Heart failure with preserved ejection fraction: An alternative paradigm to explain the clinical implications of atrial fibrillation

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Atrial fibrillation (AF) is associated with exercise intolerance, stroke, and all-cause mortality. However, whether this can be solely attributable to the arrhythmia itself or alternative mechanisms remains controversial. Heart failure with preserved ejection (HFpEF) commonly coexists with AF and may contribute to the poor outcomes associated with AF. Indeed, several invasive hemodynamic studies have confirmed that patients with AF are at increased risk of underlying HFpEF and that the presence of HFpEF may have important prognostic implications in these patients.

Mechanistically, AF and HFpEF are closely linked. Both conditions are driven by the presence of common cardiovascular risk factors and are associated with left atrial (LA) myopathy, characterized by mechanical and electrical dysfunction. Progressive worsening of this left atrial (LA) myopathy is associated with both increased AF burden and worsening HFpEF. In addition, there is growing evidence to suggest that worsening LA myopathy is associated with poorer outcomes in both conditions and that reversal of the LA myopathy could improve outcomes. In this review article, we will present the epidemiologic and mechanistic evidence underlying the common coexistence of AF and HFpEF, discuss the importance of a progressive LA myopathy in the pathogenesis of both conditions, and review the evidence from important invasive hemodynamic studies. Finally, we will review the prognostic implications of HFpEF in patients with AF and discuss the relative merits of AF burden reduction vs HFpEF reduction in improving outcomes of patients with AF and HFpEF.

KEYWORDS Atrial fibrillation; Atrial myopathy; Cardiovascular risk factors; Heart failure with preserved ejection fraction; Left atrial hemodynamics

(Introduction)

Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) are 2 highly prevalent chronic cardiovascular conditions that commonly coexist (AF-HFpEF). AF is the most common cardiac arrhythmia, while HFpEF is a myocardial functional disorder associated with abnormal intracardiac hemodynamics. Mechanistically, however, both conditions are associated with a progressive left atrial (LA) myopathy driven by the presence of common cardiovascular risk factors. Historically, HFpEF has been difficult to diagnose in patients with AF, but several recently published invasive hemodynamic studies of patients with AF have demonstrated a high prevalence of occult HFpEF. HFpEF commonly afflicts patients with AF, raising important questions that challenge current thinking; are the clinical implications associated with AF due to the rhythm disturbance of AF or underlying HFpEF? Do evidence-based AF treatments work through reduction of AF burden or treatment of underlying HFpEF?

In this article we will review the epidemiologic evidence for the close association between AF and HFpEF as well as describe the mechanisms that drive the development of both HFpEF and AF, focusing on the importance of underlying cardiovascular risk factors. Specifically, we will highlight the role of LA myopathy in both conditions and discuss the contribution of invasive hemodynamic studies that have progressed our understanding of the symbiotic relationship between AF and HFpEF. We will then discuss the growing controversy regarding the relative contributions of cardiac rhythm disturbance and HFpEF in predicting the poor outcomes associated with AF. Finally, we will review established treatment strategies for AF, discussing their mechanisms of efficacy in the context of cardiac rhythm control vs HFpEF reduction and discuss how further development of our understanding of HFpEF in AF may allow for improved treatments and outcomes.

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**KEY FINDINGS**

- Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) commonly coexist. Large-scale epidemiological studies estimate a high prevalence of AF in patients with HFpEF and vice versa. Invasive hemodynamic studies suggest the coexistence of AF and HFpEF may be even more common than epidemiological studies suggest and is likely underappreciated in clinical practice.

- AF and HFpEF are both underpinned by several common cardiovascular risk factors, including obesity, hypertension, diabetes, obstructive sleep apnea, alcohol consumption, and smoking. The mechanisms by which these risk factors lead to AF and HFpEF include systemic inflammation, hemodynamic alterations, coronary microvascular dysfunction, and atrial fibrosis.

- AF and HFpEF are both associated with a progressive and comprehensive left atrial (LA) myopathy, encompassing structural, mechanical, and electrical dysfunction.

- Progressive worsening of the LA myopathy is associated with poorer outcomes in AF and HFpEF, including increased risk of all-cause mortality and systemic thromboembolism.

- Several evidence-based treatments for AF focus on reducing AF burden. However, outcomes may be further improved by reversing LA myopathy and reducing HFpEF. Renewed focus on reversing LA myopathy and reducing HFpEF may provide prognostic benefit in patients with AF.

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**Epidemiology**

**AF and HFpEF**

AF and HFpEF represent growing worldwide epidemics. Current estimates suggest that 37.5 million people (0.51% of the worldwide population) suffer with AF globally, with ever-rising prevalence and incidence. An even larger proportion of people suffer with heart failure, with an estimated 64.3 million people (0.9% of worldwide population) affected. HFpEF is thought to account for at least half of these cases, meaning the overall prevalence of HFpEF is likely to be very similar to that of AF. Future projections suggest that the global burden of both AF and HFpEF will continue to rise in the coming years, with significant implications for healthcare such as an exponential rise in hospitalizations and healthcare costs.

