Left atrial volume index and left atrial strain in the assessment of left atrial myopathy in heart failure with preserved ejection fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a disease caused by inadequate filling of the left ventricle. Left atrial (LA) myopathy plays an important role in HFpEF and can be used as a diagnostic and prognostic marker.
LA size and strain are echocardiographic parameters to assess LA myopathy. Currently, only LA size, measured as maximum LA volume index, is incorporated in diagnostic guidelines. LA size is similar in healthy men and women, but there are indications that LA size is increased in women compared to men in advanced HFpEF. Minimum LA volume index has better predictor of adverse outcomes in HFpEF, but it is unclear if diagnostic guidelines would benefit from its inclusion. LA reservoir strain is a better marker for early left ventricular diastolic dysfunction than maximum LA volume index. Moreover, LA reservoir strain shows better diagnostic and prognostic value for HFpEF than other echocardiographic parameters. Minor differences in age-related changes in LA strain between men and women are observed. Sex differences in LA strain in HFpEF have not been studied. Future studies should focus on optimally incorporating LA reservoir strain into diagnostic guidelines for HFpEF.

Introduction

Heart failure (HF) is a disease characterised by inadequate pump function and/or filling of the left ventricle and is associated with increased mortality (LV, Heidenreich et al. 2022). HF symptoms may include shortness of breath (dyspnea) during rest and/or exercise, peripheral oedema, and fatigue (Redfield and Borlaug 2023). Approximately 64.3 million people worldwide suffer from HF and prevalence is expected to increase as the population ages (Dunlay, Roger, and Redfield 2017).

HF is classified in three different subtypes according to the LV ejection fraction (LVEF), which is the fraction of blood that is pumped out of the LV during systole (Heidenreich et al. 2022; Schwinger 2021). LVEF is measured using echocardiography and is generally above 50% in healthy conditions. When HF is accompanied by a dilated LV with thinner walls, which is not able to pump blood effectively during systole, it is defined as HF with reduced ejection fraction (HFrEF, LVEF<40%). Myocardial infarction, which leads to impaired contraction in a portion of the LV, frequently precedes this condition. When HF is due to reduced filling of the LV because of impaired LV relaxation and/or increased LV stiffness, it is defined as HF with preserved ejection fraction (HFpEF, LVEF>50%). Finally, when LVEF is between 40% and 50%, it is called HF with mildly reduced ejection fraction (HFmrEF). Diagnosis of HFpEF can be difficult because HF symptoms are non-specific and can be attributed to other non-cardiac disorders as well (Dunlay, Roger, and Redfield 2017). Therefore, the first priority is to rule out non-cardiac causes of HF symptoms.

HFpEF

HFpEF accounts for 50% of all HF patients, with women forming the majority of HFpEF patients, while, on the other hand, men are more commonly affected by HFrEF (Dunlay, Roger, and Redfield 2017). This difference in prevalence of HF subtypes emphasises the importance of performing sex-stratified analyses when investigating HF. Besides female sex, other HFpEF risk factors include older age, hypertension, diabetes, obesity, and coronary artery disease (Redfield and Borlaug 2023). It is thought that these risk factors promote a proinflammatory state in the vasculature, which can eventually lead to HFpEF onset and progression. Treatment options for HFpEF are limited and mostly consist of the management of comorbidities, such as exercise and weight loss for obesity and diabetes, and drugs to manage hypertension. Sodium glucose type 2 (SGLT2) inhibitors, which reduce glucose levels by inhibiting glucose reuptake by the kidneys, are the only drugs that are effective at preventing hospitalization and cardiovascular death (Omote and Borlaug 2021).

Abnormal pressures in the heart-lung circulation cause symptoms in HFpEF. These are caused by LV diastolic dysfunction (LVDD). Impairments in relaxation and compliance of the LV in HFpEF are typically accompanied by concentric hypertrophy or remodelling of the LV wall, resulting in a reduction in LV volume. To adequately fill the LV during diastole and sustain the required cardiac output, LV filling pressure will increase. This increase in pressure can further impair LV diastolic function by impairing LV relaxation and compliance, which can aggravate HFpEF progression. While

impairments in LV systolic function can be present in HFpEF, they play a substantially smaller role because of the preserved LVEF.

Left Ventricular Diastolic Dysfunction

Isolated LVDD is considered the preclinical stage of HFpEF and it is characterized by impaired LV relaxation and/or increased LV stiffness (Nagueh et al. 2016), leading to increased LV filling pressure (Obokata, Reddy, and Borlaug 2020). LV relaxation and compliance naturally decrease with age, which can be exacerbated by the presence of comorbidities, such as obesity, diabetes, and hypertension. LVDD is able to progress into HFpEF, but this does not happen in the majority of cases (van Ommen et al. 2022). While both sexes have the same risk of progression from LVDD to HF, this has not been studied for HFpEF specifically (van Ommen et al. 2022). Therefore, the higher prevalence of women in HFpEF could be caused by an increased risk of progression from LVDD to HF.

