Review Article

Progress of echocardiography in the evaluation of left atrial function in patients with heart failure with preserved ejection fraction: a narrative review

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Background and Objective: About half of all heart failures are heart failures with preserved ejection fraction (HFpEFs). As the population ages and metabolic disorders become more common, the prevalence of HFpEF continues to increase annually. Patients with HFpEF typically show a decline in various reserve capacities after exercise. According to recent research, patients with HFpEF may have significant clinical symptoms due to left atrial (LA) dysfunction. Patients with HFpEF may benefit greatly from the early detection of LA myocardial damage using echocardiographic measurements, particularly LA strain. This article examined state-of-the-art echocardiography as it relates to the assessment of LA function in patients with HFpEF.

Methods: Databases such as PubMed, Google Scholar, and Baidu Scholar were searched to retrieve the latest articles on research advances in the field from 1998 to 2024. The article searches were not limited by rigid language or publication date constraints.

Key Content and Findings: This article outlines LA strain measurements using echocardiography, and provides the current normal reference range for LA strain values. Further, the features of differences in LA strain during exercise and rest are outlined for HFpEF patients in varying stages of heart failure. Finally, the clinical significance of LA strain in HFpEF is highlighted, including its substantial advantages in diagnosing diastolic dysfunction and left ventricular filling pressures, as well as its diagnostic and prognostic utility and potential as a therapeutic target.

Conclusions: When evaluating the structure and function of the left atrium in patients with HFpEF, echocardiography shows a great deal of clinical promise. Specifically, LA strain may provide additional useful information for the early identification of LA dysfunction in HFpEF patients. The measurement of LA size is currently the only clinical test available for evaluating the left atrium in individuals with HFpEF. This review will enable ultrasonographers and physicians to better understand the clinical utility of LA strain in patients with HFpEF, and also provides important resources for future LA strain-related scientific research and clinical practice.

Keywords: Left atrium; strain imaging; echocardiography; heart failure with preserved ejection fraction (HFpEF)

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is the most common kind of heart failure today (1). Due to the complex etiology, numerous comorbidities, and diverse pathologic profile of HFpEF, it is difficult to diagnose and treat (2-5). Previous study has shown that left ventricular systolic function is generally preserved in patients with HFpEF (6). However, numerous studies using advanced echocardiography (e.g., speckle-tracking techniques and myocardial work) (7-10) and cardiac magnetic resonance imaging (MRI) (11,12) have found reduced longitudinal myocardial strain in the left ventricle in a significant proportion of patients, suggesting that patients with HFpEF have impaired left ventricular systolic function. Recent research has found a strong correlation between the onset of HFpEF and impaired left atrial (LA) function (13-15). The early evaluation of LA function may aid in the diagnosis and prognosis of HFpEF (16,17). Moreover, studies have shown that enhancing LA activity may be a crucial therapeutic goal for HFpEF (18,19).

Today, LA size and function can be accurately evaluated by echocardiography, computed tomography (CT), and MRI (20,21). However, the routine use of CT and MRI in the evaluation of LA function is limited due to the radiation risk associated with CT, and the lengthy examination time and costs associated with MRI (22). Due to its non-invasiveness, and real-time, comprehensive imaging, and increased repeatability capabilities, echocardiography is becoming a popular imaging modality for evaluating the structure and function of the left atrium in clinical settings (23). Notably, LA strain imaging can identify anomalies in the function of the left atrium prior to anatomical alterations occurring when used to evaluate LA myocardial deformation (24).

This review details specific methods for assessing LA size and function by echocardiography. Specifically, it presents two currently used LA strain imaging analysis methods: the real-time three-dimensional (3D) automatic LA quantitative technique; and the two-dimensional (2D) speckle-tracking technique. Further, it outlines the evolving features of LA function in individuals with HFpEF. In conclusion, this article emphasizes the specific value of LA strain in HFpEF. This article's distinctive strength is its emphasis on the evaluation of LA function using echocardiography in cases of HFpEF. From the standpoint of LA strain, the study's findings shed light on the assessment of LA function using echocardiography, and offer fresh perspectives on the diagnosis and management of HFpEF. We present this article in accordance with the Narrative Review reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-993/rc).

Methods

For this comprehensive review, the PubMed, Google Scholar, and Baidu Scholar databases were searched to retrieve articles published from 1998 to 2024 on echocardiographic studies on LA function in patients with HFpEF. Particular attention was paid to the last 5 years of research on LA strain analysis in patients with HFpEF. Case study reports and conference abstracts were excluded from the review. The following search terms were used: heart failure with preserved ejection fraction, left atrium, pathophysiology, LA remodeling and reverse remodeling, left ventricular diastolic dysfunction, LA strain, strain imaging, echocardiography, cardiac magnetic resonance, normal reference values, diagnostic value, prognosis, treatments, and interatrial shunt devices (*Table 1*).

HFpEF: definition, pathophysiology, and clinical diagnosis

Definition

Patients with HFpEF exhibit a wide range of heart failure symptoms and signs, but their left ventricular ejection fraction (LVEF) is greater than 50% (25). HFpEF is a common and extremely diverse clinical condition. According to recent epidemiological research, HFpEF affects about half of all heart failure patients (26), has a mortality rate similar to that of heart failure with reduced ejection fraction (HFrEF) (27), and has a low 5-year survival rate of only approximately 65% (28). Additionally, as the population ages and metabolic disorders, particularly obesity, metabolic syndrome, and diabetes mellitus, become more common, HFpEF is becoming a serious issue that is endangering human health. In clinical practice, the early detection and diagnosis of HFpEF remain extremely challenging. Unlike HFrEF, HFpEF develops silently, does not show obvious alterations in echocardiographic or biomarker measures, and is associated with a wide range of clinical comorbidities (29,30).

