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ORIGINAL PAPER

LA reservoir strain: a sensitive parameter for estimating LV filling pressure in patients with preserved EF

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Abstract

An elevated left ventricular (LV) filling pressure is the main finding in patients with heart failure with preserved ejection fraction (HFpEF), and LV filling pressure is estimated with an algorithm in the recent American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guideline. In this study, we sought to determine the efficacy of LA global longitudinal strain to estimate elevated LV filling pressure. Seventy-one consecutive patients (mean age of 63.2 ± 9.75, 70% male) who underwent left ventricular catheterization were included. Transthoracic echocardiography was performed within 24 h before catheterization. The LV filling pressure was estimated using echo parameters based on the 2016 ASE/EACVI algorithm. LA GLS was measured using 2D speckle tracking echocardiography in a four-chamber view (GE, Vivid E9 USA). Invasive LV pre-A pressure corresponding to the mean left atrial pressure (LAP) was used as a reference, and > 12 mm Hg was defined as elevated. Invasive LV filling pressure was defined as elevated in 41 (58%) and normal in 30 patients (42%). The LV filling pressure of 9 (13%) of 71 patients was defined as indeterminate based on the 2016 algorithm. Using the ROC method, 25.5% of LA reservoir strain (LASr) had a higher sensitivity (AUC = 0.79, specificity 77%, sensitivity 80%) in estimating LV filling pressure than the 2016 ASE/EACVI algorithm (AUC = 0.75, specificity 77%, sensitivity 70%). LASr, with higher sensitivity than 2016 ASE/EACVI algorithm, may be used as a single parameter to estimate LV filling pressure and hence may add incremental value toHFpEF diagnosis.

Keywords LV filling pressure · Left atrium · Strain · Echocardiography · Diastolic dysfunction

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Abbreviations

HF	Heart failure
LV	Left ventricular
LA	Left atrial
LVEF	Left ventricular ejection fraction
HFpEF	Heart failure with preserved ejection fraction
DD	Diastolic dysfunction
TTE	Transthoracic echocardiogram
TR	Tricuspid regurgitation
AUC	Area under the curve

Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) is increasing due to the aging population with comorbidities [1, 2]. Patients with HFpEF commonly have normal LV systolic function with a normal systolic and diastolic diameter but often have an increased LV wall thickness and left atrial (LA) dilatation. Increased LV filling pressure is an essential finding in patients with HFpEF. Although cardiac catheterization is the gold-standard method to demonstrate elevated LV filling pressure, it is not practical [3]. Therefore, the estimation of LV filling pressure using transthoracic echocardiography has become a standard method due to its feasibility and reproducibility. Conventional Doppler methods such as diastolic mitral inflow measurement from the tip of mitral leaflets with pulse-wave Doppler (PW) and tissue Doppler imaging were previously used to define diastolic dysfunction [4]. To simplify the estimation of LV filling pressure, the 2016 EACVI/ASE guideline provided a new algorithm [5] using similar echo parameters, such as E/e' and left atrium volume index (LAVi).

The left atrium has an essential role in diastole, with its reservoir, conduit, and contraction functions to modulate left ventricular (LV) filling, and both the structure and mechanics of the left atrium change to adapt to diastolic dysfunction (DD) [6]. The atrial functional parameters were impaired at the earliest stage of LVDD before the enlargement of the left atrium [7, 8]. LA speckle tracking strain is a novel method to assess LA function. In particular, peak LA strain has become an essential parameter to evaluate LA compliance, which is highly crucial for LV filling and hence normal diastolic function [9].

In this study, we aimed to evaluate whether LA strain measurement is feasible and reproducible in estimating LV filling pressure in patients with preserved EF. In addition, we sought to determine the incremental value of LA strain as a single parameter for noninvasive estimation of LV filling pressure.

Materials and methods

Patient data

A total of 78 consecutive adult patients who had been prospectively enrolled in a previous study for invasive validation of traditional diastolic echo parameters were reviewed. Patients had undergone clinically indicated coronary angiography, left heart catheterization and transthoracic echocardiography immediately before coronary angiography. Seventy-one of those who had feasible views for LA strain measurement were included in the study. Those with ST-elevation and non-ST elevation myocardial infarction (MI), reduced EF, moderate to severe valve disease, a history of cardiac surgery, any cardiomyopathies, right or left bundle branch block, a prolonged PR interval, and prolonged QRS and atrial fibrillation were excluded. The medical histories, including all clinical and demographic data, were obtained from the electronic medical records. Laboratory results received within 24 h before catheterization were obtained. The study protocol was reviewed and approved by the ethical committee.

