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Left atrial strain as a predictor of left ventricular filling pressures in coronary artery disease with preserved ejection fraction: a comprehensive study with left ventricular end-diastolic and pre-atrial contraction pressures

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Abstract

Assessing left ventricular (LV) filling pressure (LVFP) is challenging in patients with coronary artery disease (CAD) and preserved LV ejection fraction (LVEF). We aimed to correlate left atrial strain (LAS) with two invasive complementary parameters of LVFP and compared its accuracy to other echocardiographic data to predict high LVFP. This cross-sectional, single-center study enrolled 81 outpatients with LVEF > 50% and significant CAD from a database. Near-simultaneous echocardiography and invasive measurements of both LV end-diastolic pressure (LVEDP) and LV pre-atrial contraction (pre-A) pressure were performed in each patient, based on the definition of LVEDP > 16 mmHg and LV pre-A > 12 mmHg as high LVFP. A moderate to strong correlation was observed between LAS reservoir (LASr), contractile strain, and LVEDP (r: 0.67 and 0.62, respectively; p < 0.001); the same was true for LV pre-A (r: 0.65 and 0.63, respectively; p < 0.001). LASr displayed good diagnostic performance to identify elevated LVFP, which was higher when compared to traditional parameters. Median value of LASr was higher for an isolated increase of LVEDP than for simultaneously high LV pre-A. The cutoff found to predict high LVFP was lower for LV pre-A than that one for LVEDP. In the current study, LASr did not provide an additional contribution to the 2016 diastolic function algorithm. LAS is a valuable tool for predicting LVFP in patients with CAD and preserved LVEF. The choice of LVEDP or LV pre-A as the representative marker of LVFP leads to different cutoffs to predict high pressures. The best strategy for adding this tool to a multiparametric algorithm requires further investigation.

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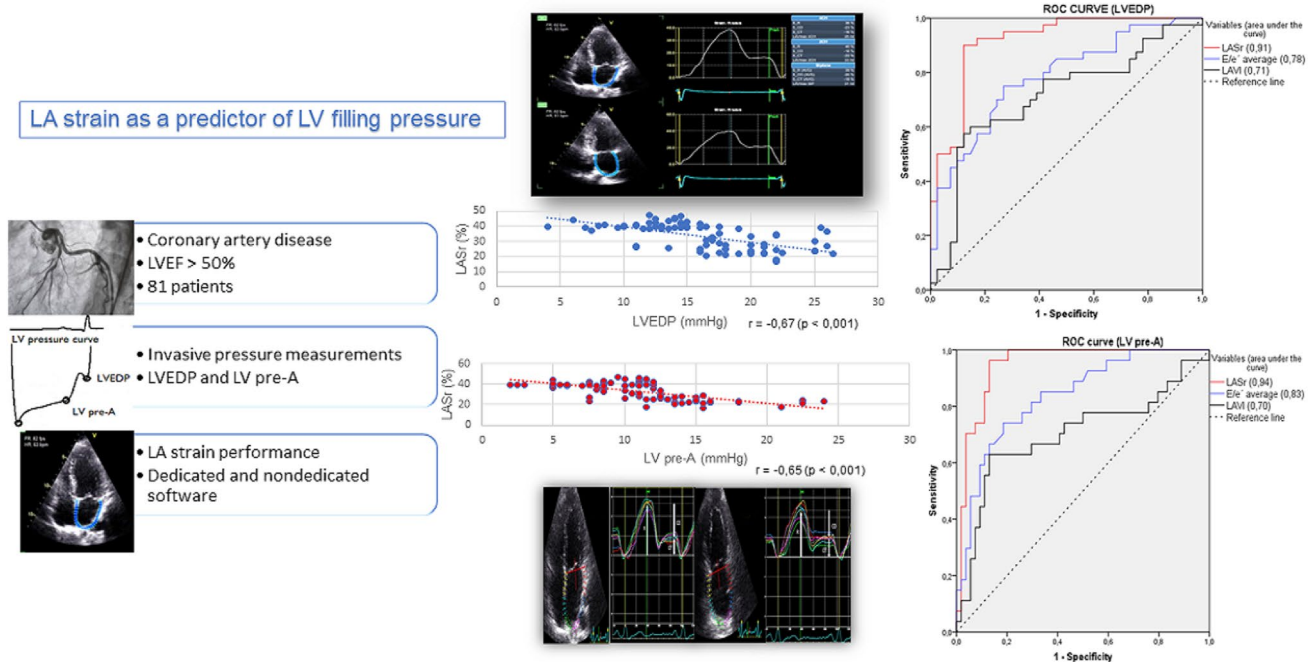
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Graphical abstract

