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Left atrial reservoir strain as a predictor for left ventricular filling pressure in patients with sinus rhythm

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We aimed to evaluate the utility of left atrial reservoir strain (LASr) as a predictor of left ventricular (LV) filling pressure measured via catheterization in patients with sinus rhythm. This prospective study collected data including pre-atrial contraction (pre-A) pressure and LV end-diastolic pressure (LVEDP) from patients undergoing LV catheterization. Transthoracic echocardiography was performed within 24 h to assess LA strain. Patients with supraventricular tachycardia or acute coronary syndrome were excluded. From June 2021 to September 2022, 365 patients (mean age 61.7 ± 11.5 years, 25.5% female) were enrolled. Mean LASr was 28.7 ± 7.4%. LASr demonstrated good discrimination for predicting LV pre-A pressure ≥ 15 mmHg (0.754, 95% CI 0.641–0.820), being significantly better than that of LVEDP ≥ 16 mmHg (0.655, 95% CI 0.592–0.719) using a 24% cutoff (*p* = 0.021). Adding LASr to a model based on HFA-PEFF components improved diagnostic performance (continuous net reclassification index 0.404, 95% CI 0.037–0.807, *p* = 0.032). In patients with indeterminate diastolic function, LASr ≥ 24% reclassified them as normal with 76.9% accuracy. When the 198 patients within the intermediate score group with LASr > 24% were reclassified as 'HFpEF unlikely,' 192 (97.0%) showed normal LV filling pressure. LASr is an independent predictor of LV filling pressure, especially LV pre-A pressure.

Keywords Left atrial function, Reservoir function, Left atrial longitudinal strain, Ventricular pressure, Left ventricular filling pressure

Heart failure with preserved ejection fraction (HFpEF) represents a heterogeneous group of conditions, with many techniques used for its precise diagnosis. Echocardiographic parameters for predicting left ventricular (LV) filling pressure are recognized as useful and have a strong predictive ability for HFpEF.[1,2] Nonetheless, it remains the case that for many patients, existing indices alone do not provide sufficient evidence for a conclusive determination.[3] The Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, and Final etiology (HFA-PEFF) diagnostic algorithm aims to non-invasively predict LV filling pressure in patients with HFpEF by integrating biomarkers such as the N-terminal pro–B-type natriuretic peptide (NT-proBNP), with morphological and functional echocardiographic parameters.[4] However, in real clinical practice, a substantial proportion of patients are classified as having intermediate likelihood, increasing the need for additional testing.[5]

Left atrial (LA) longitudinal strain (LAS), assessed through the cardiac cycle for both systolic and diastolic performance using the speckle-tracking method in echocardiography, shows reduced dependency on the angle and loading conditions. This technique offers a more accurate representation of the LA function. LA reservoir strain (LASr) is used to predict the recurrence of atrial fibrillation (AF), diagnose HFpEF, and is a prognostic factor for cardiomyopathy.[6–9] Additionally, LASr has been studied as a marker for estimating the LV filling pressure.[3,10–13] However, studies suggest a variable cutoff value of LASr for the prediction of elevated LV filling pressure, ranging from 18 to 25, which complicates its adoption in clinical practice due to inconsistencies.[3,7,10,11,13] AF is one of the most common causes of heart failure (HF) and consistently shows lower LASr values compared

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to sinus rhythm, which is also presumed to be a reason for the various cutoffs.[7,11,13] Previous studies have also used varying definitions of elevated LV filling pressure, including LV pre-A pressure, LV end-diastolic pressure (LVEDP), or pulmonary capillary wedge pressure, contributing to the lack of a standardized LASr cutoff.[1,2,14,15] We aimed to investigate which invasively measured LV pressure parameter obtained via LV catheterization is most closely associated with LASr in patients with suspected HF in sinus rhythm. Furthermore, we sought to clarify the potential clinical utility of LASr in this context.

Results

Baseline characteristics, echocardiographic parameters, and invasive hemodynamics

Between June 2021 and September 2022, we registered 365 participants with a mean age of 61.7 ± 11.5 years; of these, 93 (25.5%) were female (Table 1). The median EF was 61.0 (IQR 55.0–65.0), there were 30 (8.2%) patients with a mildly reduced EF and 21 (5.8%) patients with a reduced EF (< 40%). LV pre-A pressure ≥ 15 mmHg and LVEDP ≥ 16 mmHg were observed in 27 (7.3%) and 112 (30.7%) participants, respectively. The average amount

