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Review

Histological substrate of human atrial fibrillation

Cristina Chimenti [a,b], Matteo A. Russo [c,d], Angelo Carpi [e], Andrea Frustaci [a,*,b]

[a] Cardiovascular and Respiratory Sciences Department, La Sapienza University, viale del Policlinico 155, 00161 Rome, Italy
[b] Cellular and Molecular Cardiology Laboratory, IRCCS L. Spallanzani, Rome, Italy
[c] Department of Experimental Medicine, La Sapienza University, Rome, Italy
[d] I.R.C.C.S. San Raffaele La Pisana, Rome, Italy
[e] Department of Reproduction and Ageing, University of Pisa, Pisa, Italy

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ABSTRACT

Histologic and ultrastructural examination of atrial tissue regarding the main entities responsible of human atrial fibrillation, is reported. The pathologic changes deriving from various disorders, like degenerative, inflammatory, ischemic diseases as well as from cardiac aging and hormonal imbalance are analysed. Structural changes associated with lone atrial fibrillation and investigated by atrial biopsy are also described, as being able to provide useful information on the disease's etiology, prognosis and treatment.

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1. Introduction

Atrial fibrillation is the most common cardiac arrhythmia, with a prevalence of 0.9% in the general population [1]. Its incidence increases with age, occurring in up to 1% of people under 60 years and in more than 9% of those over 80 [1,2]. For men 65 to 74 and 75 to 84 years old, the incidences are 17.6 and 42.7, respectively, and for women, 10.1 and 21.6 events per 1000 person-years [3].

Various disorders, such as ischemic, valvular, inflammatory and degenerative heart diseases, as well as hormonal disorders and systemic hypertension predispose to atrial fibrillation. The arrhythmia may also occur in patients with no detectable heart or systemic disease, a condition known as lone atrial fibrillation [4,5].

Although it has been documented that electrical, structural and molecular remodeling of the atria may account for the self-promoting nature of the arrhythmia (atrial fibrillation begets atrial fibrillation) [6], the presence of a pre-existent pathologic substrate is required for its first manifestation [7].

We briefly review the histologic and ultrastructural atrial substrates that can determine the development of the arrhythmia in different cardiac pathologies and in the lone atrial fibrillation, reporting known pathological abnormalities but also undescribed structural changes analyzing 146 endomyocardial and surgical atrial biopsies (Table 1).

2. Cardiac aging

Several cardiac structural and functional alterations, which occur in healthy humans with advancing age may account for the age-dependent increase in atrial fibrillation. Progressive accumulation of collagen tissue, atrophy and vacuolar degeneration of myocytes with accumulation of lipofuscins, increase in the quantity of adipose tissue, gradual loss in nodal fibers with fibrofatty substitution of the sino-atrial node may all represent a structural substrate for atrial fibrillation, causing conduction inhomogeneities and reentry circuits [8–11].

Mitochondrial DNA deletions and oxidative damage increase during human aging, and may contribute to the impairment of the bioenergetic function of mitochondria, playing a role in the pathogenesis of atrial fibrillation [12]. Moreover, cell loss increases in the aged heart [13] and regenerative potential declines [14].

Another common structural atrial change observed with increased age is amyloid deposition in the atrium, which may also impair atrial conduction [15]. Heart tissue may contain two types of age-related amyloid: senile cardiac amyloid, which involves extracardiac and cardiac tissue as well and is characterized by the deposition of amyloid-derived transthyretin, and isolated atrial amyloid, which incidence reaches 90% in the ninth decade [16]. This form is limited to the atrial myocardium, characterized by the deposition of a fibrillar material derived from atrial natriuretic peptide, a hormone normally synthesized and secreted by atrial cardiomyocytes [17].

* Corresponding author. Tel.: +39 06 55170575; fax: +39 06 55170577.
E-mail address: biocard@inmi.it (A. Frustaci).

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Table 1
Atrial histology in the major clinical entities associated with atrial fibrillation.