Echocardiography plays a key role in assessing LVDD and is used to diagnose and monitor the progression of HFpEF (Silva et al. 2023). With this technique, various parameters are measured to evaluate LV filling pattern, LV geometry, and LA size. These parameters are used to indirectly estimate whether LV filling pressure is elevated. The most recent 2016 guidelines by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) recommend the use of four main echocardiography parameters to evaluate LVDD (Nagueh et al. 2016): E/e' ratio, which is the early mitral valve inflow (E) velocity divided by the average mitral valve annular early filling tissue Doppler velocity (e'), septal and lateral e' velocities, tricuspid regurgitation velocity (TRV), and maximum left atrial volume index ($LAVi_{max}$). If echocardiographic results are inconclusive and the diagnosis is uncertain, LV filling pressure can be more directly measured using right heart catheterization (RHC), but this comes with increased costs and complexity (Reddy et al. 2018). $LAVi_{max}$ is an important parameter, because an elevated $LAVi_{max}$ is an indicator of left atrial (LA) dilation, which is associated with LA myopathy.

LA Myopathy

LA myopathy is associated with HFpEF and is characterised by impairments in the structure, electrical conduction, or function of the LA (Peigh, Shah, and Patel 2021). In LVDD, LA pressure increases to adequately fill the less compliant LV and sustain the required cardiac output. This increase in LA pressure is the main factor contributing to the myocardial remodelling that gives rise to these impairments. The increase in LV filling pressure associated with LA myopathy, exacerbates LVDD, which, in turn, can exacerbate LA myopathy. Therefore, dysfunction in the two chambers is linked (LV-LA coupling). Eventually, the increase in LA pressure in LA myopathy can also induce pulmonary hypertension and dysfunction in the right ventricle (Redfield and Borlaug 2023), as well as dilation of the anulus of the mitral valve causing mitral regurgitation (Omote and Borlaug 2021). Structurally, the myocardial remodelling in LA myopathy triggers dilation of the LA. This dilation is also associated with disturbances in electrical conduction, which are able to induce arrhythmias in the form of atrial fibrillation (AF). The presence of these arrhythmias is harmful, as HFpEF combined with AF is linked to worse disease prognosis. Additionally, disturbances in normal sinus rhythm trigger prothrombotic conditions, increasing the risk of stroke.

Because of the link between LA myopathy and LVDD, measures of LA dilation, such as $LAVi_{max}$, and the presence of AF, can be used as markers for LVDD and, therefore, HFpEF. However, LA function can also serve as an effective marker for LVDD. LA function can be divided into three phases (Figure 1) (Ferkh, Clark, and Thomas 2023). First, the reservoir phase where blood from the pulmonary veins is stored during the LV systole. Second, the conduit phase where blood passively enters the LV. Third, the booster pump or contractile phase where blood is actively pumped into the LV by the LA contraction.

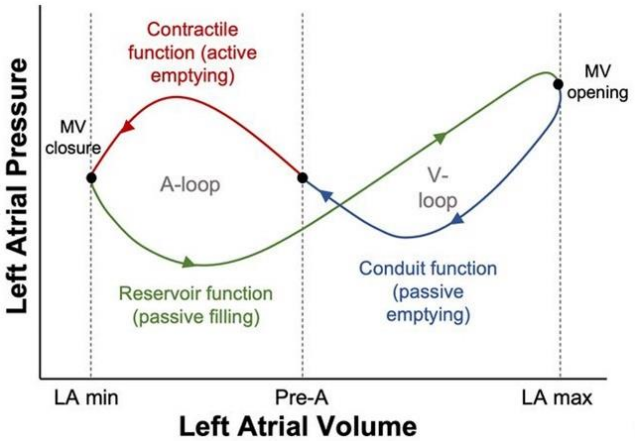

Figure 1: Pressure-volume loop of the left atrium (LA), representing the left atrial function phases. (Ferkh et al. 2023)

All three phases and their functions can be impaired in LA myopathy, which can be assessed by measuring LA strain with 2D speckle tracking echocardiography (2D-STE) or tissue doppler echocardiography (Thomas et al. 2019). Strain is the amount of myocardial deformation expressed as a percentage, which is positive during relaxation and negative during contraction. When LA function is impaired, LA strain is reduced in all three phases. Therefore, LA strain could serve as an effective marker for HFpEF (Silva et al. 2023).

Current diagnosis guidelines for diagnosis of HFpEF have limitations, with the two main scoring systems, H_2FPEF(Reddy et al. 2018) and HFA-PEFF(Pieske et al. 2019), being able to yield divergent

results (Sanders-van Wijk et al. 2021). The influence of LA myopathy is taken into account by inclusion of $LAVi_{max}$ and presence of AF, but LA function as measured by LA strain is not part of the diagnostic algorithm. In this context, reevaluating LA size as a marker of LA myopathy and comparing it against LA strain would offer substantial insight in the mechanisms of LA myopathy in HFpEF.

Objectives

LA myopathy and LVDD are strongly linked. Therefore, it is important to study the possible mechanisms implicated in the development of LA myopathy in people with HFpEF. Furthermore, given the disparity in prevalence of HF subtypes between men and women, it is crucial to investigate possible sex-differences in markers of LA myopathy and the underlying pathology. Lastly, investigating the impact of LA myopathy on AF and AF-related stroke between men and women would be of interest.

Methods

Defining scope

To define the scale of this scoping review, recent (<5 years) review articles on HFpEF and LA myopathy from PubMed were studied. Following this, we opted for topics that matched our objectives. It was decided that LA size and LA function would be the best aspects of LA myopathy to focus on, because these are the most effective markers of LA myopathy and are backed by the most research. As a result, these markers are the ones most likely to have been investigated for sex-related differences.

