Pathophysiology and clinical relevance of atrial myopathy

Title/running title:

Pathophysiology and Clinical Relevance of Atrial Myopathy

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Abstract

Atrial myopathy is a condition that consists of electrical, structural, contractile and autonomic remodeling of the atria and is the substrate for development of atrial fibrillation, the most common arrhythmia. Pathophysiologic mechanisms driving atrial myopathy are inflammation, oxidative stress, atrial stretch, and neurohormonal signals, e.g., angiotensin-II and aldosterone. These mechanisms initiate the structural and functional remodeling of the atrial myocardium. Novel therapeutic strategies are being developed that target the pathophysiologic mechanisms of atrial myopathy. In this review, we will discuss the pathophysiology of atrial myopathy, as well as diagnostic and therapeutic strategies.

Introduction

Atrial fibrillation (AF) is caused by underlying alterations in the atrium that often take decades to culminate in the arrhythmia. Various risk factors, such as aging, hypertension, and obesity, contribute to atrial wall stretch, activation of the renin-angiotensin-aldosterone (RAAS) system, oxidative stress and inflammation. These detrimental stimuli induce phenotypic alterations in different cardiac cell types, collectively referred to as atrial remodeling. Atrial remodeling encompasses structural, electrical, contractile, autonomic and endothelial remodeling. Consequently, atrial myopathy can induce clinically relevant manifestations, including AF, stroke and exertional dyspnea.[82, 263] (Fig. 1)

The complex interplay between AF and atrial myopathy involves electric remodeling, which leads to ectopic firing, decreased refractoriness and conduction slowing, thereby increasing susceptibility to AF initiation and sustainability.[197] Structural remodeling, particularly atrial fibrosis, creates conduction heterogeneity, stabilizes re-entrant circuits and perpetuates AF.[195] Additionally, the rapid atrial depolarizations during AF perpetuate electric remodeling, establishing a vicious cycle known as "AF begets AF".[113, 296] However, AF persistence cannot solely be attributed to this phenomenon, as atrial myopathy can progress even with adequate anti-arrhythmic drug or ablation strategies, contributing to therapy refractoriness.

Atrial myopathy is not only implicated in AF but also plays a significant role in thromboembolism.[246, 263] Endothelial remodeling in atrial myopathy causes a shift towards a procoagulant phenotype of the endothelium, elevating the risk of thrombo-embolism independent of AF. Stroke can be the first symptom of atrial myopathy, preceding the first episode of AF.[25, 80, 146, 266] Although atrial myopathy develops before AF, mechanistic data from patients with atrial myopathy, but before development of AF are scarce. For this reason, most clinical papers included here concern patients with atrial myopathy associated with AF.

Understanding the broader concept of atrial myopathy is instrumental in elucidating the pathophysiology of AF and may inspire novel therapeutic approaches. Intensive research has been conducted on atrial myopathy in recent years. This paper reviews the latest insights in the pathophysiology of atrial myopathy and its clinical implications.

Pathophysiology

Atrial myopathy is a complex disorder characterized by diverse pathophysiologic mechanisms, resulting in distinct phenotypes observed among individual patients. Various subtypes of atrial remodeling, including structural, electrical, contractile, autonomic, and endothelial remodeling, are

consistently present in all patients with atrial myopathy, albeit in varying proportions. Figure 1 provides an overview of the key pathways implicated in this condition.

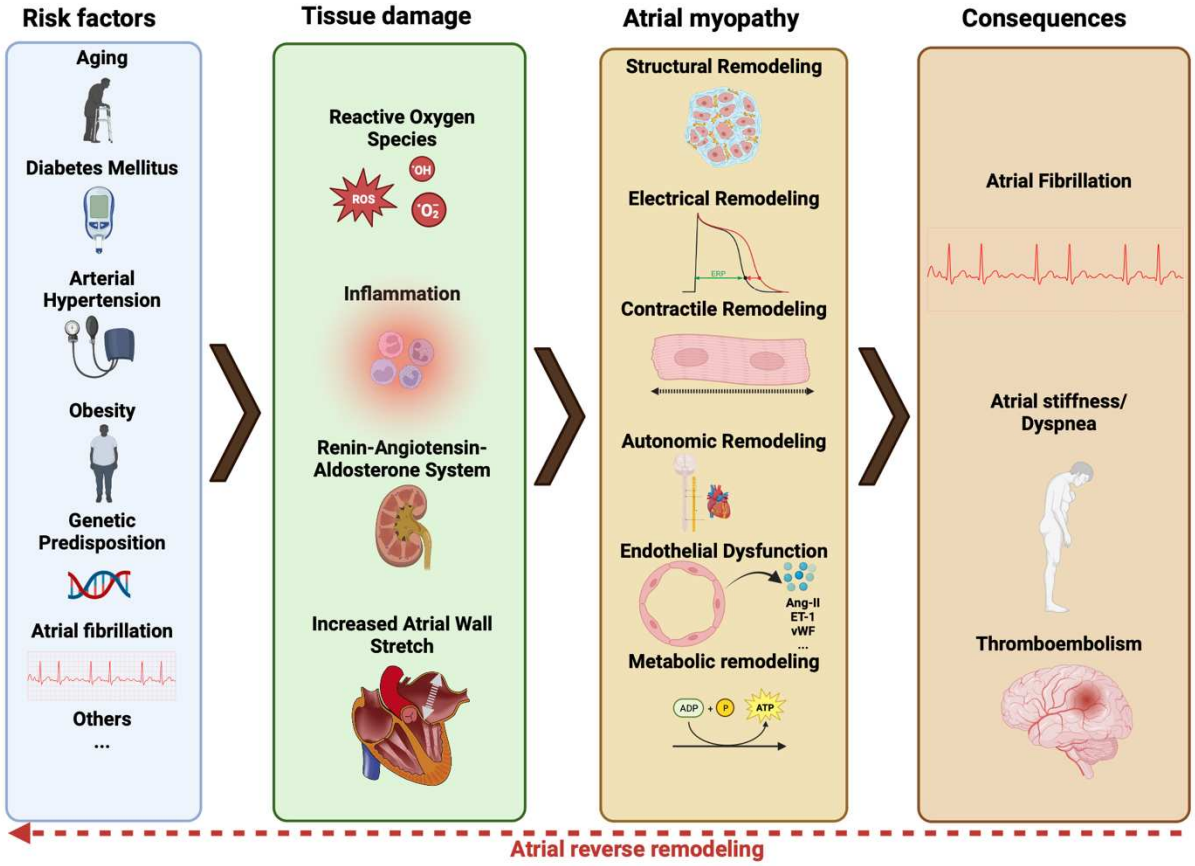

Fig. 1 Central illustration *Overview of the different pathophysiological aspects of atrial myopathy. Different risk factors induce tissue damage to the atrium through various mechanisms. All cardiac cell types react by phenotypic alterations, leading to a state of atrial myopathy, characterized by structural, electrical, contractile, autonomous, and endothelial remodeling. These changes lead to atrial fibrillation, exertional dyspnea ('stiff left atrium syndrome', a form of heart failure) and thromboembolism.*

Initiating factors

Genetic predisposition

Despite the classical paradigm that AF and atrial myopathy are acquired, heritability studies with monozygotic twins reported an estimated heritability of AF of 62%.[39] Linkage analysis identified genes in selected families with Mendelian inheritance patterns of early-onset lone AF phenotypes. The first to be discovered this way was a mutation in the KCNQ1 gene, encoding the α-subunit of the K^+-channel responsible for the I_{Ks} current.[36] Later, mutations were identified in the NPPA gene encoding for atrial natriuretic peptide (ANP), TBX5 encoding for T-box transcription factor 5 which is associated with Holt-Oram syndrome, and MYL4 encoding for myosin light chain.[243] The fact that genes like MYL4 unrelated to electrophysiology are involved in AF pathogenesis formed a clue to the importance of structural remodeling in AF pathophysiology and the role of the myopathic substrate. Another

surprising finding was the observation of frequent early-onset AF in patients with SCN5A mutations leading to long QT syndrome by *prolongation* of atrial refractoriness, while classically ERP shortening is seen as a causative factor for the development of AF.[204]