Transthoracic echocardiography

Seventy-one patients who met the clinical criteria for study inclusion underwent two-dimensional echocardiographic imaging at the Ankara University Cardiology Department. Two experienced physicians performed two-dimensional, color flow, continuous pulse-wave, and tissue Doppler TTE using a Vivid E9 imaging system (GE Medical Systems, Chicago, USA) on the same day (within 1 h) but before left heart catheterization, and measurements were obtained in a standard manner as recommended by the American Society of Echocardiography. LV dimensions were measured in the parasternal long-axis view at end-systole and end-diastole. LV ejection fraction was calculated from 4-chamber views using the modified Simpson method.

TTE parameters assessed LV diastolic function

Diastolic filling periods, including rapid filling, diastasis, and atrial contraction, were assessed by pulsed-wave Doppler. Mitral inflow at the level of mitral valve leaflet tips was used to measure the peak early (E-wave) and late (A-wave) diastolic flow velocities and to calculate the E/A ratio. In addition, tissue Doppler imaging (TDI) using PW was performed with the sample volume at the lateral and septal mitral annulus to obtain lateral e' and medial e' velocities. The arithmetic mean of lateral and medial e' was defined as the average e', which was used to calculate the E/e' ratio.

The peak velocity of the tricuspid regurgitation (TR) jet was measured using continuous-wave Doppler. Left atrial volume was measured using a 4-chamber view and divided body surface area (BSA) to calculate the left atrial volume index (LAVi).

Left atrial global longitudinal strain

A four-chamber view with 50–70 fps was selected in the Echo Pack imaging workstation (Echo Pack imaging systems). 2D speckle-tracking echocardiography measurements of LA strain and strain rate were obtained according to the standardized measurement recommendations of the 2018 EACVI/ASE consensus document [10]. If the LA image quality was not suitable for measurements or if tracking quality could not be improved by adjusting the region of interest (ROI), the image was not used to measure LA strain. Zero reference was defined as end-diastole. The LA cycle was defined as follows:

- Reservoir phase: Reservoir function was assessed by reservoir strain (LASr): LASr is calculated as LASr = peak systolic strain – the strain value at the end-diastole. This value is always positive.
- Conduit phase: Conduit function was assessed by the negative peak strain rate in early diastole (pLASRcd) and conduit strain (LAScd). In sinus rhythm, LAScd is calculated as LAScd = the strain value at the onset of atrial contraction—the peak value of the curve, and this value is always negative. In patients with atrial fibrillation, LAScd has the same value as LASr but with a negative sign.
- Contraction phase: Contraction function was assessed by the negative peak strain rate in late diastole—(pLASRct) and contraction strain (LASct) LASct is calculated as LASct = the strain value at end-diastole (by definition zero)—the value at the onset of atrial contraction. LASct occurs as a result of atrial contraction; thus, it is measured only in sinus rhythm and always has a negative value [10, 11] (Fig. 1).

LV catheterization

Left heart catheterization was performed according to the standard procedure by an interventional cardiologist. Invasive LV systolic and diastolic pressure measurements were performed using a 6-Fr pigtail catheter (Boston Scientific, Marlborough, MA) placed in the left ventricle through the femoral or radial artery before the evaluation of coronary artery visualization. The measurements were obtained after the fluid-filled transducer was balanced with the zero level at the mid-axillary line. Continuous pressure tracings were acquired for at least three consecutive respiratory cycles. As recommended by the 2016 ASE/EACVI guideline, LV pre-A pressure, which corresponds to the mean left atrial pressure (LAP), was defined as the LV filling pressure, and a pre-A pressure > 12 mm Hg was defined as an elevated LV filling pressure [5].

Statistical analysis

Baseline characteristics are presented as the mean ± SD for continuous variables and were compared using Student's **t**-test, or percentages for categorical variable differences were compared using the chi-square test. A p-value < 0.05 was defined as statistically significant. Correlations between LASr and diastolic parameters were analyzed using the Pearson correlation method. Correlations of invasive LV filling pressure with echocardiographic parameters were analyzed using the Pearson correlation method. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of echocardiographic parameters were analyzed using receiver operating characteristic (ROC) curves based on the logistic