Characteristic	Elevated LV filling pressure (n = 25)	Normal LV filling pressure (n = 340)	*P* value
Age, years	59.0 [52.0–70.0]	63.0 [54.0–71.0]	0.635
Female sex	7 (28.0)	86 (25.3)	0.951
Body mass index (BMI), kg/m^2	27.5 [25.2–30.0]	25.3 [23.2–27.4]	0.010
BMI ≥ 30 kg/m^2	7 (28.0)	37 (10.9)	0.027
Symptom			0.370
Typical chest pain	9 (36.0)	126 (37.1)	
Dyspnea/SOB	13 (52.0)	137 (40.3)	
Atypical/nonspecific symptom	3 (12.0)	77 (22.6)	
Cardiovascular risk factors			
Hypertension	13 (52.0)	184 (54.1)	0.999
Diabetes mellitus	11 (44.0)	123 (36.2)	0.570
Chronic kidney disease	4 (16.0)	11 (3.2)	0.010
Coronary artery disease	7 (28.0)	166 (48.8)	0.071
Medication			
RAS inhibitor	9 (36.0)	139 (40.9)	0.788
Beta-blocker	9 (36.0)	111 (32.6)	0.901
Calcium channel blocker	8 (32.0)	108 (31.8)	0.999
SGLT2i	0 (0.0)	38 (11.2)	0.154
Furosemide	3 (12.0)	4 (1.2)	0.002
Spironolactone	9 (36.0)	139 (40.9)	0.788
Vital signs and laboratory data			
Systolic blood pressure, mmHg	139.0 [120.0–143.0]	135.0 [123.5–146.0]	0.990
Diastolic blood pressure, mmHg	80.0 [69.0–87.0]	79.5 [72.0–87.0]	0.978
Heart rate, beats per minutes	73.0 [61.0–81.0]	66.0 [60.0–76.0]	0.200
Hemoglobin, g/dL	13.9 [11.6–14.6]	14.2 [13.1–15.2]	0.179
eGFR, mL/min/1.73m^2	92.0 [60.0–99.0]	92.0 [81.5–100.0]	0.307
NT-proBNP, pg/mL	20.0 [12.0–142.0]	10.0 [6.0–17.0]	< 0.001
Echocardiographic parameters			
Ejection fraction, %	57.0 [46.0–65.0]	61.0 [56.0–65.0]	0.137
Septal e', cm/s	5.5 [4.6–6.5]	5.9 [5.0–7.2]	0.374
Lateral e', cm/s	7.3 [7.0–8.5]	8.2 [7.2– 9.5]	0.081
Average E/e'	10.7 [8.0–13.7]	8.9 [7.5–10.6]	0.032
LA volume index, mL/m^2	30.4 [24.6–43.7]	28.4 [23.9–33.5]	0.161
LA maximal length, mm	51.8 [49.5–60.0]	50.7 [48.5–53.4]	0.044
Peak TR velocity, m/s	2.2 [2.1–2.5]	2.2 [2.1–2.4]	0.934
LV-GLS (%)	15.1 [12.5–16.6]	16.5 [14.9–17.9]	0.003
LASr (%)	22.0 [19.0–28.0]	29.0 [25.0–33.0]	< 0.001
Invasive hemodynamic parameters			
LV pre-A pressure, mmHg	15.8 [15.0–17.0]	6.0 [3.0–9.0]	< 0.001
LV end-diastolic pressure, mmHg	24.0 [21.0–27.0]	12.0 [10.0–16.0]	< 0.001

Table 1. Baseline characteristics. Continuous variables are presented as medians [interquartile ranges]. Categorical variables are presented as numbers (%). RAS, renin-angiotensin-system; SGLT2, sodium-glucose cotransporter 2 inhibitor; GFR, glomerular filtration rate.

of contrast media used for the participants was 118.2 ± 69.5 mL. There was no statistically significant difference in the amount of contrast media used between groups classified by changes in LV filling pressure.

Association between LASr and previously established parameters estimating elevated LV filling pressure

LASr demonstrated a modest overall correlation with established echocardiographic indicators of LV filling pressure, which showed a positive correlation with septal e' (r = 0.329) and a negative correlation with average E/e' (r = −0.324), LA volume index (r = −0.340), and peak velocity of tricuspid regurgitation (r = −0.270). LASr exhibited a modest negative correlation with NT-proBNP, a known biomarker for the diagnosis of HF (r = −0.330). The LASr showed a weak correlation with the invasively measured LV filling pressure. It had a slightly higher correlation coefficient with LV pre-A pressure (r = −0.288) than with LVEDP (r = −0.215). LASr tended to decrease with increasing diastolic dysfunction grade based on the 2016 guidelines and with higher categories classified by the HFA-PEFF diagnostic algorithm (Table 2).

Cutoff and predicting value of LAS for estimating invasive LV pressure

The diagnostic performance of LASr in predicting elevated LV filling pressure was assessed using two criteria: LV pre-A pressure ≥ 15 mmHg and LVEDP ≥ 16 mmHg. The corresponding AUC for LASr were 0.754 (95% CI 0.641–0.820), and 0.655 (0.592–0.719), respectively. Using the 24% cutoff derived from the Youden index, LASr more accurately identified LV pre-A pressure ≥ 15 mmHg compared to LVEDP ≥ 16 mmHg ($p = 0.021$) (Fig. 1). To assess the predictive performance of LASr for elevated invasive LV pressure across different age groups, participants were stratified into tertiles by age. LASr showed a decreasing trend with increasing age (Supplementary Table S1). However, the LASr cutoff values for predicting LV pre-A pressure ≥ 15 mmHg ranged from 23–24%, respectively, without significant variation across age groups.

In the sequential models predicting LVEDP ≥ 16 mmHg, adding LASr to Model B (Model C) did not show a statistically significant additional benefit in AUC or NRI (c-statistics, 0.707 [0.648–0.765], $p = 0.491$; NRI, 0.176 [−0.046–0.398], $p = 0.061$) (Table 3 and Fig. 2A). However, for predicting LV pre-A pressure ≥ 15 mmHg, LASr as a continuous variable added incremental value to Model B (c-statistics, 0.752 [0.635–0.869], $p = 0.442$; NRI, 0.404 [0.037–0.807], $p = 0.032$), indicating that 40.4% of patients were reclassified in a more accurate direction (Table 3 and Fig. 2B).

