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Critical Role of the LA in Cardiovascular Homeostasis

The left atrium (LA) plays a vital role in modulating LV filling by acting as a reservoir, passive conduit, and active booster pump, as well as a regulator of blood volume through A-type natriuretic peptide secretion in response to stimulation by mechanical stretch of the cavity. LA myopathy has emerged as one of the most important non-LV contributors to disease progression in heart failure with preserved ejection fraction (HFP EF). LA dysfunction is common in HFP EF and is associated with more severe pulmonary vascular disease and right ventricular dysfunction, and increases the risk of incident atrial fibrillation or atrial functional mitral regurgitation, leading to limitations in cardiac output reserve and reduced exercise capacity. LA deformation assessed by 2-dimensional speckle-tracking echocardiography is useful for estimating abnormal hemodynamics or exercise capacity, differentiating HFP EF from non-cardiac dyspnea and is an independent predictor of adverse outcome in HFP EF. Thus, interventions directly targeting LA myopathy may improve outcomes in HFP EF with LA myopathy. This review provides information regarding the physiology of the LA in patients with HFP EF and discusses the importance of evaluation of LA function, management issues, and future directions through ongoing trials of medical interventions.

Key Words: Heart failure; Heart failure with preserved ejection fraction; Left atrial myopathy

Heart failure with preserved ejection fraction (HFP EF) accounts for approximately half of all heart failure (HF) patients, and the prevalence and incidence of HFP EF are rapidly growing in the community. Although HFP EF was previously thought of exclusively as a disorder of the left ventricle (LV), there are multiple cardiac, vascular, and non-cardiac abnormalities that contribute to the condition. Among these, abnormalities in the left atrium (LA) play a key role in the pathophysiology and disease progression of HFP EF. Patients with this form of “LA myopathy” are characterized by a distinct phenotype with more severe disease and poorer outcomes. LA dysfunction in patients with HFP EF is related to more severe pulmonary vascular remodeling, right ventricular (RV) dysfunction, and an increased risk of new-onset atrial fibrillation (AF) or atrial functional mitral regurgitation (MR) due to mitral annular dilation, leading to reduced exercise capacity and adverse outcomes. Further research is needed to identify therapies targeting LA myopathy in HFP EF to improve outcomes. In this review, we focus on the current understanding of the role of the LA in cardiovascular homeostasis, pathophysiological mechanisms underlying LA myopathy in HFP EF, tools to evaluate LA dysfunction, and potential treatment strategies for this specific HFP EF phenogroup.

Critical Role of the LA in Cardiovascular Homeostasis

The LA plays a vital role in modulating LV filling by acting as a reservoir to store venous return during ventricular systole, without untoward elevation in LA pressure, as a passive conduit to conduct blood from the pulmonary vein to the LV during early to mid-diastole and as a priming pump to boost LV filling during active atrial systole. The LA pressure-volume relationship in health under normal circumstances during one cardiac cycle is shown in Figure 1. During LV systole and isovolumic relaxation, blood flows into the LA anterograde from the pulmonary veins, increasing LA volume and pressure to the peak of the v wave. During early LV diastole and diastasis, the LA functions as a passive conduit, where blood flows into the LV from the pulmonary veins. During late LV diastole and diastasis, the LA functions as an active conduit, where blood flows into the LV from the pulmonary veins. During late LV diastole, active atrial emptying leads to a reduction in LA volume accompanied by an increase in LA pressure (i.e., an a wave). All 3 phases can be accurately measured with high feasibility and reproducibility by 2-dimensional (2D) speckle-tracking echocardiography analysis for the calculation of LA strain (Figure 2).

In addition to these reservoir, conduit, and booster functions, the LA plays another important role in maintaining mitral valve competence. In an earlier or milder stage of HFP EF, the LA is able to compensate for LV diastolic dysfunction through its reservoir and booster functions,
dysfunction and the development of atrial functional MR due to dilatation of the mitral annulus. Findings in patients with these features demonstrate exaggerated peri-cardial restraint and a failure to augment cardiac output, which is related to poor functional capacity and adverse outcomes in HFpEF (Figure 3).

