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# Atrial cardiomyopathy: from cell to bedside

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## Abstract

Atrial cardiomyopathy refers to structural and electrical remodelling of the atria, which can lead to impaired mechanical function. While historical studies have implicated atrial fibrillation as the leading cause of cardioembolic stroke, atrial cardiomyopathy may be an important, underestimated contributor. To date, the relationship between atrial cardiomyopathy, atrial fibrillation, and cardioembolic stroke remains obscure. This review summarizes the pathogenesis of atrial cardiomyopathy, with a special focus on neurohormonal and inflammatory mechanisms, as well as the role of adipose tissue, especially epicardial fat in atrial remodelling. It reviews the current evidence implicating atrial cardiomyopathy as a cause of embolic stroke, with atrial fibrillation as a lagging marker of an increased thrombogenic atrial substrate. Finally, it discusses the potential of antithrombotic therapy in embolic stroke with undetermined source and appraises the available diagnostic techniques for atrial cardiomyopathy, including imaging techniques such as echocardiography, computed tomography, and magnetic resonance imaging as well as electroanatomic mapping, electrocardiogram, biomarkers, and genetic testing. More prospective studies are needed to define the relationship between atrial cardiomyopathy, atrial fibrillation, and embolic stroke and to establish a prompt diagnosis and specific treatment strategies in these patients with atrial cardiomyopathy for the secondary and even primary prevention of embolic stroke.

**Keywords** Atrial cardiomyopathy; Atrial fibrillation; Embolic stroke; Pathogenesis; Diagnosis

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## Introduction

Atrial fibrillation (AF) is the most common arrhythmia, affecting ~60 million adults worldwide.<sup>1</sup> AF is thought to be the main driver of left atrial (LA) thrombogenesis and the resultant cardioembolic stroke (CS). However, this classical theory has been questioned by more recent studies.<sup>2–4</sup> If AF is the major cause of CS, then embolic risk should be reduced after reversing and maintaining sinus rhythm, yet some studies have failed to demonstrate this observation.<sup>5–7</sup> Moreover, the temporal dissociation between AF and stroke had been examined by several recent clinical studies. For instance, only 27.5% and 8% of the patients in the TRENDS and ASSERT trial, respectively, were detected to have an atrial tachycardia/AF episode within 30 days prior to stroke.<sup>3,8</sup> In the LOOP study,

continuous electrocardiographic monitoring increased the rate of AF detection [31.8% vs. 12.2%, hazard ratio (HR): 3.17] and anticoagulation initiation (29.7% vs. 13.1%, HR: 2.72) compared with the usual care group, but the risk of stroke or systemic arterial embolism was not significantly reduced (4.5% vs. 5.6%,  $P = 0.11$ ).<sup>4</sup> The STROKESTOP study, which included 27 975 older participants, found that screening for AF significantly reduced the overall incidence of stroke, systemic embolism, hospitalization for major bleeding, and all-cause mortality compared with the control group (31.9% vs. 33.0%,  $P = 0.045$ ). However, there was no significant difference in the incidence of ischaemic stroke (5.5% vs. 5.9%,  $P = 0.084$ ) or systemic embolism (0.43% vs. 0.38%,  $P = 0.60$ ) between the two groups.<sup>9</sup> The aforementioned results indicate that AF may not always be directly associated

with stroke or systemic embolism.<sup>4,9</sup> Meanwhile, patients with a CHA2DS2-VASc score of 0 are unlikely to have a stroke even with persistent AF.<sup>2</sup> As a result, a more complex relationship between AF and CS exists.

While AF may worsen underlying atrial structural and functional abnormalities, impaired mechanical function of LA is associated with increased risks of CS independent of AF.<sup>10</sup> In addition, some studies have reported that atrial cardiomyopathy (ACM) was a potential source of embolic stroke of undetermined source (ESUS) in ~45% of ESUS patients.<sup>11</sup> These studies suggest that ACM may be the primary cause of LA thrombogenesis and resultant CS.<sup>12</sup> Therefore, identifying the value of ACM may help to better understand the risk of CS in patients without AF.

## Definition of atrial cardiomyopathy

The atria are a critical, and often overlooked, component of normal cardiac function. For example, the atria serve as a reservoir, a conduit, and a booster pump to regulate ventricular filling. In addition, the atria are responsible for cardiac conduction and the secretion of natriuretic peptides. While the concept of ACM was initially proposed a decade ago, it was not widely accepted at that time.<sup>13</sup> According to EHRA/HRS/APHS/SOLAECE expert consensus, ACM refers to 'structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations'.<sup>14</sup> This concept is impractical for the clinical diagnosis of ACM. While there is no unified diagnostic standard for ACM at present, previous studies have used criteria such as LA enlargement, increased P-wave terminal force in lead V1 (PTFV1) of the electrocardiogram (ECG), and elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) for the diagnosis of ACM.<sup>15–18</sup>

## Aetiologies of atrial cardiomyopathy

There are various aetiologies of ACM, including genetic factors, aging, congestive heart failure (CHF), AF, myocarditis, valvular heart disease, hypertension, obstructive sleep apnoea,<sup>14</sup> chronic systemic inflammatory, often autoimmune, diseases (e.g. rheumatoid arthritis, psoriasis, and systemic sclerosis), metabolic disorders characterized by adipose tissue inflammation (e.g. obesity, diabetes mellitus, and non-alcoholic liver disease), and hormonal diseases promoting adipogenesis and adipose tissue dysfunction (e.g. hypothyroidism and primary hyperaldosteronism).<sup>19</sup> In addition, mental disorders can increase the risk of cardiovascular disease and worsen its prognosis.<sup>20</sup> A recent study showed that anxiety was also independently associated with ACM.<sup>21</sup>

In this review, we focused on the effect of heart failure (HF) on atrial pathologies. The prevalence of atrial enlargement in patients with chronic HF ranged from 19% to 66% with great differences between studies, likely attributable to the heterogeneous aetiologies and stages of HF.<sup>22</sup> A recent study investigated the progression of atrial fibrosis in 42 non-AF patients and showed that patients with CHF had significantly more atrial fibrosis progression than those without HF after 25.5 ± 18 months (mean  $\Delta$ fibrosis 8.80 ± 8.88% vs. 3.50 ± 5.81%,  $P = 0.0338$ ).<sup>23</sup> In addition, atrial electrophysiological remodelling is common in patients with HF. AF is a typical representative of electrophysiological remodelling. A study from Swedish Heart Failure Registry observed that the prevalence of AF was 65%, 60%, and 53% in HF with ejection fraction (EF)  $\geq 50\%$ , 40–49%, and  $\leq 39\%$ , respectively.<sup>24</sup> In patients with HF, both pressure and volume overload of the left ventricle can increase LA wall stress and myocyte stretching, thereby triggering adrenergic activation and atrial remodelling. Risk factors of HF may synergistically aggravate atrial remodelling.<sup>22</sup> In a rat model of HF with preserved ejection fraction (HFpEF), mediated by metabolic syndrome, atrial myocytes exhibited enhanced mitochondrial fission, increased production of reactive oxygen species (ROS), abnormal  $Ca^{2+}$  handling, and interleukin (IL)-10 can attenuate the dysfunction of  $Ca^{2+}$  handling.<sup>25</sup> Dual inhibition of sodium-glucose linked transporter type (SGLT)-1 and SGLT-2 also ameliorated LA remodelling in metabolic HFpEF.<sup>26</sup> Therefore, HF mediated by differing aetiologies may participate in atrial remodelling through different mechanisms. Furthermore, HF may promote atrial thrombosis. A substudy of the ENSURE-AF trial analysed determinants of LA thrombus detected by transoesophageal echocardiography in patients with AF scheduled for electrical cardioversion. The results of this ENSURE-AF trial substudy showed that LA thrombus was reported in 91 of 1183 subjects (8.2%) and that only age  $\geq 75$  years [odds ratio (OR): 2.13,  $P = 0.0202$ ] and HF (OR: 1.97,  $P = 0.0064$ ) were independent risk factors of LA thrombus.<sup>27</sup> A meta-analysis including 20 516 AF patients also showed that HF is associated with LA thrombus presence [OR: 3.67, 95% confidence interval (CI): 2.40–5.60].<sup>28</sup>