Selection process

References from the previously mentioned review articles, which pertain to LA size and LA function in healthy and HFpEF patients were saved. Additional papers were derived from PubMed with the following search queries: “HFpEF left atrial size”, “HFpEF left atrial volume” and “HFpEF left atrial strain”. Papers describing sex differences were found in review articles or with the addition of “sex” to the previous queries. Sex was chosen over gender, because it would align better with physiological and anatomical differences of the body that we are interested in.

Articles published within the last ten years were preferred, but older papers were included if they were deemed relevant. Papers not directly focussed on HFpEF were included to compare HFpEF results against those in healthy individuals and HFrEF patients. Conference abstracts, editorials, commentaries, case reports and studies not written in English were excluded in our selection. The selection of used studies with information on relevant markers of LA size and strain in LVDD or HFpEF patients were collected and summarised in Table 1.

Results

LA size as a measurement of LA myopathy in HF

There are multiple methods to assess LA size (Thomas et al. 2019). While 2D echocardiography is used most frequently, 3D echocardiography has been shown to be more accurate (Wu et al. 2013). However, normative values for LA size with 3D echocardiography have only been established in a small number of subjects (Thomas et al. 2019). Other three-dimensional methods, such as cardiac magnetic resonance (CMR) and computerized tomography, are more accurate as well, but their expense and impracticality hinder their regular utilization in general practice.

The most basic LA size parameters are LA diameter and area. While these parameters are linked to cardiovascular events, it has been shown that LA volume is a more effective predictor (Tsang et al. 2006). Three-dimensional methods are most accurate in measuring LA volume. Results measured with these methods are slightly higher and more reliable because they do not make assumptions on LA geometry (Wu et al. 2013). In the analysis of LA size, diversity in body size needs to be taken into account because it tends to correlate with LA size. Hence, it is recommended that LA volume is indexed to body surface area, based on previous research (Lang et al. 2015). Most research has centred around $LAVi_{max}$, but other volumes, such as minimum LA volume index ($LAVi_{min}$), have been studied as well (Thomas et al. 2019).

$LAVi_{max}$ is associated with AF, HF, hypertension, and coronary artery disease (Rønningen et al. 2020). Age also plays a role, with older HFpEF patients having greater LA dilation (Gehlken et al. 2021). However, it is not entirely clear if $LAVi_{max}$ is affected by age in the healthy population. Some studies show an age-related increase in $LAVi_{max}$ (Singh et al. 2022; Zemrak et al. 2017) and $LAVi_{min}$ (Singh et al. 2022) in healthy individuals. On the other hand, a meta-analysis of 117 studies including 31,201 healthy participants showed no statistically significant difference in $LAVi_{max}$ between different age groups (D’Ascenzi et al. 2019). Their hypothesis is that LA dilation, in the form of increased $LAVi_{max}$, is primarily caused by accumulation of pathological processes, such as hypertension and obesity, and is not caused by natural aging.

LA dilation is associated with HFpEF, but also with HFrEF (Melenovsky et al. 2015). Interestingly, while $LAVi_{max}$ and $LAVi_{min}$ are increased in HFpEF, the increase in HFrEF is even more pronounced. For $LAVi_{max}$, the disparity between the two subtypes is corroborated by a recent meta-analysis (Jin et al. 2022). However, $LAVi_{max}$ seems to be more important in HFpEF, with $LAVi_{max}$ predicting mortality in HFpEF, but

not in HFrEF (Melenovsky et al. 2015). This difference in LA size is also accompanied by other changes. LA dilation in HFpEF is characterised by increased LA stiffness and pressure pulsatility, while in HFrEF eccentric remodelling of the LA plays a more important role. This indicates that the pathology of LA dilation could be different between patients with reduced and preserved LVEF. Therefore, associations with LA size that are found in HF patients are maybe not applicable to HFpEF patients.

LA size as a measurement of LA myopathy in HFpEF

There is significant correlation between LA size and AF in HFpEF. $LAVi_{max}$ (Lam et al. 2017; Reddy et al. 2020, 200) and $LAVi_{min}$ (Reddy et al. 2020, 200) have been shown to rise with increasing AF burden in HFpEF. One study investigated whether a genetic predisposition to AF was causally linked to an increase in LA size. (van de Vegte et al. 2021). Using data from the UK biobank, they found that predisposition to AF causally increased $LAVi_{max}$ and $LAVi_{min}$, independent from hypertension markers. However, it is unclear if LA dilation is the cause or consequence of AF.

AF is known to increase the risk of stroke (Son et al. 2020), and since LA dilation increases the risk of AF, it logically follows that LA dilation also increases the risk of stroke. However, it is unknown if LA dilation is a risk factor for stroke independent of AF. One meta-analysis of 6 studies with 66,007 participants found that LA size was a predictor of stroke independent of AF (Xu et al. 2020). However, this study was not specific for HFpEF, and LA size was determined with LA diameter, which is less accurate. Therefore, it is uncertain if LA dilation is an independent risk factor for stroke in HFpEF.