**AF-HFpEF**

In addition to being highly prevalent conditions, epidemiologic studies also show that AF and HFpEF frequently coexist. Figure 1 shows the epidemiologic relationship between both conditions. In large heart failure registries recruiting both inpatients and outpatients, the overall prevalence of AF is estimated to be around 51%. Similarly, in AF cohorts, the average prevalence of HFpEF is around 21%. Both values are likely to represent underestimates; the diagnosis of AF in patients with HFpEF is often limited by its paroxysmal nature and the absence of continuous rhythm monitoring, while the diagnosis of HFpEF in patients with AF is challenged by the overlapping symptomatology and clinical presentation. As a result, the nature of the close relationship between the 2 conditions may be significantly underappreciated epidemiologically.

Community cohort studies examining the temporal relationship between AF and HFpEF provide unique insight into the bidirectional relationship between the 2 conditions. The Framingham Heart Study, which followed individuals with new-onset AF or heart failure for up to 7.5 years, showed that patients with AF had more than double the risk of developing HFpEF compared to those without AF. Similarly, patients with HFpEF were more than 3 times more likely to develop AF. The PREVEND study, which invited the entire population of the city of Groningen, the Netherlands, to participate showed that AF increased the risk of HFpEF development by almost 7 times compared to those without AF over the course of a longer follow-up period (almost 10 years). These studies highlight the symbiotic nature of the relationship between AF and HFpEF and the impact that each condition has on the development of the other.

**Risk factors**

Epidemiologic studies have also been important in highlighting the common risk factors underlying both conditions (Table 1). Age, hypertension, body mass index, diabetes, and obstructive sleep apnea have all been identified as frequent comorbidities associated with both conditions. Furthermore, the coexistence of AF and HFpEF also appears to be underpinned by the presence of the same risk factors.

**Mechanisms**

The shared risk factors described above lead to the development of both AF and HFpEF via a variety of mechanisms, all of which appear to be inextricably linked (Figure 2). Systemic inflammation, hemodynamic alterations, microvascular dysfunction, epicardial adiposity, and myocardial fibrosis are all important consequences of cardiovascular risk factors and play key roles in the development of the atrial and ventricular myopathies underlying both AF and HFpEF. However, these mechanisms are not independent of each other but rather represent a complex network of interacting processes. In addition to these mechanisms, development of AF and HFpEF potentiate the development and progression of each other, resulting in the creation of a vicious cycle that, left untreated, results in the rapid, unabated progression of both AF and HFpEF. The final common pathway of all these mechanisms appears to be the development and
progression of LA disease, which is increasingly recognized as the most important linking factor between AF and HFpEF.

Systemic inflammation

Systemic inflammation plays a central role in the pathophysiology of both AF and HFpEF. The risk factors associated with AF and HFpEF are associated with high circulating levels of proinflammatory mediators. For example, the activation of the renin-angiotensin-aldosterone system (RAAS) in hypertension has been shown to mediate the production of a vast number of proinflammatory cytokines and activation of immune cells. Similarly, diabetes, obesity, the metabolic syndrome, renal disease, and smoking have all been shown to drive systemic inflammation.

The importance of systemic inflammation in both AF and HFpEF is highlighted by longitudinal observational studies in which systemic inflammatory mediators at baseline were used to predict the onset of the 2 conditions. In large population-based cohorts, elevated plasma levels of proinflammatory TNFα, E-selectin, ICAM-1, and VCAM were all found to be associated with increased risk of incident HFpEF during long-term follow-up. Similarly, elevated levels of numerous inflammatory biomarkers, including TNFα, CRP, and IL-6, as well as increased white blood cell count, have been shown to be associated with increased risk of incident AF. In addition, they were shown to be associated with increased AF recurrence after ablation or electrical cardioversion. Furthermore, patients with systemic inflammatory disorders such as rheumatoid arthritis and systemic sclerosis have been shown to be at significantly increased risk of both incident AF and HFpEF. These studies highlight the significance of systemic inflammatory processes in patients with AF and HFpEF.

The mechanisms by which systemic inflammation leads to AF and HFpEF remain incompletely understood. However, cardiac fibrosis, coronary microvascular dysfunction (CMD), cardiomyocyte hypertrophy, decreased cardiomyocyte distensibility owing to titin alterations, and increased myocardial accumulation of degraded proteins have all been implicated. Interestingly, statins have been shown to reduce the incidence of AF in patients with HFpEF, possibly via anti-inflammatory effects.