## Pathogenesis of atrial cardiomyopathy

Atrial cardiomyopathy is caused by atrial structural and electrophysiological remodelling stimulated by various aetiologies. Structural remodelling manifests as cardiomyocyte abnormalities (the absence of sarcomeres, accumulation of glycogen, dedifferentiation of mature cells, expression of a foetal gene pattern, and display of homogeneous chromatin), atrial fibrosis (fibroblast proliferation and excessive accumulation of extracellular matrix),<sup>29</sup> changes of atrial endothelial cells (irregularly hypertrophied, disorganization, the forma-

tion of different-sized gaps along the border of cells, and the enhanced expression of monocyte chemoattractant protein-1 and adhesion molecules),<sup>30</sup> the infiltration of adipose tissue and inflammatory cells,<sup>31</sup> glycosphingolipids and amyloid deposition, and granuloma formation.<sup>14</sup> Electrophysiological remodelling involves the alterations of excitation–contraction coupling, ion channels, gap junctions, and autonomic nerve distribution.<sup>29</sup> To date, the pathogenesis of ACM has not been completely clarified.

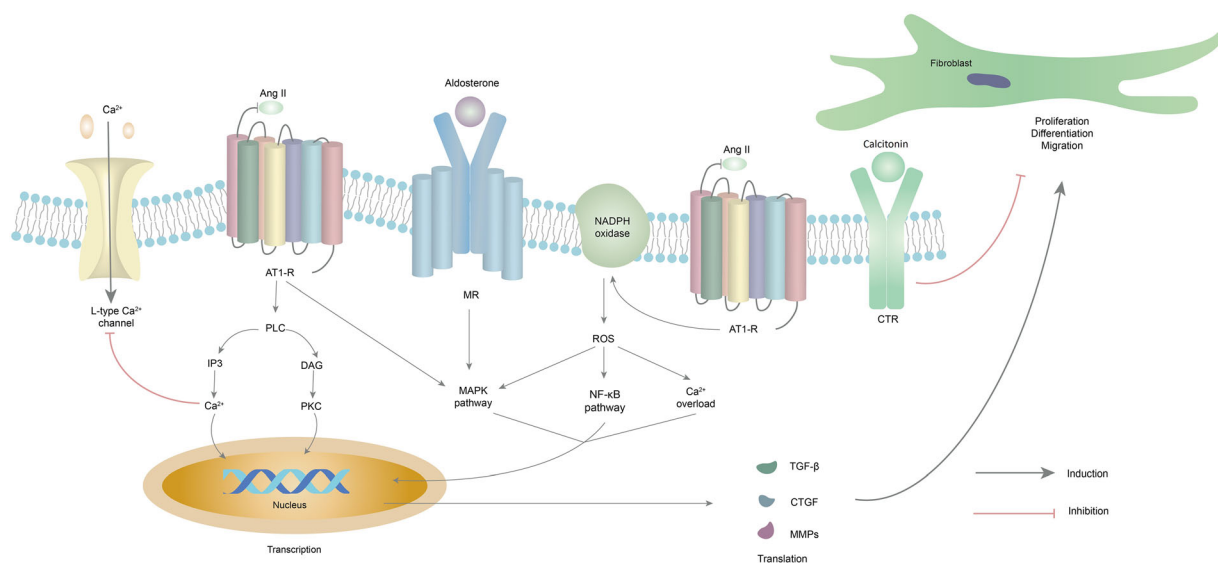
## Neurohormonal mechanisms

Normally, the renin-angiotensin-aldosterone system (RAAS) is essential for regulating haemodynamic stability. However, increased angiotensin II (Ang II) plays a key role in promoting atrial remodelling by binding to angiotensin receptor 1 (AT1-R). Firstly, the combination of Ang II and AT1-R activates the mitogen-activated protein kinase (MAPK) pathway and thus regulates the expression of pro-fibrotic molecules, such as transforming growth factor  $\beta$  (TGF- $\beta$ ), connective tissue growth factor (CTGF), and matrix metalloproteinases (MMPs).<sup>32</sup> Secondly, AT1-R is a G-protein-coupled receptor, and its activation hydrolyses phospholipase C (PLC) to generate inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG). Abnormally increased IP3 can lead to intracellular  $\text{Ca}^{2+}$  overload that promotes the proliferation and differentiation of fibroblasts and down-regulates the L-type  $\text{Ca}^{2+}$  current.<sup>33</sup> Thirdly, Ang II stimulates ROS excessive release by activating

nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which induces intracellular  $\text{Ca}^{2+}$  overload and activates MAPK, nuclear factor- $\kappa\text{B}$ , and cytokines to participate in myocardial fibrosis.<sup>34,35</sup> Sacubitril/valsartan can prevent Ang II from binding AT1-R. Li *et al.*<sup>36</sup> observed that sacubitril/valsartan reduced the extent of atrial fibrosis and alleviated susceptibility to AF in rats stimulated by Ang II. This result may be conducive to therapies targeting both ACM and AF (Figure 1).<sup>36</sup> While angiotensin-converting enzyme (ACE) is a key enzyme for Ang II production, ACE2 can convert Ang II to Ang 1–7, largely counteracting Ang II effects.<sup>37</sup> There seems to be a gender difference in allele types of *ACE1* encoding ACE as the *I* allele is more commonly seen in females and the *D* allele (associated with high expression of ACE) is more frequently observed in males.<sup>38</sup> An accumulating body of evidences suggest that the balance between ACE/Ang II/AT1-R pathways and ACE2/Ang(1–7)/Mas receptor and angiotensin receptor 2 pathways was affected by gender as oestrogen may contribute to this difference given that the prevalence of cardiovascular disease in premenopausal women is lower than in aged-matched men.<sup>39</sup> Bukowska *et al.* showed that oestrogen in atrial tissue significantly down-regulated the ratio of ACE/ACE2 and inhibited the atrial expression of nuclear factor- $\kappa\text{B}$  target genes that had pro-inflammatory or pro-oxidative effects. However, whether oestrogen or selective oestrogen receptor modulators can be used to delay the progression of atrial remodelling should be further studied.<sup>37</sup>

Aldosterone can activate MAPK pathway in atrial myocytes to promote fibrosis by binding the mineralocorticoid receptor

**Figure 1** The neurohormonal mechanisms involved in atrial remodelling. Ang II, angiotensin II; AT1-R, angiotensin receptor 1; CTGF, connective tissue growth factor; CTR, calcitonin receptor; DAG, diacylglycerol; IP3, inositol-1,4,5-triphosphate; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; MR, mineralocorticoid receptor; NADPH, nicotinamide adenine dinucleotide phosphate; NF- $\kappa\text{B}$ , nuclear factor- $\kappa\text{B}$ ; PKC, protein kinase C; PLC, phospholipase C; ROS, reactive oxygen species; TGF- $\beta$ , transforming growth factor  $\beta$ .