Application of LASr to current diagnostic algorithms

Among 26 (13.5% of patients with normal ejection fraction) patients classified as 'indeterminate' based on the 2016 diastolic function guideline, 19 had LASr > 24% and were reclassified as 'normal'. Of these, 18 (94.7%) had normal LV pre-A pressure, while only one had elevated LV filling pressure, yielding a normal prediction accuracy of 76.9% using LASr. The remaining 7 patients with LASr ≤ 24% were evaluated using the guideline's 'estimating increased LA pressure' algorithm and all were classified as having grade I (Fig. 3). None of these 7 patients were diagnosed with elevated LV filling pressure. When applying the algorithm from the expert consensus of 2022 EACVI,[16] 8 patients in our study were classified as 'inconclusive', with a LASr of 31.4 ± 7.3%. All patients had an LASr ≥ 24% and normal LV filling pressure, resulting in a predictive accuracy of 87.5%.

Based on the HFA-PEFF diagnostic algorithm, 64 participants (17.5%) were categorized as high likelihood, and 258 (70.8%) as intermediate likelihood for HFpEF. When the 198 patients within the intermediate score group with LASr > 24% were reclassified as 'HFpEF unlikely,' 192 (97.0%) showed normal LV filling pressure. This approach showed superior diagnostic performance compared to using a high HFA-PEFF score alone for identifying HFpEF (AUC from 0.545 to 0.697, $p = 0.002$).

Sensitivity analyses

To validate our study endpoint, we undertook three sensitivity analyses. First, we excluded 90 (24.7%) participants who had received percutaneous coronary intervention and conducted the same analysis. LASr, as a cutoff of 24%, showed similar incremental value to the main analysis (NRI 0.626, $p = 0.010$) (Supplementary Table S2 and Fig. S1). Second, we excluded 135 (37.0%) participants who reported typical chest pain or discomfort. As in the main analysis, LASr had incremental value in estimating LV pre-A pressure ≥ 15 mmHg (NRI 0.669, $p = 0.007$)

	LASr	*p* for trend
2016 diastolic function guideline		
Normal (n = 134, 36.7%)	31.7 ± 6.1	< 0.001
Grade I (n = 171, 46.8%)	27.4 ± 6.9	
Grade II (n = 21, 5.8%)	23.5 ± 7.9	
Grade III (n = 5, 1.4%)	12.8 ± 6.1	
HFA-PEFF diagnostic algorithm		
Low score (n = 43, 11.8%)	33.0 ± 5.7	< 0.001
Intermediate score (n = 258, 70.7%)	29.2 ± 6.8	
High score (n = 64, 17.5%)	24.0 ± 8.2	

Table 2. LASr According to the Grading of Left Ventricular Diastolic Dysfunction Based on Current Guideline Recommendations. LASr indicates left atrial reservoir strain.

