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Review Article

Atrial fibrillation from the pathologist's perspective

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ABSTRACT

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia encountered in clinical practice, is associated with increased morbidity and mortality. Electrophysiologically, it is characterized by a high rate of asynchronous atrial cell depolarization causing a loss of atrial contractile function and irregular ventricular rates. For a long time, AF was considered as a pure functional disorder without any structural background. Only in recent years, have new mapping and imaging techniques identified atrial locations, which are very often involved in the initiation and maintenance of this supraventricular arrhythmia (i.e. the distal portion of the pulmonary veins and the surrounding atrial myocardium). Morphological analysis of these myocardial sites has demonstrated significant structural remodeling as well as paved the way for further knowledge of AF natural history, pathogenesis, and treatment. This architectural myocardial disarrangement is induced by the arrhythmia itself and the very frequently associated cardiovascular disorders. At the same time, the structural remodeling is also capable of sustaining AF, thereby creating a sort of pathogenetic vicious circle. This review focuses on current understanding about the structural and genetic bases of AF with reference to their classification, pathogenesis, and clinical implications.

1. Background and aims

Atrial fibrillation (AF) is the most common sustained arrhythmia with undisputed individual and social *sequelae*. Electrophysiologically, it is characterized by a high rate (400–600 beats/minute) of asynchronous atrial cell depolarization causing a loss of atrial contractile function and irregular ventricular rates [1]. Its prevalence in the developed world is approximately 1.5–2% of the general population, with the average age of patients with this arrhythmia being 75 to 85 years. In both genders, lifetime risks for the development of AF are about one in four people aged 40 and older, this magnitude being similar to that for congestive heart failure (one in five people, for the same interval) [2]. Recent evidence suggests a trend of increased incidence and prevalence over time for AF which cannot merely be explained by an aging population. In fact, in addition to well-known conditions capable of favoring this arrhythmic disorder (i.e., valvular disease, congestive heart failure, lung disease, coronary artery disease, hypertension, diabetes mellitus, and thyroid disease) [3] new risk factors are emerging, such as obesity and obstructive sleep apnea, which might significantly predispose to AF [4]. However, in approximately 12–13% of cases, AF occurs without any clinically detectable abnormalities ("lone" or "idiopathic" AF) [5]. In turn, AF is associated with a 5-fold increased risk of ischemic stroke as a consequence of a thrombus formation in the left atrial appendage [6].

AF was long thought to represent a purely functional disorder without any distinctive anatomical characterization. However, in recent years, new mapping and imaging techniques have identified atrial sites which are predominantly involved in AF initiation and maintenance, i.e., the pulmonary veins (PVs) and the surrounding left atrial posterior wall (Fig. 1) [7,8]. Ablation procedures performed in these specific left atrial sites has very often proved efficient in restoring sinus rhythm in patients suffering from AF [9]. This increased understanding of AF pathogenesis has also generated great curiosity about its underlying histopathologic substrate and, as a consequence, its electrophysiologic implications [10]. Therefore, AF has been seen in a new light according to which it is not a purely functional disease but rather the result of diverse histological changes capable of sustaining this arrhythmic disorder [11].

This review article will focus on current understanding about the structural and genetic bases of AF as seen from the perspective of a morphologist. Their clinical implications will also be discussed. A complete PubMed search was performed in order to identify original manuscripts focusing on structural remodeling in AF and published between 1973 and 2014. Selected study papers, recently published review articles, editorials from peer-reviewed journals, book sections). In addition, the reference lists of each searched publication were reviewed. All of these were full-text English-language manuscripts.

2. Classification and natural history of atrial fibrillation

Currently, AF is classified by the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) as "paroxysmal", "persistent", "long-standing persistent", or

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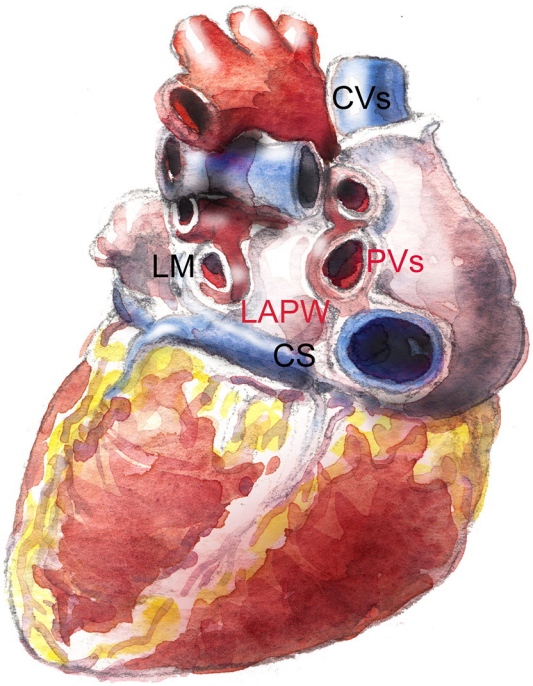

Fig. 1. Trigger points for atrial fibrillation. Postero-inferior view of the heart showing the most (red abbreviations) and the less (black abbreviations) common atrial trigger points for atrial fibrillation. Abbreviations: CS, coronary sinus; CVs, caval veins; LAPW, left atrial posterior wall; LM, ligament of Marshall; PVs, pulmonary veins.