(MR) (Figure 1). Eplerenone, an MR antagonist, attenuates the effect on atrial fibrosis of animals through an unclear mechanism.<sup>32</sup> Yi *et al.* explored the influence of osteoblast MR on atrial fibrosis, finding that the osteoblast MR deficiency alleviated atrial fibrosis by reducing the expression of osteocalcin. Osteocalcin promoted the proliferation and migration of atrial fibroblasts and thus may be a potential target for atrial fibrosis.<sup>40</sup>

Transforming growth factor  $\beta$  is one of the most effective stimulators of cardiac fibrosis. It correlates with phosphorylation of the Smads family to form complexes that translocate into the nucleus of myofibroblasts to up-regulate the generation of fibrin.<sup>35</sup> It should be noted that Ang II cannot cause cardiac hypertrophy and fibrosis in the absence of TGF- $\beta$ . TGF- $\beta$  can also induce cardiomyocyte apoptosis and stimulate the expression of AT1-R.<sup>32,41</sup> Similarly, platelet-derived growth factor (PDGF), fibroblast growth factor, CTGF, and MMPs are also significant participators in atrial remodelling.<sup>32</sup>

Calcitonin, a hormone involved in bone metabolism, is mainly secreted from the thyroid parafollicular cells. Recently, it has been demonstrated that the atrial myocardial cell is also an active source of calcitonin. Moreira *et al.*<sup>42</sup> found that the mRNA level of calcitonin in human atrial myocardial cells is half that in human medullary thyroid carcinoma TT cells. Interestingly, calcium-induced calcitonin secretion in atrial myocardial cells was 16 times higher than that in TT cells. Calcitonin from atrial myocytes acts on adjacent atrial fibroblasts to inhibit their proliferation and migration as well as collagen 1 production (Figure 1). In addition, this study revealed that the calcitonin content was markedly reduced and subcellular localization of calcitonin receptors was transformed from cell surfaces to intracellular spaces in patients with persistent AF. In the final analysis, the calcitonin gene knockout and overexpression mouse model further verified the importance of calcitonin–calcitonin receptor signalling in atrial remodelling.<sup>42</sup> Hence, restoring damaged calcitonin–calcitonin receptor signalling of the myocardium may provide a new strategy for inhibiting atrial fibrosis.

## Inflammatory mechanisms

Cardiac inflammation (myocarditis, pericarditis, infective endocarditis, etc.), noncardiac inflammation (pneumonia, intestinal inflammatory disease, etc.), and systemic subclinical inflammatory conditions (obesity, hypertension, ischaemic heart disease, etc.) are prone to promote the initiation and maintenance of AF.<sup>32</sup> C-reactive protein (CRP) was shown to be a strong predictor of new onset or recurrence of post-operative atrial fibrillation (POAF).<sup>43</sup> Inflammation can activate the RAAS and oxidative stress, thereby bringing about atrial remodelling. A variety of inflammatory cytokines are involved in atrial structural and electrophysiological re-

modelling, such as tumour necrosis factor (TNF), PDGF, and IL-6.<sup>44</sup> In the sterile pericarditis rat model, intraperitoneal injection of anti-rat-IL-6 antibody not only ameliorated atrial fibrosis but also reversed the abnormalities of Ca<sup>2+</sup> handling, particularly ryanodine receptor 2 (RyR2) dysfunction. Moreover, vascular leakage and consequent cardiac oedema caused by inflammation can induce intercalated disk remodelling and slow atrial conduction.<sup>45</sup>

Inflammasomes, macromolecular protein complexes contained in the cytoplasm, are of significance in reaction to cellular stress. The best known inflammasome is NOD-like receptor protein 3 (NLRP3) composed of NACHT, LRR, and PYD domain containing protein 3. The NLRP3 inflammasome activates caspase-1, regulates the maturation and release of IL-1 $\beta$  and IL-18, and possibly induces pyroptosis.<sup>46</sup> Yao *et al.*<sup>47</sup> have confirmed that NLRP3 inflammasome is activated in atrial cardiomyocytes from AF patients. They also found that the cardiomyocyte-specific knockin (CM-KI) mouse model expressing constitutively active NLRP3 manifested abnormal Ca<sup>2+</sup> release of atrial myocardial sarcoplasmic reticulum (SR), shortened atrial effective refractory period, and a hypertrophic and fibrotic atrium. At the molecular level, the mRNA level encoding RyR2, acetylcholine-activated K<sup>+</sup> channel, ultrafast delayed rectifier K<sup>+</sup> channel, and fibrosis markers (collagen 1a and galectin 3) were increased in the CM-KI mouse model. In contrast, the cardiomyocyte-specific knockdown of NLRP3 reduced susceptibility to AF.<sup>47</sup> These results revealed the pathophysiological role of NLRP3 inflammasome in atrial remodelling. The detailed upstream factors activating NLRP3 are not entirely clear. A recent study indicated that gut microbiota dysbiosis induced the up-regulation of atrial NLRP3 level by increasing lipopolysaccharide and glucose and thus promoted atrial fibrosis.<sup>48</sup> Suppressing the NLRP3 inflammasome signalling of atrial cardiomyocytes established a new potential target for the treatment of ACM or AF.

## Role of adipose tissue in atrial cardiomyopathy

Being overweight and clinical obesity have presented a significant threat to the global public health system. It is estimated that there are currently 2 billion adults and 43 million children under the age of 5 who are overweight or obese in the world.<sup>49</sup> Obesity is a known risk factor for ACM and AF. The incidence of pacing-induced AF in obese mice (100%) is dramatically higher than that in lean controls (25%). In addition, diet-induced obese mice exhibited the remodelling of ion channels and corresponding atrial fibrosis.<sup>50</sup> Another study demonstrated that a chronic high-fat diet also altered the expression and distribution of atrial connexin that is an essential component of gap junction.<sup>51</sup>

Epicardial adipose tissue (EAT) is a beige fat located between the visceral pericardium and myocardium, accounting

