Atrial Failure: What Do We Know About It?

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ABSTRACT

Heart failure is the end of all pathological conditions in the heart. Most accepted paradigms in heart failure are always preceded by left ventricle disfunction. Currently, there are several clinical studies that show that heart failure may occur without prior left ventricular dysfunction. Left atrial dysfunction may play a more important role in heart failure than previously expected. Failure of the left atrium can exist independently of left ventricle dysfunction and mitral valve abnormalities. Atrial failure, just like left ventricular failure, can lead to global heart failure. Etiology, pathomechanism and clinical symptoms of atrial failure are complex and not well understood. This review will explain atrial failure.

Keywords*: atrial dysfunction, failure, etiology, pathomechanism, clinical symptoms*

INTRODUCTION

To date, heart failure (HF) has been a never-ending story for cardiologists. Despite many attempts to untangle its complexity, there is no single conceptual paradigm that can rationalize this precise event. HF syndrome is defined as the inability of the heart to provide adequate blood to the body and is classified according to whether it is systolic and/or diastolic, acute/ chronic, compensated or uncompensated, and uni- or bi-ventricular.[1] Many cardiologists consider neurohormonal factors and ventricular function to be one the key player in the pathomechanism of HF and under-estimate the role of the atria.[2] HF is initiated when either the cardiac myocytes are damaged or myocardium are altered while generating force. As a consequence, the heart is not able to contract normally. Recently, through the development of cardiac imaging modalities, many clinicians have agreed that the atria play a more critical role than previously expected. Alteration of atria function arises as a result of alteration of its mechanical or hemostatic function, or electrical physiology of the ventricle.[3]

HF has an extensive variety of clinical symptoms, although in left ventricle (LV) dysfunction, asymptomatic conditions may occur and there is no rigid explanation to explain this phenomenon.[2] However, many scientists believe that neurohormonal and cytokine interactions result in heart remodeling, including the atria chambers.[2-3] The left atrium (LA) is not only involved in LV filling, but also has a bigger role via its multiple mechanisms, such as its endocrine function (atrial natriuretic peptide/ ANP) and regulator function (regulation of the autonomic nervous system and antidiuretic

hormone/ADH).[4] Recently, concerns have risen considering atrial failure to be a new separate entity, which may reduce heart function without significant valvular or ventricular abnormalities.[3] Failure of the LA may trigger neurohumoral overactivity, vasoconstriction, and volume overload.[5]

STRUCTURE AND FUNCTION OF THE LEFT ATRIUM

McAlpine classifies the muscular wall of the LA into the superior, posterior, left lateral, septal/ medial, and anterior regions, especially for interventionist purposes.[6] Nevertheless, the thickness of the muscular LA wall is varied, and the anterior part is especially thin near the vestibule of the mitral annulus and is defined as the "unprotected" area by McAlpine, in that it has a greater risk of perforation.[6-7] Posteriorly, the area around the orifices of the left and right pulmonary veins tend to be thinner and also border with the vagal nerve.[6] Muscle sleeves that spread from the left atrium to the outer aspects of the venous wall are considered to be important in electrical heart activity, especially due to their association with focal activity which initiates atrial fibrillation (AF).[8] The epicardial fat pads at the veno-atrial junction contain autonomic nerve bundles and intrinsic ganglia.[6]

Anatomically, the pulmonary vein (PV) is a varied anastomosis connected to the left atrium and found at the posterior aspect of the LA.[9] At the veno-atrial junction, there are no clear separating structures between the atrium and vein. The atrial musculature extends to the pulmonary vein and acts as a sphincter avoiding reflux during atrial systole. It has been associated as a source of ectopic beats.[8] Moreover, PV attachment also favors early diastolic LV filling and avoiding blood stasis.[10] In the LA wall, there is an infolding that protrudes to the external part of the heart called the left atrial appendage (LAA). It is small, narrow, and tubular in shape, and the left appendage mirrors the right appedage.[6] A postmortem study showed that the atrial appendages from patients with atrial fibrillation had 3 times the volume of those with a normal heart beat.[11] Several investigations also concluded that the LAA is associated with atrial fibrillation and thrombus formation.[11,12]

