Review

Atrial Fibrillation, Atrial Myopathy and Thromboembolism: The Additive Value of Echocardiography and Possible New Horizons for Risk Stratification

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Atrial Fibrillation, Atrial Myopathy and Thromboembolism: The Additive Value of Echocardiography and Possible New Horizons for Risk Stratification

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Abstract: This article explores the emerging concept of atrial myopathy (AM) and its potential role as a risk factor for stroke and dementia, both independently and in association with atrial fibrillation (AF). AM refers to structural and functional abnormalities of the atria, potentially causing blood clots formation and their subsequent embolization even in patients without AF. Echocardiography, particularly Left Atrial (LA) strain analysis, is a promising non-invasive tool for AM evaluation and might offer additional risk stratification beyond the established CHADS2-VASc score, potentially impacting anticoagulation decisions. By understanding AM and utilizing advanced imaging techniques like LA strain, clinicians can achieve a more comprehensive understanding of thromboembolic risk in specific patient groups. Integrating LA strain analysis into routine clinical practice holds promise for improved patient management and targeted therapies, allowing for better risk stratification in AF patients. However, standardized definitions and diagnostic criteria for AM are essential for consistent evaluation and research. Further studies are needed to explore the efficacy and safety of anticoagulation in AM patients without AF.

Keywords: atrial fibrillation; atrial myopathy; left atrial strain

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia among adults, and it is associated with significant morbidity and mortality, including increased risk of stroke and dementia. While the established paradigm attributes these complications to blood stasis within the atria and subsequent thrombus formation with cerebral embolization, recent evidence suggests a key role for atrial myopathy (AM).

AM is characterized by structural and functional abnormalities of the atria, which can occur with or without AF. The study of left atrial (LA) deformation with 2D speckle tracking echocardiography, which measures the ability of the LA to contract and relax, has demonstrated high sensitivity and specificity in identifying myocardial fibrosis and increased atrial stiffness, both markers of AM. Recently, different studies have shown that LA strain can be used to stratify the risk of stroke and dementia, even in patients who do not have AF, suggesting that LA strain alterations, reflecting the presence of underlying AM, may be a more sensitive risk stratifier of thromboembolic events than

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the presence of AF itself. By exploring these aspects, this article aims to provide a comprehensive understanding of the emerging role of AM in AF-related complications and its potential to refine risk stratification and patient management strategies.

2. Atrial Fibrillation: The Size of the Problem

AF is a supraventricular tachyarrhythmia characterized by an incoordinate atrial electrical activation and consequently ineffective atrial contraction. Electrocardiographic (ECG) characteristics of AF include:

- Irregular R-R intervals (when atrioventricular conduction is not impaired)
- Absence of distinct repeating P waves
- Irregular atrial activations. [1]

AF is the most frequently sustained cardiac arrhythmia among adults [2], with estimated prevalence of 0.4–1% in the general population which increases with age, affecting 9% of people above 80 years. [3] The symptoms associated with AF are heterogeneous, as it may vary from asymptomatic AF incidentally diagnosed during a routine ECG, to highly symptomatic form which manifests through chest pain, shortness of breath, syncope, palpitations, or even stroke or transient ischemic attack (TIA). A diagnosis of AF is associated with a 1.5 to 2-fold increased risk of all-cause mortality and increased morbidity in the general population [4] and diminished quality of life [5] particularly due to higher risk of ischemic stroke and dementia. [6]

3. Pathophysiological Pathway of Atrial Fibrillation

Significant effort has been made over the years to define the underlying cellular, molecular and electrophysiological changes that predispose to the occurrence and maintenance of AF in patients. [7] Progress has been limited by the understanding that AF is a complex arrhythmia that can be the final result of various different pathophysiological processes, with significant heterogeneity between patients. [7] Age is a prominent AF risk factor, but there is an increasing burden of other comorbidities including hypertension, diabetes mellitus, heart failure (HF), coronary artery disease (CAD), chronic kidney disease, [8] obesity, and obstructive sleep apnoea, [9–13] which are all potent contributors to AF development and progression to persistence AF. [14,15]

The development of AF and its lifetime risk depends on age, genetic, and (sub)clinical factors. [16–18] The impact of clinical risk factor burden and multiple comorbidities on AF suggests that an early intervention and optimum risk factors control could reduce the incidence of AF.