Genome-wide association studies (GWAS) have identified more than 140 AF loci of interest (reviewed in [125]). The advantage of GWAS is that AF cases can be compared to controls in a more general population to identify regions of interest. [125, 235, 243] From these data, polygenic risk scores have been derived, which can potentially guide personalized medicine in the future.[134, 265, 294] Furthermore, GWAS data were used to inform pathway analysis to identify transcriptional networks underlying AF.[279]

A limitation of GWAS is the fact that only SNPs are analyzed, focusing on loss-of-function mutations, potentially overlooking numerous mutations in other parts of the genome. Technological advancements reduced the price of whole exome and whole genome sequencing, which made it possible to perform sequencing-based studies, as was done in an Icelandic study that included 14255 AF and 374939 control patients, identifying missense mutation in the PLEC, MYH6 and TTN genes.[274]

Table 1 gives an overview of the most common genetic mutations associated with AF and atrial myopathy, classified according to the function of the proteins they encode. However, this is not a complete overview of every single genetic mutation associated with AF in humans. For further reading we advise review articles focusing on AF genetics.[8, 59, 125, 235, 243]

CLASS	GENE	PROTEIN	CARDIAC PHENOTYPE	REF.
ION CHANNELS	SCN5A	Na^+ channel	AF, Atrial standstill	[82]
	GJA5	Connexin-43	AF, Atrial standstill	[82]
	KCNQ1, KCNH2, KCND3, KCNE5, KCN5A KCNN2, KCNN3, KCNJ5, KCNH2	K^+ channel	Repolarization disturbances, AF	[82, 125, 235]
	HCN4	HCN-channel	AF, conduction defects, sick sinus syndrome	[125, 261]
PARACRINE SIGNALING	NPPA	Atrial natriuretic peptide	Massive atrial enlargement, AF, atrial standstill, ERP shortening	[56, 82, 221]
CONTRACTILE APPARATUS	DMD, BMD	Dystrophin	Diffuse atrial fibrosis, AF, atrial standstill	[82, 88, 101]
	LMNA	Lamin A/C	Diffuse atrial fibrosis, AF, atrial standstill	[82, 88, 101]

	SGCG	Sarcoglycan	Diffuse atrial fibrosis, AF, atrial standstill	[82, 88, 101]
	DMPK	Dystrophia myotonica protein kinase	Diffuse atrial fibrosis, AF, atrial standstill	[82, 88, 101]
	MYL4	Myosin light chain 4	Atrial dilation, sarcomere disruption, atrial standstill, AF	[215, 235]
	MYH6	α-Myosin heavy chain	Sick sinus syndrome, AF	[243]
	TTN	Titin	Atrial dilation, prolonged PR, AF	[4, 235]
CELL STRUCTURE	AKAP9	A-kinase anchoring protein 9	Atrial dilation, AF	[59]
	PRRX1	Paired related homeobox 1	Patent ductus arteriosus and AF	[90, 125, 130]
	SYNE2	Nesprin-2	Emery-Dreifuss muscular dystrophy, increased nuclear stiffness, AF	[92]
	SYNPO2L	Synaptopodin 2-like protein	Disorganized sarcomeres, contractile dysfunction, AF	[44]
	CAV1	Caveolin-1	Atrial fibrosis, AF	[314]
	SLC35F1	Solute carrier family 35 member F1	Associated with AF	[40]
	NEBL	Nebulette	Various cardiomyopathies: dilated, hypertrophic, non-compaction	[217]
	PLEC	Plectin	Associated with AF	[243, 274]
ATRIAL DEVELOPMENT AND TRANSCRIPTION FACTORS	PITX2	Paired-like homeodomain transcription factor 2	Impaired expression of Shox2, Cx-40 and ion channels, leading to AF	[72, 141, 235]
	TBX5	T-box transcription factor 5	Holt-Oram syndrome AF, atrial septal defect, conduction defects	[125]
	ZFHX3	Zinc fingers and homeoboxes protein 3	Atrial (and ventricular) dilation and fibrosis, conduction delay, shortened refractoriness, atrial thrombus, AF	[114, 235]
	PRRX1	Paired related homeobox 1	Associated with AF	[90]
	NEURL	Neuralized E3 ubiquitin protein ligase 1	APD prolongation, AF	[38]
	CAND2	Cullin associated neddylation dissociated 2	APD prolongation, AF	[267]
	GATA6	GATA-binding factor 6	Conduction defects, sick sinus syndrome, AF	[79]
	NKX2-5	Homeobox protein Nkx-2.5	Atrial septal defect, AF	[116]
	HAND2	Hand and Neural crest Derivatives expressed 2	Associated with AF	[173]

Table 1: Common genetic mutations leading to atrial fibrillation and atrial myopathy.

Aging

Increasing age is one of the most important risk factors and affects various types of remodeling: structural, electrical, contractile, autonomic and endothelial. Aging indirectly affects the atria by increasing the prevalence of hypertension, diabetes, heart failure, ischemic or valvular heart disease, among others.[168] With age, cumulative atrial damage by hypertension, diabetes, inflammation, etc. increases. Aging also directly induces deleterious effects on the atrial tissue: senescence and apoptosis of atrial cells lead to cell loss with fibrotic replacement, which creates conduction heterogeneity and a substrate for AF. [91, 145, 258] Aging also increases leakiness of the ryanodine receptor (RyR) and impairs SERCA function, leading to calcium dysregulation and delayed afterdepolarizations (DAD).[91, 145, 258] Aging leads to decreased expression and activity of muscarinic and beta-adrenergic receptors, leading to autonomic dysregulation.[31] Furthermore, elderly patients have elevated levels of the inflammatory cytokines C-reactive protein (CRP), Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α), as well as reactive oxygen species (ROS).[91, 145, 258] Finally, aging is associated with endothelial dysfunction, which is reflected by capillary rarefaction, reduced nitric oxide (NO) bioavailability, and increased thromboembolic risk.[50, 51, 102, 212]

Arterial hypertension (AHT)

Hypertension correlates strongly with AF and is the most frequent underlying condition, present in 80% of AF patients.[9, 286] Various pathophysiologic mechanisms link AF to AHT. First, AHT increases LA pressure, which leads to atrial dilation, but also to activation of stretch-activated channels (see below) which increase cytosolic Ca^{2+}, a trigger for AF. Second, atrial stretch induces Angiotensin-II (Ang-II), TGF-β1 and platelet derived growth factor (PDGF) release, stimulating profibrotic pathways. Third, pathophysiologic mechanisms of hypertension, including autonomic dysfunction, neurohormonal activation, chronic inflammation, and renin-angiotensin-aldosterone system (RAAS) activation, are important drivers of AF pathogenesis.[286]

Obesity

Obesity is strongly correlated with the prevalence of AF. [288] Not only is obesity often accompanied by other risk factors, e.g., AHT or sleep apnea, but factors secreted by the epicardial adipose tissue—e.g., adipokines—have a direct effect on atrial inflammation and fibrosis.[177, 282] It has been shown that the extent of epicardial adipose tissue measured with CT or MRI is a strong predictor of AF occurrence, severity and recurrence.[300] A recent study demonstrated upregulation of the NLRP3 inflammasome (see below) in obese patients. The NLRP3 inflammasome upregulates profibrotic pathways, abnormal sarcoplasmic reticulum (SR) Ca^{2+}-release, and ultra-rapid delayed-rectifier K^+ channels (Kv1.5) that shorten the effective refractory period (ERP). Genetic ablation of *Nlrp3* in mice

prevented these obesity-induced alterations.[255] Interestingly, limited data reported ERP-*prolongation* in cardiomyocytes in response to adipokines.[147]

Diabetes mellitus

Diabetes is associated with increased levels of Ang-II and TGF-β as well as thickened epicardial adipose tissue, leading to inflammation, fibrosis and atrial enlargement, all of which lead to higher risk of AF, faster progression and recurrence after ablation.[22, 34, 52]

Heart disease

Atrial myopathy can exist solitary but is often observed in the presence of other cardiovascular diseases, including heart failure, ischemic and valvular heart disease.[82] An observational study by *Molina et al.* illustrates the electrophysiological changes in right atrial cardiomyocytes of heart failure patients, where proarrhythmogenic alterations were observed, including increased expression of pro-fibrotic markers and abnormalities in Ca^{2+}-handling.[191] The mechanism through which heart disease leads to atrial tissue damage is not only due to overlap of risk factors of these syndromes, but atrial volume overload leads to oxidative stress, inflammation, wall stress and RAAS activation.[82, 84, 122, 146, 214, 237, 263] Finally, AF itself can further induce progression of atrial myopathy.[296] How these mechanisms lead to atrial myopathy will be described in the following section.

