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Indian Journal of Cardiovascular Disease in Women

*Review Article* *Cardiovascular*

# Unraveling Atrial Myopathy

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Received: 04 June 2023
Accepted: 17 July 2023
Epub Ahead of Print: 06 September 2023
Published: 16 December 2023

**DOI**
10.25259/IJCDW_42_2023

**Quick Response Code:**

## ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia encountered, especially in the elderly. AF leads to fivefold risk of stroke. However, there is a no temporal association found when we compare the onset of AF and stroke suggesting that the presence of AF is not mandatory for stroke occurrence. This has led to concept of atrial myopathy suggesting that a diseased atrium can provoke stroke without AF. Atrial interstitial fibrosis, inflammation, and extracellular matrix deposition can initiate and perpetuate atrial myopathy leading to stasis of blood flowing through the atria and may lead to stroke without intervening AF. AF may be just a marker of atrial myopathy. The present paper reviews the emerging concept of atrial myopathy, its pathogenesis, precursors, and diagnosis.

**Keywords:** Atrial myopathy, Atrial fibrillation, Stroke, 4D flow magnetic resonance imaging, Left atrium

## INTRODUCTION

Atrial fibrillation (AF) affects about 37,547 million cases worldwide of which 33% of cases have added up in only the last 2 decades.[1] In India, the prevalence ranges from 0.1% to 1.6%.[2] The most common risk factor for AF is hypertension and due to this high systemic pressure left ventricular hypertrophy occurs followed by left atrial (LA) enlargement. This gives a fertile anatomical ground for development of AF. Back in 1995, it was Allessie's group which gave term "atrial electrical remodeling" for the 1st time. The research conducted by this group showed that AF shortens the atrial action potential, thus proving the phrase "AF begets AF."[3] Till date all the guideline for diagnosing AF focus on the factors that predispose to or may precipitate AF, none of them talk about the involvement of heart or rather LA, to be specific. To date, apart from LA size, no other anatomical feature is taken into consideration when evaluating for AF and even this has not been proven to be useful in clinical decision-making.[4] Stroke due to AF is more fatal and is attributable to clots formed in LA appendage due to the abnormal fibrillation occurring. Hence, ideally restoration of sinus rhythm should decrease the chance of stroke. However, trials like ASSERT showed a temporal dissociation between the occurrence of stroke and onset of AF.[5] It has been observed that any abnormality in the structure of LA foretells the development of AF which is independent of history of myocardial infarction (MI), heart failure, or hypertension.[6] Thus, there seems to be some lacunae in understanding the concept of AF and its clinical consequences and the need for understanding the concept of "Atrial Myopathy."

## WHAT IS ATRIAL MYOPATHY?

In 2016, for the 1st time, various societies and associations such as European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and the Latin American

Society of Electrophysiology and Cardiac Stimulation came together and created a task force which defined LA myopathy as "Any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations."[7] Further, it was classified based on the type of damage that occurs to LA. Class I was changes in cardiomyocytes, Class II was fibrotic changes, Class III was combined pathology of Class I and II, and lastly Class IV was mainly non collagen infiltration with or without cardiomyocyte damage. Whatever may be the pathology, at least one of the three physiological functions of atria which are – reservoir, conduit, and booster – is affected. This can be diagnosed clinically but now there are modalities which help to detect myopathy very early in the course of its development. They are – electrocardiography (ECG) with continuous rhythm monitoring, echocardiography (ECHO) with special focus on speckled imaging, cardiac magnetic resonance imaging (MRI), 4D flow cardiac MRI, and electromapping of LA.[8] Atrial myopathy and its various investigational modalities are depicted in Figure 1.[9]