Figure 1. (A) Left atrial (LA) pressure-volume loop and (B) instantaneous changes in LA pressure and LA volume during one cardiac cycle.

Figure 2. Sample of 2-dimensional speckle-tracking echocardiography analysis for the calculation of left atrial reservoir, conduit, and booster strain. ES, end systolic; GLS, global longitudinal strain; Pk, peak; Seg., segment; TTP, time-to-peak.

acting as an important barrier between the LV and pulmonary circulation. However, in many patients, LA dilation and dysfunction progress over time for reasons that, as yet, remain unclear, increasing the risk of new onset AF. This progression is collectively referred to as LA myopathy and is associated with pulmonary hypertension (PH), then RV dysfunction and the development of atrial functional MR due to dilatation of the mitral annulus. Findings in patients with these features demonstrate exaggerated peri-cardial restraint and a failure to augment cardiac output, which is related to poor functional capacity and adverse outcomes in HFpEF (Figure 3).
LA Myopathy in HFpEF

LA Myopathy in HFpEF with LA myopathy leads to an increase in total heart volume. The elastic pericardium exerts a compressive contact force on the surface of the myocardium that becomes more substantial when total heart volume increases. Pericardial restraint plays an important role in determining hemodynamics, LV preload, and ventricular function. Total heart enlargement and cardiomegaly in HFpEF with LA myopathy creates the substrate for increased pericardial restraint and diastolic ventricular interaction (DVI), where right heart pressure-volume relationships more strongly influence those in the left heart in parallel. When DVI is enhanced, left heart filling pressures can be elevated disproportionate to the degree of LV diastolic stiffness, and LV end-diastolic volume is lower than expected (i.e., LV end-diastolic pressure and LV end-diastolic volume become uncoupled), resulting in failure to augment cardiac output through failure of Frank-Starling reserve.

LV transmural pressure (LVTMP), which reflects LV preload independent of right heart pressure and pericardial restraint, can be estimated by subtracting extrinsic pericardial pressure (estimated from right atrial pressure [RAP]) from pulmonary artery wedge pressure (PAWP).

This impairment in perfusion is coupled with abnormal increases in PAWP that are related to right heart congestion and DVI rather than primary left heart lesions, because LVTMP decreases with exercise in these patients with higher pericardial restraint, such as LA myopathy with permanent AF, CpcPH, or severe tricuspid regurgitation, which consist with inadequate LV preload, despite elevated PAWP.

Atrial Functional MR

Functional MR, also known as secondary MR due to LV dysfunction, develops because of tethering of the mitral valve.
is difficult to evaluate non-invasively, and many patients exhibit hemodynamic abnormalities only during exercise. LA strain is useful for the discrimination of HFpEF patients from those with dyspnea due to other conditions. Reddy et al showed that LA reservoir strain and conduit strain are significantly impaired in HFpEF compared with non-cardiac dyspnea. Among all the common echocardiographic indices, including E/e', e', LA volume index, tricuspid regurgitation velocity, LV mass, and LV global longitudinal strain, LA reservoir strain could discriminate invasively proven HFpEF (PAWP \(\geq\) 15 mmHg at rest and/or \(\geq\) 25 mmHg with exercise) from non-cardiac dyspnea most accurately, where indexing of the LA reservoir strain to estimate LA pressure (i.e., E/e') as a surrogate for LA compliance further improves the diagnostic performance. Telles et al reported that a cut-off value of <33% for LA reservoir strain predicts invasively proven HFpEF with 88% sensitivity and 77% specificity, providing a net reclassification improvement of 12% compared with the 2016 European Society of Cardiology criteria for the non-invasive diagnosis of HFpEF.