More recently, indications emerged that $LAVi_{min}$ is a better predictor of HF hospitalization than $LAVi_{max}$ in HFpEF patients (Issa et al. 2017). This is corroborated by another study (Shin et al. 2021). Their composite outcome, which contained HF hospitalization, aborted cardiac arrest and cardiovascular death, was also better predicted by $LAVi_{min}$. This indicates that $LAVi_{min}$ is a more effective prognostic marker for adverse outcomes in HFpEF and could represent a more physiologically relevant parameter for assessing LA myopathy in the context of HFpEF. If $LAVi_{min}$ is a better diagnostic marker of LVDD or HFpEF has not been adequately studied.

Sex differences in LA size in the healthy condition

Generally, LA volume is greater in men compared to women because of their larger body size. Indexing with body surface area does take this size difference into account, but it is unclear if this makes LA volume comparable between men and women. Therefore, it is helpful to examine potential sex differences in LA size in a healthy population. We will primarily focus on $LAVi_{max}$, because it is included in guidelines for HFpEF and because sex differences in $LAVi_{min}$ have not been extensively studied.

Rønningen et al. reported that in a healthy population of 832 Norwegians, $LAVi_{max}$ measured with 2D echocardiography was one ml/m^2 lower in women (Rønningen et al. 2020). Since the cutoff for LA dilation in the EACVI/ASE guidelines is 34 ml/m^2 for both sexes, this could potentially lead to underdiagnosis of HFpEF in women. This disparity in $LAVi_{max}$ between men and women is corroborated by Pritchett et al (Pritchett et al. 2003). They showed that in 767 subjects without cardiovascular disease or cardiac dysfunction, female sex was negatively associated with $LAVi_{max}$, indicating that women have a smaller LA. However, they only provided the median $LAVi_{max}$ of men and women (22 vs 21 ml/m^2), which is only one point apart.

On the other hand, Singh et al. found the opposite (Singh et al. 2022). They found that in a healthy population of 1765 subjects with normal cardiac anatomy and function, $LAVi_{max}$ measured with 2D echocardiography was one ml/m^2 higher in women than men (26.3 ml/m^2, SD: 8.0 vs. 25.2 ml/m^2, SD: 7.9, $p < 0.05$). Despite this, when measured with 3D echocardiography, there was no significant difference in $LAVi_{max}$ between women and men (28.0 ml/m^2 vs. 28.1 ml/m^2) and $LAVi_{min}$ (10.5 ml/m^2 vs. 10.8 ml/m^2). Zemrak et al. also did not find a significant difference between sexes with CMR. They measured $LAVi_{max}$ in 283 subjects without cardiovascular disease and found no significant difference between men and women. These results indicate that potential differences in LA size between healthy men and women are minor and could be caused by variation in measurements.

Sex differences in LA size in HFpEF

Differences in $LAVi_{max}$ in men and women with HFpEF has not been extensively studied. However, some studies do exist on the relationship between $LAVi_{max}$ and sex in HFpEF. Hoshida et al. found in a population of 898 HFpEF patients, that women had a greater $LAVi_{max}$ than men (58, SD: 32 vs. 52, SD: 25, $p = 0.014$) (Hoshida et al. 2022). Their results also indicated that $LAVi_{max}$ was a significant predictor for re-admission for HF in women, but not for men. However, no significant sex interaction was found for $LAVi_{max}$. Moreover, in 422 patients with HFpEF, higher $LAVi_{max}$ was correlated with female sex (linear regression coefficient: -2.88, $p < 0.001$) (Edelmann et al. 2013).

However, Dewan et al. indicated that there were no differences in $LAVi_{max}$ between men and women (36.9 ml/m^2, SD: 17.9 vs. 37.1 ml/m^2, SD:16.8, $p = 0.85$) in 1399 subjects from the I-PRESERVE and TOPCAT trials (Dewan et al. 2019). While the primary focus of these trials was HFpEF, their exclusion criteria, with a LVEF cutoff of 45%, are outdated. Another study in HFpEF patients also indicated that there was no significant difference in $LAVi_{max}$ between sexes in HFpEF (Schulz

et al. 2023). Although, their conclusions may be unreliable, considering their low sample size (25 women vs. 9 men).

There is limited information available on the subject of sex differences in LA size concerning AF and AF-related stroke. Female sex is a risk factor for AF and AF related stroke. However, it is not known if this effect is caused by differences in LA dilation.

LA strain as a measurement of LA myopathy in HFpEF

LA strain is a relatively new parameter to measure LA function and has not been included in any guidelines or scores for HFpEF. While tissue doppler imaging has been used to assess LA function, it is hindered by reproducibility challenges because measurements are influenced by the insonation angle (Thomas et al. 2019). 2D-STE has better reproducibility, but inconsistencies can still arise because differences in apical view selection, timing of initial zero reference, and inclusion or exclusion of the roof of the LA. However, this problem can be overcome by the standardised protocols, which were introduced in 2018 (Badano et al. 2018).

LA function during the three cardiac phases is influenced by different aspects of cardiac function. The reservoir function is affected by LA relaxation and compliance, the conduit function by LV relaxation and stiffness, and the contractile function by LA contractility, as well as LV end-diastolic compliance and pressure (Thomas et al. 2019). Therefore, these aspects of cardiac function can be assessed using LA strain. Alternatively, cardiac function can be assessed using LA strain rate. This is the rate of myocardial deformation, which can be measured during systole, early diastole, and atrial contraction. However, these parameters have not been thoroughly researched. Therefore, our focus will primarily be on LA reservoir, conduit, and contractile strain.