If asked to name one pathology which acts as the main mediator for the development of structural and electrical remodeling of atria finally ending up in atrial myopathy is "oxidative stress."[10] Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are uptitrated immediately after new onset AF and in animal models of rapid atrial pacing.[11] At the genetic level, analysis of atrial tissue samples from AF patients in sinus rhythm or in active AF revealed an increase in the various ROS and RNS producing genes alongside with the decreased expression of anti-oxidative genes.[12] Animal models of rapid atrial pacing show decreased expression of peroxiredoxin, superoxide dismutase and thioredoxin reductase.[13,14] Despite this, trials with antioxidants have been largely disappointing. During the initial period of AF, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase acts as the main source of ROS. Gradually as the duration of disease progresses, the source shifts to xanthine oxidase, monoamine oxidase and uncoupled endothelial nitric oxide synthase. This explains why statins, which decrease ROS production by inhibiting NADPH oxidase through Rac1 gene, are effective in acute models of AF and not in long standing or permanent AF.[15]

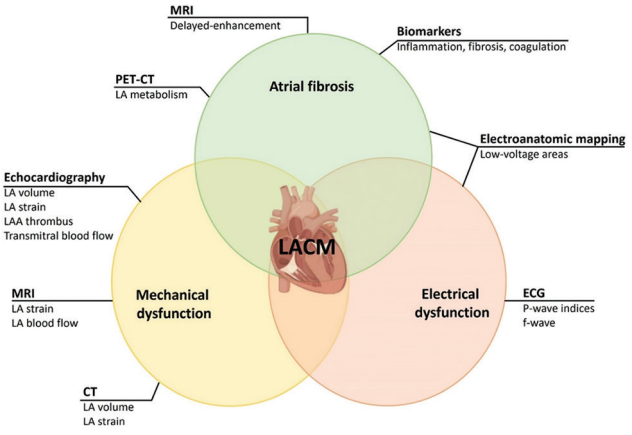


**Figure 1:** The gestalt of atrial myopathy and the investigational modalities for detection of individual components. LACM: Left atrial cardiomyopathy.

One of the important contributors for electrophysiological remodeling is a disordered autonomic nervous system. It can occur with many disease processes and most common, it occurs diabetic patients. This process serves a key component for development of AF and myopathy. Both sympathetic and parasympathetic system helps in inception and perpetuation of AF.[16] The parasympathetic system contributes more to AF by shortening and heterogeneity of the refractory period of atria whereas sympathetic system helps to modulate the disordered relationship.[4] Structural remodeling mainly occurs in the form of LA fibrosis. There are various mechanisms for LA fibrosis which include activation of Renin-Angiotensin Aldosterone System (RAAS), impaired myocardial hemodynamics, and inflammation. Due to overactive RAAS, there is increase in angiotensin II level which stimulates fibroblasts and subsequently leads to LA fibrosis. This is the reason that the newer classification of anti-arrhythmic drugs have angiotensin receptor blockers and Angiotensin converting enzyme inhibitors as an upstream therapy backed by the studies which demonstrate attenuation of atrial fibrosis in patients taking these medications.[17] Even aldosterone has been implicated to cause atrial fibrosis and supporting this fact, evidences have emerged after studies showed that Spironolactone reduces LA fibrosis and the duration of P wave on ECG in animal model.[18,19] Impaired hemodynamic profile is very much evident in patients with hypertension. Dilated LA is said to be the hemoglobin A1C for long standing uncontrolled hypertension.[20] When LA pressure increases due to the early onset of diastolic dysfunction in hypertensive patients, LA becomes more and more stiff and consequently the wall stress increase in an unequal manner. This uneven distribution of stress over atrial myocytes creates a seedbed for further fibrosis.[21] AF patients are found to have higher levels of inflammatory markers like interleukin 6 (IL-6) and tumor necrosis factor-α. These proteins have been well associated with development of LA fibrosis by activating the various metalloprotease enzymes.[22] Another major contribution of inflammation comes from the epicardial adipose tissue which creates a local inflammatory milieu and since epicardium and myocardium are connected through a continuous microcirculatory connections, any derangement in epicardial fat right away affects the underlying myocardium.[23] It has also been proven that altered activity of aldosterone along with decreased activity of natriuretic peptides increases this epicardial fat mass and metamorphose its biology from a nourishing tissue to a pro-inflammatory tissue.[24]

