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Review

Left atrial cardiomyopathy: Pathophysiological insights, assessment methods and clinical implications☆

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ABSTRACT

Atrial cardiomyopathy is defined as any complex of structural, architectural, contractile or electrophysiological changes affecting atria, with the potential to produce clinically relevant manifestations. Most of our knowledge about the mechanistic aspects of atrial cardiomyopathy is derived from studies investigating animal models of atrial fibrillation and atrial tissue samples obtained from individuals who have a history of atrial fibrillation. Several noninvasive tools have been reported to characterize atrial cardiomyopathy in patients, which may be relevant for predicting the risk of incident atrial fibrillation and its related outcomes, such as stroke. Here, we provide an overview of the pathophysiological mechanisms involved in atrial cardiomyopathy, and discuss the complex interplay of these mechanisms, including aging, left atrial pressure overload, metabolic disorders and genetic factors. We discuss clinical tools currently available to characterize atrial cardiomyopathy, including electrocardiograms, cardiac imaging and serum biomarkers. Finally, we discuss the clinical impact of atrial cardiomyopathy, and its potential role for predicting atrial fibrillation, stroke, heart failure and dementia. Overall, this review aims to highlight the critical need for a clinically relevant definition of atrial cardiomyopathy to improve treatment strategies.

1. Abbreviations

ACM	atrial cardiomyopathy
AF	atrial fibrillation
AI	artificial intelligence
APD	action potential duration
ARIC	Atherosclerosis Risk in Communities
Ca^{2+}	calcium
CI	confidence interval
CMR	cardiac magnetic resonance
EAT	epicardial adipose tissue
HFpEF	heart failure with preserved ejection fraction
IAB	interatrial block
I_{CaL}	L-type calcium current
K^+	potassium
LA	left atrium/atrial
LGE	late gadolinium enhancement
MAFLD	metabolic-associated fatty liver disease
PTFV1	P-wave terminal force in lead V1

2. Introduction

Atria play an important role in cardiac function, including haemodynamic regulation and endocrine function, and host an important part of the conduction system (i.e. pacemaker cells and atrioventricular node). The term "atrial fibrotic cardiomyopathy" was introduced by Kottkamp in 2012 as a common denominator of all forms of atrial fibrillation (AF) [1]. This concept was further developed in a specific consensus paper published in 2016 by the European Heart Rhythm Association, the Heart Rhythm Society, the

☆ Tweet: Atrial cardiomyopathy (ACM) challenges the conventional approach focused solely on managing atrial fibrillation. Ninni et al. explore ground-breaking research that elucidates the current understanding of ACM's pathogenesis, the tools available for clinical evaluation, and the related outcomes.

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Table 1
Classification of atrial cardiomyopathy.

EHRA class	Histological characterization
I	Morphological or molecular changes affecting "primarily" the cardiomyocytes, in terms of cell hypertrophy and myocytolysis; no significant pathological tissue fibrosis or other interstitial changes
II	Predominantly fibrotic changes; cardiomyocytes show normal appearance
III	Combination of cardiomyocyte changes (e.g. cell hypertrophy, myocytolysis) and fibrotic changes
IV	Alteration of interstitial matrix without prominent collagen fibre accumulation
IVa	Accumulation of amyloid
IVf	Fatty infiltration
IVi	Inflammatory cells
IVo	Other interstitial alterations

EHRA: European Heart Rhythm Association.

Asia Pacific Heart Rhythm Society and the *Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiología*, in collaboration with the American College of Cardiology and the American Heart Association [2].

In this consensus paper, the term "atrial cardiomyopathy" (ACM) is defined as "any complex of structural, architectural, contractile or electrophysiological changes affecting atria, with the potential to produce clinically relevant manifestations" (Table 1). Although these changes were first associated with AF occurrence, accumulating evidence suggests a link between ACM and major adverse cardiovascular events, independent of AF. Therefore, the clinical relevance of patient management based on atrial phenotype, rather than AF, is an emerging question. In this review, the mechanisms, assessment and clinical impact of ACM will be discussed.

3. Conditions leading to ACM

Several clinical conditions are associated with ACM (Fig. 1 and Table 2).

3.1. Aging

Among the factors associated with ACM, aging and senescence processes have been reported as cornerstones. The senescence process is characterized by several changes involving a stable cell-cycle arrest associated with specific physiological, cellular and molecular alterations. Electrophysiological studies performed in elderly patients revealed increased effective refractory periods, as well as low voltage areas associated with slow conduction [14]. Moreover, electrophysiological remodelling, suggesting acquired calcium (Ca^{2+}) handling impairments, was also found in isolated human cardiomyocytes, with a decrease in the sarcoplasmic reticulum Ca^{2+} content, a reduction in L-type Ca^{2+} current (I_{CaL}) amplitude and a decrease in the Ca^{2+} transient amplitude [21]. Importantly, the senescent phenotype resulting from alterations in the p16 and p53–p21 related pathways is characterized by senescent cell-secreted products known as the "senescence-associated secretory phenotype" [66]. The senescence-associated secretory phenotype encompasses proinflammatory cytokines (e.g. interleukin-6, tumour necrosis factor) and chemokines (e.g. C-X-C motif chemokine ligands 1 and 2), but also growth factors (e.g. vascular endothelial growth factor), matrix remodelling proteases (e.g. matrix metallopeptidases 1 and 3) and lipids, produced by cardiomyocyte and non-cardiomyocyte cells (e.g. fibroblasts and endothelial cells) [66,67]. Components of senescence-associated secretory phenotype have been shown to be involved in atrial remodelling, especially as a result of a shift toward a cardiac fibroblast profibrotic phenotype [68].

Previous studies have reported metabolic atrial remodelling associated with ageing, such as impaired fatty acid oxidation, depressed respiratory performances and increased susceptibility to mitochondrial permeability transition pore opening [69]. Advanced age is also accompanied by extracardiac processes, such as an increase in arterial stiffness, leading to increased left atrial (LA) pressure [70]. Thus, in elderly patients, atrial remodelling is believed to be a multifactorial process, involving cardiac senescence as well as age-related clinical conditions.

3.2. Metabolic disorders

Metabolic disorders have been closely linked to changes in the structure and function of the atria. Most research has focused on the impact of obesity and diabetes on atrial remodelling. In humans, obesity is associated with electrophysiological, structural and haemodynamic impairment of the LA [71]. In obese patients, electrophysiological remodelling is suggested by shorter effective refractory periods and regional slow conductions related to low voltage areas in the LA [25]. This electrophysiological remodelling has been further characterized in animal models, demonstrating several alterations, such as depressed action potential duration (APD) involving increased K^+ current, such as adenosine triphosphate-activated K^+ current (I_{KATP}) [24], but also alterations to connexin 43 expression [31]. Structural changes are a prominent characteristic of atrial remodelling in the context of obesity. Consequently, individuals with obesity exhibit a significant increase in LA volume, and histopathological investigations have unveiled concurrent fibrosis and apoptosis processes [26,29,32]. Metabolic remodelling was also observed in the context of obesity, with depressed mitochondrial respiration despite increased fatty acid β-oxidation, thereby leading to myocardial lipidosis [72].

Whereas diabetes and obesity are often intertwined, several observations have hinted at a distinct influence of diabetes on the atria [73]. In humans, this association is proposed based on electrophysiological studies that revealed intra-atrial conduction delays and reduced voltages [74]. Animal studies conducted on streptozotocin-induced diabetic rat models confirmed these findings. These studies showed alterations in connexin 43 expression, prolonged APD, impaired Ca^{2+} handling, and heightened atrial vulnerability, as evidenced by the prolonged duration of atrial tachyarrhythmia induced by rapid atrial stimulation [33,75]. Additionally, a recent study has shed light on the impact of impaired mitochondria-mediated Ca^{2+} handling. More specifically, this study highlighted dysfunction in the mitochondrial Ca^{2+} uniporter complex in the context of metabolic syndrome, an insulin-resistant condition that precedes diabetes [76].

The mechanisms underlying the association between atrial remodelling and metabolic disorders are poorly understood, but potential mediators have been identified. More specifically, inflammatory processes involving immune cell recruitment, nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 inflammasome activation and epicardial adipose tissue (EAT) have been suggested [77].

EAT is a metabolically active tissue located around the heart, directly interacting with cardiomyocytes. Increasing evidence points to EAT playing a crucial role in connecting metabolic disorders with ACM. For instance, in obese individuals, EAT mediators have been linked to the release of factors associated with monocyte recruitment, a subset of innate immune cells shown to be involved in AF pathogenesis [78]. Moreover, diabetes-induced changes in the EAT secretory profile have been connected to altered sarcomere shortening and impaired cytosolic Ca^{2+} fluxes [79]. The EAT secretome is also implicated in atrial fibrogenesis, primarily through the secretion of activin A [80]. The radiodensity of EAT has been correlated with low voltage areas in the LA in patients