Pathophysiology

The etiology of HFpEF is still unknown and extremely complicated. Initially, most researchers thought that HFpEF

Table 1 A summary of the literature search strategy

Items	Specification
Date of search	April 13, 2024
Databases and other sources searched	PubMed, Google Scholar, and Baidu Scholar
Search terms used	Free-text search terms: heart failure with preserved ejection fraction, left atrium, pathophysiology, left atrial remodeling and reverse remodeling, left ventricular diastolic dysfunction, left atrial strain, strain imaging, echocardiography, cardiac magnetic resonance, normal reference values, diagnostic value, prognosis, treatments, interatrial shunt devices
Timeframe	1998 to 2024
Inclusion and exclusion criteria	Inclusion criteria: clinical trials, cross-sectional study, cohort study, literature review, and systematic review. Articles published in any language were included Exclusion criteria: case study reports and conference abstracts
Selection process	C.L. and D.Y. jointly selected the articles for the review

was caused by ventricular diastolic dysfunction. However, a thorough examination of the pathophysiologic mechanisms underlying HFpEF revealed that the condition frequently causes significant alterations in addition to diastolic dysfunction. These alterations include abnormalities related to left ventricular systolic function, abnormalities related to LA function, pulmonary hypertension, abnormalities/reconfigurations of right ventricular function, increased vascular stiffness, microvascular circulatory disturbances (31), and peripheral abnormalities involving skeletal muscle (32), and fat (33,34). Heart failure symptoms are often caused by multiple impairments in reserve capacity that are present in patients with HFpEF. However, the pathophysiology of HFpEF varies greatly among patients (35), making it difficult to diagnose and treat HFpEF clinically.

Clinical diagnosis

The 2016 European Society of Cardiology (ESC) Heart Failure Guidelines (25) detail the current, widely accepted diagnostic criteria for HFpEF. The diagnosis criteria include: (I) symptoms and signs consistent with heart failure; (II) LVEF ≥50%; (III) elevated levels of natriuretic peptide (brain natriuretic peptide levels >35 ng/L and/or N-terminal pro-brain natriuretic peptide levels >125 ng/L); and (IV) at least one of the following signs of impairment of cardiac structure and function: abnormal diastolic function of the heart; left ventricular hypertrophy and/or LA enlargement.

Echocardiography is largely used to assess aberrant diastolic heart function and compromised cardiac anatomy and function. Diagnosing HFpEF in a large number of dyspneic patients is incredibly difficult. Thus, American academics established the H2FPEF score (36), which is recommended by the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) Heart Failure Guidelines (37), to estimate the probability of HFpEF in patients with unexplained dyspnea. The H2FPEF has a total possible score of nine points. A score of six or more indicates that the likelihood of developing HFpEF is greater than 95%, while a score of zero to one indicates that the likelihood is less than 25%. Further testing (e.g., exercise/rest right cardiac catheterization or Doppler echocardiography) is necessary for those with moderate results (i.e., a score of two to five). In 2019, a consensus recommendation from the Heart Failure Association (HFA) of the ESC proposed the HFA-PEFF scoring system for the diagnosis of HFpEF (38). This system comprises a pre-test assessment, a score derived from echocardiography and natriuretic peptide levels, functional testing (invasive hemodynamic testing or exercise stress echocardiography), and a final etiologic assessment.

Even though the guidelines for HFpEF diagnostic criteria and the related scoring system are constantly being improved, the current diagnosis rate for HFpEF remains quite low. A large epidemiological study (39) of older adults living in the community found that both the H2FPEF score and the HFA-PEFF score inconsistently classified 179 (28%) of 641 participants with unexplained dyspnea. The study also found that high-risk determinations of either score were linked to an increased risk of hospitalization for

heart failure or death in patients. Based on these findings, the present HFpEF diagnostic scores may not accurately identify patients with HFpEF, which will undoubtedly affect their clinical results. The current inability to make an early diagnosis and initiate early therapeutic management is the primary reason for the poor prognosis of HFpEF. Due to the highly heterogeneous nature of HFpEF and its many clinical comorbidities, further studies need to be conducted in the future to further clarify the pathogenesis and diagnostic criteria of the various subtypes of HFpEF. Only then, will targeted, clinical intervention be possible for a sizable HFpEF population.

Echocardiographic assessment of the structure and function of the left atrium

Echocardiography plays an important role in assessing left ventricular diastolic function, and cardiac structure and function in HFpEF. The left ventricle is the main focus of the current clinical evaluation of myocardial function in HFpEF. As our understanding of the overall myocardial and systemic abnormalities in HFpEF has increased, we have come to understand that abnormalities in LA structure and function are intrinsically linked to HFpEF, and LA function plays a critical role in both the early detection and prognostic evaluation of HFpEF. In the following sections, we provide an overview of the recent developments in the evaluation of LA anatomy and function in HFpEF using echocardiography.

LA size

To determine whether the left atrium is enlarged, the internal diameter of the left atrium is currently largely assessed using M-mode and two-dimensional echocardiography (2DE) in the parasternal left ventricular long-axis view and the left ventricular end-systole. It is unreliable to quantify the size of the left atrium using a single diameter, as the left atrium does not expand evenly in pathologic situations. Research indicates that left atrial volume (LAV) evaluation can identify 76% of patients with an enlarged left atrium, while LA diameter evaluation can only identify 49% of patients with an enlarged left atrium (40). Current recommendations (41) advise that the area-length or Simpson approach be used to measure LAV. Further, the phasic volume can be obtained by measuring the LAV at the following three different points during the cardiac cycle: left atrial minimum volume (LAV_{min}) at end-diastole (before mitral valve closure); left atrial pre-systolic volume (LAVpreA) before the P wave on electrocardiogram (ECG); and left atrial maximum volume (LAV_{max}) at end-systole (before mitral valve opening). Based on the measurements above, the following formulas can be used to calculate the left atrial total emptying fraction (LATEF), left atrial expansion index (LAEI), left atrial passive emptying emptying fraction (LAPEF), and left atrial active emptying fraction (LAAEF) (42):

$$LATEF = \left(LAV_{max} - LAV_{min}\right) / LAV_{max} \times 100\% \quad [1]$$

$$LAEI = \left(LAV_{max} - LAV_{min}\right) / LAV_{min} \times 100\% \quad [2]$$

$$LAPEF = \left(LAV_{max} - LAV_{preA}\right) / LAV_{max} \times 100\% \quad [3]$$

$$LAAEF = \left(LAV_{preA} - LAV_{min}\right) / LAV_{preA} \times 100\% \quad [4]$$