While strong data...
regarding anti-inflammatory agents for the treatment of AF or HFP EF remain lacking, there is some evidence to suggest that steroids may reduce postablation and postsurgical AF32,33 and studies investigating the use of anti-inflammatory agents in HFP EF are underway.21

Hemodynamic alterations
Several cardiovascular risk factors are associated with significant intracardiac hemodynamic changes that promote the development of both AF and HFP EF. Chronic hypertension is associated with increased afterload and left ventricular (LV) hypertrophy, impaired LV filling, and the raised LV diastolic pressures diagnostic of HFP EF.34,35 Moreover, these mechanisms further lead to increased LA stretch, dilatation, and increased risk of AF.36 In spontaneously hypertensive rats, similar LV and LA structural changes were identified and these were associated with lower atrial effective refractory period, increased atrial interstitial fibrosis, and increased inducibility of AF.37 In addition to the direct effects of pressure changes on cardiac structure, these hemodynamic alterations are also associated with neurohormonal activation of the RAAS, which has been shown in animal models to cause atrial and ventricular myocardial remodeling.23

Similarly, obesity is also associated with significant hemodynamic alterations leading to AF and HFP EF.38 Chronically obese sheep exhibited raised LA pressures and significantly reduced filling pressures compared to nonobese patients with AF.38 These studies highlight the important influence of obesity on LA hemodynamics and the development in AF. Obesity is also closely associated with diastolic function and HFP EF; obesity has been shown to be associated with concentric LV remodeling, reduced LV diastolic function, and raised LV end-diastolic pressures.40–42 Furthermore, recent data suggest that hemodynamic effects of obesity represent a specific phenotype of HFP EF patients within the heterogeneous HFP EF clinical syndrome.43 Patients with obesity-related HFP EF exhibited markedly different hemodynamics compared with nonobese HFP EF, including greater plasma volume expansion, worse right ventricular dysfunction, higher intracardiac pressures at rest and during exercise, and increased exertion-induced pericardial restraint.43 These findings highlight the marked effects of obesity on intracardiac hemodynamics, which contribute to the development of both AF and HFP EF.

Coronary microvascular dysfunction
Myocardial ischemia in the absence of macrovascular epicardial coronary artery disease is defined as CMD.44 CMD has been shown to be highly prevalent in patients with both HFP EF and AF and has been shown to be associated with systemic and local inflammatory processes resulting from the presence of cardiovascular risk factors.45 CMD causes abnormalities in LV systolic function despite the presence of normal ejection fraction. These abnormalities in systolic function are subtle and include reduced LV longitudinal strain, midwall fractional shortening, and mitral annular
systolic excursion.\textsuperscript{48} In addition, CMD likely accounts for the exercise-induced myocardial ischemia and subendocardial systolic dysfunction often seen with HFpEF.\textsuperscript{49} These subtle deficits result in the impaired systolic reserve characteristic of patients with HFpEF and AF.

CMD has been shown to be closely associated with elevated LV filling pressures at rest and during exercise and reduced cardiorespiratory fitness.\textsuperscript{50} The most extensive clinical investigation of CMD in HFpEF, showed that up to 75\% of patients with HFpEF had underlying CMD.\textsuperscript{51} Of note, 58\% of these patients had coexisting AF while the prevalence of AF in those without CMD was only 25\%. Furthermore, atrial microvascular dysfunction has been identified in patients with AF but without HFpEF.\textsuperscript{52} These findings suggest that CMD may play a significant role in the pathogenesis of both AF and HFpEF and could also be potential targets for treatment.

Of note, occult but clinically significant macrovascular coronary artery disease has been identified in half of patients with confirmed HFpEF undergoing coronary angiography, further emphasizing the relevance of myocardial ischemia in the pathogenesis of HFpEF. These patients with obstructive coronary artery disease had higher rates of adverse clinical outcomes, suggesting a possible role for revascularization in selected HFpEF patients.\textsuperscript{53}

**Epicardial adiposity**

Adipose tissue has important proinflammatory, neurohormonal, and hemodynamic effects on the cardiovascular system, all of which increase the risk of both AF and HFpEF (as discussed in previous sections). However, deposition of adipose tissue around the heart (epicardial adipose tissue [EAT]) is particularly relevant to both. When compared with overall body mass index, EAT confers a 2-fold increased risk of AF,\textsuperscript{54} while patients with HFpEF have almost 40\% more epicardial fat compared to non-HFpEF patients with matched body mass index.\textsuperscript{55}