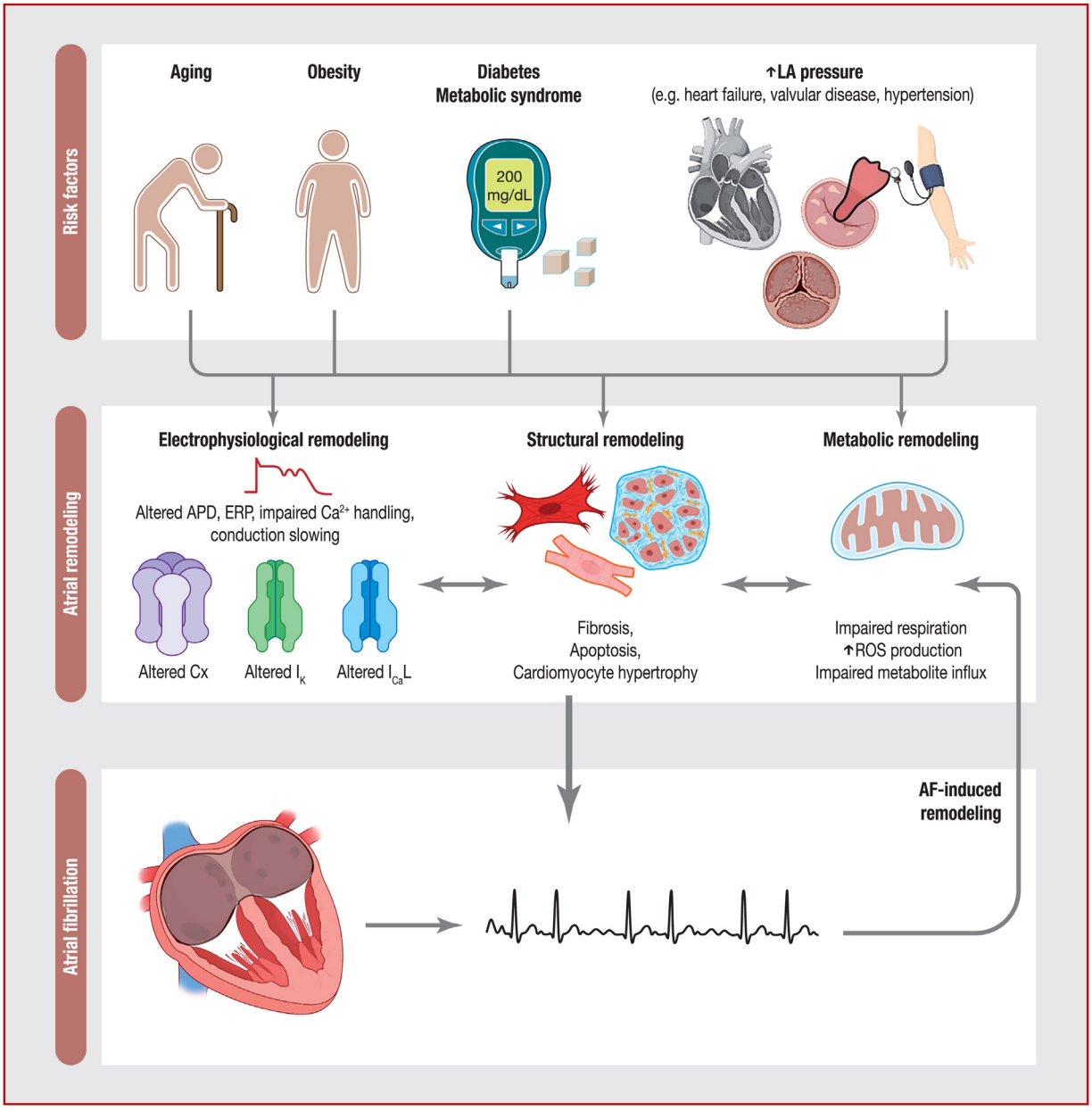


Fig. 1. Clinical conditions leading to atrial cardiomyopathy. AF: atrial fibrillation; APD: action potential duration; Ca^{2+}: calcium; Cx: connexin; ERP: effective refractory period; I_{CaL}: L-type calcium current; I_K: potassium current; LA: left atrial; ROS: reactive oxygen species.

undergoing AF ablation [81]. Associations have also been reported between EAT volume or thickness and atrial conduction delays, such as prolonged P-wave duration, interatrial conduction block and longer P-R interval [82]. Interestingly, atrial natriuretic factor secreted by atrial myocytes in response to mechanical stress has adipogenic properties that can contribute to atrial EAT development [83]. Importantly, the epicardium undergoes reactivation during the development of ACM, and contributes to fibro-fatty infiltration of the subepicardium [84].

Previous studies have suggested that metabolic disorders may trigger atrial remodelling through a liver-mediated process. Obesity and diabetes are often associated with liver steatosis, leading to metabolic-associated fatty liver disease (MAFLD), which is represented by a wide spectrum of liver alterations, including steatosis, inflammation and, ultimately, fibrosis. In a recent study, patients with MAFLD carrying advanced liver fibrosis presented several hallmarks of advanced atrial remodelling, such as increased LA volume, altered LA strain and increased low voltage areas [46]. However,

Table 2
Main clinical conditions leading to atrial cardiomyopathy.

Clinical condition	Atrial remodelling			
	Electrophysiological	Structural	Metabolic	Haemodynamic
Aging	APD↑/↓ [3–6][a] ERP↑ [14][a] Regional conduction slowing [14,17][a] Cx 43 expression↓ [19][a] SR Ca^{2+} content↓ [21][a] L-type Ca^{2+} current↓ [4,21][a] Low voltage areas [22] AF burden↑ [23]	LA volume↑/≈ [7–9][a] Cardiomyocyte hypertrophy [15][a] Fibrosis [4,15][a]	Global respiration↓ [10][a] Impaired FFA and ketone flux [16][a] Fatty acid oxidation↓ [16,18][a] Susceptibility to MPTP opening↑ [20]	Atrial compliance↓ [11–13][a]
Obesity	APD↓ [24][a] ERP↓ [25][a] Regional conduction slowing [27,28,32][a] Cx 43 expression↓ [31][a] K_{ATP} current↑ [24][a] Low voltage areas [32] AF burden↑ [28,31]	LA volume↑ [25–28][a] Fibrosis [27,28,31][a] Apoptosis [29][a]	Global respiration↓ [29][a] β-oxidation activation [24][a] Myocardial lipidosis [24,27][a]	Atrial compliance↓ [25,30] LA pressure↑ [31][a]
Diabetes	APD↑ [33][a] Regional conduction slowing [33,38,39][a] Lower bipolar voltage [38] Cx 43 phosphorylation↓ [42][a] Cx 40 expression↓ [33][a] Impaired Ca^{2+} handling [44,45][a] AF burden↑ [33]	LA volume↑ [26][a] Fibrosis [33,39,40][a]	Global respiration↓ [34][a] Myocardial lipidosis [41][a] Glutamate and fatty acid-supported respiration↓ [41][a] ROS production↑ [41][a] Susceptibility to MPTP opening↑ [43][a]	Atrial compliance↓ [35–37][a]
MAFLD	Low voltage areas [46]	Fibrosis [46][a]		Atrial compliance↓ [46]
LA pressure/volume overload[b]	APD↑ [47,48][a] ERP↑/↓ [50–52][a] Regional conduction slowing [51,52][a] L-type Ca^{2+} current↓ [56][a] Impaired Ca^{2+} handling [57][a] AF burden↑ [49–52,56]	LA volume↑ [49,50][a] Cardiomyocyte hypertrophy [51,52][a] Fibrosis [49–52,54,55][a]		LA pressure↑ [49][a] LA systolic function↓ [53][a]
AF-induced remodelling	APD↓ [58] L-type Ca^{2+} current↓ [58] I_{K1}↑ [63] I_{KACh} dysregulation [64] Impaired Cx 40–43 expression/localization [65]	LA volume↑ [8] Fibrosis [62]	Global respiration↓ [59–61] ROS production↑ [59]	Atrial compliance↓ [8]

AF: atrial fibrillation; APD: action potential duration; Ca^{2+}: calcium; Cx: connexin; ERP: effective refractory period; FFA: free fatty acids; I_{K1}: inward rectifier potassium current; K_{ATP}: adenosine triphosphate-sensitive potassium channel; LA: left atrium; MPTP: mitochondrial permeability transition pore; ROS: reactive oxygen species; SR: sarcoplasmic reticulum.

[a] Studies providing association independent of AF.

[b] Including hypertension, heart failure and valvular diseases.

conflicting findings arose from epidemiological studies [85,86]. This inconsistency may be attributed to differences in screening methods and diagnostic criteria used to identify MAFLD, liver fibrosis and AF. Consequently, further research is needed to thoroughly explore and establish the relationship between MAFLD and AF.

Hence, the process of atrial remodelling induced by metabolic disorders appears to be intricate, encompassing both cardiac and extracardiac mechanisms. Further research is warranted to enhance our understanding of this area.

3.3. LA pressure and volume overload

Various clinical and physiological factors can increase LA pressure. Pathologically, hypertension, heart failure, shunts and valvular diseases are common chronic contributors. Physiological factors, such as exercise and pregnancy, also elevate LA pressure. Importantly, the impact on electrophysiological and structural remodelling varies depending on the underlying clinical context.

Hypertension, heart failure and valvular diseases lead to similar hallmarks of atrial remodelling. More specifically, electrophysiological remodelling is a prominent hallmark of pathological LA pressure overload, resulting in APD increase, impaired Ca^{2+} handling and regional conduction slowing [87]. Structural remodelling involving cardiomyocyte hypertrophy and fibrosis is frequently associated [49–52,54,55], typically caused by the release of mediators, such as angiotensin II, endothelin 1, transforming growth factor beta and inflammatory cytokines [88].

Of note, LA pressure alterations can result from conditions primarily inducing LA volume overload, such as exercise and mitral regurgitation.

The impact of increased LA pressure during exercise depends critically on the intensity of the exercise [89]. Exercise promotes cardiac remodelling, leading to proportional symmetrical enlargement of all four cardiac chambers [90]. In healthy individuals, there is a linear increase in LA pressures (measured using pulmonary capillary wedge pressure) during exercise [91]. Consequently, athletes experience a significant increase in atrial pressure during exercise, which can be similar to that observed in disease settings. These pressure changes are expected to manifest as increased atrial volumes during exercise, a phenomenon demonstrated through exercise cardiac magnetic resonance (CMR) and, to varying degrees, in some echocardiography studies [92]. Notably, fibrosis has been observed in rodent models in response to extreme endurance exercise [93], but not during regular exercise [94]. In a rat model of treadmill running for 16 weeks, biatrial fibrosis was detected, and this was associated with an increased susceptibility to AF [93]. In mice subjected to 6 weeks of intense exercise, inflammation-induced atrial fibrosis was noted [95]. In a recent study, highly trained endurance athletes were found to have greater atrial fibrosis (as assessed by late gadolinium enhancement [LGE] CMR) compared with control subjects [96].

Mitral regurgitation leads to an excess LA volume load. Additionally, LA dilation, serving as an indicator of LA remodelling, is associated with higher cardiovascular morbidity and mortality, irrespective of LV function, in patients with mitral regurgitation [97]. In cases of acute mitral regurgitation in animal models, there is an initial adaptive response in the LA, characterized by increased reservoir and contractile function. However, this adaptative state progresses towards decompensation at 4 weeks, marked by evolving changes in LA structure and function as a result of a combination of progressive eccentric remodelling and fibrosis [98]. The long-term atrial remodelling observed in mitral regurgitation is probably a result of atrial myocardial overstretching and elevated myocyte oxidative stress, leading to programmed myocyte death, independent of AF [99,100]. Although fibrosis is a common occurrence in various cardiac pressure and/or volume overload scenarios, the evidence regarding direct activation of cardiac fibroblasts by mechanical forces remains controversial. Key responses, such as fibroblast proliferation, collagen production and differentiation into myofibroblasts, exhibit divergent and sometimes opposing changes in different studies in response to stretch [101]. Resolving these discrepancies could be crucial to the development of innovative and more efficient therapies to prevent the onset and progression of atrial remodelling, subsequently mitigating adverse clinical outcomes.