Under the area-length approach or Simpson method for assessing LAV, the left atrium is assumed to be a regular elliptical sphere with a normal form. However, the left atrium does not have a regular morphology; its lateral wall is attached to the LA appendage, and its superior and posterior walls receive four pulmonary venous inflows (43). Therefore, there are some restrictions on the use of this measurement approach.

Following the swift advancement of diagnostic ultrasound technology, three-dimensional echocardiography (3DE) has emerged as the preferred modality for evaluating the volume of heart chambers. With no geometric assumptions about the chambers, 3DE allows for 3D, full-volume imaging of the actual shape of the chambers. It also incorporates a semi-/fully automated endocardial tracing technique that improves accuracy and repeatability (44). Research has shown that 3DE has outstanding accuracy and repeatability, and that the agreement between cardiac magnetic resonance and 3DE measurements of LAV in healthy people is better than that of measurements using 2DE (45,46). Currently, the primary limitations of 3DE are the high requirements for picture quality, and a lack of data regarding normal 3DE values in the healthy population.

It should be noted that to prevent underestimating LA size due to LA shortening, measurements of LAV, whether obtained using 2DE or 3DE, are necessary for apical views of the focused left atrium. The series of standardized apical views, which are based on the criterion of displaying the optimal left ventricle morphology and size, are not applicable in the quantitative assessment of LA size because the long axis of the left ventricle and the long axis of the left atrium are not parallel to each other (41,45). Therefore, for

the purposes of obtaining the largest and most reliable LA size data, apical views of the focused LA should be used for the quantitative assessment of LA size.

LA strain

Myocardial strain refers to the amount that the myocardium has deformed from its initial length (L_0) to its maximal length (L), and is expressed as a percentage. It is calculated using the following formula:

$$strain(\varepsilon) = (L - L_0)/L_0 \times 100\% \quad [5]$$

where negative strain indicates myocardial shortening, and positive strain indicates myocardial lengthening (47). The pace at which myocardial deformation happens is known as the strain rate (SR). Tissue Doppler imaging, cardiac magnetic resonance feature tracking (CMR-FT), and speckle-tracking echocardiography (STE) may all be used to measure myocardial strain. The CMR-FT approach is not commonly used to evaluate myocardial strain because it is time consuming, complex to operate, and expensive, while the clinical application of the tissue Doppler technique is limited due to its angle dependence in detecting myocardial strain (48). Myocardial strain is currently primarily analyzed by STE, which can quantitatively assess cardiac function and ventricular wall motion by accurately measuring myocardial strain, SR, velocity of motion, and displacement. STE can also identify passive or active myocardial motion by tracking myocardial motion frame by frame during each cardiac cycle without angle dependence. STE is typically used to analyze myocardial deformation in the left ventricle; however, in recent years, due to interest in the anatomy and physiology of the left atrium, the method has also been used to examine LA function (49-52). However, as the anatomy and function of the left atrium differ to those of the left ventricle, it is recommended that LA-specific analysis techniques be used for research.

Based on 3D volumetric data, the real-time 3D automatic LA quantitative technique was created specifically for the quantitative analysis of the left atrium. It relies on automatic myocardial tracing to quantitatively assess the LA myocardium, and can be used to analyze not only the LAV and emptying rate, but also the LA longitudinal and circumferential strain (53,54).

Quantification of LA strain

The 2D speckle-tracking technique is based on 2DE. In this method, the subject is connected to the ECG and told to hold their breath for the duration of the image acquisition (three to five cardiac cycles). The examiner then uses the best ultrasonic angle of incidence, depth, and gain to acquire the apical four-chamber and apical two-chamber heart sections, preventing the left atrium from shortening, and obtaining a complete image of LA motion during the cardiac cycle (55). After importing the acquired images into offline software, the LA myocardium's region of interest (ROI) is manually drawn in the apical two-chamber and apical four-chamber heart sections. The recommended width of the ROI is adjusted to 3 mm based on the thickness of the atrial wall (45). The software then records the motion of each myocardial segment based on the ROI, resulting in the acquisition of the phasic strain parameters and the LAV parameters at each time. The LAV parameters include the LAV_{max}, LAV_{min}, LAV_{preA}, and LATEF. The phasic strain parameters include the left atrial reservoir strain (LASr), left atrial conduit strain (LAScd), and left atrial contractile strain (LASct); the left atrial SR parameters include the left atrial reservoir strain rate (LASRr), left atrial conduit strain rate (LASRcd), and left atrial contractile strain rate (LASRct) (*Figure 1*).

With the subject attached to an ECG, the real-time 3D automatic LA quantitative technique uses a 3D volumetric probe to assess LA strain. The subject is instructed to hold their breath while the apical four-chamber cardiac view of the optimal left atrium is adjusted and displayed. Three dynamic images of three cardiac cycles are taken consecutively, and the system automatically stitches the 3D full-volume images together into a full-volume 3D image that includes the intact left atrium. The dynamic images are loaded into offline software and examined to determine the longitudinal and circumferential strains throughout all time phases, as well as the LAV parameters (*Figure 2*). The real-time 3D automated LA quantitative technique assesses myocardial deformation and LAV from a 3D stereoscopic spatial perspective. It is simple to apply, fast to operate, free of geometric assumptions and angular dependence, and thus has a promising future in medicine.