EAT has several characteristics that render it detrimental to cardiac structure and function and increasing the risk of both AF and HFpEF. Anatomically, there is no fascial plane separating the adipose tissue from the myocardium, meaning adipocytes can communicate directly with cardiac myocytes. As a result, EAT can directly infiltrate the myocardium, causing reduced voltages and conduction heterogeneity and thereby creating the electrophysiological milieu for the development of AF.\textsuperscript{56,57} Additionally, EAT and the myocardium share the same microcirculation, leaving the myocardium vulnerable to paracrine effects from the adipose tissue. EAT is a particularly active secretory tissue (more than visceral adipose tissue), expressing high levels of proinflammatory cytokines and atherogenic molecules, which lead to local inflammation, tissue fibrosis, and cardiomyocyte dysfunction.\textsuperscript{58,59} Finally, the presence of EAT can directly affect cardiac mechanics, its encasing of the myocardium causing pericardial restraint and increased left-sided pressures at rest and during exercise.\textsuperscript{60}

**Fibrosis**

Cardiac fibrosis is the histologic hallmark of the structural remodeling associated with both AF and HFpEF and is closely linked with the presence of cardiovascular risk factors. Fibrotic change is driven by neurohormonal and inflammatory mediators released in response to cardiovascular risk factors.\textsuperscript{61} Animal models of hypertension, diabetes, obesity, and sleep apnea have all demonstrated increased levels of atrial fibrosis on histology.\textsuperscript{62} Furthermore, clinical electroanatomical mapping studies show increased low-voltage areas and complex fractionated atrial electrograms associated with chronic hypertension,\textsuperscript{63} obesity,\textsuperscript{64} and obstructive sleep apnea,\textsuperscript{65} suggestive of increased atrial fibrosis. These changes in the cardiac architecture lead to anistropic conduction, facilitating the stabilization of electrical reentry and the development of AF.\textsuperscript{66}

Patients with AF exhibit both atrial and ventricular myocardial fibrosis, suggesting a ubiquitous rather than localized phenomenon, possibly in response to systemic disease. HFpEF is also characterized by global myocardial fibrosis. An autopsy study comparing ventricular histology between HFpEF patients and age-matched controls demonstrated significantly increased ventricular fibrosis in HFpEF.\textsuperscript{67} Ventricular fibrosis has been linked with LV stiffening,\textsuperscript{68} which is a characteristic feature of the HFpEF syndrome.\textsuperscript{69,70} Moreover, both clinical studies and experimental models of HFpEF have identified significant atrial fibrosis,\textsuperscript{69–71} which likely contributes to the increased LA stiffness seen in patients with HFpEF. Global myocardial fibrosis is therefore a common pathophysiological mechanism in both AF and HFpEF, causing both mechanical and electrical dysfunction and likely contributing to the epidemiologic overlap between the 2 conditions. Fibrosis likely represents the final common pathway of all the pathophysiological mechanisms described above, but noninvasive methods for quantifying fibrotic change within the atria remain rudimentary. Given the association between increasing fibrosis and poorer outcomes, novel methods to quantify atrial fibrosis have the potential to provide new possibilities for the investigation and management of both AF and HFpEF.

**Vicious cycle**

While shared risk factors and common pathophysiological mechanisms contribute significantly to the frequent coexistence of AF and HFpEF, additional and important contributory factors are the direct influences that each condition has on the other.\textsuperscript{72} The 2 conditions interact with each other in a vicious cycle, each potentiating the risk of the other.

The unifying hemodynamic abnormality in HFpEF is raised LV end-diastolic pressure (LVEDP) and this ineluctably increases LA pressures. Increased LA pressures lead to LA stretch, dilatation, and structural remodeling. LA stretch activates stretch-sensitive ion channels and promotes ion channel dysregulation within the LA, altering ionic currents and resulting in reduced LA voltages, slowed conduction, and increased susceptibility to AF.\textsuperscript{73,74} In addition,
HFpEF results in neurohormonal activation of the RAAS owing to renal underperfusion. RAAS activation is associated with fibrotic change within the LA, partly mediated through inflammatory cytokines. Hemodynamic, neurohormonal, and proinflammatory mechanisms therefore all contribute to the development and potentiation of AF in patients with HFpEF.

Similarly, AF can promote the development of HFpEF. The loss of atrial systole associated with AF results in a 20% reduction in cardiac output owing to reduced ventricular filling. This reduced LV filling results in impaired cardiac output at normal diastolic filling pressures, leading to HFpEF. Furthermore, AF has been shown to be associated with increased LV fibrotic change, which is known to cause LV stiffening and therefore elevated LVEDP. Finally, the fast ventricular rate and irregularity associated with AF can result in abnormal hemodynamics, structural remodeling, and neurohormonal activation, all of which can increase the risk of HFpEF in patients with AF.

**Left atrial myopathy**

LA disease is characterized by structural, mechanical, electrical, and thrombogenic dysfunction. While AF is primarily considered an electrical lesion of the left atrium and HFpEF is increasingly associated with mechanical LA dysfunction, these abnormalities likely do not occur in isolation, but rather occur in conjunction with each other. Indeed, AF is associated with LA dilatation, mechanical dysfunction, and increased risk of thrombus formation, highlighting a comprehensive failure of the left atrium. Similarly, HFpEF has been shown to be associated with LA dilatation and increased risk of AF, suggesting a similar comprehensive LA myopathy may occur.