The LA mechanically consist of three phases; the filling phase, passive emptying phase and active emptying phase.[3,13] The LA stretches during the filling phase and blood flows from the PV into the LA chamber. The filling phase is followed by passive emptying, which is marked by the opening of the mitral valve and the blood flowing passively downstream from the atria to the ventricle. The filling phase is affected by the size, function, relaxation and stiffness of the LA.[13,14] Then, the muscle in the LA is immediately shortened (active emptying) to ensure that the entire volume of the LA is transferred into the ventricle chamber. This process is referred to as the atrial systolic or LA booster pump function. The LA's systolic function is affected by the diastolic myocardial length, afterload, and myocardial contractility.[14] This can be seen in **Figure 1**.

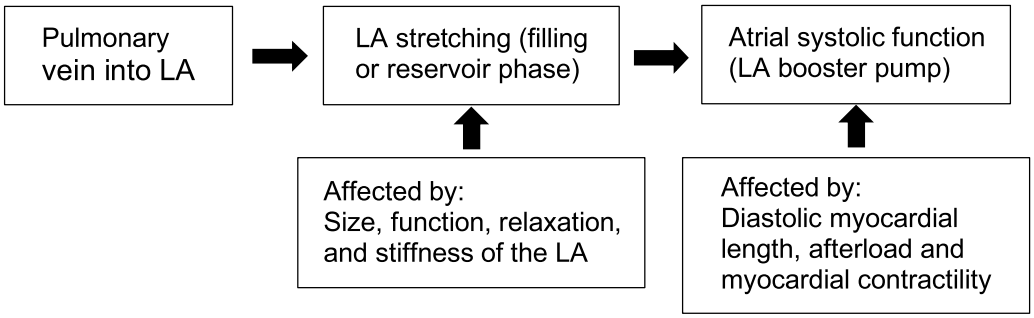

Figure 1. LA mechanism. LA: left atrium

LEFT ATRIA FAILURE

Recent studies have shown LA dysfunction without prior LV disfunction and/or mitral valve abnormalities.[3,15-17] Bisbal, et al. suggest that atria failure be defined as any dysfunction (anatomical, mechanical, electrical, and/or rheological, including blood stasis) that could alter heart performance and symptoms, and worsen quality of life or life expectancy, in the absence of significant valvular or ventricular abnormalities.[3] Additionally, another study defines LA dysfunction as an LAA peak emptying velocity of < 40cm/s, or the presence of spontaneous echo contrast, and/or thrombus in the LA/LAA detected by transesophageal echocardiography (TEE).[16]

Several anatomical spots in atria can initiate their own (ectopic) rhythm.[8,11] Electrical conduction problems in the atria, such as atrial fibrillation (AF), are a common rhythm problem encountered by cardiologists. As a result, LA pumping may be altered and the LA chamber dilatated, which could result in LA failure.[5] A cohort of studies found a correlation between LA disfunction in AF patients, despite having recovered for 3 months.[16] The alteration of LA function in sinus rhythm patients who have previously been diagnosed with AF conditions may occur as a result of mechanical and neurohormonal remodeling, leading to atrial failure.[16,18] Moreover, in subpopulations that receive different types of drugs (beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers/ARB, anti-arrhythmic drugs, digitalis, diuretics, and calcium channel blockers/CCB), the incidence of LA dysfunction was not significantly different. The LA dimension chamber was significantly larger in patients with LA dysfunction compared to the control group (40±6mm vs 36±8mm, p=0.018).[16] Atrial Fibrillation Investigators concluded that there are several clinical risk factors independently associated with LV dysfunction, such as being aged >65 years old, or having a history of hypertension, diabetes mellitus, coronary artery disease (CAD), and previous TIA or stroke.[19] Other than AF, distortion of the atrioventricular (AV) conduction system and atrial dyssynchrony may also trigger atrial failure.[3]