Normal values for LA reservoir, conduit, and contractile strain have been reported to be 39%, 23%, and 17%, respectively (Pathan et al. 2017). However, LA function and LA strain will naturally change with increasing age. Among the healthy population, both LA reservoir and conduit strain decline with age (Nielsen et al. 2021; Singh et al. 2022). In contrast, LA contractile strain will increase with age. This enhanced in LA contractile function in later life is believed to compensate for impairments in the other LA functions, helping to sustain the required cardiac output.

Because of LV-LA coupling, impairments in LVDD can be assessed using LA strain. Higher grades of LVDD are associated with a decline in reservoir function (Morris et al. 2018). Studies on the effect of LVDD grade on LA conduit and contractile strain are limited. One study of 131 women did show that LA conduit strain was impaired in LVDD (Brecht et al. 2016). However, LA contractile strain was higher in grade 1 compared to grade 0, but this can also be explained by older age of the grade 1 group. Grade 2 did show a significant decrease in LA contractile strain compared to controls. Interestingly, the decrease in LA reservoir strain was observed to precede LA dilation in LVDD (Morris et al. 2018). This is corroborated by another study which found a significant decline in LA reservoir strain in patients with hypertension and/or obesity in the absence of LA dilation (Mondillo et al. 2011). This suggests that LA reservoir strain could be a more reliable indicator of early LVDD than LA size.

The association between LVDD grade and LA strain extends further. One study examined 101 patients undergoing RHC, and found that LA reservoir strain significantly correlated with LV filling pressure (Wakami et al. 2009). Of all tested echocardiographic parameters, LA reservoir strain had the best accuracy. A meta-analysis of 7,787 HF patients in 17 studies found that LA reservoir function was a significant independent predictor of all-cause death and cardiac hospitalization, irrespective of HF subtype (Jia et al. 2022). Additionally, a study of 4,901 participants without HF indicated that LA reservoir, conduit and contractile strain were significantly decreased in patients that developed incident HF or death (Inciardi et al. 2022). This indicates that LA strain has prognostic value for HF.

Still, it is important to examine if there are differences in LA strain between HF subtypes. One study that illustrates this importance used cutoffs of 18% for LA reservoir strain and 8% for LA contractile strain to predict elevated LV filling pressure in 332 cardiovascular disease patients (Inoue et al. 2022). Their results indicated that these cutoffs have higher accuracy than conventional parameters. However, their cutoffs were most effective in patients with LVEF < 50%. This can be attributed to the fact that LA function, and consequently LA strain, is poorer in HFrEF compared to HFpEF (Jin et al. 2022). Because impairments in LA strain are not HFpEF specific and its role in LA myopathy could be different between HF subtypes, it is important to examine LA strain in HFpEF populations.

Interestingly, LA strain seems to have incremental prognostic value over $LAVi_{max}$ in HFpEF. LA reservoir, conduit and contractile strain were predictive for cardiovascular hospitalization and death in HFpEF, even after correcting for factors, such as AF and $LAVi_{max}$ (Freed et al. 2016). Additionally, in LVDD patients with normal $LAVi_{max}$, LA reservoir strain was significantly linked to risk of HF hospitalization at 2 years, even after adjusting for age and sex (Morris et al. 2018). This indicates that LA strain holds additional prognostic value over $LAVi_{max}$.

Moreover, LA strain could aid in the diagnosis of HFpEF, particularly in distinguishing between HFpEF and non-cardiac dyspnea. One small study showed that in a population of 49 HFpEF and 22 non cardiac dyspnoea patients that LA reservoir and contractile strain

were significantly lower in HFpEF. Additionally, LA reservoir and contractile strain were shown to be better than E/e' at diagnosing HFpEF (AUC: 0.83 and 0.88 vs. 0.68) (Telles et al. 2019). This is meaningful because E/e' is the best non-invasive predictor of elevated LV filling pressure. Another study with 238 HFpEF and 125 non-cardiac dyspnea patients showed that LA reservoir and conduit strain were significantly lower in HFpEF patients (Reddy et al. 2019). The lack of a significant difference in LA contractile strain between the two groups may be attributed to the HFpEF group having an average age that is 10 years older. They also found that LA reservoir strain was a good predictor of HFpEF (AUC = 0.719), but a composite with E/e' showed the best prediction (AUC = 0.772). This indicates that addition of LA reservoir strain to current guidelines could be beneficial in the diagnosis of HFpEF.

Venkateshvaran et al. investigated if the 2016 ASE/EACVI guidelines for identifying elevated LV filling pressure could be improved by inclusion of LA reservoir strain with the cutoff of < 18% in 210 patients with preserved LVEF (Venkateshvaran et al. 2022). They tested three different models where they (1) substituted TRV with LA reservoir strain, (2) substituted missing data with LA reservoir strain and (3) added LA reservoir strain as an additional parameter. They found that model 1 was had the highest accuracy (AUC: 0.77), but model 2 had the highest feasibility (98%). Their results also indicated that a cutoff of <21% had better balanced sensitivity and specificity. However, they chose a cutoff of <18%, most likely because that had higher accuracy for their cohort where only 21% had elevated LV filling pressure.