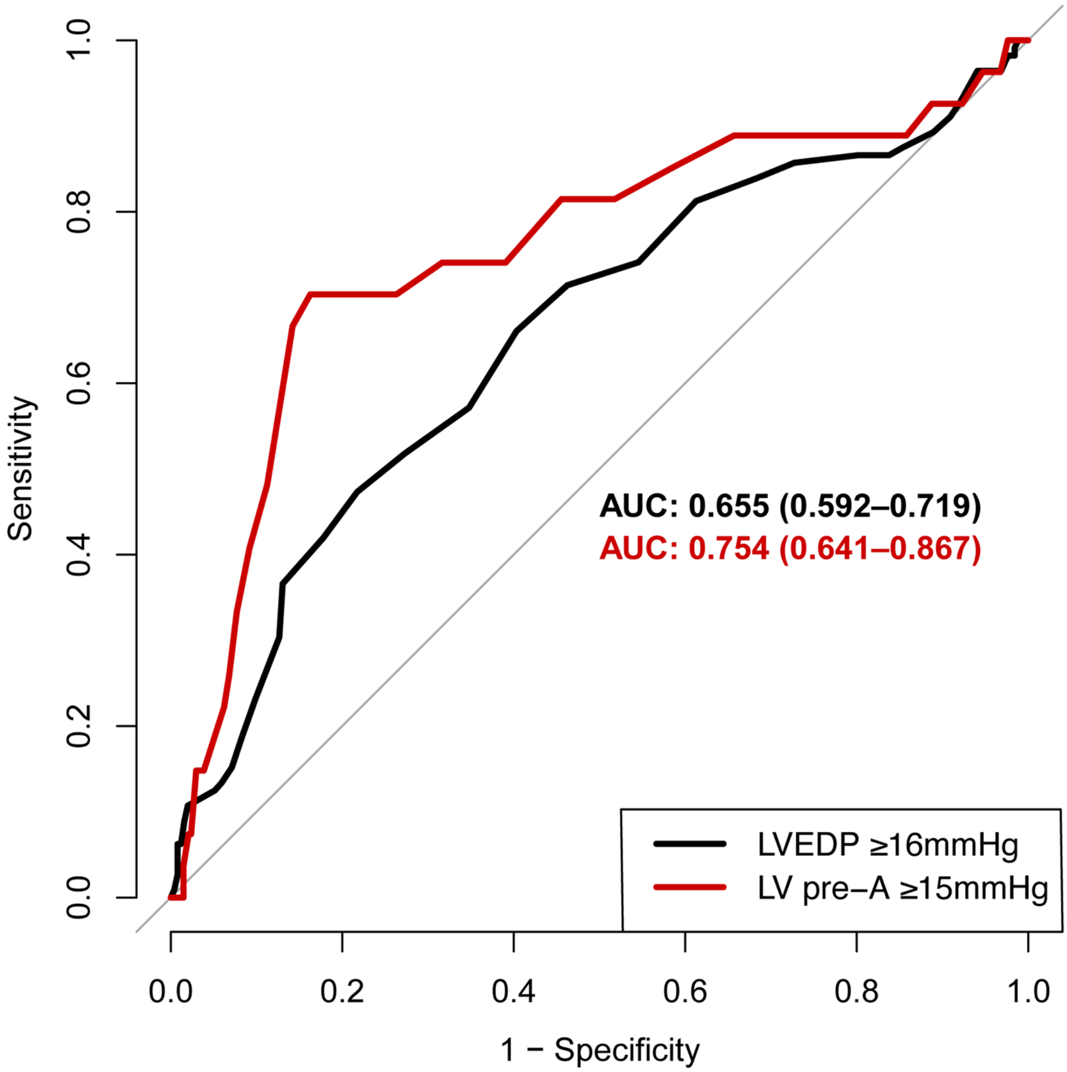

Fig. 1. AUC of LASr to predict elevated LV filling pressure of LVEDP ≥ 16 mmHg and LV pre-A pressure ≥ 15 mmHg. LV pre-A ≥ 15 mmHg had a higher AUC than LVEDP ≥ 16 mmHg with an LASr cutoff of 24% ($p = 0.021$). LVEDP, left ventricular end-diastolic pressure; pre-A, pre-atrial contraction.

	C-statistic		Net reclassification index	
	95% CI	*p*-value for difference	95% CI	*p*-value for difference
LV pre-A pressure ≥ 15 mmHg				
Model A (NT-proBNP)	0.707 (0.592–0.822)			
Model B (Model A + Echocardiographic variables*)	0.714 (0.613–0.815)	0.919	0.359 (-0.030–0.749)	0.071
Model C (Model B + LASr)	0.752 (0.635–0.869)	0.422	0.404 (0.037–0.807)	0.032
LVEDP ≥ 16 mmHg				
Model A	0.663 (0.601–0.725)			
Model B	0.695 (0.637–0.753)	0.385	0.532 (0.317–0.748)	< 0.001
Model C	0.706 (0.648–0.765)	0.491	0.176 (-0.046–0.398)	0.061

Table 3. Incremental value of LASr compared to established variables for predicting invasively measured LV pressure. *Echocardiographic variables included septal e', average E/e', LV-GLS, peak velocity of tricuspid regurgitation, LA volume index, relative wall thickness, LV mass index, which are the components of HFA-PEFF diagnostic algorism.

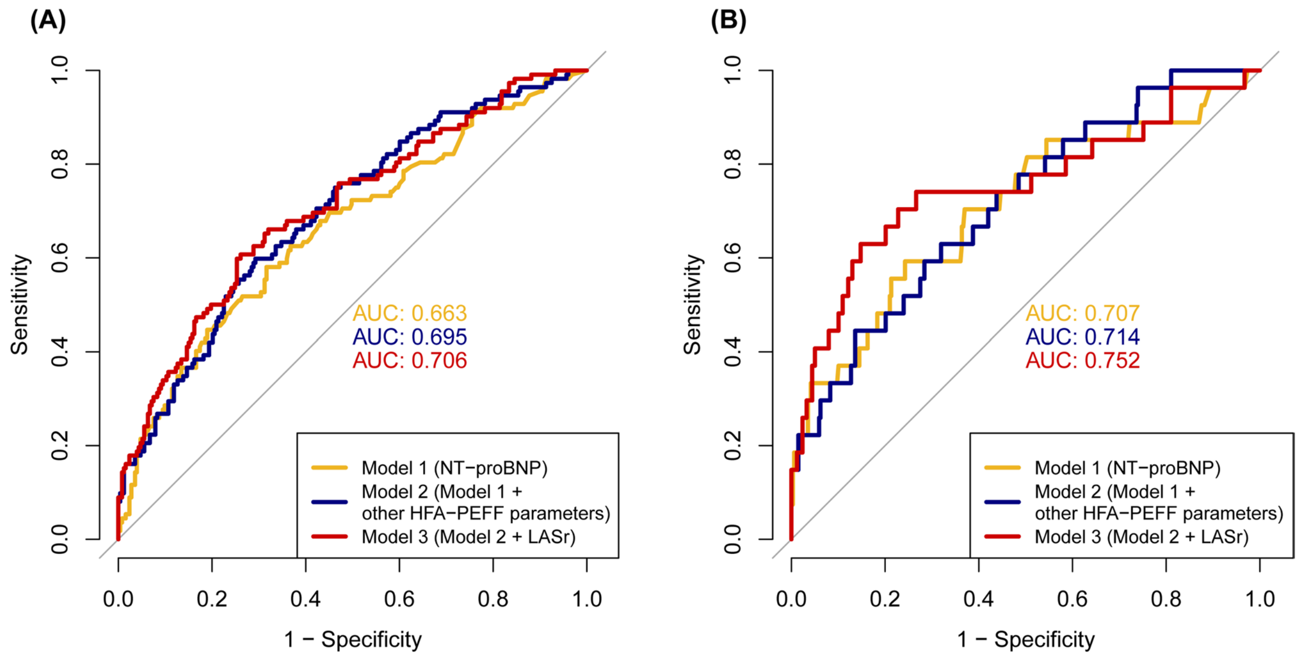

Fig. 2. AUC of sequential models to predict elevated LV filling pressure of (**A**) LVEDP ≥ 16 mmHg and (**B**) LV pre-A pressure ≥ 15 mmHg. LASr demonstrated incremental value in sequential models for predicting LV pre-A pressure ≥ 15 mmHg, but not for LVEDP ≥ 16 mmHg. Model A includes the biomarker NT-proBNP, and Model B expands on Model A by incorporating various echocardiographic parameters from the HFA-PEFF diagnostic algorithm (septal e', average E/e', LV-GLS, peak velocity of tricuspid regurgitation, LA volume index, relative wall thickness, LV mass index). Model C expands on Model B by incorporating LASr as continuous variable. LASr, left atrial reservoir strain.