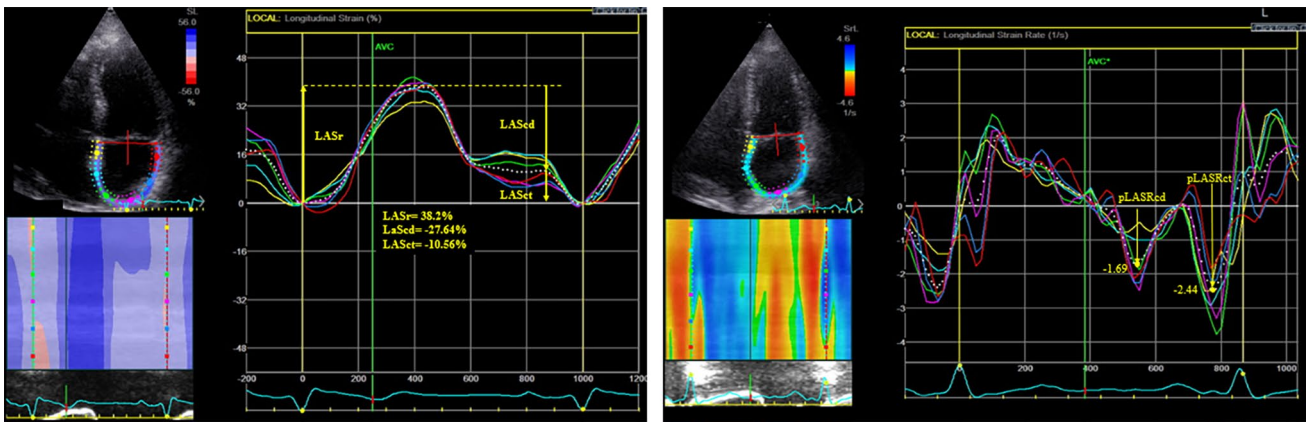

Fig. 1 An example of a study patients' LA strain and strain rate results. LASr = 38.2%. LAScd = − 27.64%, LASct = − 10.56% pLASRcd = − 1.69 and pLASRct = − 2.44

regression method. A cutoff value of LASr was also found using ROC analysis. All data were analyzed using JMP version 14.0 (SAS Institute Inc., Cary, North Carolina).

Interobserver and intraobserver variability

Images from 10 patients were randomly selected, and a second independent blinded observer measured the images to assess the interobserver variability. The first observer who measured all patients' views remeasured the same randomly selected 10 patients' views at least 6 weeks apart from the first measurement. Interobserver and intraobserver variability were assessed using the intraclass correlation coefficient (ICC) method.

Results

Baseline characteristics

The study population included a total of 71 patients (mean age 63.2 ± 9.75, 70% male) who underwent left heart catheterization. All patients were divided into two groups on the basis of their invasive LV pre-A pressure value. The > 12 mmHg group (41 patients; 58%) was defined as the elevated LAP group, and the ≤ 12 mmHg group (30 patients, 42%) was defined as the normal LAP group. In addition, all patients were asymptomatic for heart failure at the time of left heart catheterization and echocardiography. Demographic and clinical characteristics, laboratory results, medication use, and TTE results were compared between groups (Table 1). There were no differences in age, sex, medication use, or comorbidities. Laboratory results (obtained within 24 h. prior LV catheterization), including hemoglobin, platelet count, NT-proBNP, ALT, and AST, were also similar between groups. In addition, baseline SBP and SBP during catheterization were not different between groups.

Echocardiographic measurements

Although (E; 0.72 ± 0.19 vs. 0.62 ± 0.11, p = 0.0055), E/e' (13.2 ± 5.44 vs. 8.65 ± 2.51, p < 0.0001) and the E/A ratio (E/A; 0.96 ± 0.32 vs. 0.73 ± 0.16,p = 0.0002) were significantly higher in patients in the elevated LAP group, there were no differences in the A value between groups. We were able to measure TR jet velocity in 50 patients among the study population, and it was significantly higher in the elevated LAP group (TR velocity; 2.74 ± 0.50 vs. 2.28 ± 057, p = 0.0054). However, LAVi was similar between groups.

LA global longitudinal strain

LA longitudinal strain was measured in 71 patients whose image quality was suitable. LASr (20.44 ± 6.52 vs. 33.1 ± 9.22, p < 0.0001), LAcd (− 9.13 ± 5.57 vs. − 13.6 ± 7.05, p = 0.0055) and LASct (− 12.0 ± 7.06 vs. − 16.2 ± 10.6, p = 0.032) were found to be significantly impaired in patients with elevated LAP. pLASRcd (− 1.43 ± 0.59 vs. − 1.84 ± 1.05, p = 0.03) and pLASRct (− 1.63 ± 0.69 vs. − 2.03 ± 1.13, p = 0.04) were also impaired in the elevated LAP group. The intraobserver (ICC 0.97, CI 95%:0.91–0.99) and interobserver (ICC 0.94, CI95%:0.78–0.98) agreement of strain measurements was excellent.