Still, there are indications that LA strain is not an effective marker in combination with AF. In permanent AF, LA conduit and contractile strain cannot be accurately assessed (Reddy et al. 2020) and while LA reservoir strain can be measured, one study with 43 HFpEF patients with AF found that LA reservoir strain was below 20% in all but one patient, regardless of LV filling pressure (Inoue et al. 2022). This finding is corroborated by another study that found no association between $LAVi_{max}$ and LA reservoir strain and LV filling pressure in 32 HF patients with AF (Lundberg et al. 2019). This suggest that LA reservoir strain should not be used in the diagnosis of HFpEF when AF is present.

However, LA strain holds prognostic relevance when it comes to AF. LA reservoir and contractile strain adds incremental predictive value in predicting AF in HFpEF patients, independent of other echocardiographic parameters, such as $LAVi_{max}$ (Jasic-Szpak et al. 2021). Additionally, progression of paroxysmal AF into permanent AF was greater in HFpEF patients with severe reductions in LA reservoir strain (Reddy et al. 2020).

Sex differences in LA strain in the healthy condition

LA strain is normalized to the initial shape and size of the LA (Silva et al. 2023). Therefore, the expectation is that size differences in the LA between men and women should not be a confounder. Despite this, some studies do indicate that there are sex differences in LA strain.

One study with a cohort of 1,641 healthy participants demonstrated than men had significantly lower LA reservoir strain (37.9 vs. 40.6, $p < 0.001$) and LA conduit strain (22.2 vs 25.0, $p < 0.001$) compared to women (Nielsen et al. 2021). Additionally, they observed differences in the age-related decline of LA strain. LA reservoir strain was higher in younger women and exhibited a more rapid decline with age compared to men, resulting in lower LA reservoir strain in women older than 65. LA conduit strain was also higher in women, but this effect balanced out with age.

Another study with 1,765 healthy subjects corroborates this difference in LA strain progression with age between sexes (Singh et al. 2022). However, their results indicate that there was no significant difference in LA reservoir strain between sexes. Still, they did show that in men LA conduit strain was lower (27.1 vs. 28.5, $p < 0.05$), and LA contractile strain was higher (14.8 vs. 13.8, $p < 0.05$). While these results are statistically significant, the absolute differences are less substantial than the previous study. As age does affect LA strain, it is important to note that the average age of the two studies was similar. Still, in both studies, sex differences in LA strain progression were not tested for statistical significance.

Sex differences in LA strain in the healthy condition

Considering that women show a sharper decline in LA strain, this could lead to sex differences in LA strain in HFpEF patients. However, to our knowledge, there have been no sex-stratified analyses of the three phases of LA strain in HFpEF.

Discussion

HFpEF is a complex disease with many different facets, with LA myopathy being involved because of LV-LA coupling. Because of this, echocardiographic markers of LA myopathy, such as LA size and strain, can be used to assess the degree of LVDD and help diagnose HFpEF. LA size, measured as $LAVi_{max}$, is already included in the diagnostic guidelines for HFpEF. Incorporation of LA strain in these guidelines could enhance their effectiveness. However, in understanding the pathology of LA myopathy, it is important to note that LA myopathy is not HFpEF specific.

In HFrEF, LA strain impairments and LA dilation are more pronounced compared to HFpEF, indicating that LA myopathy is also present in patients with LVEF <50%. However, it is not known how similar LA myopathy is in the two HF subtypes. LA reservoir strain

has comparable prognostic value for predicting all-cause death and cardiac hospitalization in all HF subtypes. However, $LAVi_{max}$ was shown to be predictive of mortality in HFpEF, but not in HFrEF. The differences in pathology of LA myopathy in HFpEF and HFrEF should be carefully considered when evaluating LA myopathy research in general HF patients. Moreover, further research is needed to investigate if and how LA myopathy differs between HF subtypes.

LA size is a good indicator of LA myopathy and is predictive for HFpEF outcomes. However, there are indications that $LAVi_{max}$, even after indexing with body surface area, is different between sexes. Studies in the healthy population measuring $LAVi_{max}$ with 2D-echocardiography showed conflicting results. However, three dimensional methods of measuring $LAVi_{max}$ found no significant difference between men and women. Because these measurements are more accurate than 2D-echocardiography, this indicates that there are no sex differences in $LAVi_{max}$ in healthy participants. The few studies investigating sex differences in $LAVi_{max}$ in HFpEF patients also show conflicting results. Still, it's worth noting that the participants in the study by Hoshida et al. showed more pronounced LA dilation and were older compared to Dewan et al.'s participants. Therefore, it is possible that differences in $LAVi_{max}$ could only become apparent in later stages of HFpEF. Therefore, sex-based cutoffs for $LAVi_{max}$ would not benefit diagnostic accuracy. In the context of diagnosis, it would be beneficial to perform sex stratified analyses in patients with different grades of LVDD or HFpEF. In such a study, confounders such as age and LA dilation affecting comorbidities should be matched between groups.

The inconsistencies in the 2D-echocardiography also indicate that a switch to 3D-echocardiography could improve diagnostic and prognostic results. A study investigating whether parameters measured with 3D-echocardiography have greater diagnostic or prognostic value compared to parameters measured with 2D echocardiography would be beneficial. Additionally, some studies indicate that $LAVi_{min}$ has better prognostic value than $LAVi_{max}$. However, the added value of $LAVi_{min}$ compared to $LAVi_{max}$ in the diagnosis of elevated filling pressure or HFpEF has not been studied.