Clinical entity	No.	Age (years)	Sex	Source of atrial tissue	Histological changes/%patients
Aging	15	81.7 ± 4.2	8M/7F	7 EMB 8 Surgical	Amyloid deposition/75 Fibrofatty substitution/28 Myocyte atrophy/75 Myocyte apoptosis/100
IHD					
Acute	3	57.3 ± 6.4	2M/1F	Surgical	Myocyte necrosis/100 Myocyte apoptosis/100 Waviness of myocardial fibers/90
Chronic	24	61.8 ± 6.8	18M/6F	Surgical	Inflammatory infiltrates/45 Fibrosis/90
Hypertension	8	53.6 ± 5.5	5M/3F	8 EMB	Myocyte hypertrophy/100 Fibrosis/100
Mitral Stenosis and Regurgitation	31	60.4 ± 8.0	18F/12M	Surgical	Myocyte hypertrophy/100 Fibrosis/100 Myocytolysis/40
Pericarditis	7	45.4 ± 15.3	4M/3F	4 EMB 3 Surgical	Focal lymphocytic myocarditis/100
DCM	9	56.1 ± 5.0	6M/3F	6 EMB 3 Surgical	Myocyte hypertrophy/100 Cardiomyopathic changes/100 Fibrosis/100
HCM	6	38.3 ± 8.3	3M/3F	5 EMB 1 Surgical	Myocyte hypertrophy/100 Fibrosis/100
Amyloidosis	11	57.7 ± 6.8	7M/4F	EMB	Amyloid deposition/100 Myocyte atrophy/100 Small vessel disease/60 Fibrosis/100
Fabry disease	12	50.5 ± 5.5	8M/4F	10 EMB 2 Surgical	Glycosphingolipid deposition in atriocytes and neuron ganglia/100 Myocyte hypertrophy/100 Fibrosis/100
Pheochromocitoma	2	58.5 ± 4.9	2F	EMB	Contraction band necrosis/100 Myocyte hypertrophy/100 Inflammatory infiltrates/50 Fibrosis/75
Hyperthyroidism	2	51.5 ± 2.1	2F	EMB	Contraction band necrosis/100 Myocyte hypertrophy/100 Inflammatory infiltrates/15 Fibrosis/100
Lone atrial fibrillation	23	40.8 ± 5.7	16M/7F	EMB	Myocarditis/66 Cardiomyopathic changes/20 Fibrosis/14

IHD: ischemic heart disease; DCM: dilated cardiomyopathy; EMB: endomyocardial biopsy; HCM: hypertrophic cardiomyopathy.

Atrial amyloid deposition could be diagnosed by endomyocardial and surgical biopsy in 75% (Table 1) of ≥ 75-year-old patients with idiopathic atrial fibrillation (AF).

The presence of amyloid could be detected histologically by the apple green birefringence with Congo red staining under polarized light and confirmed by electron microscopy (Fig. 1) and immunohistochemistry with antibodies specific for the proteins involved.

It could be found in the wall of small atrial vessels which focally showed lumen obstruction and a potential source of ischemic damage. Amyloid deposition induces permanent structural alterations of the atria, disturbing myocyte contractility and conduction. Moreover, amyloid may cause cellular toxicity by increasing free radical accumulation, lipid perossidation and apoptotic cell death [18]. It has been recently shown that in aged patients with chronic atrial fibrillation, isolated atrial amyloid deposits in the atria are heavier than in aged subjects on sinus rhythm [19].

3. Ischemic heart disease

Atrial fibrillation can occur both in acute and in chronic stages of ischemic heart disease. When this arrhythmia complicates an acute myocardial infarction, it begins early and is frequently associated with coronary occlusion proximal to the origin of the sinus node artery. Atrial infarction is usually associated with ventricular infarction, but isolated atrial infarction manifesting with chest pain and atrial fibrillation has also been described [20]. At necropsy, the focus of infarction is typically located at the junction of the sinus node and right atrium. Microscopic examination may reveal the histological changes of the acute ischemia and necrosis, including waviness of myocardial fibers, eosinophilia, karyolisis and pyknosis of nuclei, and sequentially infiltration of neutrophils and lymphocytes followed by fibroblasts and collagen fibers (Fig. 2). Patients with AF complicating an acute myocardial infarction had higher hospital death rates, even if a trend of improved survival for these patients has been recently observed [21].

In patients with chronic coronary disease, prior atrial infarction with fibrous replacement of atrial myocardium can constitute the structural basis of the arrhythmia. The prevalence of atrial fibrillation in patients with chronic ischemic heart disease has been shown to be positively correlated with older age, mitral regurgitation and congestive heart failure [22,23].

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