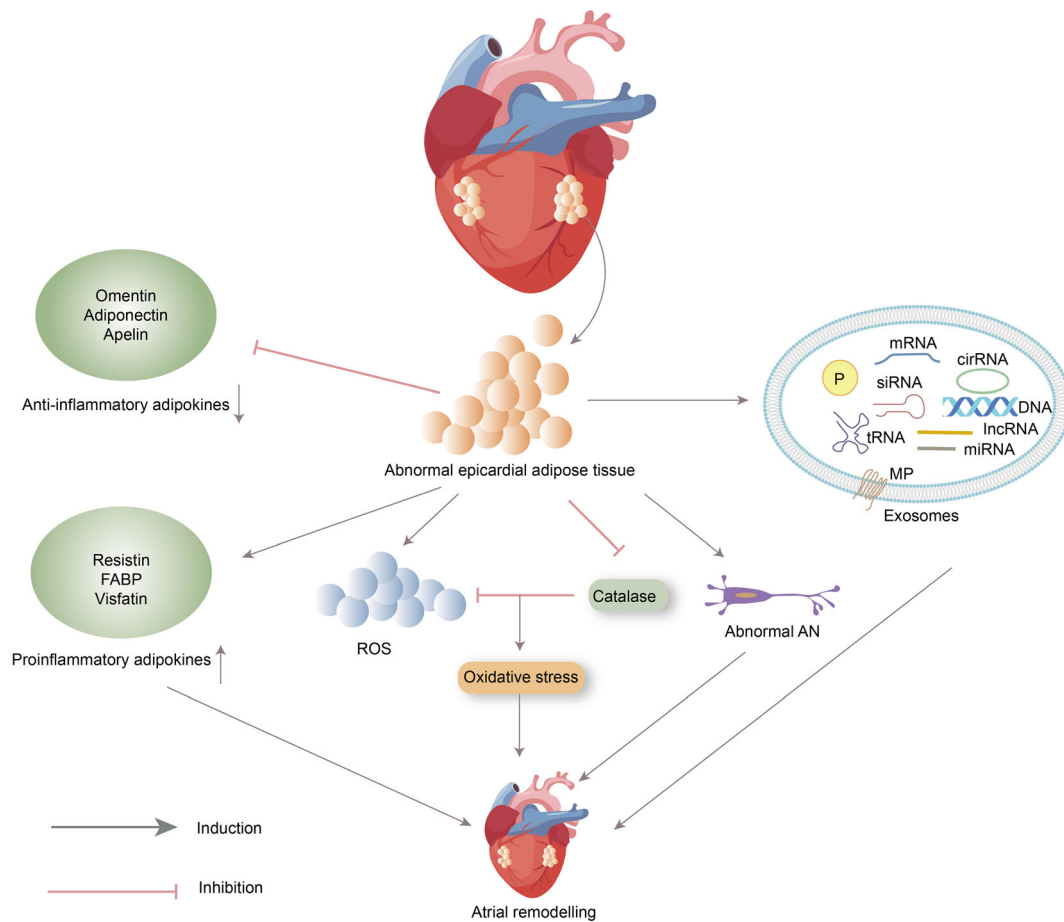


for ~20% of heart weight and covering nearly 80% of the cardiac surface. The volume of EAT may be affected by various factors such as age, gender, weight, and race. EAT consists of a variety of different cell types including adipocytes, preadipocytes, adipose-derived stem cells, monocytes, fibrocytes, immunocytes, ganglion, and stromal vascular cells.<sup>52</sup> Normally, the function of EAT are to provide energy, protect myocardium from hypothermic injury, serve as a mechanical buffer to avoid distortion of coronary arteries, and secrete cytokines to regulate coronary circulation and myocardial structure. In the pathologic state, EAT participated in the development of atrial fibrosis and atrial arrhythmia.<sup>53</sup>

The LA appendage specimens from AF patients were analysed histologically and biochemically with results showing that the extent of infiltration and fibrotic remodelling of EAT affected LA myocardial fibrosis and that the collagen content of the LA myocardium was positively related to the expression level of pro-inflammatory and pro-fibrotic

cytokines/chemokines in EAT.<sup>54</sup> EAT can secrete multiple adipokines to regulate fibroblasts, myocytes, and leukocytes in the myocardium. This imbalance between anti-inflammatory (omentin, apelin, adiponectin, etc.) and pro-inflammatory adipokines (resistin, fatty acid binding protein, visfatin, etc.) contributes to the atrial remodelling. Activin A and angiotensin-like protein 2 in EAT have been confirmed to play a key role in the atrial fibrosis process.<sup>55,56</sup> In addition, extracellular vesicles from EAT are also a significant participator in atrial remodelling. Shaihov-Teper *et al.*<sup>57</sup> collected and cultured EAT of AF patients and then extracted exosomes from culture medium. The proteomic analysis, *in vivo* and *in vitro* experiments, all showed that the exosomes from EAT of AF patients have a distinctive pro-inflammatory, pro-fibrotic, and pro-arrhythmic properties. In patients with cardiovascular diseases, EAT has more ROS, less catalase, and different post-translational modifications of oxidative stress-related proteins compared with subcutaneous

**Figure 2** The possible mechanisms of epicardial adipose tissue promoting atrial remodelling under pathological conditions. AN, autonomic nerve; cirRNA, circular RNA; FABP, fatty acid binding protein; lncRNA, long non-coding RNA; miRNA, microRNA; MP, membrane protein; mRNA, messenger RNA; P, proteins; ROS, reactive oxygen species; siRNA, small interfering RNA; tRNA, transfer RNA.



adipose tissue (SAT). These differences make the level of oxidative stress in EAT higher, thereby resulting in atrial remodelling (Figure 2).<sup>58</sup>

Moreover, EAT has potential arrhythmogenic properties. Jhuo *et al.* analysed the association between EAT volume and various ECG findings, showing that the PR interval, P-wave duration, and inter-atrial conduction block were correlated with EAT volume.<sup>59</sup> Epicardial adipocytes-incubated LA myocytes exhibited different electrophysiological characteristics and ionic currents from the control.<sup>60</sup> Adipokines and exosomes secreted from EAT promote atrial arrhythmias through paracrine signalling. Abundant autonomic nerves are distributed in epicardial fat pads. Abnormalities of autonomic nerves can also lead to atrial electrophysiological remodelling (Figure 2). Stimulating autonomic nerves of EAT can shorten the duration of the action potential, increase Ca<sup>2+</sup> release from SR, reduce atrial conduction velocity, and raise the heterogeneity of conduction.<sup>61</sup> Botulinum toxin (BTX) may block parasympathetic nerves to release acetylcholine. Recently, it was found that BTX injections into epicardial fat pads significantly reduced the incidence of atrial arrhythmias and the burden of AF in patients with AF during a 3 year follow-up.<sup>62</sup> However, the study from Waldron *et al.* showed that BTX injections into epicardial fat pads did not reduce the incidence of POAF during hospitalization.<sup>63</sup> In this study, patients without AF accounted for the majority of patients and the atrial diameter of patients without AF was smaller than that of the former study. These differences indicate that BTX injections into epicardial fat pads may represent a potential POAF prevention strategy more suitable for AF patients with severe atrial remodelling. In addition, whether epicardial BTX injection is more effective than antiarrhythmic drugs in the prevention of POAF deserves attention.