Most myocardial fibers in the left atrium are oriented obliquely and in layers (56). In theory, longitudinal, circumferential, and radial strains in the left atrium can all be measured numerically. Based on the current expert consensus, because the LA wall is extremely thin (43) and varies in thickness (57), strain analysis of the LA wall in segments is not advised (55).

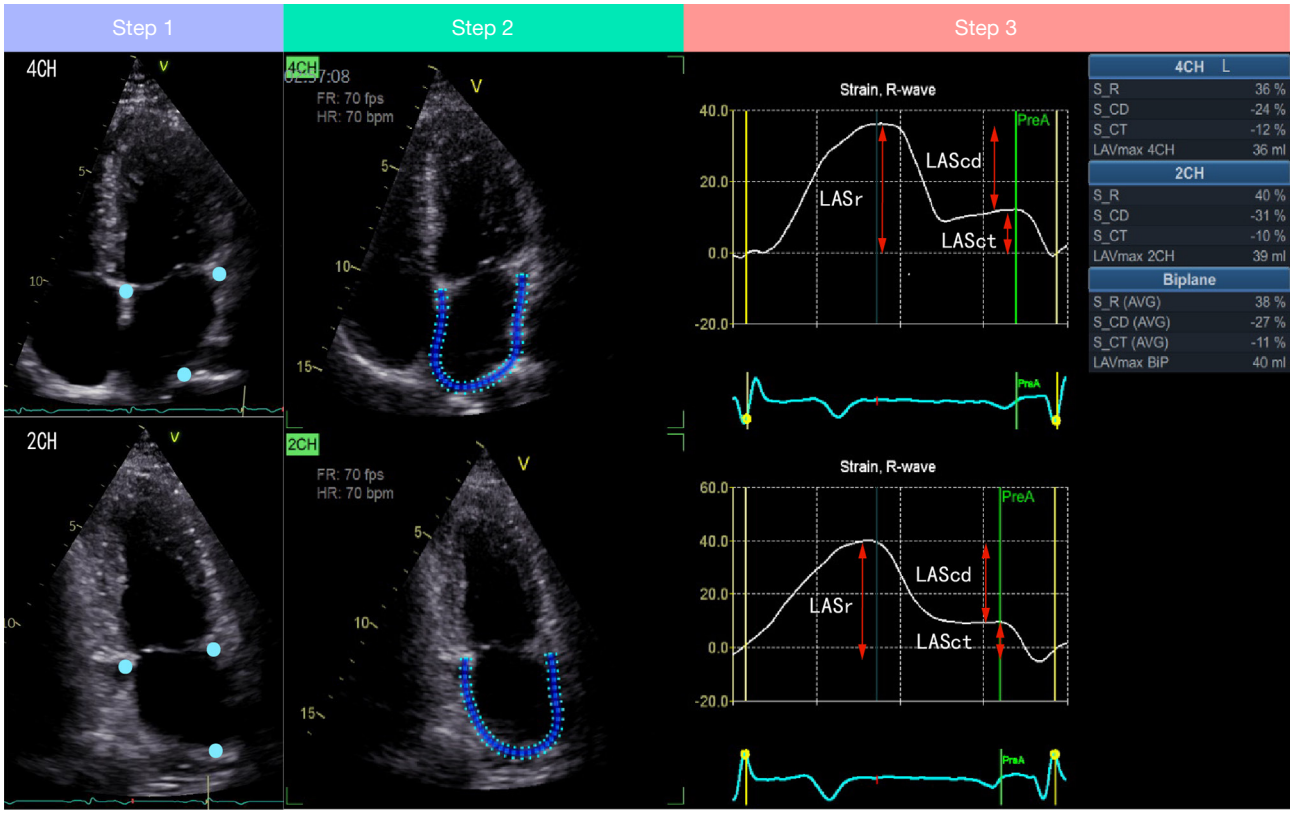

Figure 1 Specific steps for measuring left atrial strain using speckle-tracking echocardiography. Step 1, the apical four-chamber view sequentially depicts the three reference points at the base of the left atrium on the septal side, the lateral wall side, and the top of the left atrium (the blue dots in Step 1); the apical two-chamber view sequentially depicts the three reference points at the base of the left atrium on the anterior wall side, the posterior wall side, and the top of the left atrium (the blue dots in Step 1). Step 2, the application tracks the mobility of the left atrial myocardium automatically and allows the region of interest to be manually adjusted (the blue area in Step 2). Step 3, the software determines the left atrial strain curves, left atrial reservoir, conduit, and contractile strain values, as well as the average strain values for each of the apical four-chamber and apical two-chamber views based on the left atrial myocardial "speckle" motion. 4CH, apical four-chamber view; 2CH, apical two-chamber view; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain.

LA phasic function

Heart output maintenance and left ventricular filling are significantly influenced by normal LA function. LA activity (also referred to as LA phasic function) comprises three phases: the reservoir phase, the conduit phase, and the systolic phase. The atrioventricular ring descends, blood enters the left atrium from the pulmonary venous return, atrial myofibers lengthen, and the atrial volume rises during the reservoir phase, which is associated with the systolic and isovolumic diastolic phases of the ventricle. In this stage, the LA functions as a blood container. Due to the left ventricle's suction force and the pressure gradient between the left atrium and left ventricle, blood from the pulmonary veins and the left atrium passively flows to the left ventricle during the conduit phase, which is associated with early ventricular diastole. In this stage, the LA functions as a blood conduit. The left atrium actively contracts to pump the remaining blood in the atrium into the left ventricle during the systolic phase of the left atrium, which corresponds to the late diastolic phase of the ventricle. This stage of the left atrium equates to the booster pump (58,59).