Keywords Left atrial function · Left atrial strain · Diastole · Left ventricle filling pressure · Coronary artery disease

Introduction

Evaluation of left ventricular (LV) filling pressure (LVFP) has been performed through both invasive and noninvasive methods, routinely by echocardiography [1]. Some challenging scenarios include heart failure with preserved ejection fraction (HFPEF) and coronary artery disease (CAD). HFPEF represents at least half of the patients with this syndrome [2]. CAD is an important cause of mortality worldwide [3]. Left atrial strain (LAS) has been described as a supplementary marker of LVFP and a useful tool for grading diastolic dysfunction (DD) in patients with preserved LVEF [4, 5].

The 2016 American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines [6] for LV diastolic function evaluation recommended key parameters—left atrial volume index (LAVI), tricuspid regurgitation (TR) peak velocity, mitral annulus velocity (e′) and ratio E/e′—in an algorithm to predict LVFP. Some studies have revealed a modest diagnostic performance in normal LVEF [7, 8]. The EACVI recommendation for imaging in HFPEF [9] has included LAS reservoir (LASr) to replace any missing parameter.

Actually, the widespread term "filling pressure" refers to different pressures such as the mean capillary wedge pressure (PCWP), mean left atrial pressure (LAP), mean LV diastolic pressure, LV pre-atrial contraction pressure (LV pre-A), and LV end diastolic pressure (LVEDP). These pressures are not necessarily interchangeable, and their elevation may occur in different stages of the cardiac disease [10, 11].

We aimed to evaluate the correlation of LAS with two different and complementary invasive parameters of LVFP in each patient with significant CAD and preserved LVEF: LVEDP and LV pre-A. In addition, we compared the LAS diagnostic accuracy with conventional echocardiographic parameters.

Methods

Study population

This cross-sectional, single-center study was conducted at Dante Pazzanese Institute of Cardiology (São Paulo, Brazil), a specialized cardiovascular center. A total of 141 outpatients referred for diagnostic left-sided heart catheterization were retrospectively reviewed from a database. Inclusion criteria were defined as: appropriate register of LVFP invasive measurements, sinus rhythm, LVEF > 50%, significant CAD (defined by invasive angiography as > 50% stenosis of the left main coronary artery, > 70% in a major coronary vessel), and no intravenous fluid administration within 24 h

prior to the test. Patients with arrhythmia, paced rhythm, prosthetic valve, or more than mild valvopathy, complex congenital heart disease, interatrial septal aneurysm, primary myocardial disease, pericardial diseases, ventricular septal defect, or an inappropriate acoustic window would be excluded. The study was approved by the Institutional Ethics Committee. All patients had provided written informed consent at the moment of recruitment.

Echocardiographic imaging acquisition and analysis

Echocardiographic images were acquired from GE Healthcare equipment, and analysis was performed on EchoPAC PC software Version 204 by an expert echocardiographer. Patients were evaluated in left lateral decubitus as the initial position. Standard exams were performed according to current recommendations [12] at the lab cath just before coronary angiography. LVEF and LAVI by Simpson´s method, transmitral peak early (E) and late atrial flow (A) velocities, septal and lateral mitral annular velocities, and TR peak velocity were measured and averaged over three cardiac cycles. Dedicated views were recorded for LV and LA analyses.

LAS reservoir (LASr), conduit (LAScd), contractile (LASct), and LV global longitudinal strain (GLS), were measured by two-dimensional speckle tracking echocardiography technique using a frame rate from 40–80/s. Biplanar calculation of LAS was based on the ASE/EACVI standardization document [13]. As recommended by this task force, the endocardial border was manually traced and the regions

of interest were adjusted to cover the myocardium (Fig. 1) according to previously described steps for nondedicated software [14]. These results were displayed on the following tables.