## Atrial cardiomyopathy contributes to embolic stroke

### Atrial cardiomyopathy, atrial fibrillation, and embolic stroke

Cryptogenic ischaemic stroke accounts for 25% of all ischaemic strokes. Compelling evidence exists suggesting that most cryptogenic strokes arise from an inapparent thromboembolic event. Thus, the term ESUS, introduced in 2014, is defined as a non-lacunar cerebral infarction without any large arterial stenoses  $\geq 50\%$  or identifiable cardioembolic causes.<sup>64</sup> ESUS comprises 17% of all ischaemic strokes with an annual stroke recurrence rate of 4–5%.<sup>65</sup> Initially, silent paroxysmal AF was implicated as the most cause of ESUS. However, further studies have challenged this opinion as described previously in this manuscript. Although the EAST-AFNET 4 trial showed that early rhythm control com-

pared with no rhythm control for patients with AF was associated with lower incidence of adverse cardiovascular events including stroke, it should be noted that most patients in this trial received anticoagulation therapy, rate control, and management of cardiovascular conditions<sup>66</sup>; such comprehensive management is actually a treatment of atrial substrate and not only rhythm control. Previous studies demonstrated that rhythm control compared with rate control failed to reduce the incidence of cardiovascular adverse events.<sup>5,6</sup> Hence, the lower risk of adverse cardiovascular outcomes in early rhythm control group may be attributed to better treatment of atrial substrate for AF patients in the EAST-AFNET 4 trial. Kottkamp<sup>67</sup> contributed one of the first reports on the relationship between ACM, AF, and CS. Kottkamp correctly observed that the fibrotic ACM supplied the substrate necessary for both AF and thromboembolic complications.

Emerging evidence suggests ACM as an important contributor to ESUS. A prospective multicentre study of 800 ESUS patients showed that 45% of patients carried ACM that was defined as mild or severe LA enlargement or frequent supraventricular extrasystoles.<sup>11</sup> A recent study defining ACM as PTFV1  $> 5000 \mu\text{V}\cdot\text{ms}$  or severe LA enlargement found that the incidence of ACM in ESUS patients was higher than that in the large artery atherosclerosis or small vessel disease group (26.6% vs. 12.1% vs. 16.9%, respectively).<sup>18</sup> There is a significant difference in the proportion of ACM in ESUS between the aforementioned two studies, which may be partly due to the different diagnostic criteria of ACM and the different populations studied.

Atrial fibrillation tends to occur in the cases experiencing atrial abnormalities, such as endothelial damage, fibrosis, decreased myocardial contractility, and atrial enlargement. These atrial abnormalities are related to stroke independently of AF.<sup>68</sup> Thus, AF may be a lagging marker of a thrombogenic atrial substrate. With sustained AF, ACM is exacerbated by AF promoting atrial remodelling. Atrial high-rate episodes, short asymptomatic episodes of AF that are detected by a pacemaker or implantable cardioverter-defibrillator but often not recognized clinically by ECG and Holter monitors, may also induce chronic atrial changes.<sup>69</sup> Atrial functional mitral regurgitation (AFMR) refers to functional mitral regurgitation caused by persistent AF or HFpEF. The prevalence of AFMR was 28% in persistent AF with duration  $> 10$  years. This proportion rose to 37–44% in patients with persistent AF and HFpEF.<sup>70</sup> Atrial remodelling in AF is one of the significant mechanisms of AFMR. Conversely, AFMR will accelerate the development of atrial abnormalities.<sup>71</sup> Rapid depolarization of the atrium during AF results in intracellular Ca<sup>2+</sup> overload that causes adaptive or inflammatory changes promoting atrial fibrosis and systolic dysfunction.<sup>72</sup> AF can induce platelet activation. Activated platelets promote atrial fibrosis by releasing significant amounts of TGF- $\beta$  into the plasma or regional atrial tissue and interacting with fibroblasts.<sup>73</sup> Recent animal experimen-

tation has shown that the hypercoagulable state during AF can also promote atrial remodelling by enhancing the expression of pro-fibrotic and pro-inflammatory molecules of fibroblasts.<sup>74</sup>

### Atrial remodelling and thrombosis

Blood stasis, endothelial injury, and hypercoagulability are the three elements of thrombosis. The mechanism underlying thrombosis in AF patients meets all three criteria<sup>75</sup> and is specifically reflected as atrial enlargement, decreased myocardial contractility, endothelial dysfunction, fibrosis, and the release of pro-thrombotic factors such as IL-6 and von Willebrand factor.<sup>76</sup> According to this description, the pro-thrombotic conditions of AF are the result of atrial remodelling rather than just a rhythm disturbance alone. Therefore, ACM may be the real cause of atrial thrombosis.

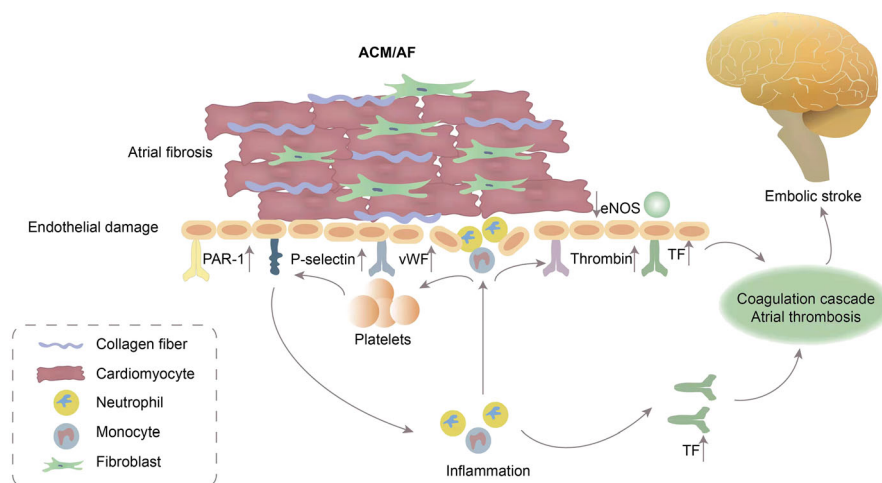
Inflammation is one of the important mechanisms of atrial remodelling. It may also play a key role in atrial thrombosis. Prospective clinical studies showed that CRP or IL-6 was an independent predictor of stroke in AF patients.<sup>77,78</sup> The infiltration of inflammatory factors and immune cells induces endothelial injury and dysfunction, decreasing the expression of endothelial nitric oxide synthase, but increasing the amount of von Willebrand factor, thrombin, tissue factor, and protease-activated receptor 1 in the atrial endocardium.<sup>44</sup> The von Willebrand factor interacts with GPIIb/IIIa proteins to mediate the adhesion and aggregation of platelets in the endocardium. This platelet aggregation-induced P-selectin expression may then recruit additional neutrophils and monocytes to the endocardial surface. Inflammatory cells and damaged endothelial cells express tissue

factors, initiating the coagulation cascade and promoting atrial thrombosis (Figure 3).<sup>79</sup>

### Atrial cardiomyopathy and antithrombotic therapy

The selection of antithrombotic drugs is crucial for stroke prevention.<sup>80</sup> At present, guidelines recommend that patients with ESUS should receive antiplatelet drugs for secondary prevention of stroke.<sup>81</sup> The multicentre, randomized, double-blind clinical studies, NAVIGATE ESUS and the RE-SPECT ESUS, concluded that rivaroxaban or dabigatran was not better than aspirin in the prevention of stroke recurrence after ESUS, and the incidence of bleeding events caused by these two anticoagulants was higher than aspirin. The failure to classify potential embolic sources, or the overlap of embolic sources, may be one of the reasons for these results.<sup>82,83</sup> Based on the secondary analysis of NAVIGATE ESUS, rivaroxaban showed significant benefits in preventing ischaemic stroke over aspirin for 361 ESUS patients with an LA diameter > 4.6 cm (HR: 0.26, 95% CI: 0.07–0.94).<sup>84</sup> The WARSS trial revealed that the incidence of recurrent ischaemic stroke or death within 2 years in the warfarin group was significantly lower than that in the aspirin group for patients with NT-proBNP > 750 pg/mL but without known AF.<sup>85</sup> The ongoing ARCADIA will further investigate whether apixaban is better than aspirin in the prevention of stroke recurrence to patients with cryptogenic ischaemic stroke and ACM.<sup>15</sup> If the primary hypothesis of this trial is successfully verified, it will be of great clinical significance for the transformation of antithrombotic therapy for patients with cryptogenic ischaemic stroke and ACM. Studies evaluating the relationship between ACM and thromboembolism will help