Additionally, measuring LA dilation for the diagnosis of HFpEF has its limitations. This is because, an increase in LA size cannot be observed in the early stages of LVDD. Therefore, early detection of LA myopathy or LVDD is not possible by measuring LA size. However, LA reservoir strain could be used for early detection of LA myopathy because it is impaired in the early stages of LVDD.

While LA strain seems to be a great marker for LVDD and HFpEF, not all phases hold equal value. Because LA contractile strain increases with age and decreases with LVDD progression, age plays a confounding factor in measuring LA contractile function. This most likely contributed to the inconsistent results in the significance of LA contractile strain in HFpEF. Moreover, LA conduit strain and contractile strain cannot be accurately measured in patients with permanent AF. While LA conduit strain does show prognostic and diagnostic value, this is trumped by LA reservoir strain. LA reservoir strain has the most research and has been shown to be the best marker for HFpEF and associated adverse outcomes. Still, research into LA conduit and contractile strain should not be discouraged, since they could hold some other diagnostic or prognostic value that has not been discovered.

How LA reservoir strain should be included in guidelines for HFpEF should be the focus of further research. Venkateshvaran et al. showed that incorporating LA reservoir strain in various ways, with a cutoff value of 18%, enhanced the prediction of elevated LV filling pressure. However, this study should be replicated with additional participants and with a more even distribution of patients with normal and elevated LV filling pressures. This should help identify the most ideal diagnostic cutoff value and the best way of incorporating LA reservoir strain into the diagnostic guidelines. Moreover, the accuracy risk scores for HFpEF could be improved by inclusion of LA reservoir strain. Still, it seems that the impairment of LA reservoir strain is not a good predictor of elevated LV filling pressure in patients with AF, highlighting its limitations as a diagnostic tool in this population.

While it is known that LA strain progression differs between men and women in the healthy population, sex stratified analyses for LA strain have not been performed for HFpEF patients. Therefore, it is not known if there are significant LA strain sex differences in HFpEF. Because the decline of LA reservoirs strain with age is faster in women and HFpEF patients are often of older age, the expectation would be that LA reservoir strain would be lower for women. Similar to LA size, LA strain should also be examined in a sex stratified analyses in patients with different grades of LVDD.

While LA size and strain are associated with AF and AF-related stroke, sex stratified analyses for the prognostic value of these parameters have not been performed. Considering that women have a higher chance of developing AF, it is possible that LA size and strain are more predictive for women than men.

Conclusion

While increased $LAVi_{max}$ has been used as an indicator of elevated LV filling pressure in HFpEF, $LAVi_{min}$ is more predictive of adverse outcomes. LA size is similar between men and women in healthy participants. Still, only limited studies are available that stratify by sex in HFpEF patients, but these studies suggest that LA size is increased in women compared to men in late-stage

HFpEF. The prognostic and diagnostic value of LA reservoir strain is better than conventionally used echocardiographic parameters. Additionally, early LVDD is better observed with LA reservoir strain than $LAVi_{max}$. Sex differences in progression of LA strain are observed in the healthy population. However, sex stratified analyses in LVDD and HFpEF populations have not been performed. LA size and strain are associated with AF and AF-related stroke, but sex differences in these associations have not been studied.

Plain English summary

Heart failure is a disease characterised by impaired heart function, leading to an increase in mortality. There are multiple heart failure subtypes based on the left ventricular ejection fraction, which is the fraction of blood pumped out of the left ventricle during systole. Patients with heart failure with a preserved ejection fraction (HFpEF) have an ejection fraction above 50%, which is normal. Patients with HFpEF often have a thicker left ventricle wall, making the left ventricle volume smaller. This impairs left ventricle filling and reduces the cardiac output. This causes heart failure symptoms, such as shortness of breath and fatigue.

In HFpEF, function of the left atrium is often impaired. This is called left atrial myopathy. With echocardiography, the extend of left atrial myopathy can be measured, using multiple parameters. These parameters can also be used to diagnose HFpEF. One of the parameters, left atrial size, is already used in diagnostic protocols for HFpEF. However, a new measure of left atrial myopathy, called left atrial strain, could also be used in the diagnosis of HFpEF. Left atrial strain, which is the amount of left atrial deformation, is lower in patients with HFpEF. Patients with decreased left atrial strain also have increased risk of death and heart failure hospitalization. In addition, diagnostic protocols for HFpEF would improve with addition of left atrial strain. Still, how to optimally include left atrial strain needs to be studied further.

A majority of HFpEF patients are women. Therefore, it is important to study if there are sex differences in left atrial size and strain. Men and women have similar left atrial sizes. However, there is evidence that left atrial volume is higher in women with HFpEF in the advanced stages of the disease. Left atrial strain, which naturally changes with age, is relatively similar in healthy men and women. However, in healthy women, the change in left atrial strain is more noticeable. It is not known if there are differences in left atrial strain in men and women with HFpEF. Currently, there is not enough evidence to advocate for different cutoff values for left atrial size and left atrial strain in the diagnosis of HFpEF.