Importantly, the LA myopathy underlying both AF and HFpEF is a progressive condition, and this is reflected in the disease processes of both AF and HFpEF. AF is characterized by the gradual progression from short, intermittent episodes (paroxysmal AF) to longer-lasting episodes (persistent AF) and finally to permanent AF. This clinical progression is associated not only with worsening electrical disease (lower LA voltages, conduction heterogeneity, increasing fractionation) but also with LA dilatation, impaired mechanical function, and increased risk of LA thrombus. Similarly, progressive worsening of LV diastolic dysfunction, which is characteristic of HFpEF, is associated with LA enlargement and reducing LA function, as determined by echocardiographic measures of LA strain. While clear evidence of electrical dysfunction and increased thrombus susceptibility in HFpEF remains lacking, there is still significant evidence to suggest that a progressive and comprehensive LA myopathy is associated with both AF and HFpEF progression.

**Diagnostic challenges**

Despite its clinical importance, the diagnosis of HFpEF in patients with AF remains a complex clinical challenge. Symptoms of AF and HFpEF overlap significantly: in patients with known AF, symptoms such as shortness of breath or exercise intolerance will often be attributed to the AF rather than coexisting HFpEF. Furthermore, routine diagnostic tests normally used for the diagnosis of HFpEF are often affected by the presence of AF, meaning their values are less clinically useful in the context of AF. In the real world, diagnosis of HFpEF relies on noninvasive echocardiographic parameters. However, echocardiographic parameters used for the diagnosis of HFpEF, including mitral valve early inflow velocities, mitral annular tissue Doppler velocities, and LA volumes, are all significantly altered by the presence of AF. Similarly, serum N-terminal pro-B-type natriuretic peptide is significantly elevated in patients with AF compared to those with sinus rhythm. These changes associated with AF make the noninvasive diagnosis of HFpEF in patients with AF particularly challenging. As a result, the gold-standard criterion for diagnosis of HFpEF remains invasive hemodynamic estimation or measurement of LVEDP at rest (>15 mm Hg) and during exercise (>25 mm Hg). However, this testing is largely restricted to specialist, high-volume centers and is therefore unavailable to the majority of the population. Historically, therefore, the coexistence of HFpEF in patients with AF has been difficult to identify.

Recently, 2 novel scoring systems utilizing integrated diagnostic approaches have been developed to assist in the diagnosis of HFpEF. The first scoring system, the HFA-PFef algorithm, was developed as part of an expert-directed consensus guideline for the diagnosis of HFpEF. This scoring system involves pretest probability assessment followed by diagnostic work-up involving resting echocardiography and serum natriuretic peptide assessment. Importantly, this scoring system accounts for alterations caused by AF by incorporating different cut-off levels for B-type natriuretic peptide and LA volume according to the presence or absence of AF. A high score reflects a definitive diagnosis of HFpEF while a low score represents low likelihood of HFpEF. However, an intermediate score necessitates further investigation involving exercise testing with either stress echocardiography or invasive hemodynamic cardiopulmonary exercise testing. Whereas invasive hemodynamic cardiopulmonary exercise testing is a proven diagnostic tool in HFpEF, stress echocardiography currently lacks the convincing evidence to support its use for this purpose.

The second diagnostic algorithm for HFpEF is the H2PEF scoring system derived by Reddy and colleagues. This algorithm was developed using clinical data from a cohort of 414 consecutive patients with unexplained dyspnea undergoing invasive hemodynamic assessment. A total of 267 of these patients were found to have HFpEF on the basis of their intracardiac hemodynamics, while the remaining 147 were diagnosed with noncardiac dyspnea. All clinical variables were then reviewed and multivariate logistic regression performed to identify those variables that reliably discriminated between HFpEF and noncardiac dyspnea. Interestingly, the variables that discriminated best were largely cardiovascular risk factors, including obesity,
hypothesis, and advancing age. Important components of the HFA-PEFF scoring system such as LA volume and natriuretic peptides were found to be poorly discriminative and not included in this algorithm. The most important multivariate predictor of HFpEF was found to be AF, providing further evidence for the close association between AF and HFpEF. Indeed, the presence of AF scores 3 points in the H2FPEF system, conferring a minimum intermediate probability of HFpEF in all patients with AF. As with the HFA-PEFF algorithm, intermediate scores necessitate further evaluation with invasive exercise hemodynamics.

A recent retrospective analysis of patients with suspected HFpEF showed that both scoring systems for HFpEF accurately identified those at highest risk for heart failure hospitalizations and all-cause mortality. Importantly, a significant proportion of these patients had coexistent AF, raising hopes that the diagnosis of AF-HFpEF has been made simpler with the use of these 2 scoring systems. However, a large proportion of the AF cohort had intermediate HFpEF scores according to these models. A definitive diagnosis of HFpEF would therefore require invasive hemodynamic testing in many AF patients.