**Figure 3** The relationship between inflammation and atrial thrombosis in patients with ACM or AF. ACM, atrial cardiomyopathy; AF, atrial fibrillation; eNOS, endothelial nitric oxide synthase; PAR-1, protease-activated receptor 1; TF, tissue factor; vWF, von Willebrand factor.





promote a conceptual reorientation that LA thrombosis is related to not only blood stasis during AF but also LA abnormalities of different aetiologies. This conceptual transformation will enable more accurate and individualized strategies for stroke prevention. In addition, it will help to develop new therapeutic targets for stroke prevention that can complement anticoagulant therapy, such as the improvement of endothelial function, interventions to halt or delay atrial fibrosis, enhancement of atrial contractility, and the comprehensive management of many risk factors of ACM.<sup>15</sup> Moreover, as ablation is the first-line treatment for AF, it has been reported that AF recurrence after ablation is associated with pre-existing atrial fibrosis. Therefore, it is worth studying whether the identification of ACM could better differentiate which patients can benefit most from AF ablation.<sup>86</sup>

## Diagnosis of atrial cardiomyopathy

### Imaging technique

Echocardiography is the first choice for screening and tracking atrial morphological or functional abnormalities due to its low cost and ease of use. Because of the three-dimensional structural characteristics of the atria and the heterogeneity of atrial remodelling, measurement of atrial volume is more accurate for evaluating the true atrial state. Compared with two-dimensional echocardiography that underestimates LA volume, the accuracy of three-dimensional echocardiography in evaluating LA volume is close to cardiac computed tomography (CCT) or cardiac magnetic resonance imaging (CMR).<sup>14</sup> Traditionally, maximal LA volume is used to evaluate LA size. Nevertheless, emerging data support the important role of minimal LA volume in assessing atrial disease.<sup>87,88</sup> Two-dimensional speckle-tracking echocardiography is a very sensitive technology to identify functional abnormalities before anatomical changes develop in the atria.<sup>89</sup> The Copenhagen City Heart Study including 1641 healthy subjects recently revealed the normal reference range for peak atrial longitudinal strain of 39.4% (23.0–67.6%), peak atrial contraction strain of 15.5% (6.4–28.0%), and LA strain during the conduit phase of 23.7% (8.8–44.8%).<sup>90</sup> Decreased peak atrial longitudinal strain is an excellent marker for assessing the fibrosis of LA.<sup>91</sup> LA strain parameters can also predict incident AF and ischaemic stroke.<sup>92</sup>

Multidetector CCT with great spatial resolution has advantages in evaluating LA volume and wall thickness, the anatomy of pulmonary veins, and the location and morphology of LA appendage.<sup>93</sup> CCT with a delayed imaging is a reliable tool with a 0.98 sensitivity and a 1.00 specificity in detecting LA appendage thrombus compared with transesophageal echocardiography.<sup>94</sup> CCT is also the preferred method for

identifying and quantifying EAT that is involved in the process of atrial remodelling.<sup>93</sup>

Cardiac magnetic resonance imaging is considered the gold standard for assessing cardiac structural and functional states. Contrast-enhanced CMR with gadolinium shows good performance in evaluating atrial fibrosis.<sup>95</sup> A study assessing the local image intensity ratio (IIR) of the LA by late-gadolinium-enhanced CMR (LGE-CMR) in 10 healthy young persons and 30 patients with AF concluded that IIR was  $\leq 1.20$  in healthy young individuals and  $> 1.32$  in dense scar with IIR values ranging between 1.2 and 1.32 for interstitial fibrosis.<sup>96</sup> Atrial fibrosis identified by LGE-CMR may help to select patients suitable for AF ablation and predict the evolution of sinoatrial node dysfunction, progression of AF, and stroke risk for AF patients.<sup>14,91</sup> However, Althoff *et al.*<sup>97</sup> found that the ability of LGE-CMR to detect ablation-induced fibrosis decreased over time. Thus, it is recommended to perform LGE-MRI at 3 months post-ablation. A multicentre study demonstrated that patients with ESUS had comparable atrial fibrosis detected by LGE-CMR with AF patients, and atrial fibrosis  $\geq 12\%$  in ESUS patients was related to a higher incidence of recurrent stroke, incident AF, or both (25.0% vs. 4.8%,  $P = 0.039$ ).<sup>98</sup> The result hinted that atrial fibrosis in ESUS patients may be a good indicator of anticoagulation therapy for secondary prevention. Some studies revealed that increased LA volume or deteriorated LA function measured by CMR could also increase the risk of AF and ischaemic stroke.<sup>10,99,100</sup> The application of CMR in ablation procedures has received attention in recent years. Quinto *et al.*<sup>101</sup> found that localizing veno-atrial gaps using delayed enhancement CMR in repeat pulmonary vein isolation (PVI) procedures could shorten the duration of ablation ( $161 \pm 52$  vs.  $195 \pm 72$  min) and decreased the rate of recurrent AF, atrial tachycardia, or flutter (30% vs. 61%) compared with the conventional group during a 2 year follow-up. Recently, the ALICIA trial showed that CMR-guided fibrosis ablation plus PVI did not improve the primary outcome nor did it reduce the risk of adverse events compared with PVI alone. This result may be partly attributed to the fact that the atrial fibrosis burden of participants was relatively mild (mean: 12%; only ~50% of patients had small-size fibrosis areas outside the pulmonary veins).<sup>102</sup> Whether CMR-guided fibrosis ablation could improve the outcomes in patients with advanced atrial remodelling and persistent AF is under study (unique identifier: NCT02529319). Advanced four-dimensional flow CMR can directly display and quantify the blood stasis of the LA and LA appendage with full volumetric coverage.<sup>95</sup> Unfortunately, although CMR has developed rapidly, it has not been widely used in clinical evaluation of atrial structure and function due to its high price and technical challenges, especially in developing regions. Thin atrial wall (2–4 mm), arrhythmias, and irregular breathing patterns are major challenges of atrial imaging using CMR.<sup>103</sup>

Electroanatomic mapping system is an invasive method to assess ACM, which can be used for anatomical replication of atria and assessing atrial substrate.<sup>14</sup> It has been regarded as the gold standard in determining atrial abnormality. Low-voltage areas detected by electroanatomic mapping systems are a powerful predictor of atrial remodelling and poor prognosis post-ablation.<sup>104,105</sup> But as an invasive procedure, electroanatomic mapping cannot be used for preprocedural and prognostic evaluation. A recent study revealed that there existed large discrepancies in identifying both extent and regional distribution of ACM between the most common LGE-CMR methods and endocardial mapping. Thus, optimizing the ACM-detection methods of LGE-CMR is required.<sup>105</sup>