(Supplementary Table S3 and Fig. S2). Lastly, we performed an analysis excluding 21 participants (5.8%) with EF < 40%. The AUC for predicting LV pre-A ≥ 15 mmHg was 0.751, which was comparable to the main analysis, and the NRI also demonstrated a statistically significant incremental value over model 2. (Supplementary Table S4 and Fig. S3).

Measurement reproducibility of LASr

The consistency of LASr measurements, when assessed by the same observer, showed strong reproducibility, as evidenced by the intra-class correlation coefficient of 0.97 (95% CI 0.92–0.99). Similarly, the intra-class correlation coefficients of inter-observer variability for LASr were recorded at 0.96 (95% CI 0.90–0.98). Bland–Altman plots are provided in Supplementary Fig. S3.

Discussion

This prospective observational study showed that LASr, when assessed noninvasively via echocardiography, shows a strong association with LV filling pressure measured invasively, especially when analyzed in combination with established biomarkers and echocardiographic parameters. LASr is more closely associated with LV pre-A pressure, which correlates better with mean pulmonary wedge pressure than LVEDP, and is particularly predictive at a cutoff of 24%, as supported by previous research. To the best of our knowledge, our study enrolled the largest cohort of participants utilizing LASr to estimate LV filling pressure by LV catheterization. Moreover, this study plays a pivotal role by comparing different previously reported cutoffs of LASr, which are known to aid in predicting LV filling pressure and may potentially provide significant assistance in real-world clinical settings.

Many investigators have studied methods for noninvasively estimating LV filling pressure. The recent expert consensus on algorithms for predicting LV filling pressure advises evaluating LASr when diastolic function is indeterminate according to the 2016 guidelines, thereby positing that an LASr of < 18% may indicate elevated LV filling pressure.[16] A multicenter study involving 322 patients who underwent LAS analysis to determine the presence of elevated LV filling pressure supported this consensus.[13] However, the study included 43 (13%) patients with AF, all but one of whom had LASr values < 20%, which may have skewed the average LASr downward. A recent expert consensus has cautioned against the use of LASr for estimating LV filling pressure in patients with AF, given their typically lower LAS values.[16] In addition, in the supporting study for the recommendation, 25% of participants had an ejection fraction < 40%, and LV filling pressure was assessed using inconsistent methodologies, including both right and left heart catheterization.[13] Another study identifying the correlation between LV filling pressure and LASr suggested a low cutoff of 12%; however, in this study, patients with AF comprised 47% of the study population.[17] According to a recently published study, the optimal value of LASr for predicting elevated LV filling pressure in patients with atrial fibrillation was as low as 10%.[18] In our

