Review Article

Left Atrial Cardiomyopathy as a Generator of Heart Failure with Preserved Ejection Fraction

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Abstract

The left atrium is an anatomical structure relevant to the maintenance of the physiological hemodynamics of the cardiovascular system. Atrial cardiomyopathy (aCMP), defined as any change in the structure, architecture, contractility or electrophysiology of the atria, is associated with adverse clinical implications, and responsible for atrial fibrillation and stroke. Heart failure with preserved ejection fraction (HFpEF) with a predominance of atrial fibrillation (AF) is a unique clinical phenotype, characterized by mechanical dysfunction of the left atrium, congestive symptoms and poor prognosis. aCMP is a common condition among patients with HFpEF and AF. Due to the strong association between aCMP and HFpEF, the diagnosis of aCMP has clinical relevance in patients with HFpEF. The objective of this review is to help identify aCMP as a risk factor for the development of HFpEF.

Introduction

The left atrium is an anatomical structure with great importance for the maintenance of the physiological hemodynamics of the cardiovascular system, serving as a reservoir, conduit and pump, functions that contribute to the left ventricular (LV) filling. Consequently, left atrial (LA) dysfunction is associated with adverse clinical implications, highlighting the importance and applicability of its diagnosis. This is particularly true and known in the setting of mitral stenosis, aortic stenosis, atrial fibrillation (AF) and has recently gained attention in the context of heart failure (HF) syndrome with preserved ejection fraction (HFpEF).[1]

HFpEF is a syndrome of high prevalence and high morbidity and mortality. The pathophysiology of the HFpEF phenotype is partially known, still with pivotal doubts, which surely led to the delay in the establishment of a disease-modifying treatment that only began to advance in recent years.[2] HFpEF is a prevalent syndrome, particularly in elderly female and hypertensive patients, and one of the mechanisms observed in this group of patients is atrial cardiomyopathy (aCMP).[3] Both aCMP and HFpEF are associated with increased left atrium, which is a recognized marker of LV diastolic dysfunction and is independently associated with increased risk of morbidity and mortality. The role of all three phases of LA function in patients with HFpEF is less well understood, especially in those patients with no history of AF and with normal left atrium.[4]

The objective of this review is to help identify aCMP as a risk factor for the development of HFpEF.

To structure this review article, two databases were searched, Medline and Scielo, for the following keywords in English "heart failure with preserved ejection fraction; atrial fibrillation; atrial myocardiopathy". The survey took place in June 2022. Prospective and retrospective studies were included and clinical cases and abstracts presented at scientific meetings were excluded. The eligibility of each study was independently assessed by two investigators. The divergent opinions regarding the relevance of the articles were resolved by consensus among the authors.

Atrial cardiomyopathy and HFpEF

The atria

The atria have a very complex structure differing from that of the ventricles and provide an important contribution to cardiac physiology. This structural complexity has important implications for the atrial mechanical function that are identified today as markers of aCMP.[5] The atria have an impact on ventricular filling and serve as a reservoir but are also important elements of the cardiac conduction system, as they protect the sinus node and the atrioventricular node. The atria also secrete atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), which are important regulators of homeostasis.[6,7]

Each atrium has a characteristic morphology of atrial body and appendage (Figure 1). In the body, there is a venous component with the orifices of the systemic and pulmonary veins and a vestibular component that surrounds the atrial outlet.[8] The interatrial septum separates the atrial bodies. The venous component of the left atrium is located posterosuperiorly and receives the pulmonary veins at the four corners, forming a prominent atrial dome.[8]

The appendix of the left atrium is smaller and narrower than the appendix of the right atrium, with different

Keywords

Atrial Function, Left; Atrial Fibrillation; Heart Failure, Diastolic

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shapes and a distinct opening to the atrial body covering the left circumflex coronary artery. There are different morphologies of the LA appendage described in the literature and it seems that the appendix morphology is correlated with the risk of developing thrombogenesis.[9] However, despite the apparent inconvenience of the existence of the LA appendix, this structure is attributed a role in volume regulation. Animal studies have shown that the elimination of the LA appendix can inhibit the manifestation of thirst because of hypovolemia.[10]

Atrial cardiomyocytes are geometrically complex cylinders and the only clear microscopic morphological difference between atrial and ventricular cardiomyocytes is in their size. The transverse diameter of the atrial cardiomyocyte is 12μm while the diameter of the ventricular cardiomyocyte is around 22μm.[11,12]