## Electrocardiogram

Various ECG markers have been associated with ACM, such as P-wave dispersion, PTFV1, and the burden of premature atrial contractions.<sup>106,107</sup> Among these markers, PTFV1 is one of the most frequently used indices for the diagnosis of ACM. Specifically, PTFV1 is defined as the negative area of the P-wave in lead V1 of the 12-lead ECG and it is calculated by the product of duration and amplitude.<sup>108</sup> These P-wave parameters have been shown to predict not only new-onset AF but also stroke independently of AF.<sup>109–111</sup>

A study conducted among 91 AF-free patients with structural heart disease showed that PTFV1 was related to increased LA volumes, decreased LA emptying fraction, and decreased LA reservoir function.<sup>112</sup> In contrast, there was no correlation between PTFV1 and LA size in 504 healthy athletes.<sup>113</sup> A recent study concluded that abnormal PTFV1 ( $\geq 4000$  ms $\cdot\mu$ V) can predict functional and electrical but not structural remodelling of the LA.<sup>108</sup> Surprisingly, this study also observed that the area of atrial fibrosis for patients with an abnormal PTFV1 was smaller than that for patients with normal PTFV1 ( $12.32 \pm 1.63\%$  vs.  $20.50 \pm 2.09\%$ ). In addition, a negative correlation between the degree of atrial fibrosis and the value of PTFV1 was observed. One possible explanation for this result is that only key cardiomyocytes, but not fibrotic tissue, have normal electroactivity. A decrease of cardiomyocytes with an accompanying progressive fibrosis will reduce P-wave terminal amplitude. But a degree of atrial fibrosis may not be enough to prolong P-wave terminal duration due to the high atrial conduction reserve.<sup>108</sup> However, the relationship between PTFV1 and atrial structural remodelling requires further study.

Non-invasive body surface electrocardiographic imaging (ECGI) is an emerging diagnostic tool for ACM.<sup>114</sup> In a study exploring the value of ECGI relative to high-density LA voltage and biatrial activation maps in diagnosing ACM before PVI ablation for AF, a total atrial conduction time (TACT)  $\geq 148$  ms in ECGI is an effective index for the diagnosis of ACM with  $>90\%$  sensitivity and specificity.<sup>114</sup> Nevertheless, the high

cost and limited clinical application make ECGI not widely used. In addition, sinus rhythm is essential in TACT measurement, so ECGI is not applicable to patients with persistent AF. Reducing electrode numbers, developing automatic analysis system, and investigating alternative imaging modalities of CT to reduce radiation damage would save cost and increase the usage of ECGI.<sup>114</sup>

## Serum biomarkers

A variety of serum biomarkers have been associated with atrial abnormalities. For example, brain natriuretic peptide (BNP) and NT-proBNP are primarily secreted in response to myocyte stretch arising from volume or pressure overload.<sup>115</sup> Elevated NT-proBNP is a predictor of LA fibrosis and has been used as one of the diagnostic criteria of ACM in some studies.<sup>15–17,116</sup> However, a recent study defining ACM as LA enlargement (diameter  $\geq 47$  mm) or NT-proBNP  $> 250$  pg/mL indicated a significant difference in the proportion of severe LA enlargement (5.3% vs. 1.4%) rather than elevated NT-proBNP (32.7% vs. 32.3%) between ESUS patients and non-cardioembolic patients,<sup>16</sup> which may be attributed to the fact that NT-proBNP was elevated in the acute stage of ischaemic stroke and thus cannot truly represent ACM.<sup>117</sup> The atrial natriuretic peptide (ANP) is secreted predominantly by the atria, which could more accurately identify ACM than BNP and NT-proBNP in theory. Mid-regional pro-atrial natriuretic peptide (MR-proANP) shows greater stability than ANP, making it widely used in clinical practice. A study including 346 patients without HF showed that both MR-proANP and NT-proBNP were both positively correlated with LA volume.<sup>118</sup> Similarly, MR-proANP was found to be a more powerful marker than NT-proBNP for atrial volume overload and LA volume index in patients with HFpEF.<sup>119</sup> In addition, amyloid deposition in the atria is a special type of pathological change of ACM. ANP, the precursor molecule of ANP, BNP, and NT-proBNP are all the main components of amyloid.<sup>120–122</sup> However, it is noteworthy to remember that the secretion of natriuretic peptides is affected by many factors besides ACM, such as body mass index and acute stage of ischaemic stroke.<sup>117,123</sup> Therefore, whether natriuretic peptides are reliable markers of ACM need individualized analysis and dynamic observation.

A disintegrin and metalloproteinases (ADAMs) are a kind of membrane-bound glycoproteins with the function of proteolysis, signal transduction, adhesion, and fusion. They play an important role in maintaining normal cardiac structure and myocardial tissue by regulating cell–cell and cell–matrix interactions.<sup>124</sup> Arndt *et al.*<sup>124</sup> found that the expression of ADAM10 and ADAM15 was significantly increased in the atrial tissue of AF patients. Importantly, the ADAM15/integrin  $\beta 1$  ratio was significantly associated with the LA diameter. Animal studies indicated that ADAM12 and ADAM19 may also

be related to myocardial hypertrophy or cardiac morphogenesis.<sup>125,126</sup> A study from Patel *et al.* showed that ADAM17 mediated the cleavage and shedding of myocardial ACE2 induced by Ang II, which established a positive feedback of RAAS.<sup>127</sup> Animal experiments revealed that ADAM17 could promote cardiac hypertrophy and fibrosis.<sup>128</sup> However, recent clinical research indicated that post-operative AF patients had lower plasma levels of ADAM17 compared with patients free from AF, suggesting a possible beneficial effect of ADAM17 against post-operative AF occurrence.<sup>129</sup> This seemingly contradictory result may be partly caused by other clinical factors. Whether the role of ADAM17 in atrial remodelling is protective or harmful should be further clarified.

Vascular cell adhesion molecule 1 (VCAM-1), a cell surface protein, belongs to immunoglobulin superfamily. It plays an important role in the adhesion and trafficking of leukocytes.<sup>130</sup> Normal endocardial surfaces express low levels of VCAM-1. Atrial VCAM-1 expression has been observed to increase during rapid atrial pacing both *in vivo* and *in vitro* models.<sup>131</sup> Local up-regulated VCAM-1 contributes to the leukocytes infiltration and inflammation that gives rise to subsequent atrial remodelling. A cohort study with a 20 year follow-up was conducted in 909 participants and revealed the association between the levels of 13 inflammation markers and incident AF, showing that only the level of soluble VCAM-1, rather than other 12 inflammation markers (including monocyte chemoattractant protein-1, P-selectin, and high-sensitivity CRP), was correlated with new-onset AF.<sup>132</sup> A recent study from Contreras-Briceño *et al.*<sup>133</sup> demonstrated that circulating VCAM-1 has direct correlation with

LA remodelling in male long-distance runners. In addition, the up-regulation of soluble VCAM-1 was reported to be linked with AF-associated cardiovascular events, which may be partly attributed to the 'endocardial remodelling' caused by VCAM-1.<sup>130,132,134</sup> The circulating levels of some molecules related to fibrosis (e.g. collagen I and III synthesis and turnover products, and galectin-3) can also reflect the ACM and predict the occurrence and maintenance of AF.<sup>35,135</sup> However, other interference factors should be comprehensively considered when serum biomarkers are used to identify ACM.