ROC analysis

Estimated LAP was determined by using the algorithm recommended by the 2016 ASE/EACVI guideline. The LAP of 9 (13%) of 71 patients was defined as indeterminate based on the algorithm. Of those nine patients, six patients had elevated pre-A pressure, and three patients had normal Pre-A pressure. According to the 2016 ASE/EACVI algorithm, 27 (38%) patients were defined as having elevated LAP, and 35 (49%) patients were defined as having normal LAP. The individual effect of parameters used in the algorithm was analyzed, and LAVi was found to be lower in accuracy (AUC: 0.61, specificity 73%, sensitivity 63%) than TR velocity (AUC:0.76, specificity 81%, sensitivity 74%) and E/e' (AUC:0.75, specificity 87%, sensitivity 63%) (Table 2, Fig. 2) in estimating LAP. Although LAScd (AUC = 0.70, specificity 67%, sensitivity 80%) and LASct (AUC = 0.69, specificity 80%, sensitivity 59%), as well as pLASRcd and pLASRct, had low accuracy in estimating LAP. LASr (AUC:0.86, specificity 77%, sensitivity 85%) had high accuracy and sensitivity in estimating LAP (Table 2, Fig. 2). The cutoff value for LASr was 25.5%, and based on the cutoff value, an LASr below 25.5% was defined as elevated LAP. An LASr of 25.5% had a higher sensitivity (AUC = 0.79, specificity 77%, sensitivity 80%) in estimating LV filling pressure than the 2016 ESC/ASE algorithm (AUC = 0.75, specificity 77%, sensitivity 70%) (Table 3, Fig. 3).

Indeterminate group analysis

The LAP of nine (13%) patients was defined as indeterminate based on the algorithm. Six of these patients had elevated invasive LAP, and three of them had normal LAP. Patients in the elevated LAP group (N = 6) had impaired LASr compared to the normal LAP group (N = 3) (19.15 ± 4.58 vs. 37.44 ± 3.61, p = 0.001). The 25.5% cutoff of LASr determined that five patients (83%) had invasive elevated LAP. Only one patient with impaired LASr had normal invasive LAP.

Table 1 Baseline characteristics divided by invasive left atrial pressure

Characteristics	Elevated LAP group (n = 41)	Normal LAP group (n = 30)	P value
Age	63.34 ± 9.11	63.0 ± 9.11	0.89
Gender			
Male (%)	27 (65.9)	23 (76.7)	0.32
Female (%)	14 (34.2)	7 (23.3)	0.32
BSA m^2	1.89 ± 0.16	1.89 ± 0.15	0.99
SBP mmHg	120.5 ± 10.5	120.1 ± 11.8	0.85
SBP-catheter mmHg	129.2 ± 10.5	128.06 ± 10.07	0.63
HT (%)	33 (80.5)	23 (76.7)	0.69
DM (%)	14 (34.2)	13 (43.3)	0.43
HL (%)	14 (34.2)	11 (36.7)	0.82
Medication			
ACE inhibitors (%)	16 (39.0)	11 (36.7)	0.83
ARB (%)	17 (41.5)	12 (40)	0.90
Beta blocker (%)	18 (43.9)	14 (46.7)	0.82
Aldosterone inhibitors (%)	4 (9.8)	2 (6.7)	0.64
Diuretic (%)*	16 (39.0)	10 (33.3)	0.62
Statin (%)	9 (22)	9 (30)	0.44
Laboratory result			
Hemoglobin g/dl	13.6 ± 1.57	14.4 ± 2.49	0.11
Platelet	249 ± 75.05	246.7 ± 64.2	0.88
Creatinine (mg/dl)	0.82 ± 0.12	0.84 ± 0.14	0.64
ALT U/L	21.4 ± 3.58	21.2 ± 3.96	0.88
AST U/L	21.3 ± 2.33	21.4 ± 2.96	0.84
NT-proBNP (pg/ml)	72.2 ± 21.07	66.4 ± 21.3	0.26
Catheter result			
Invasive Pre-A pressure	17.1 ± 2.96	7.4 ± 2.14	< 0.0001
Echocardiography			
LVEDD mm	48.3 ± 4.55	48.9 ± 5.38	0.61
LVESD mm	27.02 ± 2.97	28.6 ± 4.84	0.15
EF%	58.8 ± 4.26	57.5 ± 3.46	0.16
E m/sec	0.72 ± 0.19	0.62 ± 0.11	0.006
A m/sec	0.81 ± 0.13	0.78 ± 0.19	0.39
E/A ratio	0.96 ± 0.32	0.73 ± 0.16	0.0002
E/e' ratio	13.2 ± 5.44	8.65 ± 2.51	< 0.0001
TR velocity/sec	2.74 ± 0.50	2.28 ± 057	0.005
LAVI ml/m^2#	33.2 ± 6.64	31.08 ± 4.78	0.11
LA myocardial deformation analysis			
LASr %	20.44 ± 6.52	33.1 ± 9.22	< 0.0001
LAScd %	− 9.13 ± 5.57	− 13.6 ± 7.05	0.006
LASct %	− 12.0 ± 7.06	− 16.2 ± 10.6	0.03
pLASRcd (s^{-1})	− 1.43 ± 0.59	− 1.84 ± 1.05	0.03
pLASRct (s^{-1})	− 1.63 ± 0.69	− 2.03 ± 1.13	0.04