The atria have a series of electrophysiological characteristics that make them different from the ventricles, and susceptible to the development of arrhythmias.[7] Atrial cardiomyocytes have action potential properties that are different from ventricular ones, mainly due to the distribution of distinct ion channels.[13] Atrial potassium current is lower than the ventricular potassium current, resulting in a less negative resting potential and a more gradual slope of phase 3 repolarization (Figure 2). These cellular electrophysiological features have implications for the mechanism of action of antiarrhythmic drugs and may also alter responses to cardiac arrhythmias.[14]

LA pump function represents the increase in LV filling due to active atrial contraction and is estimated by measurements of cardiac output with and without effective atrial systole. The relative importance of the LA contribution to LV filling and cardiac output remains controversial.[7]

The conduit function performed by the left atrium occurs mainly during ventricular diastole and represents the transport of blood volume that cannot be attributed to reservoir or pump functions, corresponding to approximately one third of atrial flow.[15] There is a reciprocal relationship between the conduction and the reservoir functions of the LA; a redistribution between these functions is an important compensatory mechanism that facilitates LV filling in the presence of myocardial ischemia, hypertensive heart disease and mitral stenosis. Conduit function is estimated by early diastolic transmitral flow, pulmonary vein flow in diastole, and LA strain during early diastole.[7]

Definition of aCMP

aCMP can be defined as any change in the structure, architecture, contractility or electrophysiology that affects the atria with the potential to produce clinically relevant manifestations, mainly arrhythmogenic.[7]

Diseases and syndromes such as systemic arterial hypertension, HFpEF HF with reduced ejection fraction (HFrEF), diabetes mellitus, and myocarditis, or conditions such as aging and endocrine abnormalities are known to induce or contribute to aCMP. However, the changes are not necessarily disease-specific and pathological features often share many similarities.[16,17] The extent of pathological changes can vary over time and location in the atrium, causing substantial intra- and inter-individual differences. Pro-inflammatory conditions such as chronic obstructive pulmonary disease, possibly mediated by interleukin-6 and tumor necrosis factor-α, are associated with atrial arrhythmias.[18] Furthermore, while some pathological processes can affect the atria very selectively, such as AF-induced remodeling, most cardiomyopathies that affect the atria also involve the ventricles to a greater or lesser extent.[7]

The EHRA/HRS/APHRS/SOLAECE Consensus[7] proposed a pathophysiological classification for atrial cardiomyopathies, with definition of four classes (EHRAS), namely: (I) main alterations of cardiomyocytes; (II) mainly fibrotic changes; (III) cardiomyocyte-pathology/fibrosis combination; (IV) mainly non-collagenous infiltration (with or without cardiomyocyte alterations) (Table 1). This simple classification can help convey the primary underlying pathology in various clinical conditions. However, the class may change over time and differ in atrial sites in some patients. Thus, this classification is purely descriptive

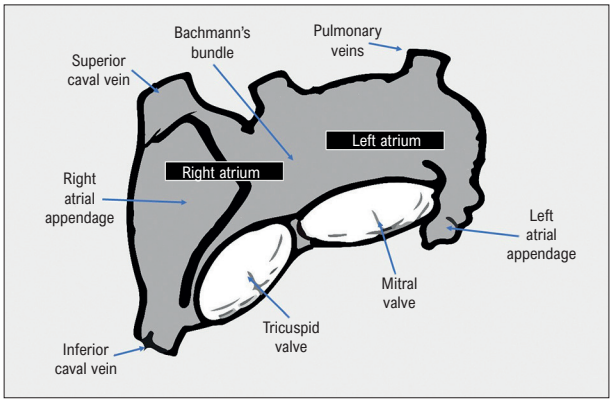

Figure 1 – *Representation of the upper and lower left and right atria; the Bachmann's bundle is part of the conduction system of the atria.*[7]

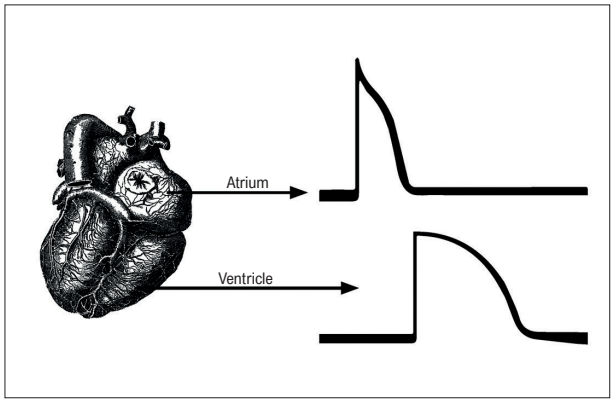

Figure 2 – *Action potential of atrial and ventricular myocytes.*[7]