Besides, more recently, novel dedicated LA tracking tool has been available in the software, so that an additional biplanar analysis of LAS was also performed for all cases (Fig. 2). This dedicated tool provided automated recognition of the chamber based on initial landmarks (two points to mark mitral ring and one point for LA roof). Diastolic function analysis was performed according to the 2016 ASE/ EACVI guidelines [6]. Pulmonary vein Doppler was also acquired and analyzed.

Echocardiographic recordings were analyzed while blinded to invasive hemodynamic data.

Cardiac catheterization and invasive measurements

Left heart catheterization was performed in the supine position, without intravenous sedation, immediately after echocardiogram, using a 5 or 6 F catheter with femoral or radial arterial access. LV pressures and simultaneous electrocardiographic recordings were taken during an expiratory pause, before contrast injection, using a hemodynamic polygraph (SP12H-TEB—Brazilian Electronic Technology). A fluid-filled catheter was used and transducers were leveled at the midaxillary line "zero" in the fluid column. A minimum of five consecutive heartbeat cycles were averaged to obtain LVEDP and LV pre-A. LVEDP > 16 mmHg [15] and LV pre-A > 12 mmHg [16] were defined as high LVFP.

Fig. 1 Biplanar LAS on non-dedicated LA tracking software
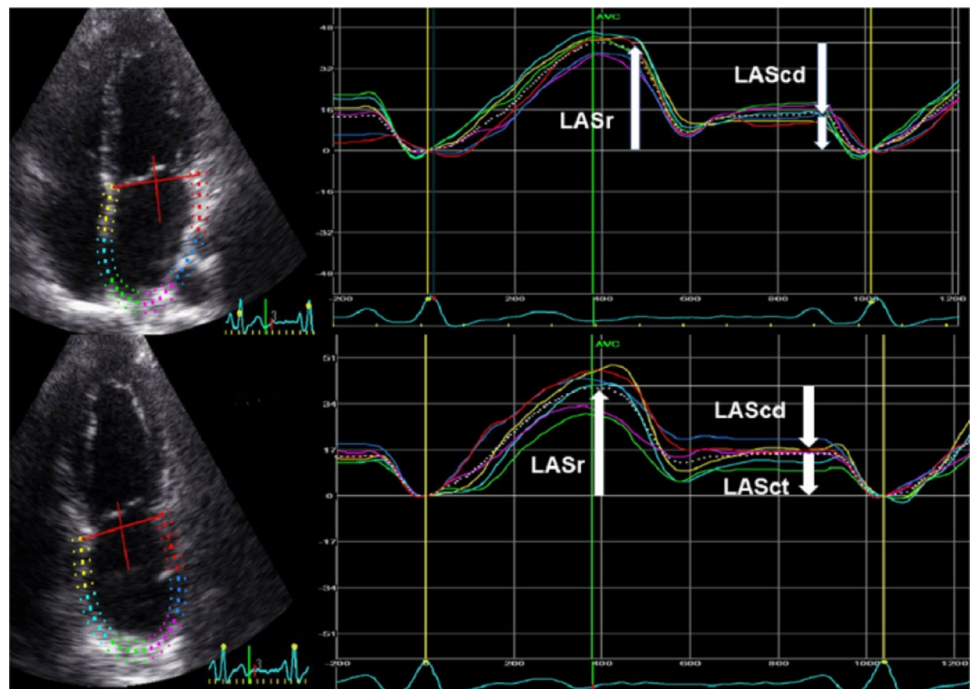
Fig. 2 Biplanar LAS on dedicated LA software
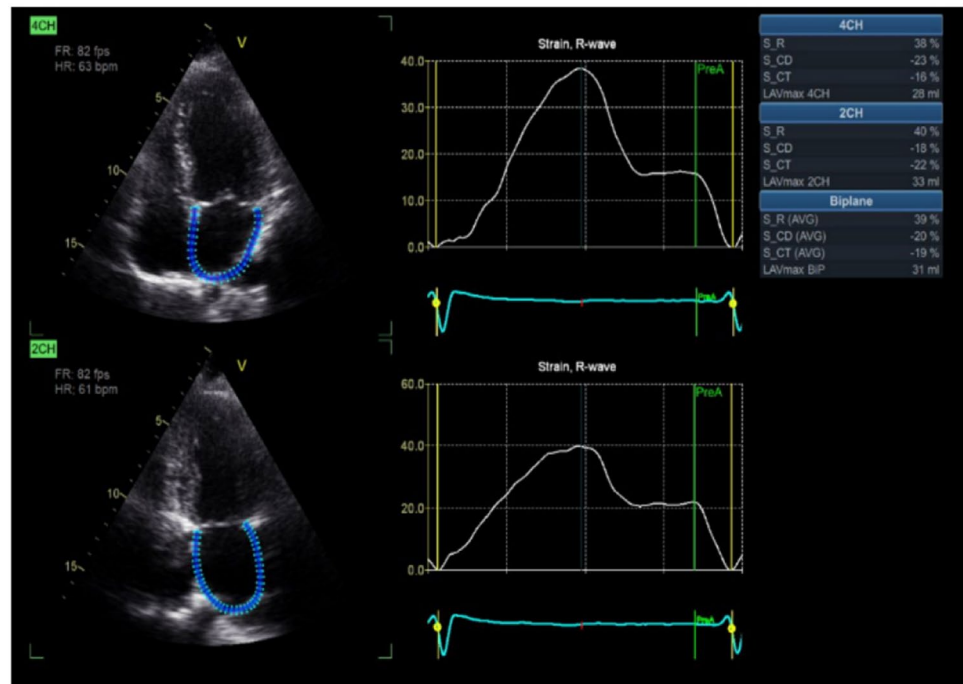
Statistical analysis