Structural remodelling in the left atrium can cause atrial fibrillation in HFpEF patients. It is known that left atrial size and left atrial strain are worse in HFpEF patients with atrial fibrillation. However, it is not known if these parameters are different between men and women in HFpEF patients with atrial fibrillation.

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Author	Year	N (mean age, %female)	Population	AF included	LA markers	Sex differences	Outcome	Study design
Wakami et al.	2009	101 (66, 26%)	Patients undergoing RHC	No	LA reservoir strain	NA	Diagnosis	Cross-sectional
Edelmann et al.	2013	422 (67, 52%)	LVDD grade 2/3 patients	Yes	$LAVi_{max}$	Yes	Diagnosis	Prospective
Melenovsky et al.	2015	HFpEF: 173 (71, 58%) HFrEF: 97 (61, 20%) Controls: 40 (63, 53%)	Patients undergoing RHC	Yes	$LAVi_{max}$, $LAVi_{min}$	NA	Mortality	Cross-sectional
Freed et al.	2016	308 (65, 64%)	HFpEF patients	Yes	LAVimax, LA reservoir, conduit and contractile strain	NA	Diagnosis	Cross-sectional
Issa et al.	2017	HFpEF: 40 (72, 50%) Controls 40 (72, 50%)	HFpEF patients and controls, age and sex matched	Yes	$LAVi_{max}$, $LAVi_{min}$	NA	Diagnosis	Cross-sectional
Morris et al.	2018	517 (68, 46%)	LVDD patients and controls	No	$LAVi_{max}$, LA reservoir strain	NA	Diagnosis	Cross-sectional
Dewan et al.	2019	Men: 625 (71,0%) Women: 774 (72, 100%)	I-Preserve and TOPCAT HFpEF patients	Yes	$LAVi_{max}$	Yes	Diagnosis	Cross-sectional
Lundberg et al.	2019	164 (73, 62%)	Patients undergoing RHC	Yes	LA reservoir strain	NA	Diagnosis	Cross-sectional
Reddy et al.	2019	HFpEF: 238 (68, 62%) NCD: 125 (58, 56%)	Patients undergoing invasive haemodynamic exercise testing	Yes	LA reservoir, conduit, and contractile strain	NA	Diagnosis	Cross-sectional
Telles et al.	2019	HFpEF cohort: 49 (69, 71%) NCD cohort: 22 (67, 77%)	Patients with cardiac and non-cardiac dyspnoea	Yes	$LAVi_{max}$, LA reservoir and contractile strain	NA	Diagnosis	Cross-sectional
Reddy et al.	2020	HFpEF no-AF: 181 (66, 60%) HFpEF paroxysmal-AF: 49 (71, 61%) HFpEF permanent-AF: 48 (75, 60%)	HFpEF patients with and without AF and controls	Yes	$LAVi_{max}$, $LAVi_{min}$, LA reservoir strain	NA	Diagnosis	Prospective
Gehlken et al.	2021	HFpEF cohort: 173 (70, 54%) HFrEF cohort: 469 (67, 31%)	HFpEF and HFrEF patients	Yes	$LAVi_{max}$	Yes	Diagnosis	Cross-sectional
Inoue et al.	2021	322 (median 62, 41%)	Cardiovascular disease patients	Yes	LA reservoir and contractile strain	NA	Diagnosis	Cross-sectional
Jasic-Szpak et al.	2021	With AF: 39 (67, 72%) Without AF: 131 (64, 73%)	HFpEF patients	Yes	$LAVi_{max}$, LA reservoir, conduit, and contractile	NA	Diagnosis	Cross-sectional

					strain			
Shin et al.	2021	HFpEF: 347 (71, 54%)	TOPCAT Americas participants	Yes	$LAVi_{max}$, $LAVi_{min}$	NA	Cardiovascular death, aborted cardiac death, or HF hospitalization	Prospective
Hoshida et al.	2022	Men: 406 (80,0%) Women: 492 (82, 100%)	PURSUIT HFpEF participants	Yes	$LAVi_{max}$	Yes	Diagnosis	Prospective
Inciardi et al	2022	4901 (75, 60%)	Healthy participants	Yes	$LAVi_{max}$, $LAVi_{min}$, LA reservoir, conduit, and contractile strain	NA	HF or death	Prospective
Inoue et al.	2022	322 (median 62, 41%)	HF patients undergoing RHC	Yes	LA reservoir and contractile strain, $LAVi_{max}$	NA	Diagnosis	Cross-sectional
Jia et al.	2022	7787 (NA, NA)	HF patients	Yes	LA reservoir strain	NA	All-cause death and cardiac hospitalization	Prospective
Venkateshvaran et al.	2022	210 (61, 65%)	HFpEF patients	Yes	LA reservoir strain	NA	Diagnosis	Cross-sectional
Schulz et al.	2023	Men: 9 (69,0%) Women: 25 (69, 100%)	HFpEF patients	Yes	$LAVi_{max}$	Yes	Diagnosis	Cross-sectional

Table 1: Overview of studies of LA markers in LVDD and HFpEF patients. AF, atrial fibrillation HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; RHC, right heart catheterization; $LAVi_{max}$, maximum left atrial volume index; $LAVi_{min}$, minimum left atrial volume index; LVDD, left ventricular diastolic dysfunction.