"permanent" merely on the basis of its (often presumed) duration. *Paroxysmal* AF is defined as recurrent AF (≥2 episodes) that terminates spontaneously within 7 days. *Persistent* AF is defined as AF, which is sustained beyond 7 days, or lasts less than 7 days but necessitates pharmacologic or electrical cardioversion. *Long-standing persistent* AF is defined as continuous AF of greater than 1-year duration. *Permanent* AF refers to a group of patients where a decision has been made not to pursue restoration of sinus rhythm by any means, including catheter or surgical ablation [12]. Although widely used, this classification has been questioned by some groups particularly on the basis of its simplistic approach which fails in expounding on the real underlying atrial substrate. On this basis, in order to improve the use of both ablation and medical treatment strategies, patients suffering from AF should additionally be categorized in terms of underlying etiology (and potential substrate), risk factors, and mechanisms [13]. Seen from a morphologic standpoint, a further weak point of the present classification is that, in the "real world", there is a definite clinicopathologic *continuum* from paroxysmal to permanent AF, while a subdivision based on arrhythmia duration with specific cut-offs forces patients into rigid and heterogeneous categories.

A structural remodeling affecting the atrial myocardial architecture seems to play a crucial role in the initiation and maintenance of AF. Aging itself and several non-arrhythmic diseases such as hypertension, heart failure, valve disorders, diabetes, and thyroid dysfunctions may induce both important histological and ultrastructural changes in the atrial myocardium [11]. Clinically, the first signs of AF usually arise after months/years of remodeling and are very often preceded by asymptomatic arrhythmic episodes. In addition, once AF has taken place, also the cardiomyocyte electrophysiology are modified (so-called "electrophysiological remodeling", see below) [14]. When established, AF behaves as a progressive disease where the arrhythmia itself may induce both further structural changes and deterioration of the underlying above-mentioned diseases, thereby creating a kind of vicious circle that does nothing but make the myocardial architecture distortion worse [15]. In this scenario, paroxysmal AF may progress to persistent or even permanent AF, whereas structural remodeling seems to be reversible only during the first phases of the arrhythmic disorder. In any event, the degree of structural remodeling appears to be crucial because it may reach a point of no return beyond which sinus rhythm cannot be restored [14].

Interestingly, the atrial distribution of structural remodeling seems to modify over the natural history of AF. Haïssaguerre et al. observed that PVs are a major source of ectopic beats and can frequently initiate paroxysms of AF (triggered AF episodes). In this situation, the anatomical and electrical isolation of PVs has become a foundation of ablation techniques [16–18]. However, the success of this PV isolation is limited in some patients with paroxysmal AF and, especially, in the great majority of those subjects with persistent/permanent AF, very likely because of more extensive atrial remodeling additionally involving extra-PV locations [19,20]. The most frequent sites of non-PV atrial triggers include the posterior wall of the left atrium, the superior vena cava, the coronary sinus, the ligament of Marshall, and the region adjacent to the atrioventricular valve annuli (Fig. 1). Furthermore, the atrial ganglionated plexi may play a significant role in the pathogenesis of AF [21].

The high rate of recurrences after PV isolation alone in patients with persistent and long-standing persistent AF, has led to the identification of further strategies aimed at improving outcomes [18]. The logic for these procedures is the fact that persistent AF seems to become pathogenetically less dependent on the PV [22] since its triggers and re-entry sites are commonly found in the left atrial myocardium around the PVs, probably as a result of greater structural remodeling which, in chronic conditions, involves the surrounding atrial myocardium [23]. Consequently, although targeting the triggers located in PVs may often be sufficient in patients with paroxysmal AF, further ablation specifically targeting the altered anatomical substrate responsible for maintaining AF may be required in chronic conditions [18].

3. Morphologic findings of atrial structural remodeling in atrial fibrillation

Large population-based investigations have associated left atrial size to the risk of developing AF. The Framingham study, which prospectively followed up adults after routine surveillance M-mode echocardiograms, showed that left atrial size is an independent risk factor for the subsequent development of AF with a hazard ratio of 1.39 for every 5-mm incremental increase in left atrial size [24]. The Cardiovascular Health Study Left atrial revealed that a diameter >5 cm was associated with a relative risk of 4.05 (1.95–8.35) for the development of AF [25]. At the same time, evidence from echocardiographic prospective studies also supports the fact that AF itself can lead to atrial dilatation. AF occurring in patients with lone AF induces a slow and progressive increase in left atrial size which is independent of left ventricular changes [26]. With the passing of time, this dilation further worsens, also because of the frequent superimposition of additional structural heart diseases, such as mitral valve dysfunctions [12]. There are contradictory data regarding right atrial enlargement in AF even though in the RACE study, performed in a patient population suffering from lone AF, both atria were enlarged with the left more that the right one [26–29]. On this basis, AF and atrial dilatation may take part in a vicious cycle which would lead to the maintenance of this arrhythmia [30].

From the histopathologic standpoint, the enlarged atrial walls are the site of profound morphologic changes affecting both the cardiomyocyte component and the myocardial *interstitium* (Fig. 2A and B). These modifications have been documented by both experimental and clinical studies [11]. The most evident modification in atrial cardiomyocytes is a progressive loss of sarcomeres starting from the perinuclear area and extending eccentrically towards the sarcoplasm (so-called "myocytolysis") (Fig. 2C). Sometimes this empty perinuclear area is filled with abundant glycogen granules