Heart failure with preserved ejection fraction (HFpEF) exhibits significant specificity for in-depth investigations into LA remodelling. HFpEF is a complex clinical syndrome marked by both cardiac and extracardiac features; it is now recognized as a systemic disease linked to a broad spectrum of clinical risk factors and co-morbidities, such as aging, female sex, hypertension, pulmonary congestion, metabolic syndrome, obesity, type 2 diabetes mellitus, hyperlipidaemia and renal disease [102]. These risk factors and co-morbidities contribute to intertwined disease mechanisms in the pathophysiology of HFpEF and the associated atrial remodelling. Given the diverse potential underlying causes of HFpEF, such as structural myocardial abnormalities or abnormal loading conditions (e.g. hypertension, valvular diseases, volume overload, or rhythm disorders), developing preclinical HFpEF models that accurately capture the complexity of the human condition is challenging. Animal models employed in research typically rely on combinations of aging, metabolic disorders, hypertension and endothelial dysfunction to induce left ventricular hypertrophy, diastolic dysfunction, LA enlargement, fibrosis and natriuretic peptide release [103]. Clinical studies emphasize the importance of LA remodelling in patients with HFpEF, demonstrating reduced emptying fractions and contractile reserve compared with control subjects and patients with hypertension [104]. Moreover, LA compliance and mechanics deteriorate progressively, with an increasing AF burden in HFpEF, elevating the risk of new-onset AF and progressive AF. These changes contribute to the development of a distinctive HFpEF phenotype, characterized by heightened ventricular interaction, right heart failure and worsening pulmonary vascular disease [105]. Whereas these observations establish a robust foundation for acknowledging the role of ACM in patients with HFpEF, further research is necessary to understand the predominant pathophysiological mechanisms involved in HFpEF-related atrial remodelling, and to tailor strategies to improve patient outcomes.

3.4. Genetic factors

Most of the evidence associating genetic factors with ACM is based on AF studies. The genetic contribution to AF has been reported extensively across various methodological approaches, based on family linkage studies, identification of rare genetic variants in AF population or genome-wide association studies. Furthermore, a variety of genes affected by mutations have been associated with AF, including genes encoding ion channels, gap junctions, structural proteins, endocrine factors and transcription factors [106]. Furthermore, the prevalence of rare variants contributing to AF has been reported as being high as 10–16% in patients presenting early-onset AF [107]. In addition, the presence of rare variants in patients presenting early-onset AF has been associated with a higher mortality rate.

However, fewer data have correlated genetic factors with other features of ACM. Two recent studies based on the genome-wide association study approach reported an association between genetic loci and ACM features, including LA volume and P-wave duration [108,109]. In a small cohort of patients presenting atrial fibrotic cardiomyopathy without AF, several rare variants were reported based on whole exome sequencing [110]. Animal studies have provided additional insights linking rare variants to advanced atrial remodelling. More specifically, a rare variant affecting the atrial-specific sarcomere protein myosin light-chain 4 has been associated with major atrial dilatation, the fibrotic process and severe atrial conduction defects [111]. Most of the variants found in ACM overlap, in some instances, with heart failure, and may be associated with a higher risk of heart failure over time. Finally, some variants found in ACM (e.g. variants affecting the *natriuretic peptide A* gene) have been associated with a higher risk of stroke [112]. Taken together, these data suggest a relatively high prevalence of genetic factors in ACM, especially in young patients, with various consequences for the atrial remodelling process. Accumulating evidence supports the role of variants in genes encoding sarcomeric proteins. However, the genetic landscape of ACM critically needs further investigation to establish its relevance in routine clinical practice.

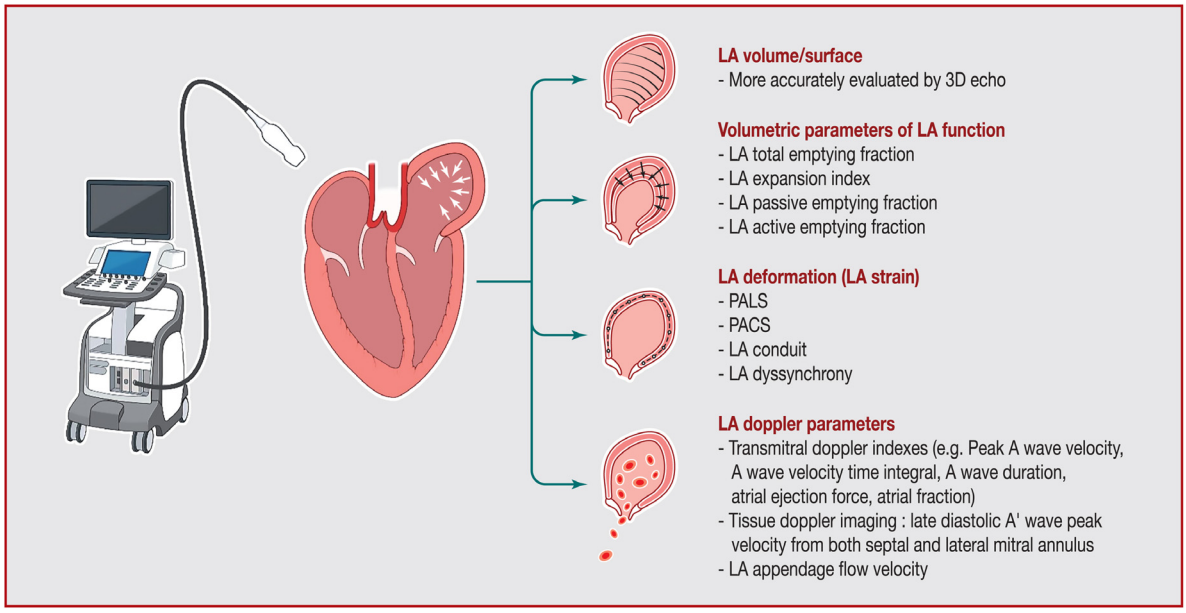


Fig. 2. Evaluation of left atrial cardiomyopathy using echocardiography. 3D: three-dimensional; LA: left atrium; PALS: peak atrial longitudinal strain; PACS: peak atrial contraction strain.

3.5. AF-induced atrial remodelling

It is now well established that electrical and structural remodelling of the atrial myocardium contributes to the progression of AF. Studies from animal models and biopsies from patients have shown that, at the cellular level, a shortening of the APD results from a decrease in inward I_{CaL} and enhanced background outward K^+ currents. In particular, the inward rectifier K^+ current (I_{K1}) is increased and the acetylcholine-activated K^+ current (I_{KACh}) is constitutively active. In contrast, voltage K^+ channel expression is reduced. Reductions in the ultra-rapidly activating delayed rectifier K^+ current (I_{Kur}) and the transient outward K^+ current (I_{to}) participate in the triangulation of action potential [113]. Ca^{2+} cycling alterations participate in cardiac arrhythmogenesis [114]. Triggered activity can result from early or delayed after-depolarization. Increased sarcoplasmic reticulum Ca^{2+} leaks, resulting from ryanodine receptor dysfunction, can produce focal ectopic firing [115]. Calmodulin-dependent protein kinase II has also been involved, and may provide a novel therapy for AF [116]. Recent studies have highlighted that Ca^{2+} cycling differences across different regions of LA are involved in the proarrhythmic activity [117,118]. At the tissue level, a reduction in the effective refractory period is observed. Alteration in conduction velocity is associated with connexin alteration (e.g. lateralization [119]). Structural remodelling, including fibrosis and hypertrophy, affects wavefront propagation and participates in re-entry. Over the last decade, metabolic remodelling has been investigated extensively. In contrast to electrical remodelling, which is fast (a few days) and structural remodelling (several weeks later), metabolic remodelling is likely to occur during the period in between [120].

4. Noninvasive assessment of LA cardiomyopathy

Based on ACM expert consensus, the classification of ACM relies on histopathological findings and the presence of fibrosis and/or non-collagen deposits [2]. Although the use of this classification is routinely limited for clinicians, several tools have been developed to assess LA remodelling and function. These tools aim to establish clinically meaningful variables for ACM. Consequently, the clinical instruments currently at hand enable the assessment of various aspects of the LA. Because of its widespread and routine application, echocardiography emerges as the primary approach for evaluating ACM and LA anatomy. Fig. 2 illustrates the measurable variables acquired through this method.

Atrial fibrosis predominantly contributes to structural remodelling, and is linked to significant alterations in the geometry of the LA. The LA size is the most widely studied variable using different imaging tools, including two-dimensional and three-dimensional echocardiography, computed tomography and CMR. LA dilatation has been widely investigated and correlated to several clinical outcomes. More specifically, LA enlargement has been extensively explored in the context of pressure and volume overload. The relationship between increased LA size and increased filling pressures has been validated against invasive measures [121,122]. LA enlargement as a result of pressure overload is usually secondary to an increase in LA afterload, in the setting of mitral valve disease or LV dysfunction. However, some studies have suggested that LA enlargement might result from the fibrotic process, resulting in impaired LA compliance and leading to an increase in LA pressure [123]. In line with other studies, LA enlargement has been associated with adverse clinical outcomes, independent of AF, such as stroke and heart failure [124].

More recently, LA strain has been proposed as an attractive tool to assess LA function. Basically, LA strain evaluates atrial wall deformation during the cardiac cycle. More specifically, LA deformation during atrial diastole is considered as a surrogate for LA reservoir function, whereas LA deformation during atrial systole is considered as an indicator of pump function. A study has demonstrated a direct correlation between atrial strain measurements obtained through two-dimensional speckle-tracking echocardiography and histologically confirmed fibrosis of the LA [125]. Watanabe et al. found a correlation between electroanatomical mapping and three-dimensional speckle-tracking echocardiography methods in patients with paroxysmal AF during sinus rhythm, even in those with less advanced anatomical remodelling [126]. Furthermore, this group showed that LA dyssynchrony is latent in patients with

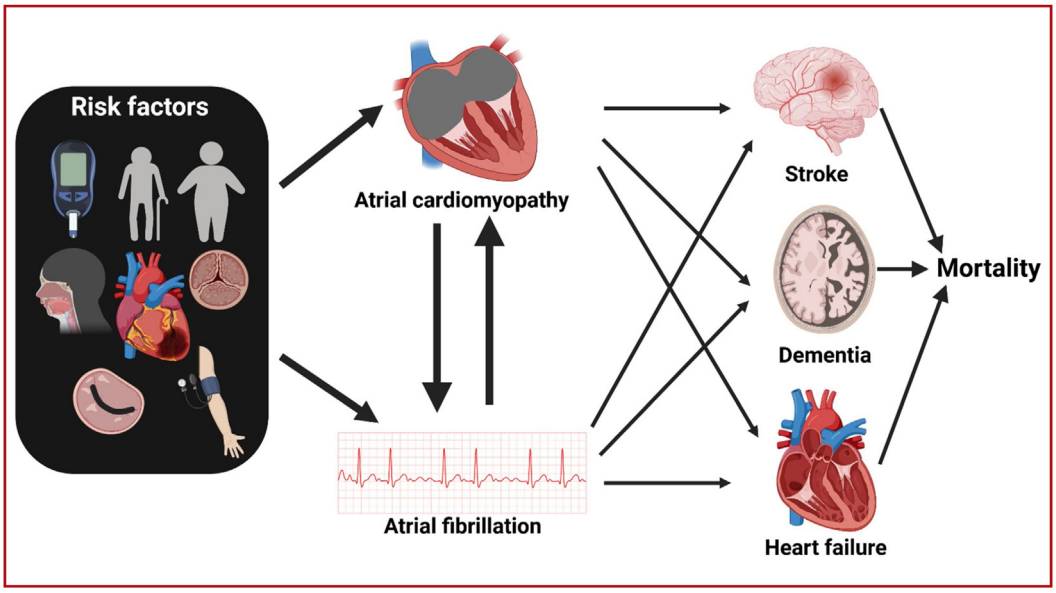


Fig. 3. Clinical impact of atrial cardiomyopathy.