## Genetic testing

Atrial cardiomyopathy can be caused by variants of genes that are important to maintain the normal atrial structure, function, and metabolism. The natriuretic peptide precursor A (*NPPA*) gene encodes for ANP and it is essential to prevent atrial remodelling. Investigators conducting a 37 year follow-up of 13 patients with atrial dilation and standstill from 6 families found that all affected patients were characterized by onset in adulthood, severe biatrial enlargement, atrial standstill, thromboembolic events, decreased ANP, and normal left ventricular function. Further genetic analysis revealed that all eight living affected patients from the aforementioned six families carried a homozygous mutation of the *NPPA* gene (p.Arg150Gln).<sup>136</sup> The myosin light-chain 4 (*MYL4*) gene encoding for myosin light chain is atrial specific and its expression is almost disappeared in the ventricles by

**Table 1** Genetic variations of atrial cardiomyopathy

Gene	Encoded protein	Mutation	Phenotype
<i>NPPA</i> <sup>136</sup>	ANP	c.G449A (p.Arg150Gln)	Severe biatrial enlargement, atrial standstill, thromboembolic events, decreased ANP, and normal left ventricular function
<i>MYL4</i> <sup>137</sup>	Myosin light chain	c.234delC	Early-onset AF or other types of arrhythmias, impaired left atrial function, ischaemic stroke, or sudden death
<i>LMNA</i> <sup>139</sup>	Lamin A/C	c.1003C > T (p.R335W)	Familial heart-hand syndrome characterized by prominent atrial lesions and brachydactyly
<i>SCN5A</i> <sup>140</sup>	The alpha subunits of cardiac voltage-gated sodium channel (Nav1.5)	Multiple	Brugada syndrome with atrial conduction abnormalities, atrial fibrosis, or atrial standstill
<i>SYNPO2L</i> <sup>141</sup>	Cytoskeletal heart-enriched actin-associated protein	rs766868752	Cardiac fibrosis, atrial cardiomyopathy, and AF
<i>PITX2</i> <sup>142</sup>	The homeobox transcription factor Pitx2	Multiple	Congenital heart diseases and AF
<i>SIX5</i> <sup>88</sup>	Sine oculis homeobox homologue 5 protein	Expansion of CTG repeats	It is related to myotonic dystrophy type 1 with atrial conduction abnormalities
<i>DMPK</i> <sup>143</sup>	Dystrophin myotonia protein kinase	Expansion of CTG repeats	Myotonic dystrophy type 1 with atrial conduction abnormalities
<i>MYO18B</i> <sup>145</sup>	Myosin 18B	Multiple	Compromised sarcomere assembly and atrial enlargement
<i>CILP</i> <sup>146</sup>	Cartilage intermediate layer protein 1	Multiple	Cardiac fibrosis
<i>TTN</i> <sup>147</sup>	A giant sarcomere protein (titin)	Multiple	Dilated or hypertrophic cardiomyopathy, and early-onset AF
<i>CASQ2</i> <sup>148</sup>	Calsequestrin-2	Multiple	AF and catecholaminergic polymorphic ventricular tachycardia

AF, atrial fibrillation; ANP, atrial natriuretic peptide.

birth in normal hearts. The expression of *MYL4* is necessary for the normal contractile characteristics of cardiomyocytes.<sup>137</sup> Patients with the *MYL4* gene mutation presented with early-onset AF or other types of arrhythmias, impaired LA function, ischaemic stroke, or sudden death.<sup>115,137</sup> Mutations in Lamin A/C gene (*LMNA*) are associated with a series of cardiac phenotypes including dilated cardiomyopathy, arrhythmia, and conduction disorders. Cardiomyopathy caused by *LMNA* mutations is characterized by ventricular dilation or non-compaction according to previous literatures.<sup>138</sup> However, a recent study revealed the *LMNA* p.R335W mutation in a heart-hand syndrome pedigree manifesting as atrial abnormality and brachydactyly. Then researchers confirmed the pathogenicity of *LMNA* p.R335W mutation in the atrial lesions.<sup>139</sup> In addition, genetic changes in other diseases, such as Brugada syndrome caused by *SCN5A* gene mutations,<sup>140</sup> hereditary AF syndromes resulting from *PITX2* gene or *SYNPO2L* gene mutations, and hereditary muscular dystrophies caused by *DMPK* gene mutations, can also induce abnormalities of atrial structure or function.<sup>76,141–143</sup> Ahlberg *et al.* used the UK Biobank to conduct genome-wide association study on LA volume and function derived from CMR. They identified 18 novel loci and provided evidence for seven plausible casual mutants related to LA function in the genes including *DSP*, *SIX5*, *MYO18B*, *CILP*, *TTN*, and *CASQ2*, and these genes are associated with cardiomyopathy or muscular dystrophy or AF (Table 1).<sup>88,143–148</sup> In a recent study of whole genome sequencing in 1293 patients with AF, the overall positive rate of disease-related gene mutation was 10.1%, and the positive proportion was highest (16.8%) in patients diagnosed as AF before 30 years of age, while lowest (7.1%) after 60 years of age. In addition, this study also suggested that the genetic overlap rate between AF and hereditary cardiomyopathy syndromes was higher than that between AF and other hereditary arrhythmia syndromes.<sup>149</sup> However, the positive rate of gene variation in patients with ACM has not been identified. Generally, genetic testing is necessary for patients with early-onset or familial atrial abnormalities, usually <60 years of age, which may be vital for the treatment and risk factor management of ACM.

## Conclusions and directions

Atrial cardiomyopathy is the common pathway of atrial structural and electrical remodelling caused by various factors. The pathogenesis of ACM is complex, including classic neuro-hormonal and inflammatory mechanisms. The role of EAT in atrial remodelling has also been important in recent years. Although many potential targets for controlling atrial remodel-

ling have been found, there is still a lack of effective strategies for intervening in the pathogenesis of ACM. The complexity of the mechanism determines that the intervention measures of atrial remodelling should be comprehensive. Future studies should explore the effect of intervening simultaneously on multiple pathways thereby targeting atrial remodelling.

Atrial cardiomyopathy is associated with embolic stroke independent of AF. ESUS patients are mainly treated with antiplatelet therapy according to established guidelines. The ongoing ARCADIA trial aims to explore whether apixaban is better than aspirin in preventing stroke recurrence of ESUS patients with ACM. The results of this trial will guide the secondary and even primary prevention strategies of stroke in the future.

Despite the rapid progression of various ACM diagnostic means, including imaging technology, ECG, serum, and genetic markers, there are no clear diagnostic criteria of ACM, which may limit the interpretability of ongoing and future studies. The diagnostic value of serum biomarkers in ACM, such as NT-proBNP, needs individualized analysis and dynamic observation. What is more, previous work regarding the relationship between ACM and the occurrence of embolic stroke is mainly confined to cross-sectional studies, which cannot prove whether there is a causal relationship between them. Hopefully, more prospective studies could further clarify this relationship, which will help to expand the strategies for the secondary and even primary prevention of embolic strokes, such as anti-inflammatory therapy, anti-oxidative stress therapy, or anti-fibrosis therapy.

## Conflict of interest

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