Normality was tested using Kolmogorov-Smirnov with Lilliefors correction. Continuous variables were provided as mean ± standard deviation for parametric variables or median and interquartile range for nonparametric variables. Categorical data were expressed as absolute numbers and percentages. Comparison of continuous variables used T-Student and Wilcoxon tests. For categorical variables, Chi-squared test was performed. Correlations of continuous variables were made using two-tailed test Pearson or Spearman method as appropriate. Receiver-operating characteristic (ROC) analysis was carried out to assess the diagnostic ability of echocardiographic parameters to identify elevated LVFP. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were calculated using standard definitions to predict high LVFP.

Reproducibility of strain measurements was tested through intraclass correlation coefficient (ICC) based on a subset of 16 exams randomly selected to be reevaluated by another experienced operator. In addition, Bland-Altman analysis was performed to evaluate the agreement between LV-software and LA-software measurements of LAS for the entire study sample.

The association of LVEDP and LV pre-A with dichotomous variables was evaluated using binary logistic regression, assuming odds ratio (OR) as the main analysis.

Statistical analysis was performed using IBM SPSS Statistics version 20 (SPSS Inc., IL, USA) software. A p-value < 0.05 was considered statistically significant.

Results

We selected a final sample of 81 patients. From the initial database, 22 did not meet the inclusion criteria due to inappropriate trace recordings of LVFP invasive measurements, and 17 presented reduced LVEF. Arrhythmia and more than mild valvopathy excluded 12 patients. A subset of 9 patients was excluded due to poor acoustic image quality.

Baseline clinical characteristics of the study population are summarized in Table 1.

Coronary angiography was requested for outpatients investigating CAD under elective conditions. Abnormal findings in noninvasive ischemic testing were noted in 41 (50.6%) patients. Prior acute coronary syndrome more than 30 days before was reported in 18 (22.2%) subjects. Symptoms were the only reason for angiogram in 22 (27.2%) patients.

Left main coronary artery disease was reported in 7 (8.6%) patients. Of the remaining group, 47 (58%) had single-vessel disease, 19 (23.5%) presented double-vessel disease, and 8 (9.9%) three-vessel disease. In 43 (53%) cases, the left anterior descending artery presented significant stenosis.

Table 1 Baseline characteristics

Variables	Number of patients (%) or mean (± standard-deviation)
Age (years)	61.1 ± 8.2
Female sex	27 (33.33%)
Body mass index (kg/m²)	28.8 ± 4.4
Systolic blood pressure (mmHg)	148 ± 21.1
Diastolic blood pressure (mmHg)	83 ± 11.1
Heart rate (bpm)	66.7 ± 11.7
Hypertension	70 (86.42%)
Dyslipidemia	64 (79.01%)
Diabetes mellitus	33 (40.74%)
Familiar history of premature CAD	2 (2.47%)
Current smoker	18 (22.22%)
Symptoms	
Dyspnea	21 (25.93%)
Angina	47 (58.02%)
Medication use	
Aspirin	74 (91.4%)
Statin	60 (74.1%)
Beta-blocker	59 (72.8%)
ACE-inhibitor	27 (33.3%)
ARB	32 (39.5%)
Calcium channel blocker	19 (23.5%)
Hydralazine	11 (13.6%)
Nitrate	21 (25.9%)
Diuretic	26 (32.1%)
Oral antidiabetic	25 (30.9%)
Insuline	6 (7.4%)
Coronary revascularization	
CABG	16 (19.8%)
PCI	14 (17.3%)