Data are expressed as mean ± SD or as (%)

BSA body surface area, *SBP* systolic blood pressure, *ACE* angiotensin converting enzyme, *ARB* Aldosterone receptor antagonist, *ALT* alanine amino transferase, *AST* aspartate amino transferase, *LVEDD* left ventricular end diastolic diameter, *LVESS* left ventricular end systolic diameter, *EF* ejection fraction, *TR* tricuspid regurgitation, *LAVI* left atrial volume index, *LV* left ventricular, *LASr* left atrial strain during reservoir phase, *LAScd* left atrial strain during conduit phase, *LASct* Left atrial strain during contraction phase, *pLASRr* peak strain during reservoir phase, *pLASRcd* peak strain rate during conduit phase, *pLASRct* peak strain during contraction phase, *p* probability

*Including furosemide and torsemide

#Calculation of left atrial volume ratio body surface area

Table 2 Receiver operating characteristic of echo parameters

Variable	Specificity %	Sensitivity %	PPV	NPV	AUC (95%CI)	P
E/e' ratio	87%	63%	87%	64%	0.75 (0.61–0.84)	< 0.0001
TR jet velocity	81%	74%	83%	71%	0.76 (0.59–0.87)	0.0034
LAVI ml/m^2	73%	63%	76%	60%	0.61 (0.49–0.73)	0.12
LASr %	77%	85%	83%	79%	0.86 (0.74–0.92)	< 0.0001
LAScd %	67%	80%	77%	72%	0.70 (0.56–0.82)	0.036
LASct %	80%	59%	79%	60%	0.69 (0.45–0.80)	0.04
pLASRcd (s^{-1})	67%	80%	76%	71%	0.70 (0.56–0.81)	0.004
pLASRct (s^{-1})	70%	59%	79%	60%	0.69 (0.41–0.80)	0.04

PPV positive predictive value, *NPV* negative predictive value, *AUC* area under curve, *GLS* global longitudinal strain, other abbreviations as in Table 1

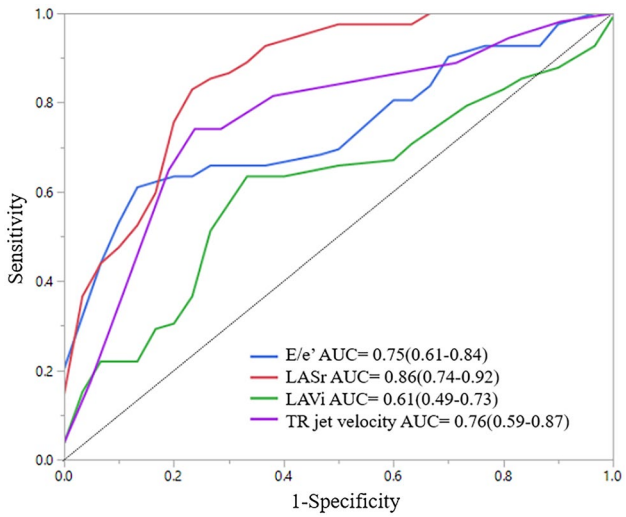

Fig. 2 Receiver operating curves of estimated LV filling pressure. E/e' AUC = 0.75 (95% CI: 0.61–0.84), LAVi AUC = 0.61 (95% CI: 0.49–0.73), LASr AUC = 0.86 (95% CI: 0.74–0.92) and TR jet velocity AUC = 0.76 (95%CI: 0.59–0.87)

Correlation analysis

The Pearson correlation method was used to assess the correlation between pre-A pressure and echo parameters. There was no correlation between pre-A and LAVi (r = 0.18). There was a weak correlation between invasive Pre-A pressure and E/e' (r = 0.34), TR velocity (r = 0.35), pLASRcd (r = 0.33) and pLASRct (r = 0.23). However, there was a moderate correlation between LASr (r = − 0.56) and invasive pre-A pressure (Table 4). There was not a good correlation between LASr and diastolic echo parameters: E/e' (r = − 0.31, p = 0.0066), LAVi (r = − 0.09, p = 0.40) and TR velocity (r = − 0.25, p = 0.043) (Fig. 4).