### Effects on Exercise Hemodynamics and Functional Capacity

Because LA dysfunction is associated with adverse hemodynamics, impaired LA strain assessed by speckle-tracking echocardiography can predict abnormal exercise hemodynamics or functional capacity. A prospective study of invasive right heart catheterization simultaneous with speckle-tracking echocardiography has shown that impairments in LA reservoir and booster strain were strongly correlated with higher peak exercise PAWP. In that study, impairments in LA reservoir strain were also shown to have a strong relationship with higher exercise mean pulmonary artery pressure and lower pulmonary artery elastance, as well as a blunted increase in forward flow with activity. These abnormalities were maintained after excluding patients with AF, suggesting that LA myopathy plays an important role in contributing to atrial functional MR in HFpEF independent of rhythm.

### Analyses of LA Deformation in HFpEF

Although abnormal LA function has been consistently identified in HFpEF and is associated with greater disease severity, measurement of LA diameter and volume is insufficient to evaluate LA function. A previous study showed that LA function assessed by deformation analysis was superior to volumetric indices in determination of hemodynamic responses in HFpEF. Indeed, recent studies have shown that LA deformation analysis using 2D speckle-tracking echocardiography is robust for detecting LA dysfunction and is useful for discriminating invasively proven HFpEF from non-cardiac dyspnea, as well as predicting abnormal invasive hemodynamics, exercise capacity, and then the risk of adverse outcomes in patients with HFpEF.

### Utility of LA Strain in the Diagnosis of HFpEF

Although the diagnosis of HFpEF is often challenging because the ejection fraction is normal, LV filling pressure
Ability in People With Diastolic Heart Failure (RELAX) trial demonstrated that the presence of AF was associated with impaired exercise capacity in patients with HFpEF. Although LA strain was not assessed in that study, exercise intolerance may also be related to LA dysfunction. Indeed, progression of AF stage was associated with impaired LA reservoir strain (Figure 4A). According to a more recent prospective study of 2,096 participants who underwent speckle-tracking echocardiography at rest, as well as after passive leg rise and the 6-min walk distance (6MWD) test, both worse LA reservoir strain and worse LA functional reserve were associated with shorter 6MWD among individuals with and without AF, indicating that impaired LA function and LA functional reserve were associated with reduced submaximal exercise capacity. Another cardiac magnetic resonance myocardial feature tracking study revealed that impaired LA conduit function was strongly correlated with peak oxygen consumption (VO2; r=0.80, P<0.01), emerging as the strongest predictor for peak VO2 even after adjustment for LV stiffness and relaxation time in multivariable regression analysis, indicating that impaired LA conduit function is also associated with poor functional capacity in HFpEF.

Prognostic Implications of LA Myopathy in HFpEF

LA dysfunction is also predictive of the prognosis of patients with HFpEF, considering the association of impairment in LA strain and abnormal hemodynamics or functional capacity. Tamargo et al reported that the presence of LA dysfunction was associated with a highly significant increased risk for the composite of HF hospitalization and death, as well as each component separately, even after adjusting for age, sex, body mass index, diabetes, and LV ejection fraction (Figure 4B). Another observational study showed that all functions of LA strain (reservoir, conduit, and booster) were predictive of cardiovascular hospitalizations and all-cause death in outpatients with HFpEF. In that study, Freed et al found that LA reservoir strain remained strongly prognostic after adjustment for AF, LA volume, LV mass, and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score. After further adjustment for LV and RV deformation, LA reservoir strain still retained prognostic value. The findings of these studies would indicate that abnormal indices of LA strain are powerful clinical and prognostic factors in HFpEF. The prognostic impact of LA dysfunction has been repeatedly shown in other studies, as summarized in a recent systematic review and meta-analysis.

Although LA structure and function are altered in most patients with HF, there are fundamental differences in LA properties between HFpEF and HFrEF. Melenovski et al demonstrated that patients with HFrEF had larger LA volumes, whereas HFpEF patients had smaller, stiffer LA, with higher LA peak pressures, lower LA minimal pressures, and higher wall stress variations. This greater phasic strain coupled with the older age (on average) in HFpEF may explain the greater burden of AF in these patients compared with HFrEF patients. Notably, Melenovski et al found that LA dysfunction was associated with higher mortality in HFpEF, but not in HFrEF, suggesting that the prognostic impact of LA dysfunction is greater in HFpEF. Given the fact that LA dysfunction is associated with poor outcome as well as functional capacity and abnormal hemodynamics, it is important to test whether interventions directly targeting unloading the LA, augmentation of LA function, and restoration of sinus rhythm may improve outcomes in HFpEF with LA myopathy.