AF in the early remodelling phase, and that the early remodelling changes can be detected using three-dimensional speckle-tracking echocardiography. Furthermore, LA strain has been associated with various clinical outcomes, such as AF [127], stroke [128,129] and heart failure [130–132].

CMR imaging has become a gold standard for assessing the volume of cardiac chambers [133], but additional methods for evaluating atrial function and fibrosis using CMR have emerged as valuable tools for ACM characterization. LGE is a well-validated method for detecting fibrosis in the myocardium. Moreover, LGE of the LA was assessed comprehensively by a group in Utah that refined the technique and developed a staging system where the degree of fibrosis is divided into stages I–IV. LGE has been investigated extensively in the field of AF ablation, and has been correlated with electroanatomical mapping and AF recurrence following ablation [134]. However, fewer works have correlated LGE of the LA with other clinical outcomes, such as sinus node dysfunction [135], LA thrombus formation [136] or stroke [137]. Beyond LGE assessment, CMR allows atrial function assessment using tissue tracking with deformation indexes similar to those applied on echocardiography speckle-tracking echocardiography.

Recently, CMR-based techniques have been improved to include four-dimensional flow that encodes velocity in all three spatial directions (three-dimensional) as well as time. This technique provides robust flow quantification in clinical practice [138], and has been used in the context of AF burden to show that LA peak velocity and vorticity are the reproducible and temporally stable novel LA four-dimensional flow biomarkers [139]. However, data acquisition using four-dimensional flow is time consuming. Therefore, efforts were undertaken recently to develop a five-dimensional flow CMR framework to reduce scan times [140]. This approach has been validated in the context of AF, and allows resolution of three-dimensional haemodynamics in less than 10 minutes [141].

Several electrocardiogram-based indexes have been developed to assess ACM. The P-wave represents the atrial depolarization of first the right atrium and then the LA, and is therefore of particular interest with regard to atrial electrical remodelling. Interatrial excitation conduction disturbances via the Bachmann bundle can also be detected on the electrocardiogram. P-wave variables comprise P-wave duration, P-wave dispersion, P-wave axis, P-wave voltage, P-wave area, interatrial block (IAB) and P-wave terminal force in lead V1 (PTFV1). These electrocardiogram markers have been associated with histological remodelling of atria, such as terminal crest fibrosis or extensive fibrosis associated with fatty tissue infiltration [142]. More recently, artificial intelligence (AI)-based electrocardiogram analysis has emerged as an attractive means of investigating ACM and ACM-related outcomes. Furthermore, AI-based electrocardiogram analysis has revealed a correlation between AI probability of AF and larger LA volumes and lower LA reservoir function [143]. Furthermore, a recent study based on saliency mapping and median waveform analysis highlighted that the electrocardiogram-AI probability of predicting AF is critically influenced by the period of atrial depolarization and repolarization (i.e. P-wave and surrounding period) [144].

Finally, several circulating biomarkers have been proposed to estimate atrial remodelling and ACM [145,146]; they include markers of inflammation (e.g. interleukin-6, matrix metallopeptidase 9, transforming growth factor beta), markers of fibrosis (e.g. galectin-3) and atrial peptides (N-terminal prohormone of B-type natriuretic peptide, natriuretic peptide A). For more details see [147].

5. Clinical impact of ACM

ACM is associated with several clinical outcomes (Fig. 3) that are reviewed below.

5.1. AF incidence and ACM

Although the clinical impact of AF screening in the general population remains controversial, the potential interest in AF screening in patients presenting hallmarks of ACM is increasing.

A recent study conducted in a large retrospective cohort of more than 30,000 patients demonstrated a strong association between LA enlargement and incident AF, independent of age, sex, hypertension, diabetes, heart failure, history of myocardial infarction, stroke and left ventricular hypertrophy [148]. In line with this, other studies have highlighted the predictive value of other LA function variables, such as LA emptying fraction [149,150]. Alexander et al. [151] proposed an AF risk score that considers P-wave characteristics and durations. The scoring system assigns points based on criteria, including P-wave morphology in the inferior leads, voltage in lead I and P-wave duration. Patients with the highest scores and those with mid-range scores had a 2-fold increased risk of developing AF compared with those with lowest scores. Furthermore, the group exhibiting highest scores took a significantly shorter average time to develop AF compared with the group presenting mid-range scores and the group with the lowest scores. Whereas other studies have corroborated these findings, there remains variability in how these P-wave variables contribute to the overall prediction of AF risk [152]. AI-based electrocardiogram analysis obtained during sinus rhythm is also emerging as a useful tool to predict incident AF, based on large-scale studies [153,154].

Previous large-scale studies have failed to demonstrate a substantial clinical benefit for AF screening in the general population [155]. In light of the limited outcomes data, the United States Preventive Services Task Force concluded that there is insufficient evidence to recommend screening for AF, and that the balance of benefits and harms of screening cannot be determined. Further studies are needed to establish the clinical impact of ACM-related variables and their relevance for the selection of elective patients for AF screening.

5.2. Risk of stroke and/or systemic embolism

AF is a major risk factor for ischaemic stroke, and one fifth of ischaemic strokes are believed to result from AF [156]. Several clinical risk factors have been identified, and have been shown to modulate the stroke risk in patients with AF. Among them, age, hypertension, diabetes mellitus, history of stroke and/or transient ischaemic attack, history of vascular disease, history of heart failure and female sex (all pooled in the CHA_2DS_2-VASc score) are the widest used in daily practice. The incremental value of ACM markers for stroke prediction is established in patients presenting AF. Previous studies have demonstrated that the CHA_2DS_2-VASc score predictive value can be improved by ACM-related variables. Maheshwari et al. enhanced the CHA_2DS_2-VASc scoring system by introducing the P-wave axis component to create the P2-CHA_2DS_2-VASc score [157]. Utilizing data from both the Atherosclerosis Risk in Communities (ARIC) and Multi-Ethnic Study of Atherosclerosis (MESA) cohorts, the authors observed that, when compared with the CHA_2DS_2-VASc score, the P2-CHA_2DS_2-VASc score demonstrated an improvement in the C-statistic, as well as net reclassification improvement and integrated discrimination improvement. In a retrospective cohort study, King et al. assessed LA fibrosis, using magnetic resonance imaging LGE in 1200 patients who underwent AF ablation, and its association with incident strokes [158]. A total of 62 strokes or transient ischaemic attacks occurred, and advanced LGE was associated with a 4-fold increased risk of stroke after adjustment.

Several studies have emphasized the possible significance of markers associated with ACM in evaluating the risk of stroke in patients who do not have documented AF. This link was first suggested by studies assessing the temporality between AF episodes and stroke [159]. In a substudy of Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), the temporal association between monitored AF and ischaemic stroke was evaluated. Interestingly, in patients presenting stroke during follow-up, only 8% presented AF within the 30 days preceding the event. Furthermore, 16% of patients presented AF after stroke. A similar observation was found in the IMPACT study (The IMPACT of Biotronik Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy With Defibrillator Devices), where 29% of thromboembolic events followed atrial tachyarrhythmia. In line with this, several studies have established associations between LA variables and ischaemic stroke in patients without a history of AF [160]. A study conducted by Benjamin et al. was the first to link atrial enlargement to stroke [161]. In this study, including over 3400 patients from the Framingham Heart Study, a strong association was found between LA size and stroke risk, even in patients free from AF. A few studies have highlighted similar associations between various LA imaging modalities, such as CMR LGE or LA strain, and stroke risk. Similarly, electrocardiographic hallmarks of ACM have been associated with stroke, such as the PTFV1.

Since the association between ACM-related variables and stroke risk was raised, the potential value of anticoagulation in patients without AF has been suggested. The Atrial Cardiomyopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA) trial has recently assessed such a strategy in patients who presented a recent cryptogenic stroke [162]. In this study, ACM was assessed using a composite criterion (including PTFV1, N-terminal prohormone of B-type natriuretic peptide and LA diameter index), and led to 1:1 randomization to aspirin or apixaban. The results of this study were recently presented at the 9th European Stroke Organisation Conference, and showed that the rate of recurrent stroke during follow-up was 4.4% both in patients treated with apixaban and in those treated with aspirin (hazard ratio: 1.00, 95% confidence interval [95% CI]: 0.64–1.55), and that lack of difference was consistent across stroke types. This result raises several questions regarding the relevant definition of ACM for stroke risk, and the need for extensive research in this field.

5.3. Heart failure

AF is a major risk factor for heart failure. In the CARDIONOR registry, in 4973 outpatients with AF, incident heart failure during follow-up (10.5% at 3 years) was five times more frequent than bleeding and three times more frequent than stroke, and these results were confirmed when the analysis was restricted to patients without a history of AF at inclusion [163]. In the Framingham Heart Study, the incidence of heart failure was 33 per 100,000 patient-years [164].

Data investigating the predictive value of ACM-related variables for new-onset heart failure are sparse. In a large general population study ($n = 1951$ without prevalent AF or heart failure), participants underwent a health examination with echocardiography. LA volumes and emptying fractions were correlated with incident heart failure [165]. After multivariable adjustment for clinical and echocardiographic variables, only minimum LA indexed volume remained an independent predictor of incident heart failure. Other studies have suggested that ACM-related variables have prognostic value in patients with heart failure. For example, in the Multicenter

Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT CRT) trial, patients with normal PTFV1 were associated with a lower risk of heart failure or death than those with abnormal PTFV1 [166]. In another study of patients with heart failure who received cardiac resynchronization therapy, the presence of IAB was associated with a 1.9-fold higher risk of AF, death or heart transplant [167].

