramide [108] and cibenzoline [109]. Disopyramide has been shown to reduce the zone of conduction delay as a result of prolongation of the atrial refractory period, in spite of prolongation of the conduction time at the basic cycle length [108] (Fig. 5). In addition, both quinidine and procainamide have been reported to prolong the action-potential duration and refractory periods in human atrial muscle preparations [110]. Flecainide has been reported to...
prolong the effective refractory period of the atrial muscle and to slow intra-atrial conduction by ~20% [111]. Among newer class III antiarrhythmic drugs, E-4031, pure IKr channel blocker, has been found to prolong the atrial refractory period in patients with paroxysmal AF. This prolongation tends to be greater at sites where repetitive atrial firing has been abolished by the drug, than at sites where the repetitive atrial firing was unchanged or newly induced [112].

Calcium channel blockers have been shown to have no effect on the electrophysiologic properties of the atrial tissue in the normal human heart [113]. Shenasa et al. [114] reported that verapamil and diltiazem prolonged the duration of electrically induced AF. In addition, Kumagai et al. [115] reported that verapamil increased the intra-atrial conduction delay without affecting the effective refractory period of the RA in patients with paroxysmal AF. Most recently, Isomoto et al. [116] demonstrated that verapamil increased the inducibility and duration of repetitive atrial firing and augmented the fragmented atrial activity in patients without a history of paroxysmal AF, but with intra-atrial conduction delay at baseline study.

Administration of calcium channel blockers before the initiation of AF, can blunt or prevent the electrophysiologic remodeling that accompanies AF [117]. Calcium overload also has been suggested to be an important factor in the initiation of arrhythmia [118]. Verapamil can attenuate short-term (less than 24 h) tachycardia-induced shortening and mal-adaptation of A-ERP and reduce the inducibility of AF. However, verapamil cannot prevent long-term (more than 1 week) tachycardia-induced change of atrial electrophysiologic properties [119]. Furthermore, verapamil increases the duration of AF in the dogs either before or after long-term rapid atrial pacing [118]. Though almost none of this deals with the human study, these findings are consistent with previously described reports [114–116]. Furthermore, Ramanna et al. [120] recently demonstrated that verapamil caused a shortening of the refractoriness and an increase in the spatial dispersion of refractoriness in patients with chronic AF.

Isoproterenol may prevent the initiation of reentrant arrhythmias by improving the conduction within the cardiac tissue [108,121].

5. The electrophysiological properties during AF

5.1. Mapping

Little information is available about the patterns of activation during AF in humans, though mapping studies in animals have suggested that AF is based on multiple reentering wavelets. Konings et al. [5] reconstructed and classified the patterns of human right atrial activation during electrically-induced AF in patients with WPW syndrome undergoing surgery for interruption of their accessory pathway(s). They concluded that three types of RA activation during AF were identified. Thus, these various types of AF in humans appear to be characterized by different numbers and dimensions of the intra-atrial reentrant circuits [5]. On the other hand, Ikeda et al. [2] recently reported that a single meandering functional reentrant wave front could result in rapid and irregular electrogram activity in human atrial tissues.

5.2. AF intervals

Recordings of electrograms have demonstrated short and variable fibrillation intervals similar to ventricular fibrillation. Opthof et al. [123] found that there was no diastolic interval between successive action potentials and that there was only a small difference in refractory periods during ventricular fibrillation.

In contrast to ventricular fibrillation, larger variations in local fibrillation intervals have been observed during AF [124]. Possible explanations for this have included either variation in the local refractory periods or the presence of a significant excitable gap [125]. Mapping of AF intervals in both canine and human AF suggested that there was a high degree of spatial organization of wave fronts [76,77] and that cells did not re-excite as soon as their refractory periods ended [6]. In the investigation of a correlation between the local AF intervals and local ERP, Ramanna et al. [76] used the mean local fibrillatory interval by measuring through the detection of intrinsic negative deflection in the unipolar electrogram recorded at the right atrial free wall and the right atrial appendage, as an index of local refractoriness. On the other hand, Kim et al. found that the AF intervals were longer than the ERPs, suggesting that reflex changes might shorten ERP in the intact heart [125]. Furthermore, Gaitz et al. proposed that the mean AF intervals did not correlate with the mean ERPs [77].

Patients with idiopathic AF showed increased dispersion of refractoriness, which may be the substrate for the observed enhanced inducibility and spontaneous occurrence of AF [76]. Botteron et al. [126] demonstrated that AF in the intact human heart was organized over a length scale consistent with reentrant excitation by using a novel method to measure the spatial organization of atrial activation during AF. This preliminary result suggests a relationship between the measured spatial organization and the clinical course of the arrhythmia [126].

Zrenner et al. [127] analyzed the electrophysiologic characteristics of paroxysmal AF and chronic AF in the human RA. They found that the majority of endocardial breakthrough points were located in the septal region and coincided anatomically with the major interatrial connection routes. Coexistence of reentrant and apparently focal activation determined the maintenance of AF in the RA in paroxysmal AF, whereas random reentry was documented more frequently in the patients with chronic
AF. Furthermore, they [128] demonstrated that differences in activation of the left and right surfaces of the interatrial septum and the preferential use and filtering effect of the interatrial connections played a significant role in explaining the differences in activation patterns of the left and right atria in patients with AF.

In typical human atrial flutter, the crista terminalis, eustachian ridge, and tricuspid annulus have been already identified as barriers to conduction. From clinical observation, it is apparent that there is a relationship between atrial fibrillation and atrial flutter in patients with atrial arrhythmias. Thus, the atrial anatomy and its relationship to the electrophysiological findings, and the role of partial or complete conduction barriers around which reentry can and cannot occur, may be of importance for AF as well [129].

6. Conclusion

Abnormal atrial electrograms during sinus rhythm and abnormal responses of the atrium elicited by programmed stimulation have been observed more frequently in patients with paroxysmal AF than in those without. A shorter A-ERP, greater dispersion of the atrial refractoriness and atrial conduction delay are also of electrophysiologic significance in the genesis of AF. Even if atrial electrical remodeling facilitates AF initiation and AF perpetuation, the initiation of AF requires a trigger. Since AF is not initiated in all patients with atrial arrhythmias, a substrate for atrial propensity to AF also is required for AF initiation. Further investigation into the electrophysiologic properties in AF will be needed in order to contribute to the future development of an appropriate treatment.

References


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