Mechanisms of tissue damage

Oxidative stress

Signs of increased oxidative stress have been widely reported in atrial tissue of patients with AF.[81, 145, 178, 238, 292] ROS originate from various sources: exogenous—e.g., alcohol or tobacco— and intracellular through activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[29, 81, 145, 194, 203, 258] Oxidative stress induces activation (phosphorylation) of the Ca^{2+}/calmodulin kinase II (CaMKII) through c-Jun N-terminal Kinase-2 (JNK2) and directly through oxidation of CaMKII at Met281/282. CaMKII activation increases the open-probability of the RyR, increasing cytosolic Ca^{2+}.[197] Interestingly, a study in old rats described how oxidative stress can acutely activate CaMKII, leading to triggered activity by *early* afterdepolarizations (EAD) in presence of a *prolonged* action potential duration, in contrast with the classical theorem of DAD-mediated triggered activity.[218] In two different transgenic mouse models that increased resistance of CaMKII to oxidative stress (overexpression of reductive enzymes and ablation of critical oxidation sites), AF was not inducible after Ang-II infusion.[225]

In the fibroblast, ROS activates mitogen-activated protein kinase (MAPK), leading to myofibroblast differentiation and tissue fibrosis.[195] Finally, oxidative stress induces a phenotypic switch in the endothelial cell, stimulating the secretion of inflammatory cytokines. [186, 197]

Inflammatory signaling

Inflammation is a central mechanism in the development and progression of atrial myopathy, which is reflected by the link between increased levels of the inflammatory markers IL-1ß, IL-6 and TNF-α and the development and persistence of AF.[256] An interesting mechanism is the nucleotide-binding domain, leucine-rich repeat (NLR)-family pyrin-domain containing protein 3 (NLRP3) inflammasome. The NLRP3 inflammasome is a multimeric protein complex present in various cell types, and consists of three molecules: NLRP3, ASC (apoptosis-associated speck-like protein containing a CARD) and procaspase-1. Activation of toll-like receptors or IL-1ß receptors induces priming of the NLRP3 inflammasome by nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB) mediated transcription of NLRP3, pro-IL-1ß and pro-IL-18. When specific stimuli are present—e.g., K^+ efflux, Ca^{2+} influx, ROS, mitochondrial DNA or cathepsin-B—they trigger the oligomerization of NLRP3, ASC and procaspase-1. In this process, procaspase-1 is cleaved into mature caspase-1, which cleaves pro-IL-1ß and pro-IL-18 into mature IL-1ß and IL-18, which both contribute to atrial fibrosis and electrical remodeling. Caspase-1 also cleaves gasdermin-D, creating pores in the sarcolemma of the cardiomyocyte, which can lead to myocytolysis through a specific type of cell death, called *pyroptosis*.[165, 197, 256] Cardiomyocyte-specific constitutive overexpression of NLRP3 in mice induced atrial dilation, shortened refractoriness, frequent premature atrial complexes (PAC) and increased AF inducibility; all of these are typical characteristics of atrial myopathy that can be abrogated by pharmacological or virally transduced short hairpin RNA targeted NLRP3 inhibition. In a CREM-transgenic mouse model of spontaneous AF, genetic ablation of NLRP3 prevented the occurrence of spontaneous AF.[310] The NLRP3 inflammasome has proven to be a central and necessary pathway in the development of atrial myopathy as a result of various stimuli: obesity, chronic kidney disease, hypercoagulation and post-operative AF.[57, 68, 99, 255, 269] Because of its central role in atrial myopathy, the NLRP3 inflammasome could be an interesting therapeutic target.

Recent insights showed that not only the initiation of inflammation but also inflammation-resolution is important in the pathogenesis of atrial myopathy. In the acute setting of inflammation, eicosapentaenoic acid (EPA) and docosaheaenoic acid (DHA) are metabolized to resolvins (series D and E), which halt the inflammatory reaction by inhibiting chemotaxis of polymorphonuclear cells, by activating phagocytosis and efferocytosis by M2 macrophages and by clearing inflammatory cells. [57,

75, 219, 259, 260] Defective reversal of the inflammatory cascade can lead to chronic inflammation, which is proarrhythmic.[75] For an excellent review on this topic, we refer the reader to [57]

Atrial stretch

Increased atrial stretch is an important driver of atrial myopathy, especially in heart failure and valvular disease. Multiple studies have proven atrial dilation to be an independent risk factor for AF.[224, 278] Several mechanisms have been proposed to explain how atrial stretch induces heterogenous conduction slowing, shortened refractoriness and triggered activity—all of them making the atria vulnerable to AF. Increased atrial wall strain activates stretch-activated channels (SAC) on cardiomyocytes. These can be divided into non-specific cation SAC (SAC_{NS}), which produce outward currents when activated during early systole (shortening ERP) or DADs when activated during late systole. Specific cation SAC include the K^+-selective SAC (SAC_K), which mediates a K^+ efflux, shortening the ERP and decreasing excitability, resulting in heterogeneous conduction block and favoring reentry. The best studied SAC_K is the TREK-1 channel, which is downregulated in AF patients.[86] TREK-1 is a mechanically gated K^+ channel, that is activated by thinning of the cell membrane, which is sensed by an amphiphatic helix that extends from within the inner leaflet of the membrane.[210] Activation of TREK-1 occurs independently from the cytoskeleton.

Cardiomyocyte stretch also stimulates cytoskeletal proteins connected to integrins, activating RyR, increasing diastolic Ca^{2+} concentration and hence the probability of DADs.[24, 86] Fibroblasts can also activated upon stretch, resulting in the secretion of collagens and matrix metalloproteases, and thus contributing to interstitial fibrosis. Increased stretch over longer periods induces differentiation into myofibroblasts, which can electrically couple to cardiomyocytes (see “fibroblast remodeling”).[30, 62, 86, 195]

Finally, atrial stretch also results in natriuretic peptide secretion. ANP not only induces natriuresis, but also cGMP-mediated decrease of the cytosolic Ca^{2+} concentration in cardiomyocytes, and thus can be antiarrhythmic.[83]

RAAS activation

Ang-II type 1 receptors (AT1R) and mineralocorticoid (MR) receptors are present on cardiomyocytes and fibroblasts. When activated, they are proarrhythmic by activating several pathways. AT1R activates NADPH oxidase, CaMKII and JNK, leading to Cx40/43 function impairment, downregulation and lateralization to transverse borders. AT1R also increases intracellular Ca^{2+} through MAPK and through JAK/STAT, resulting in transcriptional activation of pathways involved in remodeling.[197, 198] Furthermore, AT1R activates Arkadia, which results in ubiquitination of Smad7 and disinhibition of

TGF-ß signaling. Combined with connective tissue growth factor (CTGF), NLRP3 and IL-1ß secretion, TGF-ß signaling leads to increased atrial-selective inflammation.[198] Activation of AT1R and MR on fibroblasts induces a profibrotic phenotype by upregulation of collagen production and differentiation into myofibroblasts.[156, 197, 198]

Clinical data also support the crucial role of RAAS activation in atrial myopathy. For instance, patients with hyperaldosteronism have a 12-fold increase in AF incidence compared to primary hypertension, despite similar blood pressures.[86, 189] Administration of deoxycorticosterone acetate (DOCA) in pigs results in increased atrial fibrosis and inducibility of AF without changes in left atrial pressures.[179] In patients, lowering of serum aldosterone after cardioversion predicts maintenance of sinus rhythm.[301] Thus, direct action of aldosterone and Ang-II on the atrial myocardium appears to be an important contributor to atrial myopathy.[52, 86]