Table 1 – Classification of Atrial Cardiomyopathy

Class	Histological Characterization
I	Morphological or molecular changes that "mainly" affect cardiomyocytes in terms of cellular hypertrophy and myocytolysis; no significant pathological tissue fibrosis or other interstitial changes
II	Predominantly fibrotic alterations; cardiomyocytes appear normal
III	Combination of cardiomyocyte changes (e.g., cellular hypertrophy, myocytolysis) and fibrotic changes
IV	Alteration of the interstitial matrix without accumulation of collagen fibers
IVa	amyloid accumulation
IVf	fatty infiltration
IVi	inflammatory cells
IVo	Other interstitial changes

EHRA/HRS/APHRS/SOLAECE Expert Consensus[7]

and, unlike other classifications such as NYHA, there is no progression in severity from EHRAS class I to class IV. This classification can be useful to describe pathological changes in biopsies and to correlate results obtained from imaging tests with diaseases.[7]

Atrial fibrillation

AF is the most common arrhythmia in patients with heart disease, affecting an estimated 33 million people worldwide.[19] It is important to emphasize that aCMP can be induced or exacerbated by AF, which has unique epidemiological, pathophysiological and clinical characteristics. AF-mediated aCMP is defined as having AF as the sole cause of ventricular dysfunction in patients with existing cardiomyopathy or HF.[20] Similar to cardiomyopathy caused by other arrhythmias, AF-induced cardiomyopathy can be at least partially reversed by restoration of sinus rhythm, thus creating a crucial opportunity for clinical intervention.[19]

Experimental and clinical studies have clarified the pathophysiological mechanisms of arrhythmia, especially on a molecular basis. Electrical, contractile and structural remodeling, calcium handling abnormalities, autonomic imbalance, and genetic factors appear to play a crucial role in the initiation and maintenance of AF. However, the exact pathophysiological mechanisms of AF are still not fully understood, and it is not known whether AF is an unclassified cardiomyopathy or a distinct disease.[21]

According to Coumel's triangle of arrhythmogenesis, three pillars are needed at the onset of clinical AF: (a) the triggering factor; (b) the arrhythmogenic substrate; and (c) the modulating factors. The interaction between these three elements determines the clinical picture of AF[21] (Figure 3).

Several modulating factors contribute to the onset and perpetuation of AF, with aging as a significant risk factor for the development of AF. Seminal studies by Spach and Dolber described microscopic evidence of fibrosis in association with an electrical uncoupling of connections in the aged human atrium. These structural changes were associated with conduction anisotropy, providing the necessary substrate for the reentry phenomenon.[22]

The role of inflammation in the onset of AF was supported by the fact that inflammatory states such as myocarditis, pericarditis and cardiac surgery are often associated with arrhythmia. Histological findings of atrial myocarditis were identified in patients with isolated AF.[23] Several prospective epidemiological studies have confirmed that inflammation may confer an increased risk of AF. The epidemiological relationship between the incidence of cancer and AF also supports the thesis that inflammation would be the common trigger between the two clinical conditions.[24]

Obesity is associated with an increased incidence of AF. There is a 3% to 8% greater risk of new onset AF with each unit increase in body mass index (BMI),[25,26] regardless of other cardiovascular risk factors such as dyslipidemia, hypertension, and diabetes. The mechanisms by which obesity can lead to AF are currently unknown. The increase in LA size correlates with BMI and is a possible explanation for the onset of AF in these patients. Diastolic dysfunction may be a result of myocardial thickening, increased plasma volume and increased neurohormonal activation.[27-30] An additional interpretation points out to the inflammatory action of extracellular vesicles of pericardial fat and its influence on cell apoptosis, fibrosis and proarrhythmic effect in the development of aCMP.[30]