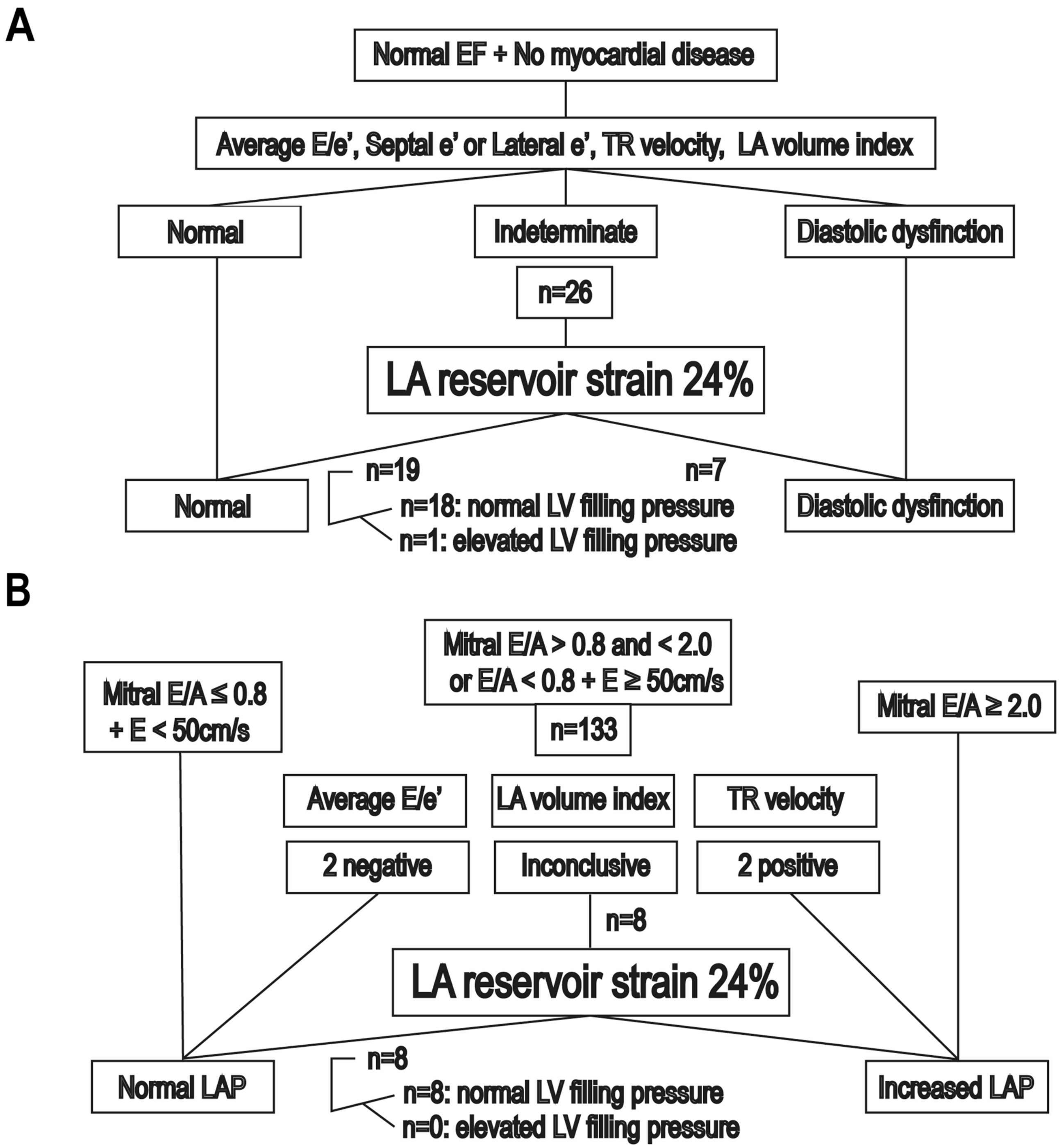

Fig. 3. Application of LASr to current diastolic function guideline. (**A**) Among 26 (13.5% of patients with normal ejection fraction) patients classified as 'indeterminate' based on the 2016 diastolic function guideline, Nineteen with LASr > 24% were reclassified as 'normal', of whom 18 (94.7%) had normal LV filling pressure. (**B**) Among 8 patients classified as 'inconclusive' (LASr 31.4 ± 7.3%), none had an LASr < 24%, and all had normal LV filling pressure.

study, we decided from the design phase to exclude supraventricular tachycardia including AF, which could affect LA function, and prospectively collected data, enabling us to attain a sample volume significant enough for statistical relevance even in patients without AF. Large-scale studies exploring the additive value of LASr in the 2016 guidelines also suggested a cutoff of approximately 23–24% for LASr.[3,11] In addition, a large-scale study (n = 2712) that excluded patients with AF and suggested the use of LASr as an indicator to predict a high HFA-PEFF score of 5 or more also sets the LASr cutoff at 25%.[19] Therefore, in patients with sinus rhythm, it may be necessary to adopt a slightly higher LASr cutoff of 24% for detecting elevated LV filling pressure compared to previously suggested thresholds.

When measuring the LV filling pressure from an invasively measured LV pressure curve, the two indicators used were LV pre-A pressure and LVEDP. Although LVEDP has been used in many studies, elevated LVEDP without an increase in mean LA pressure does not cause pulmonary venous hypertension, pulmonary vascular congestion, and the resulting respiratory distress.[14,20] Previous studies validating the 2016 diastolic function guidelines also showed that when predicting invasively measured LVEDP ≥ 15 mmHg, the predictive power decreases when EF > 50%.[21] In another study validating the 2016 diastolic function guidelines using PCWP or LV pre-A pressure, the predictive power of echocardiographic indicators was demonstrated across large sample sizes.[1] According to a study of LASr and pre-A pressure, the AUC value of LASr for predicting elevated LV filling pressure was 0.79, which is higher than the 0.75 value in the 2016 guidelines.[10] Furthermore, in a previous study based on another invasive measurement, LASr predicted pulmonary capillary wedge pressure better than the E/e', which is known for predicting LVEDP.[12] In our study, LASr of 24% cutoff showed higher AUC value than LVEDP in predicting LV pre-A pressure. Considering LA mechanics, LASr measures the expansion of the LA from late systole to the onset of diastole, which is temporally closer to the LV pre-A pressure than to the end-diastolic pressure. This temporal proximity explains the superior predictive ability of pre-A pressure.

In previous studies evaluating LA function, maximal LA length was reported to confirm the absence of foreshortening prior to assessing LA function. The average LA maximal lengths measured from apical four- and two-chamber views among participants in their 60 s were 50.0 mm for women and 53.0 mm for men—values comparable to those in our cohort (50.3 mm for women, 51.6 mm for men).[22] The LAVI in participants with normal LV filling pressure was comparable not only to the values reported in a cohort of the same ethnicity that investigated normal reference ranges for LA strain (27.0 ± 6.0 mL/m^2), but also to the international multicenter reference value of 25.7 ± 7.9 mL/m^2.[23,24] Given the low median LAVI of 29 mL/m^2 in our cohort, the LASr cutoff proposed in this study may be suitable for patients with pre-clinical or early-stage HF, before significant LA structural remodeling occurs.