Clinical manifestations of atrial myopathy

Atrial fibrillation

Atrial myopathy increases the vulnerability to AF through various abnormalities in impulse generation, impulse conduction and electrical refractoriness (Figure 2).[197] In the early stages of atrial myopathy, abnormal impulses typically originate from within the pulmonary veins (PVs) due to triggered activity or micro-reentry. As the disease progresses, AF-induced remodeling and the advancement of atrial myopathy lead to the emergence of ectopic sources and reentry outside the PVs.[197] Clinically, this is characterized by frequent PACs.[66] Impaired conduction arises from dysregulation of sodium channels or connexins, and from tissue fibrosis (or other interstitial depositions).[197] The rapid depolarizations of cardiomyocytes result in an increase in Ca^{2+} loading, leading to a reduction in $I_{Ca,L}$ and an upregulation of I_{K1}, $I_{K,ACh}$, I_{Kur}, I_{K2P} and I_{SK}.[100, 197, 254] Consequently, this shortens the action potential duration (APD) and subsequently, the effective refractory period (ERP), thus promoting micro-reentry in the PVs and the atrium.[197]

Increased atrial stiffness

The “stiff left atrium syndrome” was initially used to describe a heart failure syndrome based on a diastolic deficit, decreased LA compliance and pulmonary venous hypertension with its onset after excessive catheter ablation of the LA.[202, 231, 309] However, decreased LA compliance caused by atrial myopathy can lead to left atrial (i.e. pulmonary venous) hypertension leading to dyspnea, even in absence of prior ablation.[132, 230, 232, 276]

Atrial contractile remodeling and dilation have mainly been investigated in the setting of heart failure and valvular disease. They are the result of Ca^{2+} dysregulation, elevated filling pressures, autonomic and neuroendocrine dysfunction, and interstitial fibrosis. Even in the absence of AF and heart failure, atrial myopathy can cause exertional dyspnea. Stiffening of the atria impedes LA filling and passive emptying, while Ca^{2+} dysregulation and conduction slowing–induced dyssynchronous atrial contractions impair LA active emptying. The LA is in direct communication with the pulmonary vasculature, hence a rise in LA pressure (measured as the pulmonary capillary wedge pressure, PCWP) can result in hydrostatic pulmonary edema, leading to dyspnea. [230, 232, 276] However, the link between stiff atria and dyspnea is dubious since many patients with atrial myopathy or AF are asymptomatic.

Regarding LA hypertension, an important overlap exists between atrial myopathy and heart failure with preserved ejection fraction (HFpEF). Not only do both conditions have common risk factors and common pathophysiologic traits (Ca^{2+} dysregulation, fibrosis, inflammation, oxidative stress, mitochondrial dysfunction). But AF can exacerbate HFpEF and vice versa: on the one hand, stiffening and decreased contractility of the LA lead to worsening of restrictive LV filling. On the other hand, increased left ventricular (LV) pressures lead to LA hypertension and congestion through atrioventricular coupling. [230, 276] Finally, AF can induce an exacerbation of HFpEF complaints due to LA hypertension caused by ineffective atrial drainage and fast and irregular ventricular contractions.

Thromboembolism

Atrial myopathy disrupts the physiological regulation of prothrombotic and antithrombotic factors. There is a dysregulation of endothelial function, resulting in impaired release of endothelial nitric oxide (NO), prostacyclin (PGI_2), and tissue plasminogen activator (tPA), which are critical for maintaining an antithrombotic state. Concurrently, there is an upregulation of procoagulant factors such as tissue factor (TF) and von Willebrand factor (vWF), promoting a prothrombotic environment.[73, 107, 220, 246]

Furthermore, structural changes such as fibrosis and atrial dilation contribute to blood stasis and altered blood flow dynamics. Turbulent blood flow patterns, particularly in enlarged and dysfunctional atria, create zones of low flow and stasis, providing a fertile environment for thrombus formation. Additionally, the loss of atrial contractility and impaired mechanical function diminish the efficacy of blood clearance, further contributing to stasis. The latter is exacerbated during an episode of AF.[85, 246]

A.

Trigger	Substrate	
Focal Ectopy (DAD)	Shortened Refractoriness	Conduction Slowing
Abnormal Ca^{2+} handling	↓ $I_{Ca,L}$ ↑ I_{K1} , I_{Kur} , I_{KACh} , I_{K2P} , I_{SK}	↓ I_{Na} Cx40/43 remodeling Tissue fibrosis

B.

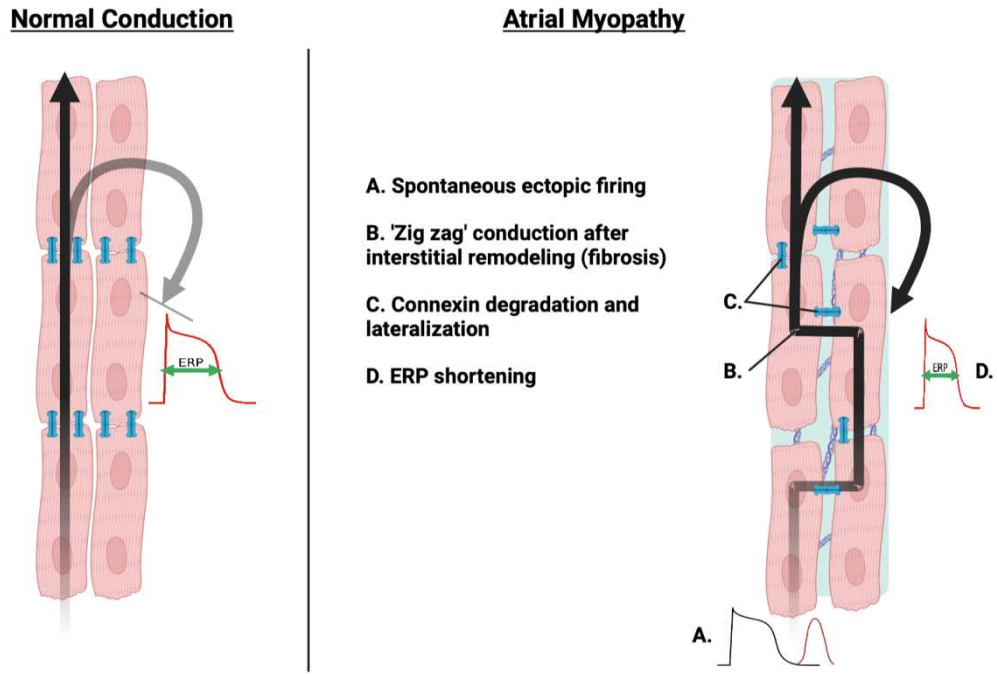

Fig. 2 *The link between atrial remodeling and AF vulnerability. A: schematic overview of the most important cellular mechanisms leading to AF vulnerability. B (left): in normal conduction, there is homogenous impulse conduction throughout the atria. B (right): In atrial myopathy, spontaneous ectopic firing triggers AF, while fibrosis, connexin remodeling and ERP shortening create a substrate for reentry, which in turn may lead to initiation and/or maintenance of AF.*

Molecular and cellular remodeling in atrial myopathy

Remodeling of the atrial interstitium

The EHRAS classification of atrial myopathy[82] distinguishes several types of atrial myopathy based on histology. Class I represents atrial myopathy characterized by myocytolysis and hypertrophy of cardiomyocytes, without fibrotic or interstitial changes. Class II represents atrial myopathy characterized by fibrotic alterations, without changes in cardiomyocytes. Class III represents atrial myopathy characterized by a combination of cardiomyocytes and interstitial changes. Class IV represents atrial myopathy with additional interstitial matrix changes, such as the accumulation of amyloid (class IV_a), fat deposits (class IV_f), inflammatory cells (class IV_i), or other interstitial changes (class IV_o), including granulomatosis or glycosphingolipids. The accumulation of these infiltrates contributes to the development of electrical conduction heterogeneity, manifesting as "zig zag" conduction patterns. Such aberrant conduction dynamics facilitate the formation of reentry circuits

and stabilize rotors at the tissue level, thereby rendering the atria susceptible to the initiation and perpetuation of AF.[52, 82, 195, 198]

Atrial fibrosis is the most common interstitial deposition. These consist of collagen (mostly type I), secreted by fibroblasts. Therefore, we refer to the paragraph “remodeling of fibroblasts”.