Obstructive sleep apnea (OSA) is a strong predictor of AF incidence. OSA induces intermittent hypoxemia and hypercapnia, sympathetic activation, and changes in blood pressure. Elevated intrathoracic pressure caused by inspiration against an obstructed airway leads to an increase in the transmural pressure gradient, which in turn can lead to atrial stretch. In addition, OSA is associated with diastolic dysfunction.[31] These pathophysiological mechanisms can lead to greater vulnerability to AF. Patients with OSA have been shown to have a higher rate of recurrence of AF after successful cardioversion than patients without OSA, and treatment with continuous positive airway pressure reduces the occurrence of AF.[32]

Atrial cardiomyopathy, FA and HFpEF

The atrial myocardium is affected by many cardiac and non-cardiac conditions and is, in some respects, more sensitive than the ventricular myocardium.[33,34] There are three important mechanisms in the development of aCMP: fibrosis, electrical dysfunction, and mechanical dysfunction. Atrial inflammation is a key factor in the formation of atrial fibrosis and the increased risk of AF.[35] Progressive fibrosis can lead to conduction abnormalities as well as structural changes in the atrium. The loss of viable myocytes and the increase in wall tissue stiffness

due to excessive fibrosis ultimately reduce atrial function[36] (Figure 4).

The atria are activated, in addition to the three specialized internodal tracts, through functional cardiomyocytes,[37] so that any change in the atrial myocardium can cause significant electrophysiological disturbances. Furthermore, atrial cells, both cardiomyocytes and non-cardiomyocyte elements such as fibroblasts and endothelial cells, react rapidly and extensively to pathological stimuli and are influenced by many predisposing genetic factors. Responses include hypertrophy and contractile dysfunction of atrial cardiomyocytes, arrhythmogenic changes in the cardiomyocyte ion channel, proliferation of atrial fibroblasts, hyperinnervation, and thrombogenic changes.[38] Thus, atrial diseases have a substantial impact on cardiac performance, occurrence of arrhythmia, especially AF, and increased risk of stroke.[39,40]

HF is a common cause of AF[33] and atrial phenotype induced the disease is complex. A particularly important component is atrial fibrosis, which in experimental models occurs earlier in the course of HF, and to a much greater extent than in the ventricles, at least in part due to phenotype differences of atrioventricular fibroblasts.[34] In HF, fibrosis is slow and the AF-promoting substrate predominantly accompanies fibrosis rather than other components of atrial remodeling, such as ionic current or connexin changes. In HF, increased ventricular pressure or volume is a strong trigger for atrial enlargement and remodeling. In chronic conditions, LA volume and tension correlate with LV end-diastolic pressures, regardless of ejection fraction. Mechanical stress induces stretching and stiffening of the atria. Atrial fibrosis is perpetuated by atrial distention and is related to activation of profibrotic signaling cascades and apoptosis/necrosis of cells, as well as activation of a fetal genetic program.[7]

Unlike AF-induced remodeling, changes in atrial ionic current in HF do not shorten the action potential duration or cause general slowing of conduction and therefore do not directly contribute to the formation of arrhythmias.[41]

AF-predominant HFpEF is a unique clinical phenotype, characterized by LA mechanical dysfunction, congestive symptoms, and poor prognosis. ACMP is a common condition among patients with HFpEF and AF, and is associated with worse pulmonary vascular resistance and right ventricular function, and higher oxygen consumption. In addition, these patients may have abnormalities in right atrial function that lead to increased venous congestion. Patients with HFpEF with predominance of AF may have marked LA remodeling without substantial changes in LV performance. While loss of LA contractile function due to AF undoubtedly contributes to the clinical manifestations of aPMC, reduced LA compliance adversely compromises hemodynamics.[38]

Recently, a new element has been identified as a contributing factor to the pathophysiology of HFpEF. Dilatation of the mitral and tricuspid valve rings contributes to valve regurgitation by worsening atrial remodeling and can lead to an overload in a small, rigid ventricle, thereby causing an increase in filling pressures.[42] In addition, mitral annulus dilatation results in functional mitral regurgitation, further contributing to LA dysfunction. These findings suggest that aPMC may occur disproportionately to LV dysfunction in HFpEF with a predominance of AF.[1]