5.4. Dementia

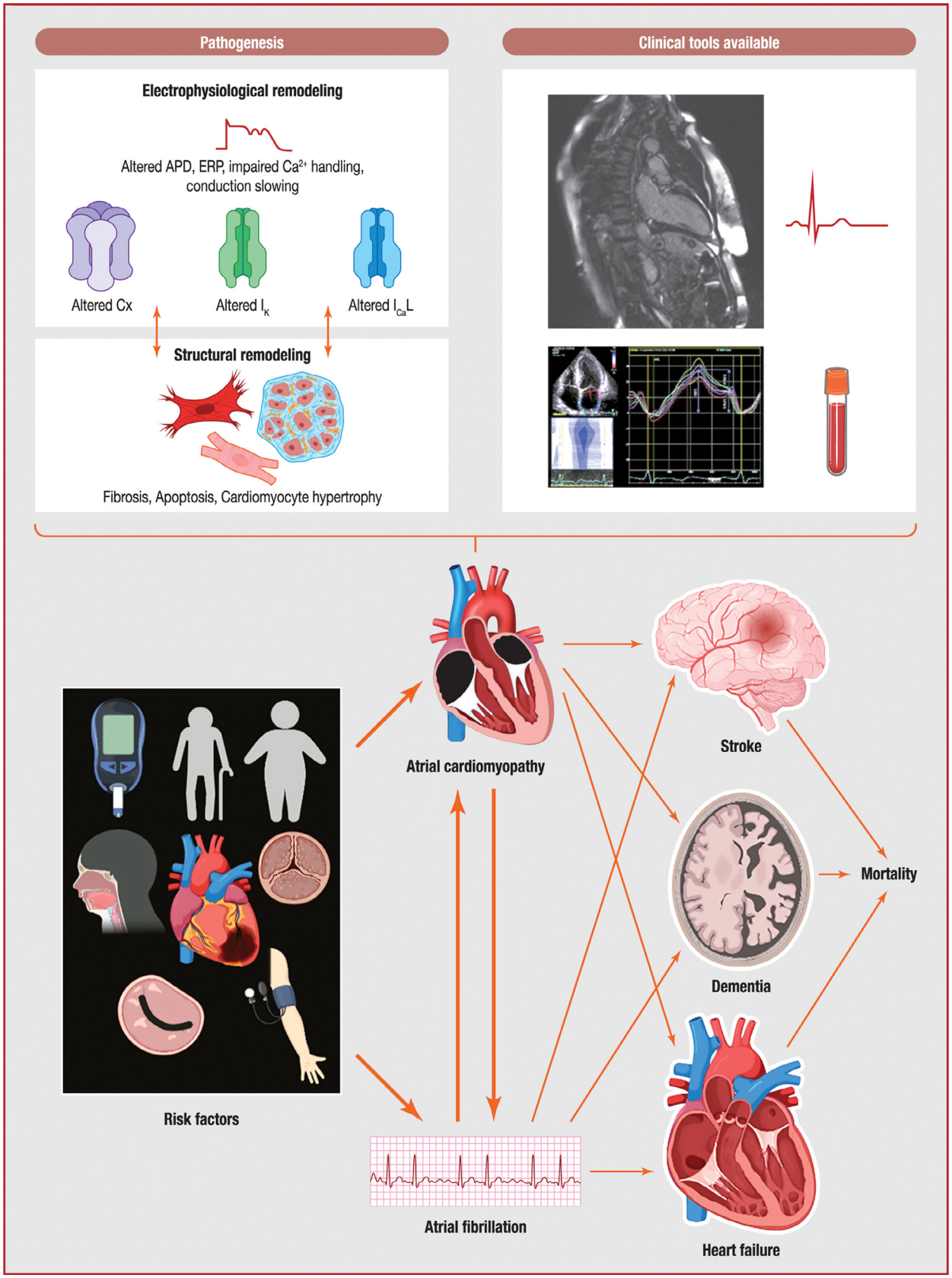
AF has been linked to the emergence of cognitive decline, and this association holds true even when considering cases without clinical symptomatic stroke. Evidence from a meta-analysis involving over 80,000 participants with AF indicates that AF, even in the absence of documented stroke, may independently contribute to cognitive impairment [168,169]. As ACM is associated with a higher risk of stroke, and both stroke and AF are linked to an elevated risk of dementia, a potential connection between ACM and dementia has been proposed.

Drawing from the ARIC study, Gutierrez et al. recently revealed that the presence of abnormal P-wave variables is linked to more pronounced cognitive decline and an elevated risk of dementia [170]. Their investigation involved 13,714 middle-aged participants, with an average age of 57 years, 56% of whom were women. These individuals were tracked for dementia occurrence and changes in cognitive function over an average follow-up period of 18 years. Abnormal PTFV1, abnormal P-wave axis, prolonged P-wave duration and advanced IAB were identified through electrocardiograms conducted during the study. All abnormal P-wave variables, except advanced IAB, were associated with a heightened dementia risk, even after accounting for the occurrence of AF and stroke. Specifically, the multivariable hazard ratio for abnormal PTFV1 was 1.60 (95% CI: 1.41–2.83), for abnormal P-wave axis was 1.36 (95% CI: 1.17–2.57) and for prolonged P-wave duration was 1.60 (95% CI: 1.42–1.80). Furthermore, the presence of abnormal PTFV1 was also linked to a more pronounced decline in overall cognitive function.

In this context, Martinez-Selles et al. conducted an assessment of the relationship between partial and advanced IAB and cognitive impairment in the BAYES registry, which consisted of 332 participants [171]. Their analysis revealed that, at baseline, the prevalence of cognitive impairment was 2.7% among individuals with a normal P-wave, 5.1% among those with partial IAB and 10.3% among those with advanced IAB, showing a statistically significant difference. Furthermore, advanced IAB was found to be independently associated with baseline cognitive impairment, with an odds ratio of 4.9 (95% CI: 1.4–16.5). Additionally, both partial IAB and advanced IAB were independently associated with cognitive impairment at follow-up. In a recent study including 4096 participants in the ARIC study, several echocardiographic measures of lower LA function were significantly associated with an increased risk of incident dementia. These findings were robust to sensitivity analyses that excluded participants with incident AF or stroke [172].

6. Conclusions

ACM is characterized by atrial structural and electrophysiological remodelling that facilitates the development of clinically relevant events. Despite the clinical tools available, including imaging, electrocardiography and biomarkers (Central Illustration), there are still no clear noninvasive diagnostic criteria for ACM. Various animal models of ACM have improved our understanding of pathophysiological mechanisms. Additional basic research is needed to investigate the complex relationship between ACM and strokes. Numerous clinical tools used to characterize ACM have shown their capacity to forecast adverse clinical events. Nevertheless, additional research is necessary to pinpoint individuals who necessitate therapeutic intervention.



Central Illustration. Atrial cardiomyopathy: pathophysiology, clinical tools, risk factors and relationship between atrial fibrillation, stroke, heart failure and dementia. APD: action potential duration; Ca^{2+}: calcium; Cx: connexin; ERP: effective refractory period; I_{CaL}: L-type calcium current; I_K: potassium current.

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Disclosure of interest

The authors declare that they have no competing interest.