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *CAD* coronary artery disease, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention
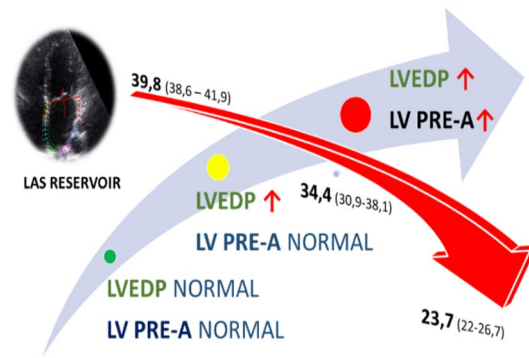
Fig. 3 Median values of LASr based on hemodynamic classification according to LVFP

There was no significant difference in regular oral medication use between normal and high LVFP groups. Prevalence of cardiovascular risk factors was also similar as well as heart rate and blood pressure at the time of echocardiographic evaluation and catheterization.

LVEDP was normal in 41 patients (group A) and > 16 mmHg in 40 patients (group B). From this last group, 27 patients presented simultaneously LV pre-A > 12 mmHg (mean 15.8 ± 3.3 mmHg), while 13 had isolated high LVEDP. Mean LVEDP and LV pre-A in group A were 12.3 ± 2.9 mmHg and 8.2 ± 2.8 mmHg respectively; in group B, they were 20.6 ± 3.1 mmHg and 14 ± 3.8 mmHg, respectively.

Echocardiographic profile

Echocardiographic parameters are described in Table 2. Median values of LASr (Fig. 3) in normal LVFP [39.78 (38.55–41.86)] were higher than in isolated high LVEDP [34.41 (30.88–38.13); $p < 0.001$] and in high LV pre-A [23.69 (21.97–26.68); $p < 0.001$].

Fig. 4 Scatter plots of correlation between LAS and LVFP
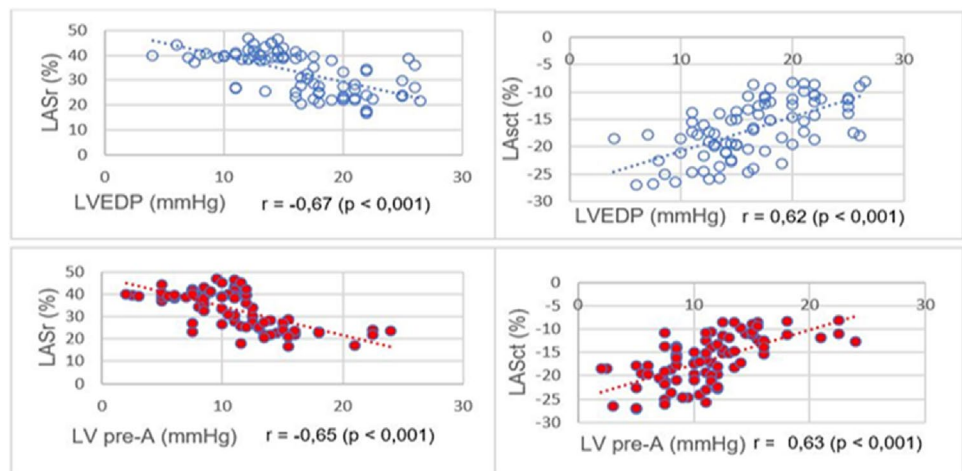
Table 2 Echocardiographic parameters across the groups classified by LVEDP and LV pre-A