Invasive hemodynamic studies

Several recent investigations have utilized invasive hemodynamic studies to identify the true proportion of AF patients with underlying HFpEF. Table 2 provides an overview of these studies. Two of the studies investigated patients going for AF ablation and assessed mean LA pressures following transseptal puncture. In the remaining 2 studies, patients with AF underwent invasive right heart catheter for assessment of mean pulmonary capillary wedge pressure (PCWP). The response of intracardiac pressures to exercise was also assessed in all studies; studies involving right heart catheter utilized supine bicycle ergometer, whereas those involving AF ablation utilized arm exercises done in the supine position following transseptal puncture.

In all 4 studies, a high proportion of AF patients exhibited the raised intracardiac pressures diagnostic of HFpEF. The highest proportion of AF patients meeting HFpEF criteria was seen in the study by Reddy and colleagues, who demonstrated elevated pressures in 94.1% of AF patients. However, it is unlikely that this study was representative of the general AF population; the patients included in this study had significant dyspnea of uncertain cause and had been investigated extensively prior to referral for invasive hemodynamic studies. Sugumar and colleagues included a smaller number (54) of patients awaiting first-time AF ablation and found that 64% met the criteria for HFpEF diagnosis. However, again this study was limited by a highly selected population of AF patients (only 20% of patients referred for AF ablation were ultimately included in the study). Of note, the majority of those meeting HFpEF criteria in this study were identified only on exercise, suggesting that these patients had early rather than established HFpEF, representing perhaps early LA remodeling. Importantly, all studies showed that AF
cohorts exhibited a broad spectrum of LA pressures, highlighting the fact that despite the diagnosis of HFpEF being reliant on meeting strict LA pressure cutoffs, the reality is that the LA myopathy progresses on a more continuous spectrum.

The studies measuring transseptal LA pressures rather than PCWP identified similar proportions of HFpEF patients at rest but lower proportions of patients meeting criteria with exercise. There are several possible reasons for these differences in prevalence: (1) the studies involving LA pressures involved larger and more representative AF populations; (2) the methods of exercise used in the transseptal studies (arm exercises) were less exhaustive than bicycle ergometry and therefore elevated intracardiac pressures to a lesser extent; (3) exercise studies undertaken immediately prior to AF ablation likely involved some level of sedation (although this was not explicitly stated in either study), which may have had some impact on exertional levels; and (4) the mean PCWP values were overestimates of LVEDP; an investigation into the relationship between mean PCWP and LVEDP showed that PCWP was consistently higher than LVEDP in patients in AF, likely owing to the poor operating compliance of a stiff LA and the uncoupling of LVEDP from PCWP.94

Aside from the prevalence of HFpEF in patients with AF, these invasive hemodynamic studies provide numerous additional insights into the association between AF and HFpEF. Sramko and colleagues3 showed that elevated LA pressures were independently associated with an increased risk of AF recurrence following ablation. Sugumar and colleagues4 further showed that patients without AF recurrence had reduced mean PCWP at follow-up, while symptomatic improvement following ablation was also associated with significantly reduced mean PCWP. In another invasive hemodynamic study investigating the impact of progressively increasing AF burden in patients with a known diagnosis of HFpEF, higher AF burden was associated with progressively increased intracardiac pressures, reduced LA function, and worse long-term survival.45 Taken together, these findings not only highlight the close links between LA myopathy, AF, and HFpEF and the progressive nature of all 3 conditions, but also suggest that reversal of this progression is possible and may be related to a reduction in LA myopathy.

Prognostic implications

Prior data regarding the prognostic implications of AF-HFpEF have considered the 2 conditions as entirely separate entities. Numerous studies have shown that patients with HFpEF fare significantly worse when they have coexistent AF, and a recently published meta-analysis confirmed a significant increased risk of all-cause mortality, cardiovascular mortality, stroke, and heart failure hospitalizations.96 Mortality is also increased in AF patients who develop incident HFpEF.11 However, these data are based on the assumption that HFpEF is a discrete entity that patients with AF either have or do not have. Increasingly, with the aid of hemodynamic testing described above, we are understanding that both HFpEF and AF are progressive conditions; in AF cohorts, some patients have severe HFpEF, while others have mild HFpEF, which may only be present during exertion. Importantly, there is growing data to suggest that the level of HFpEF and LA myopathy progression within the cohort of patients with AF has direct consequences on cardiovascular outcomes (including mortality and systemic thromboembolism), symptoms, and quality of life (Figure 3).97