Isolated atrial amyloidosis (IAA) represents the atrial-specific deposition of insoluble misfolded proteins, for instance ANP.[108] Like fibrotic depositions, these induce local conduction block and prolong P-wave duration but are also directly toxic to atrial cardiomyocytes. The prevalence of IAA strongly increases with age: up to 8.2% of people older than 80 years in one post-mortem study. In people undergoing cardiac surgery, a prevalence of 16% has been reported. In both studies, IAA strongly correlated with AF, independent of age or sex. These data indicate that IAA is a common cause of intra-atrial conduction block and AF in older people.[148, 239, 283]

Fatty infiltration of the atrium arises from the epicardial adipose tissue and causes local conduction block. Adipocytes secrete adipokines—e.g., Activin A—that decrease Ca^{2+} influx and contractility in cardiomyocytes [87] and induce fibrosis.[107, 282] Over time, fatty infiltrates can evolve into subepicardial fibro-fatty infiltrations, observed in more advanced stages of atrial myopathy with persistent AF. [93, 237]

Rare forms of interstitial infiltration in the atria are inflammatory infiltrates in myocarditis,[50, 155] granulomatosis in cardiac sarcoidosis[185] or glycosphingolipids in Anderson-Fabry disease.[137]

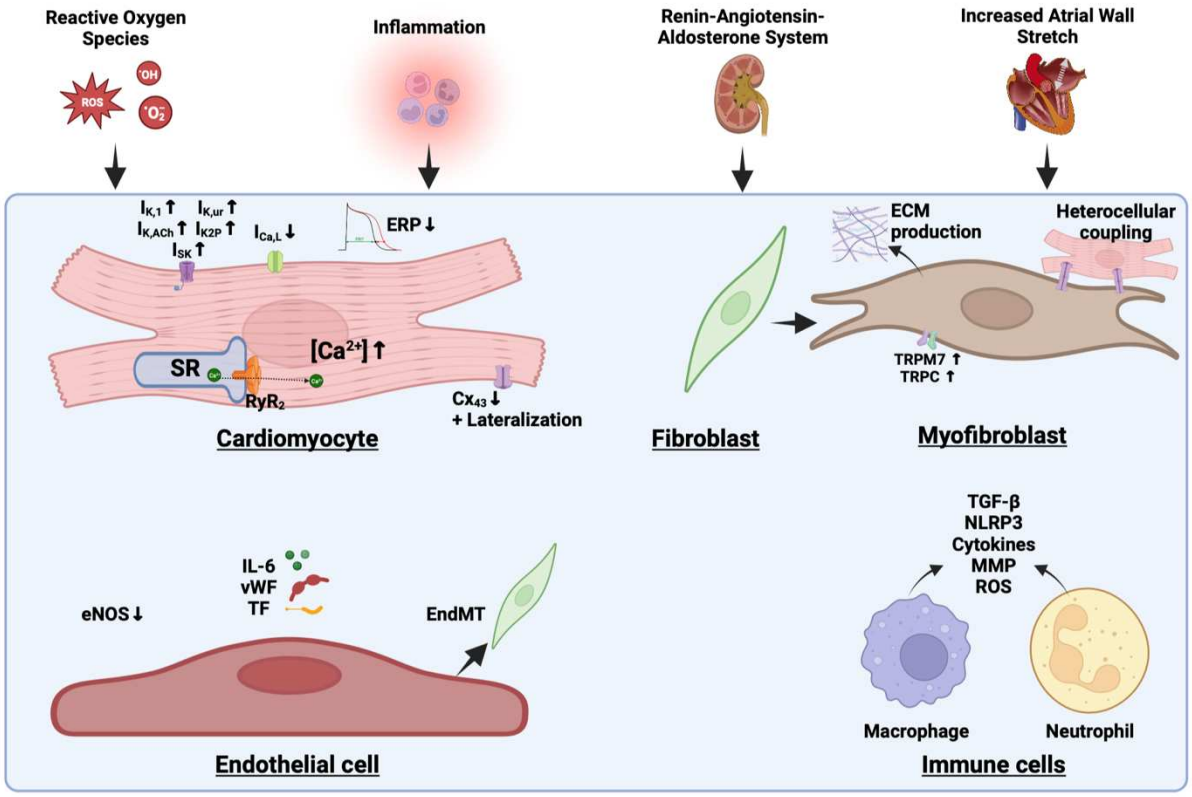

Fig. 3 *Overview of cellular remodeling in atrial myopathy*

Cx_{43} = connexin-43, ECM = extracellular matrix, EndMT = endothelial-mesenchymal transition, eNOS = endothelial nitric oxide synthase, ERP = effective refractory period, IL-6 = interleukin-6, MMP = matrix metalloprotease, NLRP3 = nucleotide-binding domain, leucine-rich repeat (NLR)-family pyrin-domain containing protein 3, ROS = reactive oxygen species, RyR2 = ryanodine receptor type 2, SR = sarcoplasmic reticulum, TGF-ß = transforming growth factor-ß, TF = tissue factor, TRP = transient receptor potential, vWF = von Willebrand Factor.

Remodeling of cardiomyocytes

Cardiomyocyte remodeling is a key process in atrial myopathy and AF, as reviewed previously [196-198]. Here, we provide a brief overview of the main mechanisms involved in this process and illustrate these in Fig 2. One of these mechanisms is the activation of the NLRP3 inflammasome and ROS, which increase the RyR_2 channel open-probability and cause sarcoplasmic reticulum (SR) Ca^{2+}-overload. This leads to spontaneous SR Ca^{2+}-release and triggered activity due to enhanced Na^+/Ca^{2+} exchanger (NCX) activity, resulting in DADs.[284] Cytosolic Ca^{2+} overload leads to ion channel remodeling due to NFAT-regulated miR-26 reduction and altered expression of $I_{Ca,L}$, $I_{K,1}$, $I_{K,ur}$ and $I_{K,ACh}$. This causes a shortening of the effective refractory period. Another mechanism is the impairment of impulse conduction by Connexin-43 dysregulation and lateralization, which are influenced by aging, IL-6, Ang-II and ROS. Moreover, fibrosis causes “zig zag” conduction, which further disrupts normal impulse propagation.[196-198]

Remodeling of fibroblasts, myofibroblasts

Myofibroblasts are fibroblasts that have been activated by various stimuli (atrial stretch, TGF-ß, PDGF, CTGF and Ang-II) to differentiate and produce more procollagen and matrix metalloproteinases (MMP), which are mediated through various intracellular profibrotic signaling pathways (MAPK, SMAD, NLRP3, ROS…).[195] During fibroblast differentiation, expression of the transient receptor potential (TRP) melastatin related 7 (TRPM7) and TRP canonical-3 (TRPC3) receptors is increased. TRPM7 and TRPC3 are inward non-selective Ca^{2+}-channels, that stimulate myofibroblast differentiation and proliferation.[60, 94] Myofibroblasts express contractile proteins, such as alpha-smooth muscle actin (α-SMA), a distinctive marker.[195] They also express connexin-43, which allows them to form electrical connections with cardiomyocytes; these connections affect the conductivity and rotor susceptibility of cardiomyocytes in vitro.[120, 190, 323] However, it is not clear whether myofibroblasts can couple with cardiomyocytes in vivo.