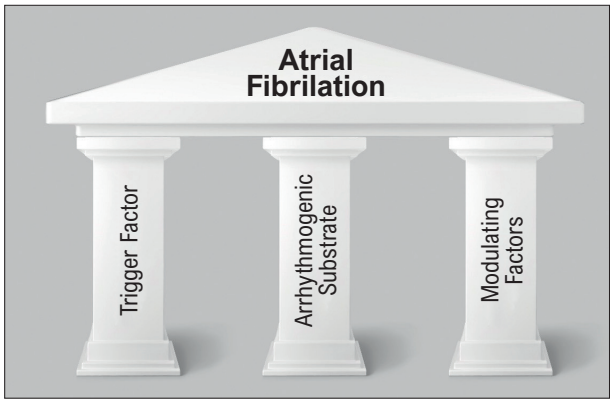

Figure 3 – *According to Coumel's triangle of arrhythmogenesis, three pillars are needed at the onset of clinical arrhythmia: the triggering factor, the arrhythmogenic substrate, and the modulating factors.*[21]

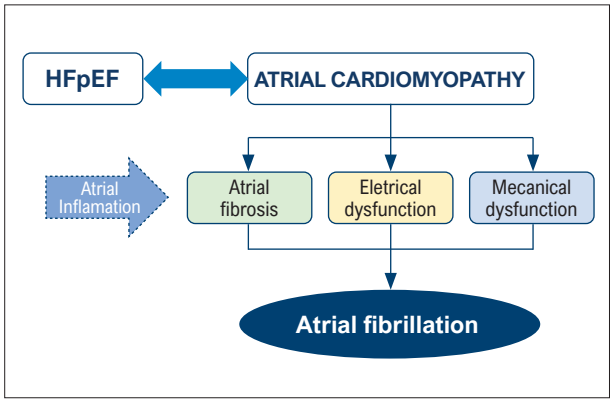

Figure 4 – *Atrial cardiomyopathy is composed of atrial fibrosis, mechanical dysfunction, and electrical dysfunction. The evaluation of these three components is done through different methods; HFpEF: heart failure with preserved ejection fraction.*[35]

HFpEF and AF share common pathophysiological features including a relative nitric oxide deficiency[34] and symptoms like dyspnea and exercise intolerance. Such nonspecific symptoms in isolated AF are commonly thought to be secondary to the arrhythmia. However, these patients likely have substantial aCMP, and restoration of sinus rhythm may not completely relieve symptoms. These patients should be considered as having HFpEF with a predominance of AF. Indeed, in a cohort of patients with AF and unexplained dyspnea, the probability of undiagnosed HFpEF was greater than 50%.[43] Recently, a risk score for HFpEF, the H2FpEF score, identified AF as the most important clinical variable to predict HFpEF among patients with dyspnea. Thus, aCMP secondary to AF is one of the main contributors to the pathogenesis of HFpEF.[43]

The left atrium stretches in HFpEF due to the chronic elevation of LV filling pressure and LA pressure, resulting in LA remodeling. Therefore, atrial size is often increased in HFpEF, which has not only become a diagnostic criterion, but is also useful as a prognostic factor.[44] Although LV diastolic dysfunction is the fundamental pathophysiological change in HFpEF, this condition is difficult to be determined solely by the occurrence of diastolic dysfunction. In fact, LA dilation (LA volume >32mL/m^2) was recommended to be included as an additional structural abnormality for the diagnosis of HFpEF in the European Society of Cardiology[45] guideline and the Brazilian Heart Failure Guideline.[46] Previous studies have shown that patients with HFpEF had a larger LA size than hypertensive patients with LV hypertrophy. Indeed, LV hypertrophy is also a common precursor of HFpEF and an indicator of elevated left atrial pressure leading to atrial remodeling.[47,48]

A population-based cohort study[3] showed that more than two-thirds of patients with HFpEF had AF before (risk factor), concomitantly or after the diagnosis of HFpEF (comorbidity), highlighting the interaction of these two conditions. At the diagnosis of HFpEF, patients with AF (previous or concomitant) were older and had larger atria, worse diastolic dysfunction, and higher BNP levels than those in sinus rhythm, consistent with more advanced HF. The development of incident AF was associated with advanced age, systemic arterial hypertension, renal dysfunction, LA dilatation and diastolic dysfunction in the diagnosis of HF. Importantly, both prevalent AF and incident AF were associated with worse survival in HFpEF even after adjusting for potential confounding factors. These data suggest that AF may be a risk factor and potentially a comorbidity of increased mortality in HFpEF, independently of other known risk factors.[3]