Treatment for LA Myopathy in HFpEF

There are few effective treatments for HFpEF, which is related, in part, to the complexity and heterogeneity within the HFpEF syndrome, limiting “one-size-fits-all” approaches that have proven so effective in HFrEF. Current treatment of HFpEF is aimed at volume control with diuretics, treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors and mineralocorticoid antagonists, lifestyle interventions, and interventional therapy targeting common comorbidities. Recently, it is hoped that better phenotyping of patients based on their predominant pathophysiologic abnormalities may enable more individually tailored therapy, and LA myopathy is one of the most representative distinct phenotypes among HFpEF. In this section we focus on the current understanding of the potential treatment strategies for HFpEF with LA myopathy.

Pharmacological Therapy

A-type natriuretic peptide (ANP) is a polypeptide hormone that is synthesized and stored in the atrial myocytes and secreted in response to atrial wall stretch, with effects of natriuresis, diuresis, and vasodilation, and so enhancing natriuretic peptide (NP) signaling is a rational treatment target in HF. A post hoc analysis of the Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function (TOPCAT) trial revealed a significant reduction in the rate of the primary outcome of cardiovascular-related death, aborted cardiac arrest, and HF hospitalization with spironolactone compared with placebo among patients who were enrolled according to elevated NP levels, with important regional variations in the trial. Neprilysin plays a significant role in the degradation of NPs, and the beneficial therapeutic effects of neprilysin inhibition may rely on NP. The Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) trial showed that treatment of patients with HFpEF with an angiotensin receptor-neprilysin inhibitor (ARNI), compared with the angiotensin receptor valsartan only, resulted in a greater decrease in N-terminal pro B-type natriuretic peptide (NT-proBNP), which was associated with a greater reduction in LA volume at the 12-week follow-up. Despite this favorable effect in the PARAMOUNT trial, in the much larger Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON) trial, LCZ696 narrowly missed showing a reduction in the frequency of the primary composite outcome of death from cardiovascular causes and total HF hospitalizations compared with treatment with valsartan only. There was no interaction between AF status and the effects of ARNI on the primary endpoint.

The Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) trial demonstrated that the SGLT2 inhibitor (SGLT2i) dapagliflozin improves outcomes in patients with HFrEF and a substudy of the Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction (Empire HF) randomized clinical trial showed that the SGLT2i empagliflozin significantly reduced LA volume index in patients.
with HFpEF. In the Empagliflozin outcome Trial in Patients With Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial, the SGLT2i reduced the combined risk of cardiovascular death or HF hospitalization in patients with HFpEF. Over half the patients participating in the EMPORER-Preserved trial had a history of AF and, in prespecified subgroup analyses, there was no difference in the efficacy of empagliflozin in patients with or without AF. Further support for SGLT2i comes from a post hoc analysis of the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) trial, which showed reduced rates of new-onset AF.

Other novel pharmacologic approaches also hold promise. The vasodilator relaxin activates the relaxin family peptide receptor RXFP1, which is expressed in atrial but not ventricular myocytes. In human atrial tissue, relaxin increases inotropy, even as ventricular effects appear to be absent, suggesting a potential role for relaxin as an LA-targeted therapy.