## ATRIAL MYOAPTHY AND STROKE

Before the concept of atrial myopathy, AF was thought to be a major risk factor for stroke. No doubt it still is, but the causal association limits itself to only "plausibility" whereas "temporality" criteria are now in question. Various articles have been published which support this lack of association between AF and onset of stroke.[25,26] As rhythm control strategies in these patients did not decrease the chance of stroke,[5,27] quest started in search of factors other than AF which could explain the temporal dissociation of these two events. Answers to all these questions came with the introduction of atrial myopathy into picture. It was found that the presence of atrial myopathy promotes a thrombogenic state which leads to stroke.[28] The various remodeling which occur in this process are also responsible for AF. Thus, atrial myopathy makes a roadmap for both stroke and AF simultaneously rather than one after the other.

There are four stages of atrial myopathy as proposed by the American College of Cardiology and American Heart Association.[29] Stage A, which represents condition having high risk which lead to development of atrial myopathy is basically the result of ageing process, inflammation, stretching of the atrial myocytes, damage due to ROS, etc. At this stage, atrial myopathy cannot be detected and patient is clinically asymptomatic. As these various insults progress, there occurs structural and autonomic remodeling along with fibrosis. It is at this stage that various changes start to occur in atria which can be detected by advanced techniques such as cardiac MRI or 4D flow cardiac MRI but still the patient is completely asymptomatic. When there is continued fibrosis and remodeling then Stage C comes into picture which is detectable clinically. Here, the disease starts to manifest itself clinically in the form of either AF or stroke. However, at this point, the disease is still reversible with appropriate intervention like catheter ablation. Even after this if the disease progresses further, then it enters a stage of irreversible end-stage atrial myopathy labeled as Stage D. Figure 2 depicts all the stages progression in a sequential manner.[30]

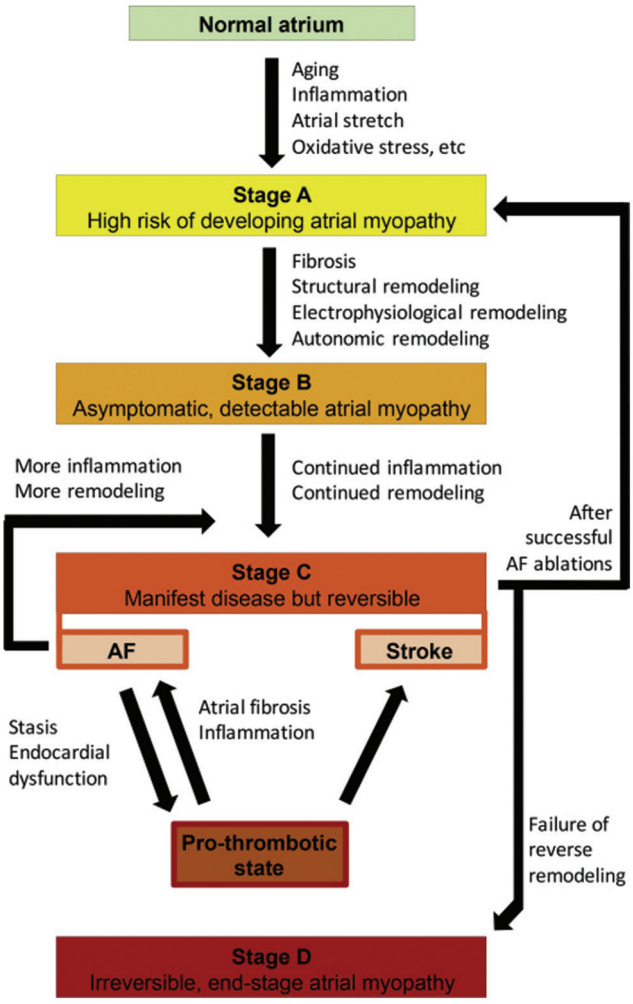


**Figure 2:** Stages of atrial myopathy.

## IDENTIFYING PATIENTS WITH ATRIAL MYOPATHY

After being accustomed to this new concept, we as clinicians should focus on how to identity atrial myopathy in early stages so as to prevent AF and related diseases. The CHARGE-AF consortium has tried to produce a risk predictive model for AF which included these 11 factors – age, race, height, weight, systolic blood pressure, diastolic blood pressure, smoking, use of antihypertensive drugs, diabetes mellitus, history of MI, and heart failure. It was surprising to see that adding ECG variables in the model did not improve its prediction probability.[31]