All phases of the cardiac cycle involve dynamic states for the LA function, which is influenced by various factors. These include the relaxation and compliance of

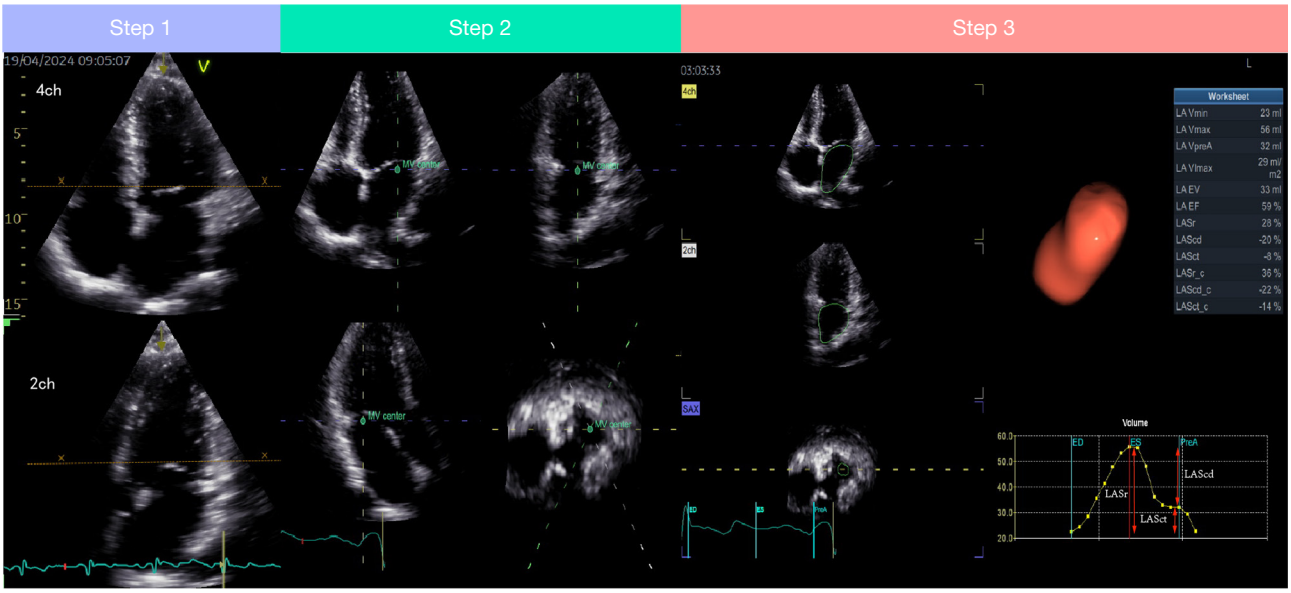

Figure 2 Specific steps for measuring left atrial strain using the real-time three-dimensional automated left atrial quantitative technique. Step 1, the three-dimensional volumetric probe is used to acquire an apical four-chamber view image of the focused left atrium, allowing for a clear demonstration of the motion of the left atrial walls; Step 2, the imaging axis is manually moved to the left atrial chamber's center in the apical four-chamber view, apical two-chamber view, and apical three-chamber view; Step 3, the left atrial myocardium is quantitatively analyzed by the software through automatic myocardial tracing. This results in the creation of a three-dimensional left atrial pattern map, a left atrial strain curve, left atrial volumetric parameters, and three-phase longitudinal and circumferential left atrial strain values. 4CH, apical four-chamber view; 2CH, apical two-chamber view; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain.

the LA myocardium, as well as the left ventricular systolic function (systolic atrioventricular ring downshift) during the reservoir phase (60), the diastolic function of the left ventricle and LA compliance during the conduit phase, and the LA compliance, left ventricular end-diastolic pressure (LA afterload), LAV/pressure (LA preload), and contractility of the left atrium itself during the LA systole phase (61). Throughout the cardiac cycle, the left atrium and left ventricular function interact. As ventricular diastolic dysfunction (such as HFpEF) progresses, LA phasic function initially undergoes compensatory alterations to preserve normal ventricular filling volumes (62). The left atrium cannot, however, provide continuous compensation. The Frank-Staring mechanism states that the LA myocardial elongates beyond its ideal length when it is endlessly subjected to pressure/volume loading. This in turn causes impairment in LA function and eventually LA remodeling (63,64). Further, a key defense mechanism for the pulmonary vasculature is normal LA function. Numerous studies have reported a correlation between impaired LA function and the development of dyspnea (65), exercise intolerance (66), and pulmonary edema (67) in patients with HFpEF. It is possible to help protect the pulmonary vasculature and stop the onset of right ventricular dysfunction by preserving or rebuilding a normal LA (68).

The LA phasic volume parameters and phasic strain parameters can be used to evaluate LA phasic function. *Table 2* shows the LAEI, LASr, and LASRr for the LA reservoir phase function; the LAPEF, LAScd, and LASRcd for the LA conduit phase function; the LAAEF, LASct, and LASRct for the LA systolic function; and the LATEF for overall LA function (61,71).

HFpEF: echocardiographic evaluation of LA function

Alterations in LA function in patients with HFpEF

In the pathophysiologic course of HFpEF, LA dysfunction

Table 2 Left atrial phasic volume, strain, and strain rate correspond to left atrial function and normal reference values*

LA phasic function	Normal values		
	Phasic volume (2DE/3DE†) (45)	Strain‡ (69)	Strain rate§ (70)
Reservoir	LAEI (204%/208%)	LASr (39.4%)	LASRr (2.4±0.5 s^{-1})
Conduit	LAPEF (41%/44%)	LAScd (23.0%)	LASRcd (–2.4±0.7s^{-1})
Contractile	LAAEF (46%/41%)	LASct (17.4%)	LASRct (–2.8±0.6 s^{-1})
Total	LATEF (67%/67%)	–	–