Cardiomyopathy of the atria, caused by isolated primary or secondary atria pathology, may lead to atrial failure.[3,6] In recent consensus, cardiomyopathies have been described as any complex structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations.[20] The isolated etiologies of atria cardiomyopathies other than AF are genetic (amyloidosis), infective (myocarditis), infiltrative, inflammatory, and toxin causes.[21] Any specific causes that affect the atrial chamber lead to tachyarrhythmias and result in impairment of atrial systolic contraction and further atrial dilatation, which can persist even after the heart's rhythm returns to normal.[22] Atrial cardiomyopathies can progress into atrial fibrosis, electrical dysfunction, or a procoagulant state, which can worsen the preexisting condition (**Figure 2**).[20,23]

The third mechanism of atrial failure is atrial remodeling.[3] Left atrial remodeling consists of a spectrum of structural and electrical alterations, which lead to atrial dilatation and disrupt atrial function.[6] The problem with atrial remodeling is that it is caused by volume/pressure overload, although not exclusively. Other clinical factors predisposing remodeling are obesity, exercise, obstructive sleep apnea, and modifiable atherosclerosis.[24] Maladaptive responses of atria cells in high stress conditions (such as volume or pressure overload) are myocyte growths, hypertrophy, necrosis, apoptosis, alteration of the extracellular matrix (ECM), recalibration of energy production and expenditure, and changes in the expression of cellular ionic channel and atrial hormones.[6,25] Maladaptive responses result in atrial fibrosis and can lead to shortening of atrial refractoriness, re-entrant wavelengths, and create local conduction heterogeneities (arrhythmias).[26] The connection between electrical arrhythmias and cardiac remodeling remains poorly understood, but the complexity of pathogenesis may involve multiple agents, such as oxidative stress, calcium overload, atrial dilatation, micro-RNAs, inflammation, and myofibroblast activation.[27] These changes are the underlying mechanisms behind atrial remodeling.

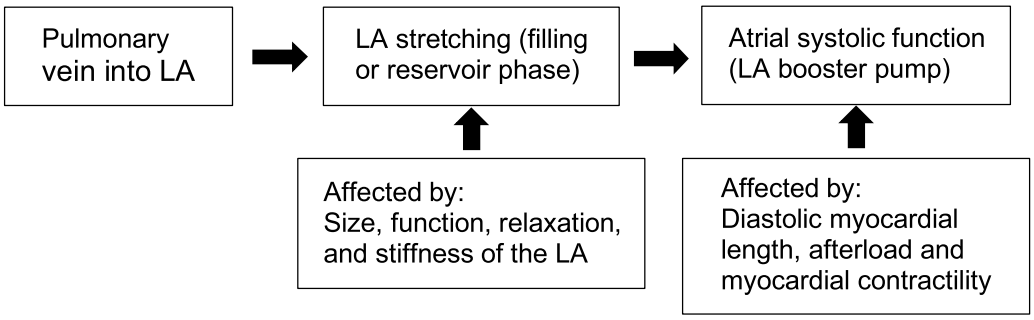

Figure 2. Concept of atrial cardiomyopathy[20-23]

DETERIORATION MECHANISM IN LA FAILURE

After several etiologies, LA function finally fails (Table 1). Fat pads around the ostium of the PV consist of ganglionated plexus (GP) and are innervated with both adrenergic and vagal nerve endings.[28] A volume receptor reflex is activated by a mechanical stretching at the pulmonary venous-atria junction. Over expansion of the blood volume leads to an inhibition of renal sympathetic nerve activity, increasing diuresis, and affecting the heart rate (Bainbridge and reverse Bainbridge reflexes).[29] On the other hand, lack of blood volume leads to thirst and vasopressin hormone release.[30] LA failure downregulates sympatho-inhibition and, unfortunately, upregulates sympatho-excitatory.[6] A recent study conducted by the New York Heart Association (NYHA) was successful in finding a correlation between sympathetic over-activation and functional capacity and prognosis in heart failure patients.[31] As a result, alteration of sympathetic regulation in LA failure can worsen the atria's condition and, in turn, overall heart performance.