Invasive Intervventional Therapies
Given the adverse functional and hemodynamic consequences of AF, restoration of sinus rhythm may improve clinical status. In a recent study from Australia, 20 patients with HFpEF and AF underwent catheter ablation and follow-up invasive exercise testing >6 months later. From this cohort, 9 patients (45%) no longer fulfilled hemodynamic criteria for HFpEF at follow-up. Patients who remained arrhythmia free experienced a reduction in left heart filling pressures with exercise and improved quality of life. The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial tested the effects of catheter ablation to drug therapy for patients with AF. In an ancillary study from CABANA restricted to patients with known HF at the time of randomization, over three-quarters of whom had HFpEF, catheter ablation resulted in a reduction in the primary endpoint of death, disabling stroke, serious bleeding, or cardiac arrest by 36%, and reduced all-cause mortality by 43%. However, there is also concern for worsening hemodynamic and clinical status in patients with HFpEF and increased LA stiffness, related to the adverse consequences of the ablation itself on LA hemodynamics through worsening of fibrosis and atrial reverse remodeling. Clinical trials testing catheter ablation and other strategies to reduce AF burden in HFpEF are urgently needed to guide clinical decision making.

Devices to reduce LA pressure with a percutaneously implanted interatrial shunt device (IASHD) have been shown to improve exercise hemodynamics, symptoms, and exercise capacity in patients with HFpEF in the A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF) trial, in which greater LA volume reduction following IASHD implantation was independently associated with higher baseline LA compliance and reservoir strain of the right atrium. LA unloading with this device is expected to improve LA myopathy in HFpEF, and is currently being evaluated in ongoing clinical trials (NCT03080803). LA unloading with the creation of therapeutic interatrial shunts may also improve pulmonary vascular function without compromising systemic perfusion in patients without significant pre-existing pulmonary vascular disease or RV dysfunction. Because pericardial restraint and enhanced ventricular interdependence contribute to elevation in LV filling pressures in HFpEF with larger LA and total heart volume, pericardial resection through a minimally invasive percutaneous approach is a potential treatment that has shown promise in both normal animals and animal models with diastolic dysfunction and is currently under investigation to determine whether it is safe and produces similar hemodynamic benefits in people with HFpEF (NCT03923673). Finally, novel assist devices to reduce LA pressure and volume overload are also under development and may come to testing in clinical trials soon.

Lifestyle Interventions
Recent studies have shown that cardiac rehabilitation improves outcome in patients hospitalized for acute HF, including HFpEF, and exercise training and weight loss through caloric restriction have been shown to improve functional capacity as well as quality of life in patients with HFpEF. Similarly, weight reduction also reduces the burden of AF and enhances the maintenance of sinus rhythm, suggesting salutary effects on LA myopathy. Although increasing activity in sedentary patients may reduce AF (and, potentially, LA myopathy), there is also evidence that excessive exercise promotes LA remodeling and increases the risk of AF (i.e., U-shaped relationship). In one study, 2 years of high-intensity exercise training in sedentary, healthy, middle-aged adults was associated with LA mechanical remodeling without electrical remodeling significantly in excess of LV remodeling, which is known to occur in the earlier stages of endurance training. The differential mechanisms that drive pathologic remodeling at the atrial level from excessive training in athletes and pressure-volume overload of HFpEF remain unclear.

Conclusions
Abnormalities in the LA play an important role in the pathophysiology and disease progression of HFpEF. Prolonged LV dysfunction leads to LA remodeling, dysfunction, and predisposition to the development of paroxysmal and permanent AF. This is then associated with the development of worsening pulmonary vascular disease, right heart dysfunction, atrial functional MR, worsening functional capacity, and an increased risk of morbidity and mortality. LA dysfunction or the loss of atrioventricular synchrony with AF are associated with marked limitations in LV preload, and total heart enlargement creates the substrate for increased pericardial restraint and DVI. These abnormalities lead to lower preload (despite high LV end-diastolic pressure), resulting in a failure to augment forward flow, which is related to exercise intolerance. Deformation analysis is useful not only for measuring LA function, but also for estimating invasive hemodynamics, exercise capacity, discriminating HFpEF from non-cardiac dyspnea, and even in predicting prognosis in HFpEF. It is hoped current and future trials targeting LA myopathy in patients with HFpEF will offer new treatments to improve outcomes in this large and expanding cohort of patients.

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None.

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