ECHO has been widely used to identify atrial myopathy using various parameters such as LA size and LA hemodynamics which include – LA ejection fraction and LA function index (LAFI). LAFI is a rhythm-independent index that combines LA emptying fraction, adjusted LA volume index, and stroke volume.[32,33] Tissue Doppler imaging measures a' velocity which evaluates the contractility of LA muscle. Newer techniques like LA speckled tracking (LA strain imaging) and 3D ECHO are providing better insight to the conduit, booster, and reservoir functions of LA.

The usual ECG recordings also very well predict the preclinical atrial myopathy, though it is very under utilized. Atrial myopathy can present itself as AF or non-AF arrhythmias such as atrial premature beats or paroxysmal atrial tachycardia.[34] These show some abnormality in the atrial morphology which can be predict atrial myopathy at very early stage. In fact, analysis of fibrillary waves gives the much needed electrical information regarding outcome of AF, response to anti-arrhythmic drugs, and catheter ablation.[4]

Cardiac MRI can assess the fibrotic changes which appear as delayed enhancement on T1 imaging. 4D flow MRI allows us to visualize velocity of blood flow in LA and predict stasis of blood if the flow velocity is <0.2 m/s. As this is the most novel technique to predict LA myopathy, so standardization of the values is yet to be done.[35]

Atrial eletroanatomic voltage mapping helps to identify the areas which can become a nidus for tachyarrhythmias in future. Various electrophysiological researches have shown that patients with persistent AF have a higher burden of low-voltage areas compared with those with paroxysmal AF.[36]

Various biomarkers are being studied for early prediction of atrial myopathy but with no much success in hand till now. It has been found that within a few minutes of onset of AF, the level of von willebrand factor (vWF) increases and these become resistant to breakdown by A Disintegrin-like Metalloprotease domain with ThrombosSpondin Type 1 motifs 13 (ADAMTS13).[37] Due to this, vWF: ADAMTS13 ratio increases which in normal healthy person is equal to one. Higher vWF: ADAMTS13 ratio may predict impending AF. Atrial natriuretic peptide, Troponin, C-reactive protein, and IL-6 are few other biomarker which are being studied as novel biomarkers for predicting LA myopathy.[4] A novel study by Liu *et al.* showed that a circulating fibrocyte level ≥4.05% of total leukocyte count was predictive of LA fibrosis and recurrence of AF after 1st-time ablation therapy.[38]

One interesting thing that is not explained by any of these novel techniques is that "why only left atrium and why not the right one." An *ex vivo* study done by Cervero *et al.* gave an insight to this entrancing question. His team found that in LA, ability to activate protein C was half and lower expression of thrombomodulin in its endocardium when compared to the right atrium. Thus, abnormal activation of protein C on the LA endocardium, due to decreased thrombomodulin expression, explains well about the higher thrombogenicity of LA.[39]

## CONCLUSION

Atrial myopathy is a new emerging concept which changes the way we look at AF. Various redox signaling pathways are being studied which contribute to tissue remodeling and self-perpetuation of AF. At present, ROS/RNS have been the main contributing elements for remodeling that leads to LA myopathy. In general, LA myopathy may antecede AF. Various methods to identify this condition in early stages have been in the pipeline and now they are coming up with exemplary results. These results will help to better delineate myopathic substrate and its association with the mechanisms of arrhythmia. Furthermore, it shall not be surprising in future if we see a new set of antiarrhythmic drugs focusing on how to prevent the onset of AF rather than how to treat AF.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Satpathy C, Mishra TK, Singh S. Unraveling atrial myopathy. Indian J Cardiovasc Dis Women. 2023;8:259-63.