Discussion

This study confirmed that the measurement of LA global longitudinal strain is practical and reproducible in estimating LV filling pressure patients with preserved EF. Our population also demonstrated that LASr has higher accuracy with higher sensitivity and specificity than LAVi in assessing LV filling pressure. We also observed that LASr measurement estimates the LAP with higher sensitivity than the 2016 ASE/EACVI algorithm.

Increased myocardial stiffness and prolongation of active myocardial relaxation are the main reasons for HFpEF, which leads to elevated LV filling pressure. Thus, invasive evaluation of elevated LV filling pressure is the gold-standard method to define diastolic dysfunction in patients with HF symptoms. However, invasive assessment is not practical or reproducible for all patients with HF symptoms. For this reason, the 2009 American Society of Echocardiography (ASE) and European Association of Echocardiography (now European Association of Cardiovascular Imaging [EACVI] [12]) guidelines were simplified, and a practical algorithm was developed in the 2016 guidelines to estimate LV filling pressure. The studies designed to validate the algorithm with invasive LV filling pressure presented conflicting results. Some of these studies demonstrated good agreement in

Table 3 Receiver operating characteristic of echo parameters

Variable	Specificity %	Sensitivity %	PPV	NPV	AUC (95%CI)	P
Estimated LAP	77%	70%	80%	66%	0.75 (0.64–0.84)	0.0002
25.5% cut point of LASr	77%	80%	83%	74%	0.79 (0.68–0.86)	< 0.0001

PPV positive predictive value, *NPV* negative predictive value, *AUC* area under curve, *GLS* global longitudinal strain; other abbreviations as in Table 1

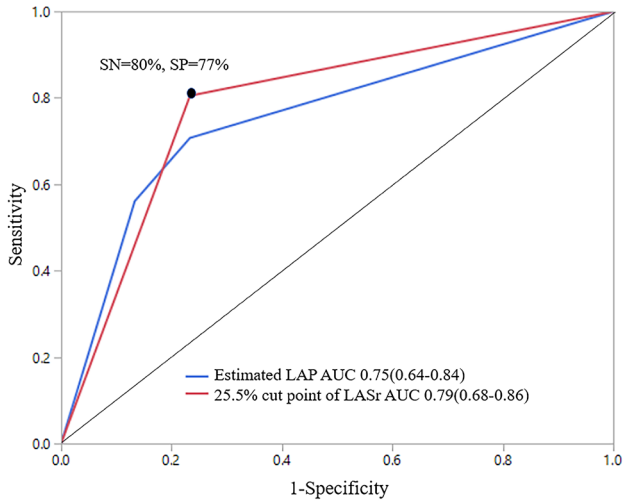

Fig. 3 Receiver operating curves of estimated LV filling pressure. Cutoff point of 25.5% for LASr AUC = 0.79 (95% CI: 0.68–0.86, p < 0.0001) and estimated LAP (the 2016 ASE/EACVI algorithm) AUC = 0.75 (95% CI: 0.64–0.84, p = 0.0002) alone

Table 4 Correlation of invasive LAP and echo parameters

Variable	r	P value
E/e' ratio	0.34	0.0028
LAVi	0.18	0.12
TR velocity/sec	0.35	0.0041
LASr%	− 0.56	< 0.0001
LAScd %	0.41	0.0003
LASct %	0.29	0.016
pLASRcd (s^{-1})	0.33	0.004
pLASRct (s^{-1})	0.23	0.05

r correlation coefficient, other abbreviations as in Table 1

results with invasive LV pressure [12, 13]. For instance, the Euro-Filling study demonstrated a substantial sensitivity to diagnose elevated LV filling pressures with the 2016 recommendations in patients undergoing invasive LV end-diastolic pressure measurement. However, they concluded that the algorithm was suboptimal in patients with preserved ejection fraction [14]. In addition, their result was conflicting when compared with those of similar studies, and they did not demonstrate the echo parameters using the algorithm as a predictor of elevated invasive LV filling pressure [5, 12]. Obokata et al. reported that the new algorithm was specific but poorly sensitive, being able to identify only 34% of individuals with HFpEF diagnosis [15]. Our study also showed that the new algorithm had good specificity but lower sensitivity to predict LV filling pressure.