Our study had some limitations. First, because this study was designed as a prospective observational study to explore the association between invasively measured LV pressure and LA strain, LV catheterization was not limited to patients with overt HF symptoms. To address this limitation, we conducted sensitivity analyses excluding patients with critical coronary stenosis or chest pain, and the findings remained consistent with the primary analysis. Moreover, as most participants in this cohort had not been previously diagnosed with HF, our results may support the clinical use of LA strain in the pre-clinical stage of HF. Second, considering the age-related decline in LASr reported in previous studies, our cutoff may potentially misclassify elderly individuals with normal LV filling pressure as false positives.[25] Age-adjusted LASr thresholds for predicting elevated LV filling pressure may be warranted as more data become available from international multicenter studies using standardized methods. Third, this was a single-center observational study. The cutoff value of LASr was determined using the Youden Index in the same population in which it was also tested. Ideally, the Youden Index should be computed in a derivation cohort and subsequently validated in an independent or prospective population, and this methodological issue should be acknowledged as a limitation of our study. Nevertheless, it should be noted that the LASr cutoff of 24% was not originally proposed in our study but has also been suggested in previous studies.[3,11,19] Lastly, this study was conducted in an East Asian population. Future external validation of our study is required in multicenter and multi-ethnic populations.

In Conclusion, LASr—with a cutoff value of 24%—showed a stronger association with LV pre-A pressure than with LVEDP in patients with sinus rhythm. LASr showed incremental value in predicting LV pre-A pressure beyond established parameters, suggesting its potential role in complementing current guidelines.

Methods
Study participants
This prospective observational cohort study was conducted at a single referral hospital (https://trialsearch.who.int. Unique identifiers: KCT0006253). We enrolled patients aged ≥ 20 years who underwent catheterization to measure LV filling pressure invasively, following invasive coronary angiography. We excluded patients requiring emergent or urgent coronary angiography for myocardial infarction or acute coronary syndrome, as well as those with supraventricular tachycardia including AF, atrial flutter, and atrial tachycardia, as evident on electrocardiograms. Patients who consented to participate in the study underwent transthoracic echocardiography for LA strain measurement, either on the same day as LV catheterization or within 24 h. Patients who did not undergo echocardiography within 24 h (n = 4), those with AF during echocardiography (n = 2), those with difficulty in accurately evaluating LV pre-atrial contraction (pre-A) pressure or LV end-diastolic pressure (LVEDP) from the catheterization pressure curve (n = 21), and those with poor image quality for LA strain measurement (n = 14) were excluded from the study. A total of 365 patients were enrolled in the study.

All participants provided written informed consent. This study adhered to the ethical standards established in the 2013 revision of the Declaration of Helsinki. The Institutional Review Board of our hospital approved this study (IRB number: 9-2021-0062).

Data collection
Participants' demographics, health histories, prescribed medications, social factors, and laboratory results upon admission, including NT-proBNP levels, were prospectively recorded. The HFA-PEFF score was then determined based on the clinical and echocardiographic findings.[4] Details of echocardiographic image acquisition are presented in Supplementary Method section. Echocardiography was performed using a commercially available equipment (Vivid E9/E95, GE Healthcare, Horton, Norway). We followed established guidelines to collect standard echocardiographic measurements, including LV global longitudinal strain (LV-GLS).[2,26].

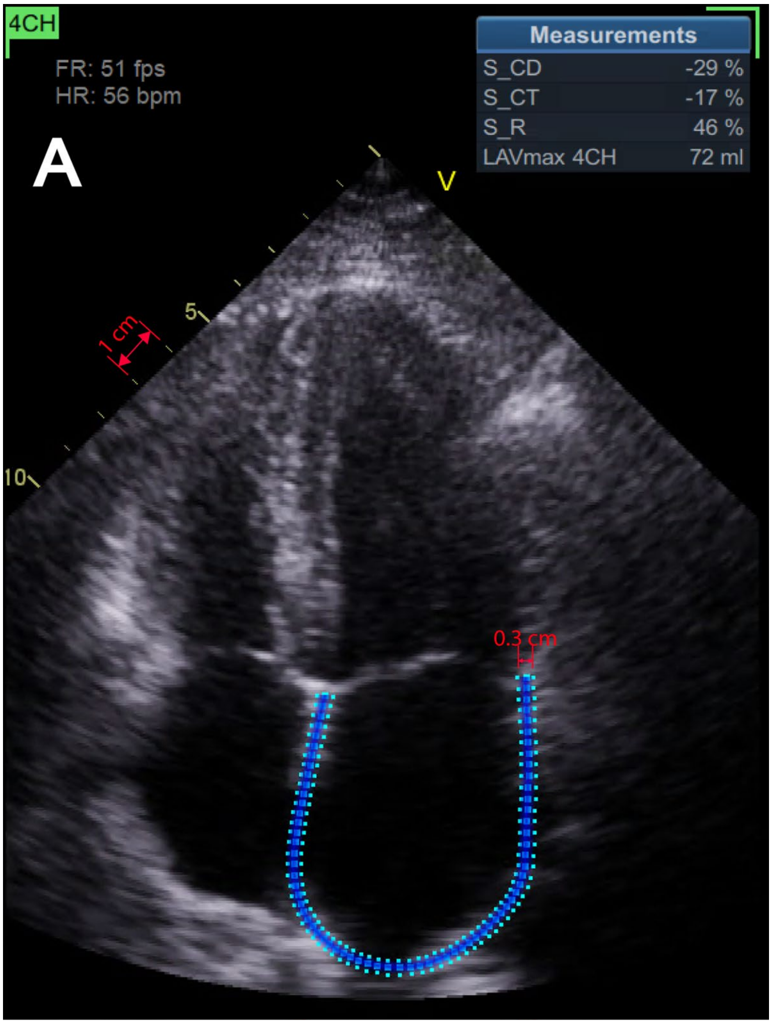

Fig. 4. Representative example to measure LAS. The width of the region of interest was set to 3 mm in accordance with guideline recommendation. LAS indicates left atrial strain.