HFpEF increases the risk of aCMP and AF

The most commonly recognized mechanism by which HFpEF gives rise to AF is the structural and functional remodeling of the left atrium, which is substrate for aCMP. In patients with HFpEF, LA volumes are 68% greater compared to age-matched controls and 40% greater than in patients with hypertensive heart disease without HF.[49] LE enlargement in HFpEF is a well-established proarrhythmic substrate associated with atrial fibrosis,[49] and the abnormal distribution of gap junctions and loss of cell-to-cell coupling in areas of fibrosis contribute to electrical remodeling, increased atrial refractoriness and development of AF.[50,51]

In aCMP, there is also the important role of gap junctions in atrial remodeling, involving atrial connexin proteins[52] and the consequent heterogeneity of impulse propagation, establishing reentry circuits that predispose to AF.[52] In this case, studies have not been able to define the underlying disorder, whether HFpEF or aCMP. Therefore, it remains a diagnostic dilemma to discriminate HFpEF from aCMP/AF due to converging symptoms like shortness of breath and exercise intolerance. However, accurately distinguishing one condition from another is important as their treatments may differ, in part because of the potentially different pathophysiology.[42] Therefore, the overlap of AF with HFpEF makes the interpretation of the definitive causal mechanism based on clinical features complex.[52]

Mechanisms by which aCMP and AF give rise to HFpEF

As aCMP leads to LA dilation, alters atrial function and causes atrial fibrosis, it can be a direct cause of HFpEF. Indeed, successful cardioversion of AF is associated with restoration of atrial booster pump function and improved ventricular filling, with the atrial contribution to ventricular filling increasing from 30% to 47% one month after return to sinus rhythm.[53] AF is also associated with LV myocardial fibrosis, which in turn contributes to diastolic dysfunction and HFpEF. In addition, atrioventricular annulus remodeling with progressive mitral and tricuspid regurgitation may be another mechanism by which aCMP causes HFpEF. ANP depletion, which occurs in permanent AF, can lead to further vasoconstriction and congestion and thus set the stage for incident HFpEF.[54]

HFpEF and aCMP share common pathophysiological mechanisms, as a substantial proportion of patients with HFpEF experience AF. Also, these conditions probably share pathophysiological mechanisms, such as systemic inflammation, neurohumoral activation, increased activity of the renin-angiotensin-aldosterone system, endothelial dysfunction, reduced ANP release, mitral and tricuspid annular remodeling, chronotropic incompetence and tachycardiomyopathy.[52]

In aCMP, it has been often proposed that HF develops due to tachycardia or cardiomyopathy induced by hemodynamic changes, cellular effects, and neurohormonal activation. The hemodynamic changes that lead to aCMP are: shortened diastasis, reduced cardiac output, structural effects such as eccentric LV remodeling, subendocardial fibrosis and impaired myocardial perfusion. The main cellular alterations related to aCMP include changes in the cytoskeleton, disruption of the mitochondrial matrix and abnormal manipulation of calcium. Finally, neurohormonal activation, such as the upregulation of the renin-angiotensin-aldosterone system and natriuretic peptides would also be involved in the development of aCMP.[55,56]

Diagnosis of aCMP

The correct diagnosis of aCMP is of clinical importance and includes electrocardiography (ECG), echocardiography, cardiac magnetic resonance (CMR) imaging, and biomarkers, which can identify and quantify structural, mechanical, and electrical dysfunction in the atria (Figure 5).

An abnormal electrocardiogram (ECG) can provide information about conduction disorders and electrical remodeling. Studies analyzing ECG parameters have reported heterogenous definitions of aCMP[57] (Figure 6).

Analysis of fibrillatory waves (f waves) may be suitable for detecting both electrophysiological and structural changes in the atria. Coarse-wave AF, defined as f-wave amplitude in