*, when actually using the normal reference values in the table, one should consider the age and gender of the individual, as these normal reference values are restricted to the overall population. †, the data are presented as the median from 276 healthy individuals; ‡, the data are presented as the mean value. The range of normal values for left atrial reservoir strain, left atrial conduit strain, and left atrial contractile strain were derived from 40, 14, and 18 studies, respectively; §, the data are presented as the mean ± standard deviation from 121 healthy individuals. LA, left atrial; 2DE, two-dimensional echocardiography; 3DE, three-dimensional echocardiography; LAEI, left atrial expansion index; LAPEF, left atrial passive emptying fraction; LAAEF, left atrial active emptying fraction; LATEF, left atrial total emptying fraction; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASRr, left atrial reservoir strain rate; LASRcd, left atrial conduit strain rate; LASRct, left atrial contractile strain rate.

is receiving a great deal of attention. Previous studies have demonstrated that most cases of HFpEF are linked to diastolic dysfunction, left atrium enlargement, and pulmonary hypertension, and that an enlarged left atrium is an independent predictor of a poor prognosis in HFpEF patients (72). One of the current criteria for the diagnosis of HFpEF is an LA volume index (LAVI) ≥34 mL/m^2; however, many studies have demonstrated that even if the left atrium is normal in size, its function is abnormally impacted (73,74). A systematic review and meta-analysis of 22 studies (with more than 1,900 patients with symptomatic HFpEF) (75) reported that all LA phasic volumes and phasic strain parameters were significantly reduced in patients with HFpEF compared with healthy controls, showing that LA dysfunction is very common in patients with HFpEF.

The 2022 AHA/ACC/HFSA guidelines for the management of heart failure classify heart failure into four stages (76): stage A (at risk for heart failure); stage B (pre-heart failure); stage C (symptomatic heart failure); and stage D (advanced heart failure). Since heart failure is a progressive disease, it is important to implement effective prevention strategies in stages A and B to prevent or slow the progression of the disease to stages C and D (76). The present investigation found that in heart failure stage A, the primary characteristics are decreased LA reservoir and conduit strain, while contractile strain remains normal; in stage B, the primary characteristics are decreased LA reservoir and conduit strain, along with increased contractile strain; and in stages C and D, the primary characteristics are decreased LA strain values in all temporal phases (reservoir, conduit, and contractile) (77). Exercise intolerance is another significant characteristic of HFpEF sufferers. One of the main reasons HFpEF is difficult to diagnose is that most patients do not exhibit evident heart failure symptoms or abnormalities on echocardiograms while they are at rest; rather, their symptoms and echocardiographic manifestations typically occur during exercise. Exercise-induced LASr is increased in healthy people (77-80); however, in individuals with HFpEF, this increase is less pronounced (*Figure 3*).

In summary, in HFpEF, abnormal changes in LA function occur before structural modifications. These abnormal changes are first observed as decreased strain in the reservoir and conduit, while systolic function remains normal. Reduced LA triphasic strain values are the ultimate sign of the condition, which develops as LA systolic function rises to compensate for the decreased reservoir and conduit strain to maintain normal left ventricular filling. More investigation is still needed on the alterations, diagnostic utility, and prognostic significance of LA phasic function in specific HFpEF subtypes.

HFpEF and LA strain

More and more researchers are focusing on the specific quantitative application value of LA strain parameters because of their accessibility, minor volume load dependence (81), and capacity to provide additional information regarding LA myocardial deformation. Currently, LA strain has shown significant value in evaluating left ventricular filling pressure and diastolic dysfunction, as well as diagnosing and prognosticating