Figure 3  Progressive left atrial disease is central to the development and progression of both atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). Deteriorating left atrial function (mechanical and electrical) is associated with poorer outcomes in both AF and HFpEF. LV = left ventricle; LVEDP = left ventricular end-diastolic pressure.
Mortality
Mortality in AF is linked to AF burden according to the classical classification scheme of paroxysmal, persistent, and permanent AF. Patients with persistent AF, who have been adequately anticoagulated, demonstrate increased all-cause mortality compared to those with paroxysmal AF, even after adjustment for other cardiovascular risk factors. However, whether this increased risk of mortality is truly attributable to AF burden or, alternatively, to the severity of the underlying LA myopathy remains unclear. Patients with persistent AF demonstrate increased LA size, reduced LA function, and lower LA voltages when compared with patients with persistent and permanent AF, suggesting that LA myopathy is significantly worse in these patients. This raises the possibility that LA myopathy rather than AF burden may underlie the increased risk of all-cause mortality in patients with increased burden of AF.

Systemic thromboembolism
As with mortality, systemic thromboembolic risk is associated with increased AF burden as well as worsening LA myopathy. However, in this case the evidence for LA myopathy as the chief mitigator of systemic thromboembolism is strong. Advancing LA myopathy is associated with all 3 components of Virchow’s triad: increased stasis of blood within the LA, increased blood coagulability, and endothelial injury. Furthermore, increasing atrial fibrosis has been shown to be directly associated with LA appendage thrombus and prior history of strokes. In addition, while rhythm control strategies and reduced AF burden have not been shown to have a significant effect on subsequent stroke risk in patients with AF, mitral regurgitation and its associated increased blood flow within the LA have been shown to protect against thrombus formation despite increasing the risk of higher AF burden. Finally, in patients with cryptogenic stroke and no evidence of AF on prolonged cardiac monitoring, stroke was associated with significantly reduced LA strain.

Exercise intolerance
Exercise intolerance is a characteristic symptom of AF. More than 60% of symptomatic AF patients suffer with exertional dyspnea or exercise intolerance and these symptoms are associated with significantly impaired quality of life. Exercise intolerance is closely linked with AF burden, and cardioversion of patients from AF to sinus rhythm significantly improves maximal exercise tolerance. However, exercise intolerance is also a classical feature of HFpEF and has been shown to be closely associated with LA function in HFpEF patients without AF. Furthermore, in a large cohort of patients with AF, cardiopulmonary exercise testing showed that diastolic function rather than cardiac rhythm predicted maximal VO2. These studies suggest that LA myopathy and HFpEF play critical roles in the development of exercise intolerance in patients with AF.

Clinical management strategies
Management of AF has traditionally focused on stroke prevention and symptom control via rate or rhythm control. However, emerging data suggest that a progressive LA myopathy and HFpEF may underlie many if not all of the prognostic consequences of AF, suggesting that a re-evaluation of the treatment strategies for AF may be needed, with renewed focus on reversal of the progressive LA myopathy. However, evidence suggests that many of the established treatments for AF may already involve reversal of the LA myopathy and treatment of the occult underlying HFpEF. While these treatments have not yet shown any proven benefit in stroke risk reduction, meaning the need for anticoagulation continues, a number of proven treatments may exert their effects through reversal of the HFpEF process. These treatments include early rhythm control, catheter ablation, and risk factor management.

Early rhythm control
Rhythm control has long been established as an important treatment strategy in AF to improve symptoms and quality of life. Recent data suggest that early rhythm control may also reduce major cardiovascular events, including cardiovascular mortality, stroke, and heart failure hospitalization. The mechanisms for these improvements in outcomes are purported to be related to a reduction in AF burden but could also be attributable to reverse remodeling and treatment of the underlying LA myopathy. It is well known that duration of time in AF is directly correlated with structural, contractile, and electrical remodeling of the LA. Indeed, it has been shown that longer time to treatment of AF is associated with increased risk of AF recurrence. Early rhythm control of AF may therefore halt progression of adverse LA remodeling, resulting in reduced likelihood of developing HFpEF and improved outcomes.

Catheter ablation
Catheter ablation for rhythm control has also been consistently associated with improvements in symptoms and quality of life. Historically, the efficacy of catheter ablation for the treatment of AF has been considered the result of a reduction in AF burden. The cornerstone of catheter ablation for the treatment of AF remains pulmonary vein isolation, a technique aimed at targeting commonly occurring AF triggers arising in the pulmonary veins. In addition, catheter ablation may also reduce AF burden through modulation of ganglionic plexi, which have also been implicated in the genesis of AF, or through atrial debulking, whereby extensive catheter ablation results in a reduction of electrically active atrial tissue capable of sustaining AF.

However, an alternative theory to explain the symptomatic benefit derived from catheter ablation is a reduction in HFpEF. The imaging substudy of the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial showed that catheter ablation was associated with significantly reduced LA volumes compared with
antiarrhythmic drug therapy. This suggests that catheter ablation may be associated with a significant reverse remodeling process, perhaps via an atrial debulking process, resulting in reduced LA myopathy and therefore improved outcomes. Evidence regarding LA mechanical function following ablation is less clear; early studies suggested that LA function decreased after ablation, although a more recent study suggested that LA strain may improve at 6 months postablation. Two meta-analyses investigating LA function postablation delivered conflicting results. More data are required to determine the effect of catheter ablation on overall LA function.