The mechanism that this risk factors potentially share is the capability to induce atrial electrical and structural remodeling. Electrical remodeling encompasses changes in the properties of ion channels affecting atrial myocardial depolarisation and conduction, while structural remodeling refers to alterations in the tissue architecture, both microscopic (eg, myocardial fibrosis) and macroscopic (eg, atrial dilatation). At this point, the initiation and maintenance of AF can be linked to the interaction between a trigger and the substrate. A ‘trigger’ is a rapidly firing focus that can act as an initiator of the arrhythmia, the maintenance of which generally requires a ‘remodeled substrate’, that is, altered electrophysiological, mechanical and anatomical characteristics of the atria that sustain AF.

It is thought that there is a progression over time from a trigger-driven disease, through to development of an atrial function substrate, followed by predominant atrial structural remodeling. [8] This would correspond to the clinical observation that AF is often initially paroxysmal, before progressing to a persistent and ultimately permanent form of arrhythmia. [19]

4. Association between AF, Stroke/TIA and Dementia - The Emerging Concept of Atrial Myopathy

The presence of AF is associated with a fivefold increased risk of stroke, in fact TIA or ischemic stroke represents the first manifestation of AF in 2-5% of patients. [6] This is usually attributed to LA appendage thrombi formation as a result of blood stasis, with subsequent clot dislodgement and

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embolization to the systemic circulation, more often to the brain, and frequently after restoration of sinus rhythm.

Furthermore, an independent correlation between AF and various forms of dementia, including Alzheimer disease, has been observed in AF population, irrespective of stroke occurrence. [20,21] The pathophysiology is thus likely to be multifactorial which has not been fully explained. [20] One plausible mechanism may be repetitive microclots/macroclots embolization, chronically leading to brain dysfunction. Studies supporting this hypothesis showed a reduction in the incidence of dementia in AF patients treated with optimum anticoagulation [22,23], or in patients undergoing effective and early AF ablation. [24,25] This would suggest a shared pathophysiology for dementia and stroke/TIA as connected to the atrial disease. The complexity of the mechanism by which these morbidities result from AF has yet to be completely understood, in particular the interaction of various factors involved in thrombus formation which should allow better clinical risk stratification and optimum targeted therapies in these patients.

It is well known that the increased risk of pathological thrombus formation is due to an alteration of the physiological haemostatic mechanisms, known as Virchow's triad, which consist of the combination of alterated blood constituents (including platelet factor 4, von Willebrand factor, fibrinogen, β-thromboglobulin and D-dimer), blood vessel wall disease and reduced blood flow. The occurrence of AF has been shown to be related to all of the Virchow's triad components. Specifically, the increased activation of the coagulation cascade and platelet reactivity and with impaired fibrinolysis, processes are also amplified by the usually pre-existing comorbidities. The presence of atrial fibrosis and endothelial dysfunction is related to the development of AF, which promotes further atrial remodeling, thereby providing an increased risk for clot formation and subsequent embolization. In addition, it is also well demonstrated that LA dilatation and the loss of atrial contractile function reduce blood flow, specifically in the LA appendage, as it has been shown with various imaging techniques. [26] For years, the atrial blood stasis hypothesis has been acknowledged as the mechanism of AF-related thromboembolism and morbidity [27], however, recent evidence has emerged to suggest the presence of atrial myopathy (AM) as an alternative hypothesis.

AM (or atrial cardiomyopathy or atrial cardiopathy) is defined as "any complex structural, architectural, contractile or electrophysiological changes affecting the atria with the potential for producing clinically relevant manifestations" and appears as LA dysfunction and dilation. [28,29] The European Heart Rhythm Association (EHRA) has proposed in 2016 a working histological/pathophysiological classification scheme for AM (Table 1) which may help to convey the primary underlying pathology that led to its development. Emerging evidence suggests that thromboembolism can occur in the setting of AM even in the absence of AF. [30] However, AM and AF are strictly correlated with a cause-consequence relationship. This relationship is based on the close association between atrial fibrosis, one of the main characteristics of AM, and AF. Even microscopic scar has been documented to affect LA compliance and mechanical function leading to the development of AF. [31] Furthermore, AF and the subsequent volume and fluid overload, may themselves cause atrial remodeling, increasing atrial wall stiffness and fibrosis, and therefore provoking or worsening AM. [32]

Table 1. The European Heart Rhythm Association (EHRAS) classification of atrial myopathy. [28].