Références

[1] Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. J Cardiovasc Electrophysiol 2012;23:797–9.
[2] Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace 2016;18:1455–90.
[3] Anyukhovsky EP, Sosunov EA, Chandra P, Rosen TS, Boyden PA, Danilo Jr P, et al. Age-associated changes in electrophysiologic remodeling: a potential contributor to initiation of atrial fibrillation. Cardiovasc Res 2005;66:353–63.
[4] Anyukhovsky EP, Sosunov EA, Plotnikov A, Gainullin RZ, Jhang JS, Marboe CC, et al. Cellular electrophysiologic properties of old canine atria provide a substrate for arrhythmogenesis. Cardiovasc Res 2002;54:462–9.
[5] Jansen HJ, Moghtadaei M, Mackasey M, Rafferty SA, Bogachev O, Sapp JL, et al. Atrial structure, function and arrhythmogenesis in aged and frail mice. Sci Rep 2017;7:44336.
[6] Toda N. Age-related changes in the transmembrane potential of isolated rabbit sino-atrial nodes and atria. Cardiovasc Res 1980;14:58–63.
[7] Aurigemma GP, Gottdiener JS, Arnold AM, Chinali M, Hill JC, Kitzman D. Left atrial volume and geometry in healthy aging: the Cardiovascular Health Study. Circ Cardiovasc Imaging 2009;2:282–9.
[8] Boyd AC, Schiller NB, Leung D, Ross DL, Thomas L. Atrial dilation and altered function are mediated by age and diastolic function but not before the eighth decade. JACC Cardiovasc Imaging 2011;4:234–42.
[9] Ronningen PS, Berge T, Solberg MG, Enger S, Nygard S, Pervez MO, et al. Sex differences and higher upper normal limits for left atrial end-systolic volume in individuals in their mid-60s: data from the ACE 1950 Study. Eur Heart J Cardiovasc Imaging 2020;21:501–7.
[10] Lemieux H, Vazquez EJ, Fujioka H, Hoppel CL. Decrease in mitochondrial function in rat cardiac permeabilized fibers correlates with the aging phenotype. J Gerontol A Biol Sci Med Sci 2010;65:1157–64.
[11] Abou R, Leung M, Tonsbeek AM, Podlesnikar T, Maan AC, Schalij MJ, et al. Effect of aging on left atrial compliance and electromechanical properties in subjects without structural heart disease. Am J Cardiol 2017;120:140–7.
[12] Evin M, Redheuil A, Soulat G, Perdrix L, Ashrafpoor G, Giron A, et al. Left atrial aging: a cardiac magnetic resonance feature-tracking study. Am J Physiol Heart Circ Physiol 2016;310:H542–9.
[13] Sun JP, Yang Y, Guo R, Wang D, Lee AP, Wang XY, et al. Left atrial regional phasic strain, strain rate and velocity by speckle-tracking echocardiography: normal values and effects of aging in a large group of normal subjects. Int J Cardiol 2013;168:3473–9.
[14] Kistler PM, Sanders P, Fynn SP, Stevenson IH, Spence SJ, Vohra JK, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. J Am Coll Cardiol 2004;44:109–16.
[15] Anderson R, Lagnado A, Maggiorani D, Walaszczyk A, Dookun E, Chapman J, et al. Length-independent telomere damage drives post-mitotic cardiomyocyte senescence. EMBO J 2019;38.
[16] Hyyti OM, Ledee D, Ning XH, Ge M, Portman MA. Aging impairs myocardial fatty acid and ketone oxidation and modifies cardiac functional and metabolic responses to insulin in mice. Am J Physiol Heart Circ Physiol 2010;299:H868–75.
[17] Roberts-Thomson KC, Kistler PM, Sanders P, Morton JB, Haqqani HM, Stevenson I, et al. Fractionated atrial electrograms during sinus rhythm: relationship to age, voltage, and conduction velocity. Heart Rhythm 2009;6:587–91.
[18] Chiao YA, Kolwicz SC, Basisty N, Gagnidze A, Zhang J, Gu H, et al. Rapamycin transiently induces mitochondrial remodeling to reprogram energy metabolism in old hearts. Aging (Albany NY) 2016;8:314–27.
[19] Koura T, Hara M, Takeuchi S, Ota K, Okada Y, Miyoshi S, et al. Anisotropic conduction properties in canine atria analyzed by high-resolution optical mapping: preferential direction of conduction block changes from longitudinal to transverse with increasing age. Circulation 2002;105:2092–8.
[20] Hafner AV, Dai J, Gomes AP, Xiao CY, Palmeira CM, Rosenzweig A, et al. Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy. Aging (Albany NY) 2010;2:914–23.
[21] Herraiz-Martinez A, Alvarez-Garcia J, Llach A, Molina CE, Fernandes J, Ferrero-Gregori A, et al. Ageing is associated with deterioration of calcium homeostasis in isolated human right atrial myocytes. Cardiovasc Res 2015;106:76–86.
[22] Huo Y, Gaspar T, Pohl M, Sitzy J, Richter U, Neudeck S, et al. Prevalence and predictors of low voltage zones in the left atrium in patients with atrial fibrillation. Europace 2018;20:956–62.
[23] Pearman CM, Madders GWP, Radcliffe EJ, Kirkwood GJ, Lawless M, Watkins A, et al. Increased vulnerability to atrial fibrillation is associated with increased susceptibility to alternans in old sheep. J Am Heart Assoc 2018;7:e009972.
[24] Suffee N, Baptista E, Piquereau J, Ponnaiah M, Doisne N, Ichou F, et al. Impacts of a high-fat diet on the metabolic profile and the phenotype of atrial myocardium in mice. Cardiovasc Res 2022;118:3126–39.
[25] Munger TM, Dong YX, Masaki M, Oh JK, Mankad SV, Borlaug BA, et al. Electrophysiological and hemodynamic characteristics associated with obesity in patients with atrial fibrillation. J Am Coll Cardiol 2012;60:851–60.
[26] Shigematsu Y, Norimatsu S, Ogimoto A, Ohtsuka T, Okayama H, Higaki J. The influence of insulin resistance and obesity on left atrial size in Japanese hypertensive patients. Hypertens Res 2009;32:500–4.
[27] Abed HS, Samuel CS, Lau DH, Kelly DJ, Royce SG, Alasady M, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. Heart Rhythm 2013;10:90–100.
[28] Mahajan R, Lau DH, Brooks AG, Shipp NJ, Manavis J, Wood JP, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. J Am Coll Cardiol 2015;66:1–11.
[29] Niemann B, Chen Y, Teschner M, Li L, Silber RE, Rohrbach S. Obesity induces signs of premature cardiac aging in younger patients: the role of mitochondria. J Am Coll Cardiol 2011;57:577–85.
[30] Di Salvo G, Pacileo G, Del Giudice EM, Natale F, Limongelli G, Verrengia M, et al. Atrial myocardial deformation properties in obese nonhypertensive children. J Am Soc Echocardiogr 2008;21:151–6.
[31] Mahajan R, Lau DH, Brooks AG, Shipp NJ, Wood JPM, Manavis J, et al. Atrial fibrillation and obesity: reverse remodeling of atrial substrate with weight reduction. JACC Clin Electrophysiol 2021;7:630–41.
[32] Mahajan R, Nelson A, Pathak RK, Middeldorp ME, Wong CX, Twomey DJ, et al. Electroanatomical remodeling of the atria in obesity: impact of adjacent epicardial fat. JACC Clin Electrophysiol 2018;4:1529–40.
[33] Watanabe M, Yokoshiki H, Mitsuyama H, Mizukami K, Ono T, Tsutsui H. Conduction and refractory disorders in the diabetic atrium. Am J Physiol Heart Circ Physiol 2012;303:H86–95.
[34] Marciniak C, Marechal X, Montaigne D, Neviere R, Lancel S. Cardiac contractile function and mitochondrial respiration in diabetes-related mouse models. Cardiovasc Diabetol 2014;13:118.
[35] Kadappu KK, Boyd A, Eshoo S, Haluska B, Yeo AE, Marwick TH, et al. Changes in left atrial volume in diabetes mellitus: more than diastolic dysfunction? Eur Heart J Cardiovasc Imaging 2012;13:1016–23.
[36] Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, et al. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. J Am Soc Echocardiogr 2011;24:898–908.
[37] Steele JM, Urbina EM, Mazur WM, Khoury PR, Nagueh SF, Tretter JT, et al. Left atrial strain and diastolic function abnormalities in obese and type 2 diabetic adolescents and young adults. Cardiovasc Diabetol 2020;19:163.
[38] Chao TF, Suenari K, Chang SL, Lin YJ, Lo LW, Hu YF, et al. Atrial substrate properties and outcome of catheter ablation in patients with paroxysmal atrial fibrillation associated with diabetes mellitus or impaired fasting glucose. Am J Cardiol 2010;106:1615–20.
[39] Kato T, Yamashita T, Sekiguchi A, Sagara K, Takamura M, Takata S, et al. What are arrhythmogenic substrates in diabetic rat atria? J Cardiovasc Electrophysiol 2006;17:890–4.
[40] Kato T, Yamashita T, Sekiguchi A, Tsuneda T, Sagara K, Takamura M, et al. AGEs-RAGE system mediates atrial structural remodeling in the diabetic rat. J Cardiovasc Electrophysiol 2008;19:415–20.
[41] Anderson EJ, Kypson AP, Rodriguez E, Anderson CA, Lehr EJ, Neufer PD. Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. J Am Coll Cardiol 2009;54:1891–8.
[42] Mitasikova M, Lin H, Soukup T, Imanaga I, Tribulova N. Diabetes and thyroid hormones affect connexin-43 and PKC-epsilon expression in rat heart atria. Physiol Res 2009;58:211–7.
[43] Montaigne D, Marechal X, Lefebvre P, Modine T, Fayad G, Dehondt H, et al. Mitochondrial dysfunction as an arrhythmogenic substrate: a translational proof-of-concept study in patients with metabolic syndrome in whom post-operative atrial fibrillation develops. J Am Coll Cardiol 2013;62:1466–73.
[44] Lamberts RR, Lingam SJ, Wang HY, Bollen IA, Hughes G, Galvin IF, et al. Impaired relaxation despite upregulated calcium-handling protein atrial myocardium from type 2 diabetic patients with preserved ejection fraction. Cardiovasc Diabetol 2014;13:72.
[45] Reuter H, Gronke S, Adam C, Ribati M, Brabender J, Zobel C, et al. Sarcoplasmic Ca2+ release is prolonged in nonfailing myocardium of diabetic patients. Mol Cell Biochem 2008;308:141–9.
[46] Decoin R, Butruille L, Defrancq T, Robert J, Destrait N, Coisne A, et al. High liver fibrosis scores in metabolic dysfunction-associated fatty liver disease patients are associated with adverse atrial remodeling and atrial fibrillation recurrence following catheter ablation. Front Endocrinol (Lausanne) 2022;13:957245.
[47] Jansen HJ, Mackasey M, Moghtadaei M, Belke DD, Egom EE, Tuomi JM, et al. Distinct patterns of atrial electrical and structural remodeling in angiotensin II mediated atrial fibrillation. J Mol Cell Cardiol 2018;124:12–25.
[48] Jansen HJ, Mackasey M, Moghtadaei M, Liu Y, Kaur J, Egom EE, et al. NPR-C (Natriuretic Peptide Receptor-C) modulates the progression of angiotensin II-mediated atrial fibrillation and atrial remodeling in mice. Circ Arrhythm Electrophysiol 2019;12:e006863.