LAS analysis

The measurement of LAS was conducted using the speckle-tracking and semiautomatic analysis method of a widely used software (EchoPAC version 204, AFI LA 3.0, GE HealthCare, Horton, Norway), following the established guidelines.[27] An expert sonographer in the core lab, without access to the participants' data, performed the LAS measurements.[19] The assessment was based on a non-foreshortened apical four-chamber view as recommended in the consensus document.[27] The start point of the measurement was set by the onset of the R-wave, or in cases of ambiguity, the lowest point of the LAS waveform was marked as end-diastole.[27] Delineation of the region of interest (ROI) was first undertaken automatically, encompassing the septal and lateral segments of the proximal part of the mitral annulus and the LA roof, and was refined to be compatible with the LA endocardial border when necessary. The ROI width was considered the anatomical thickness of the LA wall, aiming to minimalize the thickness (3 mm) to prevent the pericardium from being included (Fig. 4).[27] Additionally, we carefully ensured that the endocardial border of the ROI was not positioned towards the pulmonary veins or LA appendage. Although the LAS curve is divided into three phases, we used LA reservoir strain (LASr), which is the peak value from the nadir of the LAS curve, in our analysis to estimate elevated LV filling pressure. Intra- and inter-observer variabilities of LASr were evaluated in 20 randomly selected cases. For intra-observer analysis, a single observer repeated measurements at a different time, blinded to initial results. Inter-observer variability was assessed by an independent observer, also blinded to prior results.

LV catheterization

LV pressure was measured immediately after the coronary angiography to ensure that both tests were conducted as part of a continuous series. The iso-osmolar agent, iodixanol, was used to minimize the increase in LV filling pressure caused by contrast media. Participants were examined in the supine position after fasting for at least 4 h and were permitted to take any long-term medications with sips of water. LV pressure data were collected during the end-expiratory period using a 5-Fr pigtail catheter (Supertorque 542-598B, Cordis, Miami Lakes, Florida, USA). Through LV catheterization, we assessed LV diastolic and systolic pressures, as well as LV pre-A pressure and LVEDP. Elevated LV filling pressure was defined as a pre-A pressure ≥ 15 mmHg—given its correlation with the pulmonary capillary wedge pressure threshold—and LVEDP ≥ 16 mmHg.[1,14,15].

Study objectives

The primary objective of this study was to determine which of the invasively measured LV pressure parameters—LV pre-A pressure or LVEDP—was more strongly associated with LA strain, and to establish appropriate cutoffs for identifying elevated LV filling pressure in patients with sinus rhythm. The secondary objective was to evaluate the clinical utility of LASr and explore its potential application within current guidelines—2016 diastolic function guideline, 2022 expert consensus document of European Association of Cardiovascular Imaging (EACVI), and Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology (HFA-PEFF) diagnostic algorithm—for practical use in clinical settings.[2,4,16].

Statistical analysis

Continuous data were depicted as either mean ± standard deviation or median with interquartile range (IQR), chosen based on normality as determined by the Shapiro–Wilk test. Categorical data frequencies are expressed as numbers and percentages. Categorical data were analyzed using the Chi-square or Fisher's exact test, whereas continuous data were compared using the Student's t-test or the Mann–Whitney U test, as appropriate. Receiver operating characteristic (ROC) curve analysis was performed to assess the degree of LASr reduction to predict elevated LV filling pressure. Differences in area under the ROC curves (AUC) were evaluated using DeLong's method. The optimal threshold for LASr was identified based on the Youden index. Except for LV-GLS (18.4%), peak TR velocity (12.6%), the other variables had missing rates below 5%. We performed multiple imputation for missing values using the mice package in R, specifying 50 imputations with predictive mean matching as the imputation method and a maximum of 10 iterations.[28] To assess whether LASr provides greater incremental value in predicting elevated LV filling pressure when added to models targeting either LV pre-A pressure ≥ 15 mmHg or LVEDP ≥ 16 mmHg, AUC and continuous net reclassification index (NRI) analyses were performed using three sequential models. Model A included the biomarker of NT-proBNP levels. Model B expanded on Model A by incorporating morphological and functional parameters of the HFA-PEFF diagnostic algorithm, such as septal e', average E/e', LV-GLS, peak velocity of tricuspid regurgitation, LA volume index, relative wall thickness, and LV mass index. Model C extended Model B by incorporating LASr. All statistical analyses were performed using R software version 4.1.2 (R Development Core Team, Vienna, Austria), and a two-sided p-value of < 0.05 was indicative of statistical significance.

Data availability

Upon a reasonable request, the corresponding authors may provide the data that supports this article.

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Author contributions

M. Kim, J W Roh, D K Cho, and I. H. Jung designed the research. J W Roh, O H Lee, and D K Cho, performed the experiments. N H Son, S Bae, performed data analysis. M.Kim, J W Roh wrote the manuscript. M. Kim, J W Roh, N H Son, S, S Bae, I. H. Jung, D K Cho reviewed and interpreted the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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