Atrial Myopathy: EHRAS classification	
EHRAS CLASS	***HISTOLOGICAL FEATURES***
I	Morphological/molecular changes affecting the cardiomyocytes (hypertrophy and myocytolysis). Absence of significant tissue fibrosis or interstitial changes
II	Predominance of fibrotic changes. Normal appearance of cardiomyocytes
III	Combination of changes in the cardiomyocyte and tissue fibrosis

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IV	Non-fibrotic alteration of interstitial matrix
a	Amyloid accumulation
f	Fatty infiltration
i	Inflammatory cells
o	Other interstitial alterations

5. Evaluation of Atrial Cardiomyopathy

The diagnosis of AM could be suggested based on ECG findings, as AF or other atrial arrhythmias [33,34], serum biomarkers, and imaging evidence for LA dilatation and dysfunction, often associated with myocardial fibrosis. [28,35,36]

LA dilation, in the absence of mitral valve disease, is usually an indicator for chronic increase in wall tension, commonly due to increased LA pressure, [37–40] paired with impairment of LA function related to AM. [41,42 CS,CT] LA dilatation has been shown to be related to increased incidence of AF and stroke, [43–52] increased risk of overall mortality after myocardial infarction, [41,42,53,54], increased risk of death and hospitalization in patients with dilated cardiomyopathy, [55–63] as well as major cardiac events or death in patients with diabetes mellitus. [64]

LA dilatation is also a well-known marker of severity and chronicity of diastolic dysfunction and its consequent raised LA pressure. [37–40] Despite that, Kojima T et al. [65] and others have shown that LA function deteriorates before cavity enlargement with 36% of patients with AF having normal LA size. [66] Such controversy suggests the need for thorough and and comprehensive assessment of atrial anatomy, structure, and function for making accurate diagnosis of AM.

Evaluation of atrial morphology is typically made with 2D or 3D echocardiography. For assessment of atrial size, the parasternal long-axis linear dimension using M-mode is the most commonly used method [44–58,64,67–69]. However, considering the complex 3D nature of the atrium and the usually non-uniform atrial remodeling, this measurement does not guarantee an accurate reflection of LA size. [70–74] Hence, measurement of LA volume has emerged as a more accurate prognostic indicator in a variety of cardiac diseases. [49,51,53–58,64,67–80] LA volume from 2D images is best measured using the disk summation algorithm since it includes fewer geometric assumptions. [81,82] 2-D echocardiographic LA volumes are typically smaller than those reported from computed tomography (CT) or cardiac magnetic resonance imaging (CMR), [83–87] however, 3-D echocardiography measured LA volumes have been shown to correlate well with cardiac CT [88,89] and CMR, [90,91], having shown a superior prognostic predictive power than 2D LA volumes. [92,93]

Overall, the recommended normal upper limit for indexed LA volume is 34 mL/m^2 for both genders which fits well with a risk-based approach for determining a cut-off between a normal and an enlarged LA. [43,77–79]

LA function can be studied by analyzing the electrical remodelling process from surface 12 lead ECG (P wave terminal force in lead V1, P wave axis alterations, P wave voltage reduction, P wave increased area, P wave dispersion or prolonged duration, PR interval (interatrial conduction block)) [94], or, more precisely during an electrophysiological study.