Recently, *Moreira et al.* discovered that cardiomyocyte-secreted calcitonin inhibits fibroblast proliferation and differentiation. In right atrial appendages of AF patients, calcitonin secretion was decreased and calcitonin receptors were internalized. In a LKB1-knockout mouse model of spontaneous AF, additional atrium-specific knockout of calcitonin increased cardiac fibrosis 2.5-fold and mean duration of spontaneous AF episodes 16-fold compared to the single-knockout LKB1 mice, while calcitonin overexpression led to reduced fibrosis and no spontaneous AF.[192]

Remodeling of immune cells

Important cells in atrial appendages from AF patients are macrophages, which contribute to inflammation and fibrosis. A recent single-nucleus RNA-sequencing study demonstrated that expansion of the macrophage population was higher than of any other cell type and that macrophage-specific genetic ablation of the inflammatory mediators *Spp1* and *Ccr2* resulted in decreased arrhythmogenicity.[109] Macrophages respond to inflammatory signals and produce TGF-ß, which induces the differentiation of fibroblasts into myofibroblasts. Through NLRP3 activation, inflammatory cytokines released by the macrophage affect electrical properties of cardiomyocytes by reducing $I_{Ca,L}$ and altering Ca^{2+} handling.[107, 171] In explanted human hearts from end-stage heart failure patients undergoing transplant, a marked tendency was observed for increased atrial NLRP3 inflammasome activation in AF patients compared to sinus rhythm.[150] In a canine rapid atrial pacing model, TRAM-34—an inhibitor of the Ca^{2+}-sensitive K^+ channel KCa3.1 which is expressed on macrophages—was able to prevent macrophage switching into a proinflammatory phenotype, decreasing AF vulnerability.[96]

Neutrophils are involved in atrial remodeling after surgery or ablation for AF. They release inflammatory mediators, matrix metalloproteases and ROS, which cause changes in the structure and

function of the atria.[107, 171] Mast cells and lymphocytes may also play a role in some cases of atrial myopathy.[171]

Remodeling of endothelial cells

Inflammation and oxidative stress induce endothelial dysfunction, endothelial activation and endothelial-to mesenchymal transition (EndMT). These processes increase the risk of thromboembolic complications. Studies have shown that patients with AF have endothelial dysfunction. For example, they have decreased flow-mediated dilation and lower levels of endothelial NO synthase (eNOS).[73, 107, 220] They also have higher levels of inflammatory and prothrombotic factors, such has IL-6, vWF and TF, all markers of endothelial activation.[107, 220] Moreover, they have more EndMT in their atrial appendages.[129] These fibroblast-like mesenchymal cells are derived from endothelial cells through the action of TGF-ß, which reduces expression of E-cadherin and enables them to migrate and secrete extracellular matrix components, leading to fibrosis.[153, 250]

Remodeling of the autonomic nervous system (ANS)

Auto-antibodies that target muscarinic receptors and $ß_1$-adrenergic receptors have been implicated in some cases of AF.[171] These receptors mediate the effect of vagal and sympathetic stimulation on cardiomyocytes and increase the risk of arrhythmia: ß-adrenergic receptor stimulation induces hyperphosphorylation of RyR_2 channels and increased intracellular Ca^{2+} concentrations, while vagal activation enhances $I_{K,ACh}$.[122] Zhou et al. showed that microinjections with Neuregulin-1 into the ganglionated plexi (GP) of dogs prevented rapid atrial pacing (RAP)-induced upregulation of GP neural activity; decreased GP neural activity suggests that it could eventually decrease AF vulnerability.[321] As a therapeutic approach, targeted ablation of the ganglionated plexi in humans on top of conventional PVI did not deliver significant increase in AF-free survival.[14, 138] However, in another attempt to target autonomic remodeling in AF patients, intermittent low-level tragus stimulation to increase vagal tone reduced AF burden in patients with paroxysmal AF.[151]

AF-related atrial remodeling

When atrial myopathy is established, it can predispose individuals to atrial fibrillation (AF). However, the presence of AF itself exerts detrimental effects on various cardiac cell types, contributing to the progression of atrial myopathy and creating a self-perpetuating cycle known as “AF begets AF”.[296]

At the electrophysiological level, the rapid depolarizations observed during AF induce Ca^{2+} loading within the cardiomyocytes. Consequently, there is downregulation of $I_{Ca,L}$ and upregulation of I_{K1}, I_{Kur}, , $I_{K,Ach}$, I_{K2P} and I_{SK}.[100, 254] These changes result in a shortened ERP, which promotes the occurrence

of reentrant circuits. Additionally, the increased diastolic Ca^{2+} levels activate NCX, enhancing the likelihood of triggered activity.[196-198]

Beyond electrical remodeling, the intracellular Ca^{2+} overload in the cardiomyocytes triggers the activation of NADPH oxidase, leading to the generation of reactive oxygen species (ROS) and the activation of the NLRP3 inflammasome. These signaling pathways extend their influence to neighboring fibroblasts, promoting their differentiation into myofibroblasts and ultimately contributing to the development of atrial fibrosis, which in turn stabilizes reentrant circuits and promotes AF.[195, 197, 198]

Metabolic remodeling

Cardiomyocytes oxidate fatty acids (FA) and glucose in the mitochondria to produce acetyl-coA that is consumed in the oxygen-dependent Krebs cycle to generate nicotinamide adenine dinucleotide and flavin adenine dinucleotide, the latter only in FA oxidation. These molecules are transported towards the electron transporter chain, where they undergo redox reactions eventually resulting in adenosine triphosphate (ATP), the universal energy source of the cell.[95] FA oxidation produces more ATP than glucose, but also requires more oxygen. During stress situations, e.g., during high atrial rates observed in AF, glucose metabolism is favored. In patients with AF, there is also increased expression of the less energy consuming, but slower contracting myofilament fetal-phenotype beta-myosin heavy chain (MHC) instead of the adult myofilament alpha-MHC.[95] In response to energy depletion, adenosine monophosphate (AMP)-activated protein kinase (AMPK) is activated (phosphorylated), increasing glucose and FA uptake in the mitochondrion. AMPK phosphorylation is increased in paroxysmal AF, but decreased in permanent AF, indicating failure of this adaptive mechanism as atrial myopathy progresses.[95]

In patients with AF, atrial myocytes have decreased ability to switch to glucose, either favoring glycolysis or FA oxidation.[227] Pyruvate dehydrogenase kinase (PDK) is upregulated in AF and inactivates pyruvate dehydrogenase, leading to uncoupling of glycolysis and glucose oxygenation, which is called the Warburg effect, originally described in tumor cells.[170] PDK is upregulated in AF patients, and its inactivation by dichloroacetic acid was able to counteract electrical and structural remodeling in a mouse model of paroxysmal AF.[106] Similar to the Warburg effect, FA transportation and oxidation are uncoupled from FA uptake, leading to FA overload and lipotoxicity, resulting in fibrosis and connexin-43 lateralization in a mouse model.[227, 253]

Finally, during AF, an imbalance can arise between energy supply and demand. On the one hand, high rates of atrial excitation and increased cardiac work (due to LA dilation) lead to increased atrial ATP consumption. On the other hand, coronary flow reserve decreases, leading to metabolic stress. This

results in mitochondrial dysfunction due to redox imbalance, resulting in increased ROS production and mitochondrial damage, a characteristic histological change in atrial tissue of AF patients.[50, 95]

Diagnosis of atrial myopathy

Atrial myopathy is a scientific concept that has not been translated to daily clinical practice yet, in part because of the lack of diagnostic criteria. However, many clinical findings indicate the presence of atrial myopathy; some of them are listed below. Future research should develop a scoring or classification system, or perhaps serum biomarkers, that reflects the degree and reversibility of atrial tissue damage and the patient's prognosis. Furthermore, a quantitative assessment of various components contributing to atrial myopathy could give insight into a hierarchical classification of these factors. Potential avenues include investigating the association between biomarkers reflecting underlying types of remodeling, and their correlation with quantitative proxies for atrial myopathy, e.g., atrial arrhythmia burden, imaging proxies like atrial size or strain, and stroke risk. Addressing these aspects could enhance our understanding of atrial myopathy, guide future therapeutic interventions, and help clustering different types of atrial myopathy.

History

A detailed history can reveal the patient's risk profile and possible mechanisms or triggers for atrial remodeling. The $CHADS_2$-VA_2Sc score is part of this risk profile. Personal and family history, lifestyle habits—such as drug use (alcohol, nicotine, caffeine, cocaine…), medication use, endurance sports and sleeping apnea—should also be investigated. These factors can increase the risk of atrial myopathy and can be modified to reduce it (see management).

Electrocardiogram (ECG)

The ECG is a widely used tool in cardiology that can reveal signs of atrial myopathy. The most obvious sign of atrial myopathy on the ECG is the presence of AF, which is a strong argument for an underlying atrial myopathy and requires treatment according to current guidelines.[104] Several studies have shown a correlation between the amplitude of fibrillatory f-waves and the degree of LA enlargement, AF chronicity, and response to therapy.[5, 23, 237, 262, 305] However, ECG findings during sinus rhythm can also provide valuable insights into the presence of atrial myopathy. Specifically, the P-wave terminal force in lead V1 (PTFV1) and P-wave duration on signal-averaged ECG (P-SAECG) serve as indicators of left atrial enlargement and conduction abnormalities. Furthermore, the frequency of PACs reflects atrial electrical remodeling. Increased PTFV1 and PAC frequencies have been associated with a higher risk of AF incidence, stroke, AF recurrence after PVI, and mortality. Although less data is available for P-SAECG, it has shown promise as a predictor of AF and AF recurrence following PVI.