Symptomatic benefits may therefore arise from reduced LA myopathy in addition to reduced AF burden. In their hemodynamic assessment of patients with AF pre- and postablation, albeit in a relatively small cohort, Sugumar and colleagues showed that patients remaining arrhythmia-free postablation showed significant reductions in their mean PCWP with exercise, reflecting an improvement in their underlying HFpEF. The resultant improvement in their heart failure symptoms was therefore possibly related to reduced arrhythmia burden as well as improved LA myopathy. While there can be little doubt that catheter ablation is an effective strategy in the treatment of patients with AF, the precise mechanisms of its efficacy remain unclear.

### Risk factor management

Numerous observational and randomized studies have demonstrated the significant benefits of aggressive risk factor management (RFM) in patients with AF. The symptomatic and quality-of-life benefits seen with RFM have been consistently associated with reductions in AF burden. However, RFM has also been associated with reverse remodeling of the LA. The LEGACY study showed that substantial weight loss was associated with structural reverse remodeling of the LA; weight loss of more than 10% resulted in significant reductions in LA volumes and improvements in LV diastolic function. In addition, animal studies of AF have demonstrated significant reversal of the LA myopathy with weight loss. While the symptomatic and quality-of-life benefits associated with RFM may be due to the significant reduction in AF burden, there is evidence to suggest that LA myopathy reversal and, therefore, improved HFpEF management may also underlie the benefits of RFM. There is also evidence to support aggressive RFM in HFpEF cohorts; a 20-week supervised exercise program and/or hypocaloric diet regimes were associated with significant improvements in exercise tolerance as measured by cardiopulmonary exercise testing compared to a control group who did not make any lifestyle changes. The majority of these patients did not have a history of AF. However, the improvements in exercise tolerance were not accompanied by significant changes in LA size. Additional research is therefore required to further delineate the precise mechanisms underlying the efficacy of RFM and to establish any long-term mortality or thromboembolic benefits.

### Pharmacological therapy

A vast number of randomized clinical trials have been carried out to investigate the use of various medical therapies in patients with HFpEF. However, the majority have reported neutral outcomes. The TOPCAT trial investigated the use of spironolactone in patients with a confirmed diagnosis of HFpEF. The primary composite outcome of cardiovascular death, aborted sudden death, or heart failure hospitalization was not reduced in the treatment arm. However, when only patients from the Americas were included in the analysis, the composite primary outcome was significantly reduced and cardiovascular death and heart failure hospitalizations were also independently reduced. For these reasons, mineralocorticoid receptor antagonists are now recommended for patients with HF and preserved ejection fraction (>45%) according to the ACC guidelines (class IIb indication). However, substudies of the TOPCAT trial showed that LA structure was not influenced by spironolactone and AF incidence and recurrences were not reduced by spironolactone, suggesting that reversal of the LA myopathy may not have been the mechanism of effect. Given the lack of pharmacological options for patients with HFpEF, the results of the EMPEROR-Preserved trial, investigating the use of the SGLT2-inhibitor empagliflozin in patients with HFpEF, are highly anticipated.

### Future directions

Establishing the true extent of HFpEF in patients with AF is critical to improving outcomes. Invasive hemodynamic studies of large, unselected cohorts of patients with AF are urgently required to develop a greater understanding of the true prevalence of HFpEF in AF. In addition, alternative noninvasive methods to diagnose and quantify LA myopathy in patients with AF should be sought, with a focus on quantifying LA fibrosis and stiffness. Prospective longitudinal outcome studies of patients with AF and known LA myopathy are required to further understand the prognostic impact of occult HFpEF on both mortality and systemic thromboembolism. Finally, Interventional studies evaluating the effect of AF treatments on the reversal of the underlying LA myopathy and HFpEF are required to determine whether improvements in mortality, stroke risk, symptoms, and quality of life can be achieved.

### Conclusion

The true nature of the relationship between AF and HFpEF is likely underappreciated; invasive hemodynamic studies suggest a large number of AF patients have occult HFpEF, associated with a progressive LA myopathy. As LA myopathy worsens, both AF burden and diastolic dysfunction increase and evidence suggests this may result in increased risk of mortality, systemic thromboembolism, and exercise intolerance. While many evidence-based treatments for AF are centered around reduction in AF burden, there is growing evidence to suggest that these treatments are also associated with reduced LA myopathy and reduced HFpEF. Further
work is required to establish whether reversal of the LA myopathy and HFpEF can significantly reduce mortality and systemic thromboembolism in AF.

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