Routine conventional echocardiographic indexes used for studying LA function have limitations, but the evaluation of longitudinal deformation by speckle tracking echocardiography has proven to be a very reliable parameter. LA function has been studied with different echocardiographic tools including pulsed-wave Doppler measurements of late (mitral A) diastolic filling and pulmonary vein atrial reversal velocity, but their absolute values are affected by many factors including age, reduced LV compliance and loading conditions. [39,95–103]

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The time between the onset of surface ECG "P" wave and the onset of "a" wave on tissue Doppler imaging (TDI), or total atrial conduction time, can be used as a non-invasive marker of atrial electromechanical delay (AEMD)[104–111], which has shown to be accurate, yet an indirect marker of atrial function. This index measures the time required for atrial depolarization to occur which results in active atrial contraction representing a more complete measure of the extent of atrial remodeling than other indices. [112] An increase in TDI-derived AEMD has been shown to predict AF recurrence in patients with paroxysmal AF [104], particularly if measured in the lateral leads, and has been shown to be non-inferior to LA volume index in identifying those patients. [113]

A correlation between TDI-derived AEMD duration and the degree of right atrial appendage fibrosis has been demonstrated in a histological validation study by Müller et al. [114] A good agreement has also been demonstrated between TDI-derived AEMD duration and total atrial conduction time measured in an electrophysiological study in healthy individuals. [115] Its duration was also shown to be affected by several risk factors which are known to play significant role in atrial remodeling including age, hypertension, valvular disease, LV diastolic dysfunction, sleep apnoea and increased body mass index [112]. Additionally, it was found to be related to increased LA volume and inversely related to LA reservoir strain, [116] hence was proposed as an independent predictor of AF after cardiac surgery [117], AF recurrence after electrical cardioversion [118], and catheter ablation [119]. In a recent prospective study of patients free of AF after successful catheter ablation who were not on anticoagulants, a prolonged TDI-derived AEMD was associated with increased stroke incidence and an improved CHA2DS2-VASc score performance [120].

Two-dimensional speckle-tracking echocardiography has emerged as a more sensitive marker for detecting early functional remodelling before anatomical alterations occur. [121–135] Strain and strain rate are two measures of myocardial deformation based on estimating spatial gradients in myocardial velocities. [121,124,128,129,136–140] This technique offers important information on early modification of LA structure and function, before volume changes, and is associated with the occurrence and persistence of AF. [35,141] Furthermore, patients with paroxysmal AF have been shown to have increased LA stiffness which is described as low relaxation properties, one of the main features of AM that can be non-invasively measured as the ratio between E/e' to LA strain. [142] Abnormalities in atrial strain have been observed in many conditions, including AF, valvular pathology, heart failure, hypertension, diabetes, and cardiomyopathies [124,125,131–135]. Population-based studies have shown the prognostic value of LA strain analysis of long-term outcome. [124,130] Interestingly, LA dysfunction with changes in strain and strain rate has been observed in patients with amyloidosis even in the absence of other echocardiographic features of cardiac involvement, thus highlighting its possible application as an early marker of cardiac involvement. [137] The study of LA deformation with 2D speckle tracking echocardiography has also demonstrated high sensitivity in identifying myocardial fibrosis and increased cavity stiffness as compared to CMR measures [35], invasive electrophysiological studies with high density voltage mapping, [143] and with invasive biopsy assessment. [144] Considering the CMR's high-cost and the risk of side-effects from Gadolinium, echocardiography has been proved as the modality of choice for screening and serially following patients with diseases involving the LA morphology and function. [67,145]

6. Potential Applications of AM Study in Clinical Practice

Based on the strong emerging evidence, many authors used these noninvasive indices to focus attention on the evaluation of AM as lone disease and started to consider AM not just as a "collateral finding" or a consequence of AF, but likely to be the primary cause of the morbidity and poor outcome previously attributed to AF. Sade et al. have demonstrated that a reduction in LA strain was able to stratify the risk of AF onset in patients with cryptogenic stroke irrespective of AF. [146] Moreover, in a low-risk general population Alhakak et al. have shown a reduction in LA reservoir strain as an independent predictor of long-term risk for AF and ischemic stroke [147].