[49] Remes J, van Brakel TJ, Bolotin G, Garber C, de Jong MM, van der Veen FH, et al. Persistent atrial fibrillation in a goat model of chronic left atrial overload. J Thorac Cardiovasc Surg 2008;136:1005–11.
[50] Verheule S, Wilson E, Everett TT, Shanbhag S, Golden C, Olgin J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. Circulation 2003;107:2615–22.
[51] Kistler PM, Sanders P, Dodic M, Spence SJ, Samuel CS, Zhao C, et al. Atrial electrical and structural abnormalities in an ovine model of chronic blood pressure elevation after prenatal corticosteroid exposure: implications for development of atrial fibrillation. Eur Heart J 2006;27:3045–56.
[52] Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Brooks AG, Worthington M, et al. Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. Heart Rhythm 2010;7:1282–90.
[53] Triposkiadis F, Moyssakis I, Hadjinikolaou L, Makris T, Zioris H, Hatzizaharias A, et al. Left atrial systolic function is depressed in idiopathic and preserved in ischemic dilated cardiomyopathy. Eur J Clin Invest 1999;29:905–12.
[54] Liao CH, Akazawa H, Tamagawa M, Ito K, Yasuda N, Kudo Y, et al. Cardiac mast cells cause atrial fibrillation through PDGF-A-mediated fibrosis in pressure-overloaded mouse hearts. J Clin Invest 2010;120:2422–3253.
[55] Ohtani K, Yutani C, Nagata S, Koretsune Y, Hori M, Kamada T. High prevalence of atrial fibrosis in patients with dilated cardiomyopathy. J Am Coll Cardiol 1995;25:1162–9.
[56] Deroubaix E, Folliguet T, Rucker-Martin C, Dinanian S, Boixel C, Validire P, et al. Moderate and chronic hemodynamic overload of sheep atria induces reversible cellular electrophysiologic abnormalities and atrial vulnerability. J Am Coll Cardiol 2004;44:1918–26.
[57] Pluteanu F, Hess J, Plackic J, Nikonova Y, Preisenberger J, Bukowska A, et al. Early subcellular Ca2+ remodelling and increased propensity for Ca2+ alternans in left atrial myocytes from hypertensive rats. Cardiovasc Res 2015;106:87–97.
[58] Qi XY, Yeh YH, Xiao L, Burstein B, Maguy A, Chartier D, et al. Cellular signaling underlying atrial tachycardia remodeling of L-type calcium current. Circ Res 2008;103:845–54.
[59] Emelyanova L, Ashary Z, Cosic M, Negmadjanov U, Ross G, Rizvi F, et al. Selective downregulation of mitochondrial electron transport chain activity and increased oxidative stress in human atrial fibrillation. Am J Physiol Heart Circ Physiol 2016;311:H54–63.
[60] Ozcan C, Li Z, Kim G, Jeevanandam V, Uriel N. Molecular mechanism of the association between atrial fibrillation and heart failure includes energy metabolic dysregulation due to mitochondrial dysfunction. J Card Fail 2019;25:911–20.
[61] Wiersma M, van Marion DMS, Wust RCI, Houtkooper RH, Zhang D, Groot NMS, et al. Mitochondrial dysfunction underlies cardiomyocyte remodeling in experimental and clinical atrial fibrillation. Cells 2019;8.
[62] Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–68.
[63] Dobrev D, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T, et al. The G protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial fibrillation. Circulation 2005;112:3697–706.
[64] Makary S, Voigt N, Maguy A, Wakili R, Nishida K, Harada M, et al. Differential protein kinase C isoform regulation and increased constitutive activity of acetylcholine-regulated potassium channels in atrial remodeling. Circ Res 2011;109:1031–43.
[65] Igarashi T, Finet JE, Takeuchi A, Fujino Y, Strom M, Greener ID, et al. Connexin gene transfer preserves conduction velocity and prevents atrial fibrillation. Circulation 2012;125:216–25.
[66] Mehdizadeh M, Aguilar M, Thorin E, Ferbeyre G, Nattel S. The role of cellular senescence in cardiac disease: basic biology and clinical relevance. Nat Rev Cardiol 2022;19:250–64.
[67] Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol 2010;5:99–118.
[68] Meyer K, Hodwin B, Ramanujam D, Engelhardt S, Sarikas A. Essential role for premature senescence of myofibroblasts in myocardial fibrosis. J Am Coll Cardiol 2016;67:2018–28.
[69] Sithara T, Drosatos K. Metabolic complications in cardiac aging. Front Physiol 2021;12:669497.
[70] Lee HY, Oh BH. Aging and arterial stiffness. Circ J 2010;74:2257–62.
[71] Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev 2008;88:389–419.
[72] Sletten AC, Peterson LR, Schaffer JE. Manifestations and mechanisms of myocardial lipotoxicity in obesity. J Intern Med 2018;284:478–91.
[73] El Hayek MS, Ernande L, Benitah JP, Gomez AM, Pereira L. The role of hyperglycaemia in the development of diabetic cardiomyopathy. Arch Cardiovasc Dis 2021;114:748–60.
[74] Demir K, Avci A, Kaya Z, Marakoglu K, Ceylan E, Yilmaz A, et al. Assessment of atrial electromechanical delay and P-wave dispersion in patients with type 2 diabetes mellitus. J Cardiol 2016;67:378–83.
[75] Allo SN, Lincoln TM, Wilson GL, Green FJ, Watanabe AM, Schaffer SW. Non-insulin-dependent diabetes-induced defects in cardiac cellular calcium regulation. Am J Physiol 1991;260:C1165–71.
[76] Fossier L, Panel M, Butruille L, Colombani S, Azria L, Woitrain E, et al. Enhanced mitochondrial calcium uptake suppresses atrial fibrillation associated with metabolic syndrome. J Am Coll Cardiol 2022;80:2205–19.
[77] Ajoolabady A, Nattel S, Lip GYH, Ren J. Inflammasome signaling in atrial fibrillation: JACC state-of-the-art review. J Am Coll Cardiol 2022;79:2349–66.
[78] Karastergiou K, Evans I, Ogston N, Miheisi N, Nair D, Kaski JC, et al. Epicardial adipokines in obesity and coronary artery disease induce atherogenic changes in monocytes and endothelial cells. Arterioscler Thromb Vasc Biol 2010;30:1340–6.
[79] Greulich S, Maxhera B, Vandenplas G, de Wiza DH, Smiris K, Mueller H, et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. Circulation 2012;126:2324–34.
[80] Venteclef N, Guglielmi V, Balse E, Gaborit B, Cotillard A, Atassi F, et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. Eur Heart J 2015;36:795a–805a.
[81] Klein C, Brunereau J, Lacroix D, Ninni S, Brigadeau F, Klug D, et al. Left atrial epicardial adipose tissue radiodensity is associated with electrophysiological properties of atrial myocardium in patients with atrial fibrillation. Eur Radiol 2019;29:3027–35.
[82] Jhuo SJ, Hsieh TJ, Tang WH, Tsai WC, Lee KT, Yen HW, et al. The association of the amounts of epicardial fat, P wave duration, and PR interval in electrocardiogram. J Electrocardiol 2018;51:645–51.
[83] Suffee N, Moore-Morris T, Farahmand P, Rucker-Martin C, Dilanian G, Fradet M, et al. Atrial natriuretic peptide regulates adipose tissue accumulation in adult atria. Proc Natl Acad Sci U S A 2017;114:E771–80.
[84] Suffee N, Moore-Morris T, Jagla B, Mougenot N, Dilanian G, Berthet M, et al. Reactivation of the epicardium at the origin of myocardial fibro-fatty infiltration during the atrial cardiomyopathy. Circ Res 2020;126:1330–42.
[85] Chen Z, Liu J, Zhou F, Li H, Zhang XJ, She ZG, et al. Nonalcoholic fatty liver disease: an emerging driver of cardiac arrhythmia. Circ Res 2021;128:1747–65.
[86] van Kleef LA, Lu Z, Ikram MA, de Groot NMS, Kavousi M, de Knegt RJ. Liver stiffness not fatty liver disease is associated with atrial fibrillation: the Rotterdam study. J Hepatol 2022;77:931–8.
[87] Jansen HJ, Bohne LJ, Gillis AM, Rose RA. Atrial remodeling and atrial fibrillation in acquired forms of cardiovascular disease. Heart Rhythm O2 2020;1:147–59.
[88] Dobaczewski M, Chen W, Frangogiannis NG. Transforming growth factor (TGF)-beta signaling in cardiac remodeling. J Mol Cell Cardiol 2011;51:600–6.
[89] Lobo HM, Naves ÍG, Marçal SB, Canzi CC, Rodrigues ABS, Menezes Jr AS. Atrial fibrillation in endurance training athletes: scoping review. RCM 2023;24:155.
[90] La Gerche A, Burns AT, Taylor AJ, Macisaac AI, Heidbuchel H, Prior DL. Maximal oxygen consumption is best predicted by measures of cardiac size rather than function in healthy adults. Eur J Appl Physiol 2012;112:2139–47.
[91] Stickland MK, Welsh RC, Petersen SR, Tyberg JV, Anderson WD, Jones RL, et al. Does fitness level modulate the cardiovascular hemodynamic response to exercise? J Appl Physiol 2006;100:1895–901.
[92] Wright SP, Dawkins TG, Eves ND, Shave R, Tedford RJ, Mak S. Hemodynamic function of the right ventricular-pulmonary vascular-left atrial unit: normal responses to exercise in healthy adults. Am J Physiol Heart Circ Physiol 2021;320:H923–41.
[93] Guasch E, Benito B, Qi X, Cifelli C, Naud P, Shi Y, et al. Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. J Am Coll Cardiol 2013;62:68–77.
[94] Olah A, Barta BA, Sayour AA, Ruppert M, Virag-Tulassay E, Novak J, et al. Balanced intense exercise training induces atrial oxidative stress counterbalanced by the antioxidant system and atrial hypertrophy that is not associated with pathological remodeling or arrhythmogenicity. Antioxidants (Basel) 2021;10:452.
[95] Aschar-Sobbi R, Izaddoustdar F, Korogyi AS, Wang Q, Farman GP, Yang F, et al. Increased atrial arrhythmia susceptibility induced by intense endurance exercise in mice requires TNFalpha. Nat Commun 2015;6:6018.
[96] Peritz DC, Catino AB, Csecs I, Kaur G, Kheirkhahan M, Loveless B, et al. High-intensity endurance training is associated with left atrial fibrosis. Am Heart J 2020;226:206–13.
[97] Messika-Zeitoun D, Bellamy M, Avierinos JF, Breen J, Eusemann C, Rossi A, et al. Left atrial remodelling in mitral regurgitation – methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. Eur Heart J 2007;28:1773–81.
[98] Bouwmeester S, van Loon T, Ploeg M, Mast TP, Verzaal NJ, van Middendorp LB, et al. Left atrial remodeling in mitral regurgitation: a combined experimental-computational study. PLoS One 2022;17:e0271588.
[99] Chang JP, Chen MC, Liu WH, Yang CH, Chen CJ, Chen YL, et al. Atrial myocardial nox2 containing NADPH oxidase activity contribution to oxidative stress in mitral regurgitation: potential mechanism for atrial remodeling. Cardiovasc Pathol 2011;20:99–106.
[100] Molnar AA, Santa A, Pasztor DT, Merkely B. Atrial cardiomyopathy in valvular heart disease: from molecular biology to clinical perspectives. Cells 2023;12.
[101] Li X, Garcia-Elias A, Benito B, Nattel S. The effects of cardiac stretch on atrial fibroblasts: analysis of the evidence and potential role in atrial fibrillation. Cardiovasc Res 2022;118:440–60.
[102] Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol 2020;17:559–73.