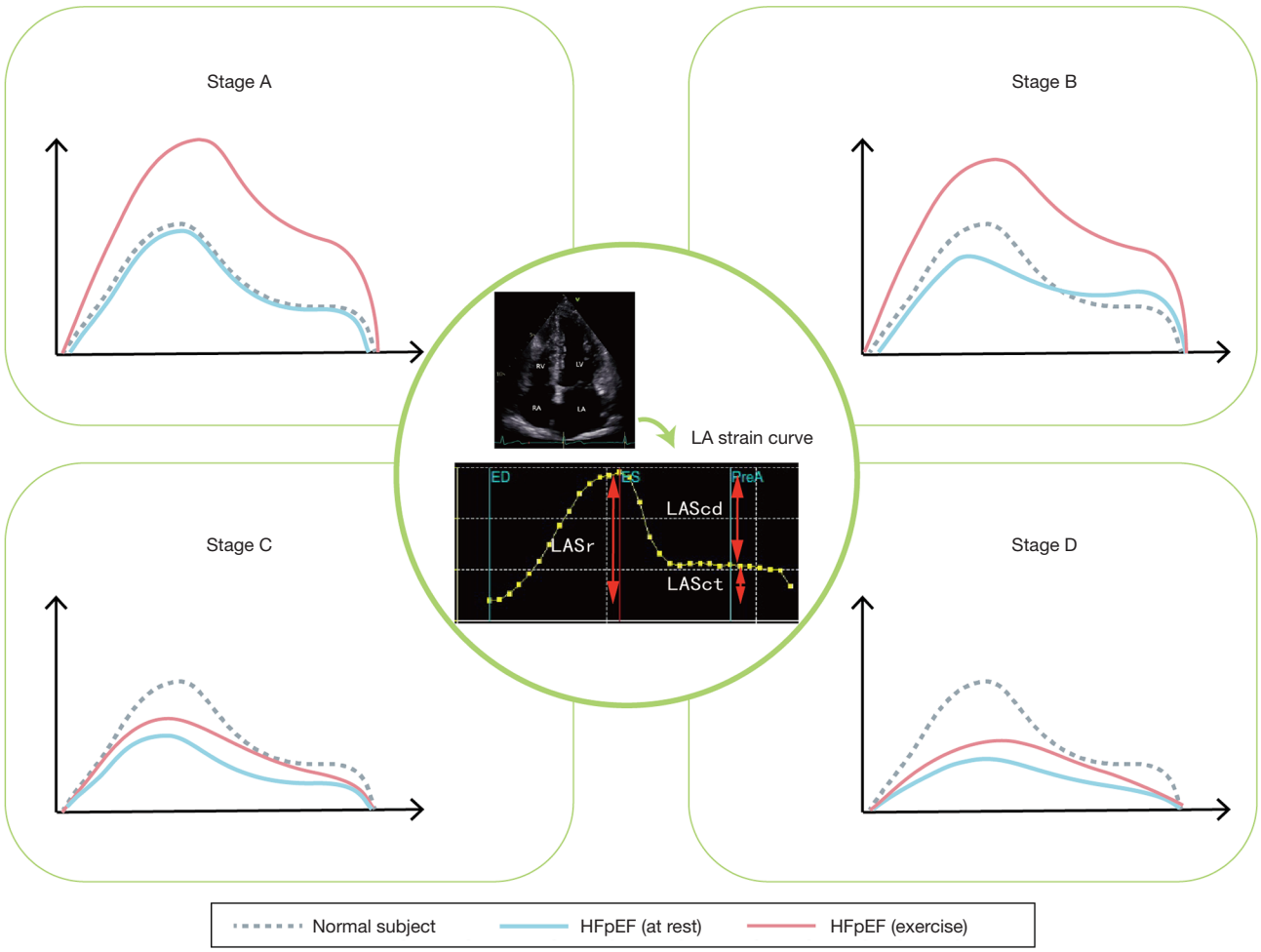

Figure 3 Diagram showing the varied left atrial strain curves in HFpEF patients at different stages of heart failure, both at rest and during exercise. Stage A is characterized by decreased left atrial reservoir and conduit strain, preserved normal contractile strain during rest, and elevated strain values in the left atrial during all phases of exercise. Stage B is characterized by increasing contractile strain and decreased left atrial reservoir and conduit strain, which mainly occurs at rest. During exercise, the extent of the increase in the left atrial three-phase strain values decrease. Stage C and Stage D are characterized by all three left atrial phases (contractile, conduit, and reservoir) having significantly lower strain values. Additionally, there is a further decrease in the degree to which strain values increase during exercise in all three left atrial phases. HFpEF, heart failure with preserved ejection fraction; stage A, at risk for heart failure; stage B, pre-heart failure; stage C, symptomatic heart failure; stage D, advanced heart failure; LA, left atrial; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain.

HFpEF. The precise application of LA strain in HFpEF is covered in more detail below.

LA strain indicates left ventricular filling pressure and diastolic dysfunction

As a sign of increased left ventricular filling pressure, left atrium enlargement is frequently observed in individuals with HFpEF (82). However, LAV measures are not very sensitive in identifying early elevated left ventricular filling pressure because left atrium enlargement reflects a long-term increase in left ventricular filling pressure (83). At present, numerous studies have reported a strong correlation between invasively determined left ventricular filling pressure and LASr (84). Venkateshvaran *et al.* (85) found an independent correlation between pulmonary capillary wedge pressure (PCWP) obtained by invasive

hemodynamics and LASr (r^2=0.41; P<0.001). A PCWP ≥15 mmHg was most accurately identified when the LASr was <21% (sensitivity: 81% and specificity: 64%). Further, the identification of high left ventricular filling pressure was enhanced by adding the LASr to the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging recommendation, before and after LASr was included, the area under the curve (AUC) was 0.69 and 0.77, respectively, with a P value of 0.001 (86). Additionally, Inoue *et al.* (87) discovered that in patients with HFpEF, LASct >14% correctly predicted normal left ventricular filling pressure (accuracy: 92%).

The algorithms used in clinical applications today to evaluate left ventricular diastolic function have many parameters and employ a complicated approach (86). Nonetheless, several studies have found a strong relationship between left ventricular diastolic dysfunction and its grades, as well as LA strain (88-91). Comparing conventional echocardiographic measures to worsening diastolic dysfunction, Singh *et al.* (88) discovered that LA strain reduced progressively, providing an accurate categorization of diastolic severity. According to Frydas *et al.* (89), LA strain was found to be negatively correlated with the severity of left ventricular diastolic dysfunction. This finding was superior to conventional echocardiographic parameters and was useful in diagnosing severe diastolic dysfunction when the longitudinal peak atrial strain of the left atrium was <14.1% (AUC =0.83, sensitivity: 80%, specificity: 77.8%). However, studies have not demonstrated that the present multiparametric assessment criteria for diastolic performance may be substituted with a single LA strain parameter. Nonetheless, LA strain is still a valuable tool for diagnosing and classifying diastolic dysfunction in HFpEF patients. Further research is required to ascertain its critical value in the diastolic function grading system.

Diagnostic significance of LA strain in HFpEF

Presently, it is difficult to diagnose the condition of HFpEF; however, numerous studies have discovered a potential link between LA strain and improved HFpEF diagnosis. In a prospective trial comparing patients with HFpEF and preHF, Rimbas *et al.* (92) found that in comparison to current standards, the highest diagnosis accuracy for HFpEF was observed when the LASRct <–1.66 s^{-1} and the distensibility index (DI) was <0.57 (AUC =0.76, P<0.001). Reddy *et al.* (93) found that an LASr <24.5% (AUC =0.719, P<0.0001) had greater diagnostic accuracy than traditional echocardiographic measures in distinguishing between patients with HFpEF and patients with non-cardiac causes of dyspnea. Additionally, Obokata *et al.* (80) found that in identifying patients with HFpEF at rest, the LASr had a considerable incremental diagnostic value over clinical and conventional echocardiographic measures (P<0.0001). The inclusion of the LASr during the exercise stress test (leg lifts) increased the diagnostic value even further (P<0.0001).

Reports on the diagnostic efficacy of LA strain in enhancing HFpEF vary somewhat among different studies; however, LA strain, especially during exercise stress echocardiography, unquestionably enhances the detection of HFpEF compared with traditional echocardiographic measures.