Even though transthoracic echocardiography is practical and reproducible in determining diastolic dysfunction, it is not feasible in some instances, including in cases of atrial fibrillation and mitral annular calcification, In addition, the LAP of the indeterminate group was found to be increased on the basis of the ASE/EACVI algorithm. Almedia et al. showed an increase in indeterminate cases with the use of the 2016 algorithm in comparison with the 2009 guideline [16]. In addition, Van Dalen et al. demonstrated an indeterminate rate of 48% in their study, which was more than that described in the guideline [17]. The inclusion of TR velocity in the new algorithm might be an important reason for the increase in indeterminate cases. TR velocity generally reflects severe HFpEF; therefore, the early stage of disease may not be evaluated. Moreover, 30% of patients show normal resting diastolic function by standard echocardiographic assessment. [18, 19] Although the cumulative effect of the parameters when using the algorithm gives substantial information about LV filling pressure, the individual parameters have some limitations. In particular, E/e' is load-dependent, might be affected by angle intonation and has poor predictivity, with 37% estimation to detect elevated

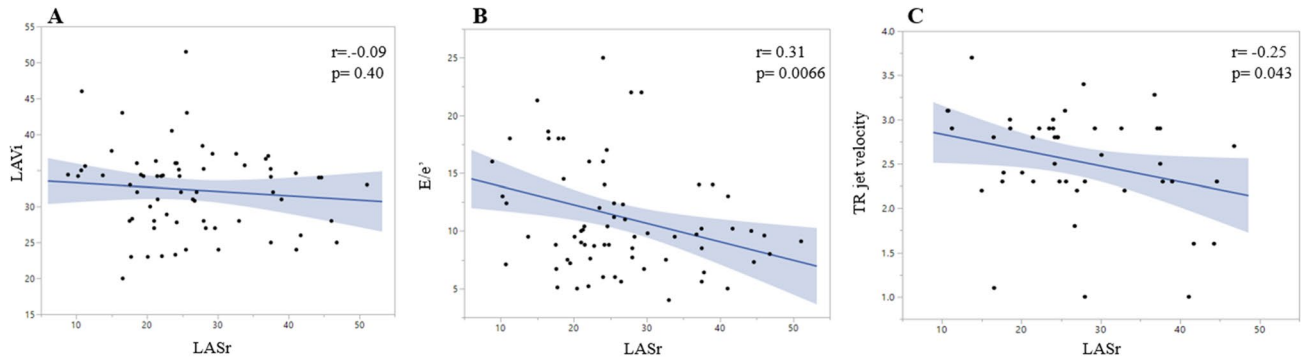

Fig. 4 Correlation of LASr with LAVi, E/e', and TR velocity. No correlation between LA reservoir strain and LAVi (r = − 0.09, p = 0.40) (**a**). Weak correlation between LA reservoir strain and E/e' (r = 0.31, p = 0.0066) (**b**). There was no correlation between LA reservoir strain and TR velocity (r = − 0.25, p = 0.043) (**c**)

LV filling pressures. [3] Nevertheless, LAVi is an adequate parameter to estimate the cumulative effect of increased LV filling pressures [4, 5, 20]. LAVi might be inadequate to detect early LV diastolic dysfunction since this volumetric parameter essentially reflects the chronic effect of elevated LV filling pressure. Our study observed a weak correlation between TR jet velocity and E/e' and invasive pre-A pressure and no correlation between LAVi and invasive pre-A pressure. Additionally, LAVi had lower specificity and sensitivity (specificity 73%, sensitivity 63%) than E/e' TR jet velocity and LASr.

Although LA enlargement is the major finding in patients with HFpEF and predicts a poor prognosis, the significance of LA function in HFpEF is not well understood. Chronic elevation of LA pressure is the essential reason for LA enlargement in patients with diastolic dysfunction. Chronic elevation of LA pressure is strictly associated with LV pressure, as the LV is exposed to the atrium during the diastolic period [21, 22]. LA enlargement is an independent predictor of morbidity and mortality in diastolic dysfunction. Furthermore, LA volume was found to be highly associated with the severity of diastolic dysfunction and disease burden [18, 23, 24].

Nevertheless, one-third of patients with HFpEF still have normal LA size [23, 25]. LA enlargement occurs in the chronic phase of diastolic dysfunction and increases with the severity of the disease. However, in the early phase of diastolic dysfunction, LA size is still normal despite the impairment of its reservoir, conduit, and contraction functions [22]. The PARAMOUNT trial showed worse reservoir, conduit, and contraction function in HFpEF patients regardless of LA size [26]. In addition, chronic dilatation of the left atrium results in deteriorated LA function due to atrial myopathy, which leads to atrial fibrosis [27, 28] and, hence, incomplete recovery of the left atrium after treatment [22]. Likewise, we did not find a correlation between invasive LAP and LAVi. We believe that our study population might have been in thebe early phase of diastolic dysfunction and did not have LA enlargement (mean LAVi = 32.3 $\pm$ 5.99).