[103] Withaar C, Lam CSP, Schiattarella GG, de Boer RA, Meems LMG. Heart failure with preserved ejection fraction in humans and mice: embracing clinical complexity in mouse models. Eur Heart J 2021;42:4420–30.
[104] Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. J Am Coll Cardiol 2016;68:2217–28.
[105] Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. J Am Coll Cardiol 2020;76:1051–64.
[106] Roselli C, Rienstra M, Ellinor PT. Genetics of atrial fibrillation in 2020: GWAS, genome sequencing, polygenic risk, and beyond. Circ Res 2020;127:21–33.
[107] Yoneda ZT, Anderson KC, Quintana JA, O'Neill MJ, Sims RA, Glazer AM, et al. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. JAMA Cardiol 2021;6:1371–9.
[108] Ahlberg G, Andreasen L, Ghouse J, Bertelsen L, Bundgaard H, Haunso S, et al. Genome-wide association study identifies 18 novel loci associated with left atrial volume and function. Eur Heart J 2021;42:4523–34.
[109] Christophersen IE, Magnani JW, Yin X, Barnard J, Weng LC, Arking DE, et al. Fifteen genetic loci associated with the electrocardiographic P wave. Circ Cardiovasc Genet 2017;10.
[110] Zhu Y, Shi J, Zheng B, Liu H, Li C, Ju W, et al. Genetic findings in patients with primary fibrotic atrial cardiomyopathy. Eur J Med Genet 2022;65:104429.
[111] Peng W, Li M, Li H, Tang K, Zhuang J, Zhang J, et al. Dysfunction of myosin light-chain 4 (MYL4) leads to heritable atrial cardiomyopathy with electrical, contractile, and structural components: evidence from genetically-engineered rats. J Am Heart Assoc 2017;6.
[112] Rubattu S, Stanzione R, Di Angelantonio E, Zanda B, Evangelista A, Tarasi D, et al. Atrial natriuretic peptide gene polymorphisms and risk of ischemic stroke in humans. Stroke 2004;35:814–8.
[113] Nattel S, Heijman J, Zhou L, Dobrev D. Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective. Circ Res 2020;127:51–72.
[114] Kistamas K, Veress R, Horvath B, Banyasz T, Nanasi PP, Eisner DA. Calcium handling defects and cardiac arrhythmia syndromes. Front Pharmacol 2020;11:72.
[115] Hove-Madsen L, Llach A, Bayes-Genis A, Roura S, Rodriguez Font E, Aris A, et al. Atrial fibrillation is associated with increased spontaneous calcium release from the sarcoplasmic reticulum in human atrial myocytes. Circulation 2004;110:1358–63.
[116] Mesubi OO, Anderson ME. Atrial remodelling in atrial fibrillation: CaMKII as a nodal proarrhythmic signal. Cardiovasc Res 2016;109:542–57.
[117] Cros C, Douard M, Chaigne S, Pasqualin C, Bru-Mercier G, Recalde A, et al. Regional differences in Ca(2+) signaling and transverse-tubules across left atrium from adult sheep. Int J Mol Sci 2023;24.
[118] Niort BC, Recalde A, Cros C, Brette F. Critical link between calcium regional heterogeneity and atrial fibrillation susceptibility in sheep left atria. J Clin Med 2023;12.
[119] Kato T, Iwasaki YK, Nattel S. Connexins and atrial fibrillation: filling in the gaps. Circulation 2012;125:203–6.
[120] Opacic D, van Bragt KA, Nasrallah HM, Schotten U, Verheule S. Atrial metabolism and tissue perfusion as determinants of electrical and structural remodelling in atrial fibrillation. Cardiovasc Res 2016;109:527–41.
[121] Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993;22:1972–82.
[122] Pape LA, Price JM, Alpert JS, Ockene IS, Weiner BH. Relation of left atrial size to pulmonary capillary wedge pressure in severe mitral regurgitation. Cardiology 1991;78:297–303.
[123] Roh SY, Lee DI, Hwang SH, Lee KN, Baek YS, Iqbal M, et al. Association of left atrial pressure with late gadolinium enhancement extent in patient who underwent catheter ablation for atrial fibrillation. Sci Rep 2020;10:16486.
[124] Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357–63.
[125] Her AY, Choi EY, Shim CY, Song BW, Lee S, Ha JW, et al. Prediction of left atrial fibrosis with speckle tracking echocardiography in mitral valve disease: a comparative study with histopathology. Korean Circ J 2012;42:311–8.
[126] Watanabe Y, Nakano Y, Hidaka T, Oda N, Kajihara K, Tokuyama T, et al. Mechanical and substrate abnormalities of the left atrium assessed by 3-dimensional speckle-tracking echocardiography and electroanatomic mapping system in patients with paroxysmal atrial fibrillation. Heart Rhythm 2015;12:490–7.
[127] Park JH. Two-dimensional echocardiographic assessment of myocardial strain: important echocardiographic parameter readily useful in clinical field. Korean Circ J 2019;49:908–31.
[128] Leong DP, Joyce E, Debonnaire P, Katsanos S, Holman ER, Schalij MJ, et al. Left atrial dysfunction in the pathogenesis of cryptogenic stroke: novel insights from speckle-tracking echocardiography. J Am Soc Echocardiogr 2017;30:71–9 [e71].
[129] Pagola J, Gonzalez-Alujas T, Flores A, Muchada M, Rodriguez-Luna D, Sero L, et al. Left atria strain is a surrogate marker for detection of atrial fibrillation in cryptogenic strokes. Stroke 2014;45:e164–6.
[130] Khan MS, Memon MM, Murad MH, Vaduganathan M, Greene SJ, Hall M, et al. Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail 2020;22:472–85.
[131] Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. Circ Cardiovasc Imaging 2009;2:10–5.
[132] Morris DA, Belyavskiy E, Aravind-Kumar R, Kropf M, Frydas A, Braunauer K, et al. Potential usefulness and clinical relevance of adding left atrial strain to left atrial volume index in the detection of left ventricular diastolic dysfunction. JACC Cardiovasc Imaging 2018;11:1405–15.
[133] Maceira AM, Cosin-Sales J, Roughton M, Prasad SK, Pennell DJ. Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2010;12:65.
[134] Siebermair J, Kholmovski EG, Marrouche N. Assessment of left atrial fibrosis by late gadolinium enhancement magnetic resonance imaging: methodology and clinical implications. JACC Clin Electrophysiol 2017;3:791–802.
[135] Akoum N, McGann C, Vergara G, Badger T, Ranjan R, Mahnkopf C, et al. Atrial fibrosis quantified using late gadolinium enhancement MRI is associated with sinus node dysfunction requiring pacemaker implant. J Cardiovasc Electrophysiol 2012;23:44–50.
[136] Akoum N, Fernandez G, Wilson B, McGann C, Kholmovski E, Marrouche N. Association of atrial fibrosis quantified using LGE-MRI with atrial appendage thrombus and spontaneous contrast on transesophageal echocardiography in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2013;24:1104–9.
[137] Daccarett M, Badger TJ, Akoum N, Burgon NS, Mahnkopf C, Vergara G, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. J Am Coll Cardiol 2011;57:831–8.
[138] Bissell MM, Raimondi F, Ait Ali L, Allen BD, Barker AJ, Bolger A, et al. 4D Flow cardiovascular magnetic resonance consensus statement: 2023 update. J Cardiovasc Magn Reson 2023;25:40.
[139] Spartera M, Pessoa-Amorim G, Stracquadanio A, Von Ende A, Fletcher A, Manley P, et al. Left atrial 4D flow cardiovascular magnetic resonance: a reproducibility study in sinus rhythm and atrial fibrillation. J Cardiovasc Magn Reson 2021;23:29.
[140] Walheim J, Dillinger H, Kozerke S. Multipoint 5D flow cardiovascular magnetic resonance – accelerated cardiac- and respiratory-motion resolved mapping of mean and turbulent velocities. J Cardiovasc Magn Reson 2019;21:42.
[141] Ma L, Yerly J, Di Sopra L, Piccini D, Lee J, DiCarlo A, et al. Using 5D flow MRI to decode the effects of rhythm on left atrial 3D flow dynamics in patients with atrial fibrillation. Magn Reson Med 2021;85:3125–39.
[142] Huo Y, Mitrofanova L, Orshanskaya V, Holmberg P, Holmqvist F, Platonov PG. P-wave characteristics and histological atrial abnormality. J Electrocardiol 2014;47:275–80.
[143] Verbrugge FH, Reddy YNV, Attia ZI, Friedman PA, Noseworthy PA, Lopez-Jimenez F, et al. Detection of left atrial myopathy using artificial intelligence-enabled electrocardiography. Circ Heart Fail 2022;15:e008176.
[144] Khurshid S, Friedman S, Reeder C, Di Achille P, Diamant N, Singh P, et al. ECG-based deep learning and clinical risk factors to predict atrial fibrillation. Circulation 2022;145:122–33.
[145] Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on Atrial cardiomyopathies: definition, characterisation, and clinical implication. J Arrhythm 2016;32:247–78.
[146] Goldberger JJ, Arora R, Green D, Greenland P, Lee DC, Lloyd-Jones DM, et al. Evaluating the atrial myopathy underlying atrial fibrillation: identifying the arrhythmogenic and thrombogenic substrate. Circulation 2015;132:278–91.
[147] Kreimer F, Gotzmann M. Left atrial cardiomyopathy – A challenging diagnosis. Front Cardiovasc Med 2022;9:942385.
[148] Edwards JD, Healey JS, Fang J, Yip K, Gladstone DJ. Atrial cardiopathy in the absence of atrial fibrillation increases risk of ischemic stroke, incident atrial fibrillation, and mortality and improves stroke risk prediction. J Am Heart Assoc 2020;9:e013227.
[149] Sardana M, Lessard D, Tsao CW, Parikh NI, Barton BA, Nah G, et al. Association of left atrial function index with atrial fibrillation and cardiovascular disease: the Framingham Offspring Study. J Am Heart Assoc 2018;7.
[150] Lim DJ, Ambale-Ventakesh B, Ostovaneh MR, Zghaib T, Ashikaga H, Wu C, et al. Change in left atrial function predicts incident atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. Eur Heart J Cardiovasc Imaging 2019;20:979–87.
[151] Alexander B, Milden J, Hazim B, Haseeb S, Bayes-Genis A, Elosua R, et al. New electrocardiographic score for the prediction of atrial fibrillation: the MVP ECG risk score (morphology-voltage-P-wave duration). Ann Noninvasive Electrocardiol 2019;24:e12669.
[152] Chen LY, Ribeiro ALP, Platonov PG, Cygankiewicz I, Soliman EZ, Gorenek B, et al. P wave parameters and indices: a critical appraisal of clinical utility, challenges, and future research – A consensus document endorsed by the International Society of Electrocardiology and the International Society for Holter and Noninvasive Electrocardiology. Circ Arrhythm Electrophysiol 2022;15:e010435.
[153] Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. Lancet 2019;394:861–7.
[154] Hygrell T, Viberg F, Dahlberg E, Charlton PH, Kemp Gudmundsdottir K, Mant J, et al. An artificial intelligence-based model for prediction of atrial fibrilla-

tion from single-lead sinus rhythm electrocardiograms facilitating screening. Europace 2023;25:1332–8.
[155] Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. Lancet 2021;398:1498–506.
[156] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373–498.
[157] Maheshwari A, Norby FL, Roetker NS, Soliman EZ, Koene RJ, Rooney MR, et al. Refining prediction of atrial fibrillation-related stroke using the P(2)-CHA(2)DS(2)-VASc Score. Circulation 2019;139:180–91.
[158] King JB, Azadani PN, Suksaranjit P, Bress AP, Witt DM, Han FT, et al. Left Atrial fibrosis and risk of cerebrovascular and cardiovascular events in patients with atrial fibrillation. J Am Coll Cardiol 2017;70:1311–21.
[159] Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation 2014;129:2094–9.
[160] Vinereanu D, Lopes RD, Bahit MC, Xavier D, Jiang J, Al-Khalidi HR, et al. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. Lancet 2017;390:1737–46.
[161] Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation 1995;92:835–41.
[162] Kamel H, Longstreth Jr WT, Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, et al. The Atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: rationale and methods. Int J Stroke 2019;14:207–14.
[163] Lemesle G, Ninni S, de Groote P, Schurtz G, Lamblin N, Bauters C. Relative impact of bleedings over ischaemic events in patients with heart failure: insights from the CARDIONOR registry. ESC Heart Fail 2020;7:3821–9.
[164] Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107:2920–5.
[165] Andersen DM, Sengelov M, Olsen FJ, Marott JL, Jensen GB, Schnohr P, et al. Measures of left atrial function predict incident heart failure in a low-risk general population: the Copenhagen City Heart Study. Eur J Heart Fail 2022;24:483–93.
[166] Baturova MA, Kutyifa V, McNitt S, Polonsky B, Solomon S, Carlson J, et al. Usefulness of electrocardiographic left atrial abnormality to predict response to cardiac resynchronization therapy in patients with mild heart failure and left bundle branch block (a multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy substudy). Am J Cardiol 2018;122:268–74.
[167] Jacobsson J, Carlson J, Reitan C, Borgquist R, Platonov PG. Interatrial block predicts atrial fibrillation and total mortality in patients with cardiac resynchronization therapy. Cardiology 2020;145:720–9.
[168] Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med 2013;158:338–46.
[169] Zhang MJ, Norby FL, Lutsey PL, Mosley TH, Cogswell RJ, Konety SH, et al. Association of left atrial enlargement and atrial fibrillation with cognitive function and decline: the ARIC-NCS. J Am Heart Assoc 2019;8:e013197.
[170] Gutierrez A, Norby FL, Maheshwari A, Rooney MR, Gottesman RF, Mosley TH, et al. Association of abnormal P-wave indices with dementia and cognitive decline over 25 years: ARIC-NCS (The Atherosclerosis Risk in Communities Neurocognitive Study). J Am Heart Assoc 2019;8:e014553.
[171] Martinez-Selles M, Martinez-Larru ME, Ibarrola M, Santos A, Diez-Villanueva P, Bayes-Genis A, et al. Interatrial block and cognitive impairment in the BAYES prospective registry. Int J Cardiol 2020;321:95–8.
[172] Wang W, Zhang MJ, Inciardi RM, Norby FL, Johansen MC, Parikh R, et al. Association of echocardiographic measures of left atrial function and size with incident dementia. JAMA 2022;327:1138–48.