Prognostic significance of LA strain in HFpEF

The prognostic value of LA strain is also important in patients with HFpEF. Many studies have reported that an increased risk of heart failure hospitalization is significantly associated with a decreased LA strain in patients with HFpEF (50,91,94,95). In a longitudinal study of 308 HFpEF patients examining adverse outcomes, Freed *et al.* (94) found that compared to left ventricular strain and right ventricular strain, LASr had the strongest correlation with increased pulmonary vascular resistance (P<0.0001) and decreased peak oxygen consumption. Echocardiographic LA function assessment can independently predict the risk of hospital admission or mortality in patients with HFpEF, as it is independently related to the composite outcome of cardiovascular hospitalization or death.

One of the most frequent comorbidities of HFpEF is atrial fibrillation (96), which is linked to worse clinical outcomes and more severe diastolic dysfunction (97). According to Reddy *et al.* (98), patients with HFpEF were more likely to experience atrial fibrillation progression when their PCWP, LASr, and LA compliance were all reduced. This suggests that LA myopathy may be a significant risk factor for the development of atrial fibrillation and a valuable target for therapy. To sum up, LA strain provides crucial guidance in clinical management and offers further prognostic information about HFpEF.

LA strain as a therapeutic target

Cardiovascular disease results are improved by LA reverse remodeling, and monitoring left atrium reverse remodeling is greatly aided by LA strain imaging (99). Patients with atrial fibrillation following radiofrequency ablation therapy and those with heart failure following cardiac resynchronization therapy (CRT) were shown to have reversal functional

and/or structural remodeling of the left atrium (100,101). CRT has complicated consequences on the structure and function of the left atrium. According to Martens *et al.*'s research (102), right atrium pacing during CRT had an adverse effect on the morphology, function, and synchronization of the left atrium in heart failure patients, and was linked to worse clinical results. In relation to medication, Kokubu *et al.* (103) found that an improvement in LA reservoir function was only seen in hypertensive patients with normal LA size who were treated with renin angiotensin system inhibitors. This finding implies that once the left atrium has undergone structural remodeling, it may be difficult to reverse its function. Further, the decrease in LA strain may be a sign of negative medications side effects. Sardana *et al.* (104) reported that compared to other antihypertensive medications, β-blocker use was significantly linked with impaired left atrium function in hypertensive patients. This was demonstrated by reduced LA strain values in all periods, which may increase the risk of atrial fibrillation and stroke in patients.

In relation to the management of heart failure, numerous studies have revealed that patients with HFpEF/HFrEF experienced reverse functional and/or structural remodeling of the left atrium following treatment with sacubitril/valsartan (105-107). Thus, sacubitril/valsartan appears to be beneficial for these patients. However according to published clinical trial results, patients with HFrEF experienced a decrease in cardiovascular death and hospitalization when using sacubitril/valsartan (108), but patients with HFpEF did not experience the same benefits (109). While recent clinical trials have shown that sodium-glucose cotransporter protein type 2 inhibitors effectively reduce cardiovascular mortality and hospitalization rates in patients with HFpEF (110,111), there is still a long way to go in the treatment of HFpEF compared to HFrEF. Recent investigations indicated that decreasing the LA pressure load improves LA function, which may be an effective means of treating patients with HFpEF (112). It may be possible to effectively decrease left atrium pressure in patients with HFpEF and enhance their clinical symptoms and quality of life by implanting a shunt device in the atrial septum, which results in left-to-right shunting at the atrial level (113,114). Reversible remodeling of LA function produced by drugs and/or atrial bypass devices may be an effective therapeutic target for HFpEF. Echocardiographic LA strain techniques provide a valuable noninvasive imaging modality for quantifying LA function and tracking the therapy response in HFpEF. Future research is required to ascertain the optimal timing for left atrium reverse remodeling, and the effectiveness and long-term safety of atrial shunt device implantation.

Strengths and limitations

In this section, we consider the limitations and strengths of this review.

The limitations of this review are as follows:

(I) It is possible that this review neglected other noninvasive imaging methods, like cardiac magnetic resonance and CT imaging, as it focused primarily on the latest developments in the evaluation of LA function by echocardiography in patients with HFpEF.

(II) Despite our best efforts, there is a chance that some of the important research on LA strain in patients with HFpEF was not included in this review. It is critical to acknowledge that discoveries and advancements will continue to surpass the scope of this article's coverage, as the mechanisms underlying HFpEF become better understood and noninvasive imaging techniques advance.

The strengths of this review are as follows:

(I) It provided a normal reference range for LA strain values, along with an overview of the two current techniques for assessing LA strain by echocardiography (i.e., the 2D speckle-tracking technique and the real-time 3D automatic LA quantitative technique).

(II) It also provided in-depth descriptions and striking images to illustrate the variability of LA strain in HFpEF patients in various stages of heart failure, both at rest and during exercise.

(III) This article focused on the unique clinical significance of LA strain in patients with HFpEF in terms of diagnosis, prognosis, and treatment. Specifically, it examined the potential utility of LA strain and whether it could serve as a therapeutic target in the future. LA strain provides additional helpful and fresh insights into the diagnosis and treatment of individuals with HFpEF. However, HFpEF is still very difficult to diagnose and treat.

Summary and prospects

The rapid developments in echocardiography have made it possible to evaluate LA function in patients with HFpEF

using a noninvasive, precise, and real-time imaging technique. The diagnosis, prognosis, and treatment evaluation of HFpEF can be further clarified by the quantitative assessment of LA strain, which can also be used to identify diastolic dysfunction and left ventricular filling pressures in certain individuals. Unfortunately, the only clinical evaluation of the left atrium that exists today is the measurement of LAVI, which is far from sufficient. In the future, reference values for normal LA strain in various age and sex groups should be established; however, this will require a greater standardization of LA strain measurements and variations among device vendors. Future research priorities should also include conducting further research into the value of LA strain in the classification, diagnosis, and prognosis of HFpEF subgroups.

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Footnote

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