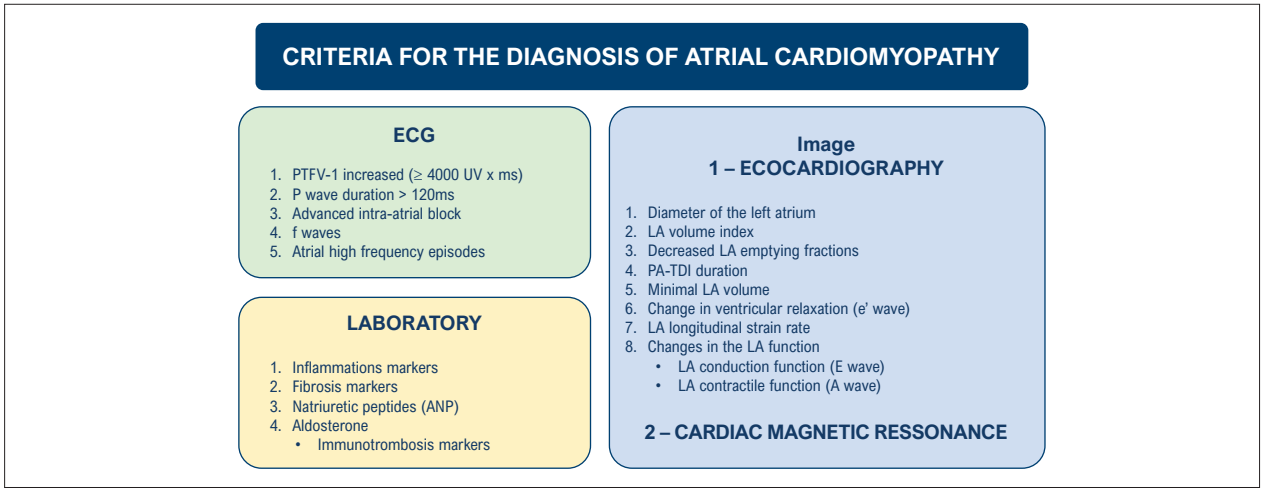

Figure 5 – *Main laboratory criteria, electrocardiogram and echocardiogram for the diagnosis of atrial cardiomyopathy;[57] PTFV-1: power terminal force on lead V1; PA-TDI: total atrial conduction time assessed by tissue Doppler; LA: left atrial.*

lead V1 ≥1mm, is associated with decreased LA appendage ejection fraction and decreased maximum atrial emptying velocity.[57] F-wave amplitude strongly correlates with LA volume measured by echocardiography.[58]

The P wave represents atrial depolarization and is associated with atrial electrical remodeling. P wave parameters include its duration, dispersion, axis, voltage, area, atrial block and terminal force in lead V1 (PTFV1).[59] P-wave parameters are predictive of ischemic stroke, regardless of AF, suggesting that they may reflect atrial remodeling independent of arrhythmogenesis.[59]

PTFV1 is an electrocardiographic marker for atrial remodeling. The P wave in lead V1 is usually biphasic, where the second negative portion of the P wave represents the propagation of excitation in the left atrium. PTFV1 is determined by multiplying the amplitude of the second portion of the P wave by its width. A PTFV1 ≥ −4,000μV × ms is considered pathological.[57]

An ECG analysis using artificial intelligence was performed to detect CMPa in 613 patients with HFpEF.[60] This method is based on a computer-aided algorithm that analyzes data of resting 12-lead ECG and includes a statement (criteria) about the probability of AF. Structural heart disease was more severe in patients with a higher probability of AF assessed by artificial intelligence, with LV hypertrophy, higher LA volumes, and decreased LA reservoir on echocardiography. Each 10% increase in the likelihood of AF by artificial intelligence resulted in a 31% higher risk of developing new-onset AF among patients with sinus rhythm and without prior AF. In the total population, every 10% increase in the likelihood of AF by artificial intelligence led to a 12% greater risk of death.

Echocardiography is the imaging technique of choice for screening and monitoring patients with abnormal LA morphology and function due to its widespread, non-invasive, and cost-effective use. Thus, echocardiography may be useful in detecting aCMP. In studies that investigated the usefulness of echocardiography, aCMP was defined by demonstrating an association of abnormal LA size with primarily clinical outcomes such as AF and AF recurrence after ablation and ischemic stroke.[57]

The LA volume (LAV) index is more accurate to estimate atrial size than LA diameter.[57] Increased LAV index has been described as a potential early marker of aCMP and is often present in patients with AF.[61]

In addition to LAV abnormalities that represent structural remodeling, assessment of atrial function can provide other important indicators for the presence of aCMP. Both increased LA and decreased LA void fraction are common phenomena