Previous studies researched a new method for the early detection of LA dysfunction in diastolic dysfunction Although the most widely used technique is LA anteroposterior measurement in the parasternal long-axis view using M-mode echocardiography due to the nonuniform dilatation and unequal geometry of LA anteroposterior dimension, LA volume measurement is the recommended method to assess LA size and remodeling [29]. LAVi is more accurate in evaluating LA volume than computed tomography (CT), and the biplane disk summation technique, which is theoretically more accurate than the area length method, is recommended to measure LA volume [29]. Although LAVi was found to be highly correlated with the severity of diastolic dysfunction (DD) and cardiovascular risk in patients without AF or valvular heart disease [23], it is not recommended as a parameter to assess LAP in patients with AF, mitral valve disease, bradycardia or high-output states [5]. Although LAVi is recognized as a method to evaluate the estimated LAP, LA enlargement is the chronic result of diastolic dysfunction, and its individual sensitivity is poor to identify elevated LV filling pressure, as we confirmed in our study.

Recently, 2D speckle-tracking measurement of LA strain has become a common tool to evaluate LA function due to its higher sensitivity and specificity, as shown in several studies. Van Grootel et al. defined reference ranges for LA myocardial and volumetric function in healthy adults. They also investigated whether LA phasic function was influenced by age and sex. Their study demonstrated that LA-strain and LA-early strain rate (LA-Sre) were lowest in older subjects, while LA-late strain rate (LA-Sra) was higher. However, they did not find any sex differences in LA phasic function. They also observed that left ventricular diastolic dysfunction is closely related to LA function [30]. In our study, there were no differences in age between groups, which could change the results. Morris, D. A., et al. observed that LA strain measurement had greater sensitivity than LAVI for estimating LV filling pressure, as recommended by 2016 guidelines. They also found a cutoff value of peak atrial longitudinal strain (PALS) of 23%, and PALS < 23% showed 73% sensitivity and 76% specificity in the determination of DD [20]. Cameli M., et al. also showed that the global PALS was a determinant of the LVEDP, and the PALS cutoff value of 18.0% was found to be a better predictor of LVDP above 12 mmHg than E/e' [31].

Additionally, PALS is more highly correlated with pulmonary capillary wedge pressure than other conventional echo parameters, including E/A, E/e', and LAVI, in patients with symptomatic HFpEF [32]. Likewise, Brecht, A., et al. observed specific alterations in different stages of DD. In particular, the reservoir and conduit functions of LA were significantly reduced before symptoms and LA enlargement occurred. In addition, Lin et al. found that the LASr/E/E' septal ratio was a better stand-alone parameter to predict elevated LV filling pressures in patients with stable CAD who had preserved LVEF [33]. Our study also confirmed that LASr has higher accuracy and better sensitivity (AUC: 0.86, specificity 77%, sensitivity 85%) for noninvasive estimation of LV filling pressure than LAVi (AUC: 0.61, specificity 77%, sensitivity 63%). We believe that left atrial strain might be more determinant than LAVI to provide early and accurate information about early-stage diastolic dysfunction, as shown in recent studies [20, 22].

Study limitation

Our study has several limitations, including that it was a single-center study with a small patient group. We included only patients with preserved EF; therefore, we could not evaluate all patient groups with diastolic dysfunction.

Because of our small number of patients, the study had only nine patients with indeterminate LAP; therefore, we could not demonstrate whether LA strain is adequate to define diastolic dysfunction in those patients. Prospective studies will be essential to demonstrate the efficacy of LA strain in the estimation of LV filling pressure.

Conclusion

LA enlargement caused by chronic elevation of LV filling pressure is an independent predictor of hospitalization and mortality in HFpEF patients. In particular, LA enlargement might be irreversible due to LA fibrosis; therefore, early detection of LA dysfunction might be crucial to improve survival in HFpEF. Our findings suggest that LASr may be used as a single parameter in estimating LV filling pressure for the diastolic dysfunction grading algorithm and may be a more effective parameter for the early diagnosis of HFpEF.

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Data availability The data that support the findings of this study are available from the corresponding author, [TST], upon reasonable request.

Declarations

Conflict of interest The authors have no relevant relationships with industry to disclose.

Ethical approval We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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