Azemi et al. have also demonstrated that patients with low-risk $CHADS_2$ scores and a history of AF, LA strain values were significantly reduced in those presenting later with stroke or TIA

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compared with age and gender-matched controls with identical $CHADS_2$ score [148] thus suggesting low LA strain as a a direct contributor to thrombogenic risk (or both). Also, Saha et al. showed a strong association between impairment of LA strain, the presence of AF and higher $CHADS_2$ score, and that in AF patients LA strain was a predictor of stroke events and cardiovascular outcomes. [149]

LA strain provided additional information on acute embolisms over and above the $CHA2DS_2$-VASc score in a population of patients with paroxysmal or permanent AF. [150] Finally, LA strain has proved to be a predictor of new onset AF in patients with heart failure [151] and those with cardiac amyloidosis, being able to identify those at high thrombotic risk, independent of AF. [152]

Evaluation of LA strain, reflecting an underlying AM, also demonstrated a potential as a preoperative predictor of postoperative AF in patients undergoing aortic valve replacement (AVR) for aortic stenosis and coronary artery bypass grafting (CABG). Cameli et al. [153] demonstrated a significant reduction in global peak atrial longitudinal strain (PALS) as the sole independent predictor of postoperative AF. Pastore et al. [154] also proposed a preoperative global PALS below 28% as a specific parameter for stratifying patients at increased risk for postoperative AF (hazard ratio, 3.6 [95% CI, 2.2-5.9]; $P<0.001$) following CABG. These findings emphasize the use of LA strain assessment in identifying patients with a higher risk of arrhythmias, and applying optimum preventive measures.

A recent interesting attempt to demonstrate the possible influence of underlying AM in increasing the risk of ischemic stroke and dementia in patients with AF has been made in the study by Zhang et al [155] in which the association of AF with stroke and between AF and dementia, adjusted by echocardiographic parameters of AM, has been investigated. The study was particularly powered by a large number of patients. The authors found that, after adjusting for LA volumes and function, particularly of LA reservoir strain, the apparent association between AF and incident stroke and dementia loses its strength and statistical significance. All these studies confirmed that LA strain may be used not only to study LA fibrosis/changes in the interstitial matrix that characterize AM, but also driving the risk of new onset of AF and stroke independent from AF, being a predictor of cardiovascular outcomes.

The main limitations of the methodology are currently the absence of consensus or standardization for the echocardiographic definition of AM. All these authors have used strain parameters that, despite being a sensitive marker of atrial structural rearrangements and fibrosis, still remain “new indices” and are yet not regarded as an objective parameter for defining AM.

LA strain has been already included as an additional parameter in detecting diastolic dysfunction in the latest recommendations of the European Association of CardioVascular Imaging (EACVI) on the use of multimodality imaging for the evaluation of heart failure with preserved ejection fraction (HFpEF). [156] Thus, if the mechanism hypothesized by Zhang et al. for the association between AM and stroke, based on impaired LA structure/function predisposing to thrombus, is confirmed, the use of LA strain in evaluating AM may be considered for better studying the underlying mechanism and better stratifying patient’s thromboembolic risk.

Considering the increasing availability, feasibility, and timelines of obtaining LA strain values, as well as being used within scores as a prognostic stratifier of cardiovascular outcomes, it may also be used to improve risk stratification for stroke and dementia, with important therapeutic consequences on anticoagulation for primary prevention of stroke. This may lead to a general optimization of anticoagulation use, not only including patients at higher risk of stroke without AF but also those in the grey-zones risk of stroke according to current indices (i.e. in the low CHADs-VASC score). These suggestions need randomized controlled trials with safety/efficacy data on AM as lone indication to anticoagulation, which are eagerly awaited in the future.