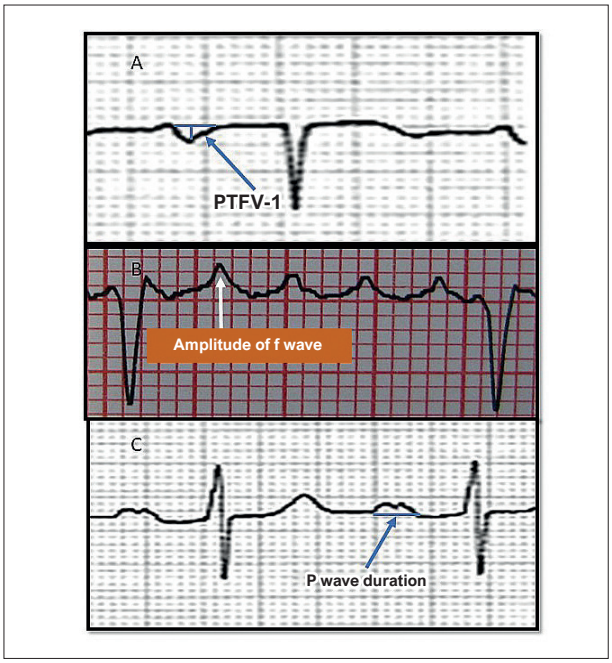

Figure 6 – *Examples of electrocardiogram changes that may indicate atrial cardiomyopathy.[57] PTFV-1: power terminal force on lead V1.*

in patients with AF, with a negative correlation between LA size and void fraction.[61]

The assessment of LA function is also possible by Doppler echocardiographic measurements, and altered LA function may be indicative of aCMP. While LA conduction function, represented by transmitral E wave velocity, increases with greater incidence of AF, there is an opposite effect on LA contractile function, represented by transmitral A wave velocity and the mitral annular tissue Doppler velocity.[61]

Another important marker of aCMP would be LA deformity (atrial strain), a cyclic process analyzed in three phases: reservoir phase, conduit phase and contraction phase. Traces of LA strain obtained by speckle-tracking echocardiography are largely a mirror image of strain in the left ventricle, since the LA and left ventricle share the mitral annulus.[62] The superiority of atrial strain over left atrial volume index, a variable already well established in the evaluation of patients with HFpEF, has been discussed.[63]

CMR imaging is considered the gold standard for assessing structural and functional changes in the heart. Gadolinium-enhanced CMR shows good performance in the assessment of atrial fibrosis, helping to identify eligible patients for AF ablation and to predict the course of sinoatrial node dysfunction, AF progression, and stroke risk in AF patients.[7]

Several circulating biomarkers, including inflammatory and fibrosis biomarkers and atrial peptides, have been proposed to estimate atrial remodeling and aCMP. However, there are conflicting results, as biomarkers related to inflammation and fibrosis are not specific to these conditions. In view of this, the clinical value of biomarkers in the assessment of aCMP is unclear and their use in routine screening is questionable.[57]

Treatment of aCMP

The treatment of aCMP should involve the control of underlying risk factors, anticoagulation, and the use of medical therapy established in the guidelines.[19] Controlling heart rate is a reasonable first step in controlling clinical symptoms and restoring cardiac function. Heart rate control with short-term cardioversion can also be attempted in the initial phase. For long-term treatment, existing evidence supports the use of AF ablation as a preferred strategy for patients who are good candidates for the method. Long-term heart rate control can be used as an alternative for patients who are not good candidates for AF ablation or who prefer a conservative management strategy even knowig it may be inferior to ablation in long-term clinical outcomes. With close monitoring, antiarrhythmic drugs can be used in a group of patients independently or as an adjunct to AF ablation to aid in rhythm control. When this control is not possible and pharmacological rate control is inadequate, atrioventricular nodal ablation with physiological stimulation may be considered.

Numerous randomized controlled trials and multicenter observational registries have demonstrated the superiority of AF ablation over drug therapy for maintaining sinus rhythm. However, late recurrences are common and associated with more advanced atrial substrate and structural heart disease.[19]

Conclusion

aCMP has been associated with HFpEF and has a significant impact on atrial function and the development of arrhythmias, especially AF. AF occurs in more than half of individuals with HFpEF, and HFpEF occurs in more than a third of individuals with AF. Although HFpEF and aCMP frequently coexist, there are numerous unanswered questions about the pathophysiology, symptomatology, diagnosis, and prognosis of both conditions. When together, aCMP and HFpEF offer a poor prognosis to patients.

Author Contributions

Conception and design of the research and Acquisition of data: Jorge AJL; Writing of the manuscript: Jorge AJL, Martins WA, Mesquita ET, Carvalho MRM; Critical revision of the manuscript for important intellectual content: Jorge AJL, Martins WA, Mesquita ET.

Potential Conflict of Interest

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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