The natriuretic peptide (NP) family consists of atrial -type, brain -type, and c-type peptides with their own receptors. Atrial natriuretic peptides (ANP) are stored inside the atria and appendages, and are released during disruption to the LA wall.[31] A precursor for atrial natriuretic peptides is proANP with 126 amino acids that are stored in secretory granules of atrial cardiomyocytes. The proANP secreted from the atria has 3 major forms: proANP with 126 amino acids, proANP with 98 amino acids N terminal peptide (NT-proANP), and pro ANP with 28 amino acids C terminal (ANP) which hormonally actives.[33] ANP plays an important role in cardioprotective mechanisms through several functions.[34,35] However, when LA failure occurs, ANP processing becomes defective and desensitized.[6]

Tabel 1. Causes and triggers of atrial failure

A	Electrical dyssynchrony:
	Atrioventricular dyssynchrony
	Atrial dyssnchrony
B	Booster-Pump and Reservoir Dysfunction
	Fast/disorganized atrial activation
	Extensive atrial fibrosis
C	Impaired Conduit Function
	LA dilation and deformation

CLINICAL MANIFESTATIONS OF LA FAILURE

LA failure has various clinical consequences, such as suboptimal LV filing, AF resulting from atrial failure which progress to pulmonary hypertension, global heart failure (HF), and increased thrombogenicity.[3] Calenda, et all. suggest that atrial myopathies may initiate atrial substrate, which causes increased thrombogenicity.[36] Moreover, the MESA population study also produced the same conclusion.[37] Numerous studies have shown the correlation between atrial remodeling and myopathies with increased risk of stroke.[38,39] Alteration of sympathetic activation leads to LA endothelial dysfunction and fibrosis and, furthermore, is associated with incidents of stroke.[40]

Atrial Fibrillation

LA enlargement is one of the atrial structural changes that can lead to atrial dysfunction. A cardiovascular health study showed that the risk of new AF is increased by 4 times when the

LA diameter > 0.5 mm.[41] Impaired LA reservoir function also increases the risk of first-time AF, independent of clinical risk factors, LA volume, LV ejection fraction, and diastolic function.[42]

Stroke

Risk of stroke in patients with atrial failure can be related to atrial fibrillation. A study on patients with AF referred for catheter ablation showed that LA structural remodelling is associated with an increased risk of stroke and that LA fibrosis severity (quantified using late gadolinium enchancement-cardiac magnetic resonance imaging) is associated with increased major adverse cardiovascular and cerebrovascular events (MACCE).[43] In elderly patients without AF, the association of LA size with stroke was studied. The study found that a LA volume index (LAVI) ≥32 mL/m^2 was independently predictive of a first ischemic stroke.[44] Leong et al. studied the role of LA dysfunction in the pathogenesis of cryptogenic stroke. This study showed that the LA reservoir strain was significantly lower, indicating LA dysfunction in patients who experienced cryptogenic strokes.[45]

Heart Failure with Preserved Ejection Fraction (HFpEF)

HFpEF is a common condition and patients with HFpEF are more likely to have LV hypertrophy, LV diastolic dysfunction, and LA enlargement. Recent studies have indicated a correlation between LA dysfunction and HFpEF. A study by Santos et al. found that worse LA strain was associated with a higher risk of HF hospitalization in HFpEF patients, independent of other potential clinical confounders, but not independent of LV systolic deformation and diastolic filling pressure.[46] Khan et al. also showed that all LA volumetric and strain parameters are significantly reduced in HFpEF patients compared to healthy controls. Impaired LA function causes atrial compliance to decrease, thus lowering the pressure gradient in the left-side of the heart during early diastole and decreasing the LV filling.[47]

CONCLUSION

Cardiologists have long believed LA failure to be a consequence of LV disfunction. However recent studies have been open to the new possibility of the LA as a potential new source of HF incidents. LA failure is defined as isolated failure of the LA without prior LV or mitral valve abnormalities. There are several etiologies of LA failure and they precipitate heart conditions related to HF, independent of LV involvement. LA failure may also have clinical significance.

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