Notably, one small study[121] demonstrated the predictive value of P-SAECG in stroke recurrence among patients with cryptogenic stroke.[2, 64, 66, 77, 89, 121, 126, 223, 226, 237, 247, 249, 298, 307]

A recent advancement in ECG analysis is the use of artificial intelligence (AI) to predict AF occurrence from sinus rhythm recordings.[268] *Attia et al.* used a deep learning system trained on a dataset of 454 789 ECGs in sinus rhythm to identify AF patients in a separate testing dataset of 130 802 ECGs with a sensitivity of 79.0% and specificity of 79.5%.[13] They also showed that AI-based screening of ECGs was more sensitive than conventional care to detect AF.[201] The deep learning system was able to extract subtle—predominantly P-wave—features invisible to the human eye to predict AF.[135] Despite promising results, implementing AI into clinical practice requires cautiousness because the outcome is strongly dependent on the learning database.[268]

Cardiac imaging

Echocardiography is the most common and accessible technique for cardiac imaging in clinical practice. It can measure several parameters related to the LA. The most typical parameter is the left atrial volume (index), but it does not correlate seamlessly with stroke risk or AF occurrence and recurrence after treatment.[84, 237] LA strain, which is the deformation of the LA wall during the cardiac cycle using speckle tracking echocardiography, has been studied extensively in recent years. Reduced LA strain reflects LA stiffness and fibrosis.[28] It also predicts stroke, and AF occurrence and recurrence after ablation.[205, 264, 311] Transesophageal echocardiography (TEE) can evaluate blood flow velocities in the LAA and detect spontaneous echo contrast, both of which indicate a higher risk of thrombo-embolism.[12, 85]

Late gadolinium enhancement *cardiac magnetic resonance* (LGE-CMR) allows the detection of fibrotic areas in the heart, where gadolinium remains longer than in normal tissue after 10-15 minutes. LGE-CMR can quantify the extent of fibrosis according to the Utah classification, which is a strong predictor for AF recurrency after catheter ablation, as shown in the DECAAF-trial.[35, 180] Moreover, increased fibrosis assessed with LGE-CMR correlates with AF occurrence, chronicity and stroke.[140, 157, 228] Another parameter that can be measured with CMR is the amount of epicardial fat, which is associated with AF occurrence, ablation outcome and stroke. [242, 300]

Besides gadolinium, new *molecular imaging* probes are being developed to target specific markers of atrial myopathy, for instance collagen, inflammatory cells, coagulation factors and ganglionated plexi. These probes can be visualized by CMR, positron emission tomography (PET) or single photon emission computed tomography (SPECT), depending on the probe.[65]

In patients undergoing an electrophysiology study, three-dimensional *electroanatomical voltage maps* can be created to visualize the substrate of the arrhythmia. On these maps, low voltage areas, electrical silence, fractionation or double potentials indicate fibrotic areas that can cause reentry. Additionally, activation maps can show zones of conduction slowing. [58, 82, 237] These abnormal areas inside the atria can be ablated to improve outcome.[241, 320] Electroanatomic mapping is probably the most accurate technique for estimating atrial substrate, but it is invasive and not suitable for patients in early stages of atrial remodeling.

Circulating biomarkers

Numerous studies aim to identify blood biomarkers signaling the presence of atrial myopathy, indicating an elevated risk of atrial fibrillation (AF), stroke, and AF recurrence post-catheter ablation. Atrial myopathy, a common endpoint for various remodeling types, has diverse biomarkers measuring specific remodeling aspects: myocyte stress, damage, inflammation, fibrosis, endothelial, metabolic, and electrical remodeling.

Micro-ribonucleic acids (miRNAs) are emerging biomarkers. These short non-coding RNA strands can bind to messenger RNA, epigenetically altering gene transcription. Some miRNAs released into serum/plasma (focused on in this article) provide clinicians with a means to assess remodeling-related pathways with targeted precision.[45, 74, 136, 144, 174, 183]

While no single biomarker directly links to myopathy, simultaneous use of multiple biomarkers offers insights into its underlying mechanisms, as highlighted in Table 2.

Parameter	Mechanism	Predicts AF	Predicts stroke	Predicts response to PVI	Ref.
ECG:					
- PTFV1	Intra-atrial conduction delay	Yes	Yes	Yes	[64, 126, 237, 249]
- P-SAECG	Intra-atrial conduction delay	Yes	?	Yes	[89, 121, 223]
- frequent PAC	Triggered activity	Yes	Yes	Yes	[2, 66, 77, 226, 247, 307]
- deep learning	Unknown	Yes	?	?	[13, 135, 201, 268]
Ultrasound:					
- atrial dimensions	Structural/contract. remodeling	(Yes)	(Yes)	No	[84, 206]
- LA strain	Contr. remod., Î stiffness	Yes	Yes	Yes	[27, 28, 205, 264, 311]
- LA emptying fraction	Contractile remodeling	Yes	Yes	Yes	[37, 119, 132, 154, 214]
- a' wave velocity	Contractile remodeling	Yes	?	?	[33, 55, 214, 315]
- LA functional index	Structural/contract. remodeling	Yes	Yes	Yes	[251, 252]
- integrated backscatter	Structural remodeling	Yes	?	Yes	[26, 54, 149, 289]
- spont. echo contrast	Endothelial/contract. remodeling	Yes	Yes	Yes	[167, 291, 317]
CT :					
- LA asymmetry index	Structural/contract. remodeling	?	?	Yes	[199]
- LAA morphology	Blood stasis	?	Yes	?	[158]
CMR:					
- atrial LGE	Fibrosis	Yes	Yes	Yes	[35, 140, 157, 180, 228]
- epicardial fat	Adipokines	Yes	Yes	Yes	[242, 300]
- LA strain	Contr. remod., Î stiffness	Yes	Yes	Yes	[19, 21, 112]
- LA emptying fraction	Contr. remodeling	Yes	Yes	Yes	[19, 21, 112]
Biochemical markers:					
- *Troponin*	Myocardial injury	Yes	Yes	?	[20, 52, 103, 229, 237]
- *NT-pro-BNP*	Myocardial stretch	Yes	Yes	Controversial	[20, 52, 103, 229, 237]
- *CRP*	Inflammation	Yes	Yes	Yes	[49, 117, 318]
- *IL-6*	Inflammation	Yes	Yes	Yes	[49, 117, 318]
- *GDF-15*	Inflammation/oxidative stress	Yes	Yes	Yes	[287, 293, 299, 322]
- *miRNA-150*	Inflammation (IL-6, IL-8, TNF-α)	Yes	?	(Yes)	[184]
- *sST2*	Fibrosis	Controversial	Yes	Yes	[124, 169, 176, 200, 209, 236]
- *Galectin-3*	Fibrosis	Yes	Yes	Yes	[46, 47, 281]
- *PIIINP/ICTP*	Fibrosis	Yes	No/Yes	Yes	[81, 220, 246, 258, 297]
- FGF23	Fibrosis	Yes	No	No	[7, 17, 41, 302]
- TGF-β_1	Fibrosis	Yes	?	Yes	[53, 74, 139, 244]
- *miRNA-29*	Fibrosis (COL1A1, COL3A1)	Yes	Yes	?	[3, 16, 61, 229]
- *vWF*	Endothelial remodeling	Yes	Yes	Yes	[220, 240, 246, 257, 295]

- *ADMA*	Endothelial remodeling	Yes	Yes	Yes	[128, 142, 163, 303]
- *IGF1*	Metabolic remodeling	Yes	Controversial	?	[128, 245, 271]
- *IGFBP1*	Metabolic remodeling	Yes	No	?	[128, 271]
- *miRNA-1*	Electrical (KCNE1, KCNB2)	Yes	No	?	[15, 18, 45, 174]
- *miRNA-328*	Electrical (CACNA1C, CACNB1)	Yes	Yes	No	[152, 183, 290]
- *miRNA-106*	Electrical (RYR2)	Yes	(Yes)	?	[172]
- *miRNA-208*	Electrical (SERCA2A)	Yes	No	?	[184, 213]
- *miRNA-21*	Electrical + fibrosis + inflammation (CACNA1C, CACNB2, MAPK/ERK, Smad7)	Yes	Yes	Yes	[53, 144, 184, 208, 222, 277, 319]
Electroanatomic mapping:					
- low voltage areas	Fibrotic/electrical remodeling	Yes	Yes	Yes	[182, 193, 272]

Table 2: Diagnostic tools to detect atrial myopathy and their predictive values for AF incidence, stroke and response to ablation therapy.