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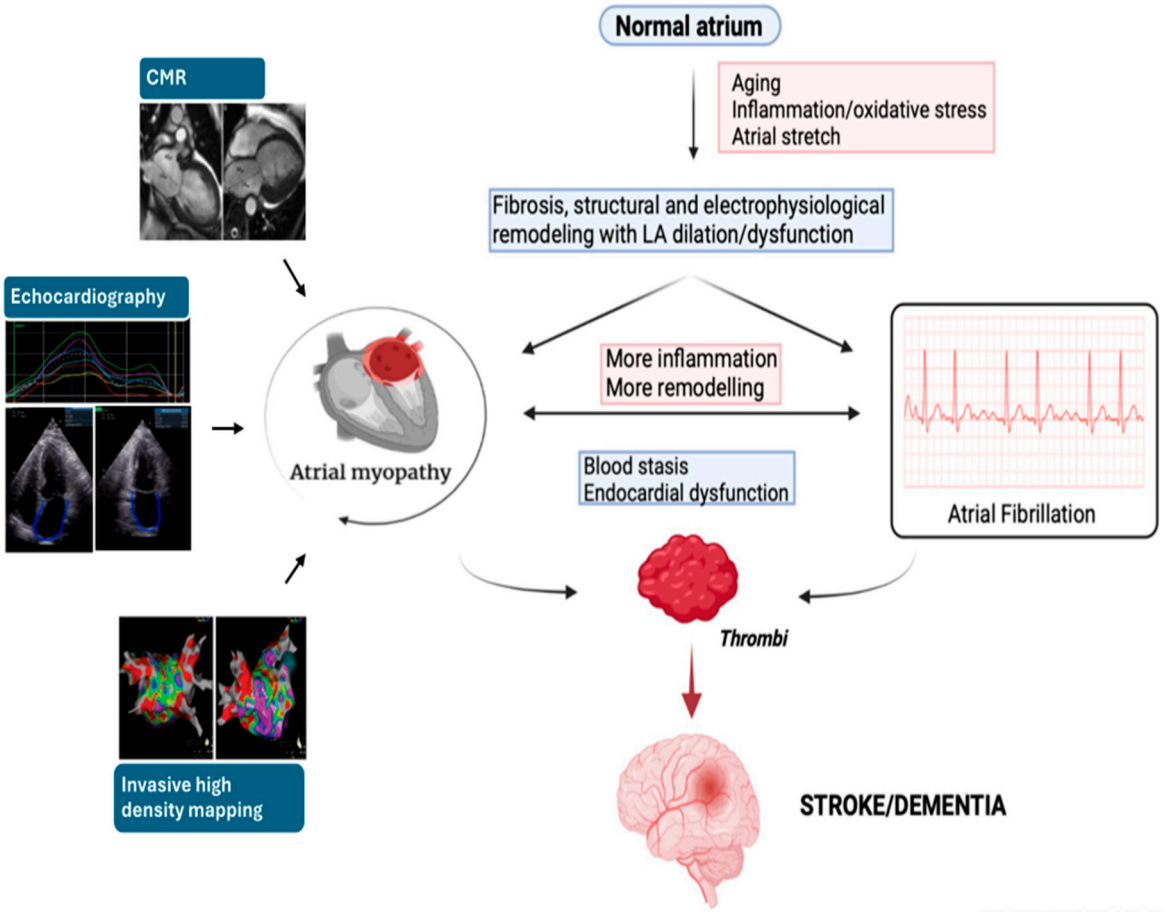

Figure 1. The interdependency and common pathophysiology of atrial myopathy and atrial fibrillation and their association with Stroke and Dementia. CMR, cardiac magnetic resonance.

7. Conclusions

This article examines the emerging concept of AM, its association with thromboembolic events and the consequent increased risk of stroke and dementia, particularly in the context of AF. While the association between AF and these outcomes is well known, AM presents a novel perspective, suggesting its possible role as an independent risk factor.

The Key Takeaway messages are three 1) AM encompasses structural and functional abnormalities of the atria, potentially contributing to thromboembolism even in the absence of AF; 2) Echocardiography emerges as a promising tool for non-invasive evaluation of AM, particularly LA strain analysis; 3) Evidence exists suggesting that LA strain may offer additional risk stratification beyond the established CHADS2-VASc, with potential impactions on anticoagulation.

By acknowledging AM potential role and utilizing advanced imaging techniques like LA strain, we can strive towards a more comprehensive understanding of the mechanism underlying an increased thromboembolic risk in specific sub-groups of patients. The integration of LA strain analysis into routine clinical practice holds promise for improved patient management and targeted therapies thus may allow better clinical risk stratification in AF patients. Nevertheless, standardized definitions and diagnostic criteria for AM are crucial for consistent evaluation and research, and further studies are necessary to explore the efficacy and safety of anticoagulation in AM patients without AF.

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