Abbreviations (alphabetically): ADMA = asymmetric dimethylarginine, CMR = cardiac magnetic resonance imaging, CRP = c-reactive protein, CT = computed tomography, ECG = electrocardiogram, FGF23 = fibroblast growth factor-23, GDF-15 = growth differentiation factor-15, ICTP = type I carboxy-terminal peptide, IGF1 = insulin-like growth factor-1, IGFBP1 = IGF-binding protein-1, IL-6 = interleukin-6, LA = left atrium, LAA = left atrial appendage, LGE = late gadolinium enhancement, miRNA = micro-ribonucleic acid, NT-pro-BNP = N-terminal pro-B-type natriuretic peptide, PAC = premature atrial contraction, PIIINP = procollagen type III N-terminal peptide, P-SAECG = P-wave duration in signal-averaged electrocardiography, PTFV1 = pre-terminal force in lead V1, PVI = pulmonal vein isolation, sST2 = soluble suppressor of tumorigenicity 2, TGF-β_1= transforming growth factor-β_1, vWF = von Willebrand factor.

Management of atrial myopathy

The ESC and AHA provide guidelines for the management of AF,[104, 115] but they do not address interventions that target the underlying atrial myopathy. This section summarizes some of the main therapeutic strategies that target the atrial substrate.

Atrial reverse remodeling

As can be appreciated in Figure 1, atrial myopathy is a heterogenous disorder that is a common endpoint of (a combination of) various pathogenic driving mechanisms. *Shen et al*. proposed 4 stages of atrial myopathy, similar to the 4 stages of AF in the recent ACC/AHA/ACCP/HRS guidelines on AF: [118] stage A (at risk of developing atrial myopathy), stage B (asymptomatic but detectable atrial myopathy), stage C (manifest disease but reversable), and stage D (irreversible).[263] Without intervention, patients progress towards stage D, but therapy directed at the driving mechanism of atrial myopathy can induce reverse remodeling, which is often objectivated by reduction in LA volume, increase in LA strain, or decrease in symptom burden.[111]

One of the most important strategies is to modify the risk factors that contribute to atrial myopathy, such as obesity, alcohol consumption, and high blood pressure. For example, weight loss can reduce epicardial fat, improve symptoms and quality of life, and lower the recurrence of AF after ablation and even reverse persistent AF to paroxysmal AF.[1, 187, 211] Quitting alcohol can improve the oxidative balance and reduce both AF recurrence and stroke risk.[161, 285]

Successful early rhythm control can lead to atrial reverse remodeling via inhibition of AF-induced atrial myopathy.[273] Successful maintenance of sinus rhythm after catheter ablation leads to a decrease in LA volume and an increase in LA strain.[275] Successful DC cardioversion also leads to a prolongation of the ERP, and sustained ERP prolongation post-cardioversion predicts longer-term rhythm control.[270] On a molecular level, sinus rhythm maintenance is accompanied by a reduction in oxidative stress[145] and inflammation parameters.[123] Thus, ample evidence exists that early rhythm control with existing therapies is effective to halt and even reverse atrial myopathy. To widen the therapeutic arsenal of anti-arrhythmic drugs, highly specific ion-channel blocking agents inhibiting I_{SK} [100] or K_{Ca}-2 [76] are currently being developed.

Combining several targets increases success rates: aggressive risk factor reduction after AF ablation not only increased arrhythmia-free survival compared to standard care, but also significantly reduces left atrial volumes, suggesting a reversing effect on atrial myopathy.[43, 211]

Therapies targeting the atrial substrate

Treating atrial myopathy in patients presenting in later stages, e.g. stage C, is challenging, because they often progress to persistent and permanent AF (stage D) despite rhythm control efforts. Current strategies targeting the atrial substrate include ACE inhibitors, Ang-II receptor blockers, and mineralocorticoid receptor antagonists. However, large clinical trials have not been able to confirm their efficacy in atrial myopathy. [6, 10, 11, 52, 71, 133, 166, 188, 234, 248] Diuretics may alleviate LA hypertension during early atrial myopathy stages, [207] but their impact on later stages of atrial myopathy is limited. [11, 70] Statins show promise in reducing inflammation and fibrosis during early stages, but their effectiveness in persistent AF is unclear. [67, 308, 316] Novel therapies targeting atrial fibrosis, such as pirfenidone, show potential but lack convincing clinical data. [160, 162]

Sodium-glucose linked transporter-2 inhibitors (SGLT2i) may reduce AF incidence in diabetic patients by targeting several mechanisms [42, 63, 143, 164, 175] with ongoing trials like the BEYOND trial to validate their efficacy in humans. [159] The NLRP3 inflammasome is a promising target; inhibitors like glibenclamide [304]and colchicine [48, 280] exhibit (weak) anti-fibrotic effects. Ongoing developments include selective NLRP3 inhibitors (oridonin, MCC950), that show promising data, [78, 216, 306, 313] but are still being clinically tested.[57] Resolvins, a novel class promoting inflammation-resolution. A

member of this family, Resolvin-D1, has proven anti-inflammatory, anti-fibrotic, and anti-arrhythmic effects in a rat model. [105] A recent drug repurposing study showed that ruxolitinib, a drug used to treat myelofibrosis, is a potent CaMKII inhibitor and is able to inhibit AF in vitro and in mouse models [110, 233] Future research should further identify possible therapies targeting and ideally reversing atrial remodeling, in order to get patients from stage C or D back to earlier stages of the disease in order to enhance rhythm control and patient wellbeing.

Anticoagulation

Another challenge in managing atrial myopathy is the initiation of anticoagulation therapy to prevent thrombo-embolic complications, particularly in the absence of AF. Some studies suggest that atrial remodeling, rather than rhythm, is a significant stroke risk factor, [246, 263] and therefore should guide initiation of anticoagulant therapy.[97, 181] The ARCADIA trial[127] is currently investigating apixaban with aspirin in stroke patients with atrial myopathy without AF. While awaiting trial results, it may be more practical to use markers for atrial myopathy to identify patients at risk for developing AF and stroke.[98, 131] However, there is a need for standardized diagnostic tools to asses and stage atrial myopathy in individual patients.

The bidirectional relationship between coagulation and AF is gaining attention. AF promotes a hypercoagulant state, contributing to atrial myopathy progression. Thrombin and Factor Xa (FXa) are serine proteases and activate protease activated receptors (PAR 1-4), which induce inflammatory signaling, oxidative stress, and inositol triphosphate (IP_3)-mediated SR Ca^{2+} release in cardiomyocytes. They also induce differentiation of fibroblasts into myofibroblasts. Furthermore, thrombin and FXa activate MMP9 and the NLRP3 inflammasome through PAR4 activation, triggering fibrosis and inflammation.[68] These detrimental effects can potentially be prevented by direct oral anticoagulants (DOACs). Additionally, DOACs exhibit direct antiarrhythmic properties by prolonging ERP through upregulation of $I_{Ca,L}$ in isolated cardiomyocytes.[32, 69] More research is needed to elucidate the clinical importance of these findings. Finally, selective PAR4-inhibitors are under investigation in clinical trials.[312]

Conclusion

Rhythm control therapy proves highly effective in many patients with AF, even those exhibiting early signs of atrial myopathy. Addressing underlying factors contributing to myopathy is a prudent approach, amplifying the impact on reverse remodeling. However, the inefficacy of long-term rhythm control in some subjects displaying signs of more advanced atrial myopathy suggests the need for interventions targeting the underlying substrate to treat this large subgroup of patients. Improved

criteria for diagnosing and staging atrial myopathy are needed for the clinical implementation of this concept.

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