Variable	LVEDP ≤ 16 mmHg (n=41)	LVEDP > 16 mmHg (n=40)	p-value	LV pre-A ≤ 12 mmHg (n=54)	LV pre-A > 12 mmHg (n=27)	p-value
LV end diastolic diameter (mm)	49.1 ± 3.80	49.4 ± 3.7	0.70	49.1 ± 3.6	49.4 ± 4.1	0.74
LV mass index (g/m²)	99 ± 15.3	98.8 ± 16.6	0.95	98.5 ± 16.1	99.7 ± 15.6	0.74
Relative wall thickness	0.42 ± 0.04	0.41 ± 0.05	0.67	0.41 ± 0.04	0.42 ± 0.05	0.77
LV geometry						
Normal	19 (46.34%)	20 (50%)	0.82	28 (51.85%)	11 (40.74%)	0.74
Concentric remodelling	10 (24.39%)	10 (25%)		6 (11.11%)	5 (18.52%)	
Concentric LVH	6 (14.63%)	7 (17.5%)		13 (24.07%)	7 (25.93%)	
Excentric LVH	6 (14.63%)	3 (7.5%)		7 (12.96%)	4 (14.81%)	
LV end diastolic volume (ml)	77.9 ± 16.6	77 ± 17	0.81	77.9 ± 18.2	76.6 ± 13.5	0.70
LVEF-Simpson (%)	63.12 ± 5.30	64.43 ± 3.64	0.20	63.54 ± 5.12	64.22 ± 3.25	0.47
GLS LV (%)	− 16.53 ± 3.42	− 16.93 ± 3.50	0.60	− 16.94 ± 3.39	− 16.30 ± 3.57	0.44
LV wall motion abnormality	14 (34.15%)	11 (27.5%)	0.63	18 (33.33%)	7 (25.93%)	0.61
E wave (cm/s)	68.07 ± 15.14	78.25 ± 19.58	***0.01***	69.61 ± 17.21	80.07 ± 18.14	***0.01***
A wave (cm/s)	74.56 ± 18.68	76.73 ± 16.9	0.59	74.61 ± 17.92	77.67 ± 17.56	0.47
E/A ratio	0.97 ± 0.34	1.06 ± 0.32	0.25	0.98 ± 0.34	1.08 ± 0.33	0.22
DT E wave (ms)	208.5 ± 50.6	215.50 ± 38.55	0.49	210.74 ± 47.60	214.41 ± 39.72	0.72
Septal e′ (cm/s)	7.37 ± 1.67	6.08 ± 1.54	***0.001***	7.20 ± 1.61	5.78 ± 1.58	***<0.001***
Lateral e′ (cm/s)	9.83 ± 2.50	8.6 ± 1.55	***0.01***	9.76 ± 2.26	8.15 ± 1.46	***<0.001***
Average e′ (cm/s)	8.60 ± 1.98	7.34 ± 1.33	***0.001***	8.48 ± 1.80	6.96 ± 1.32	***<0.001***
E/e′ average	8.14 ± 2.00	10.89 ± 2.84	***<0.001***	8.39 ± 2.15	11.72 ± 2.65	***<0.001***
TR velocity (m/s)	2.03 ± 0.38	2.41 ± 0.33	***<0.001***	2.11 ± 0.39	2.47 ± 0.29	***<0.001***
IVRT (ms)	87.71 ± 16.46	81.93 ± 13.43	0.09	85.63 ± 16.46	83.30 ± 12.55	0.48
S/D ratio	1.32 ± 0.47	1.33 ± 0.47	0.94	1.35 ± 0.48	1.26 ± 0.45	0.40
Ar-A duration (ms)	21.85 ± 20.15	16.25 ± 25.93	0.28	21.33 ± 22.42	14.59 ± 24.53	0.24
Ar wave velocity (cm/s)	26.78 ± 3.23	28.63 ± 6.03	0.09	27.37 ± 4.29	28.33 ± 5.92	0.46
S′ RV (cm/s)	10.76 ± 1.07	10.79 ± 1.09	0.56	10.79 ± 1.08	10.73 ± 1.08	0.82
FAC RV	0.44 ± 0.04	0.43 ± 0.04	0.94	0.44 ± 0.04	0.43 ± 0.04	0.34
LA diameter (mm)	37.2 ± 2.95	38.03 ± 3.70	0.27	37.7 ± 2.91	37.48 ± 4.15	0.84
LAVI (ml/m²)	28.68 ± 4.95	32.70 ± 5.83	***0.001***	29.28 ± 4.71	33.43 ± 6.58	***0.006***
LASr	39.8 (38.6–41.9)	25.7 (22.5–32)	***<0.001***	39.3 (36.4–40.8)	23.7 (22–26.7)	***<0.001***
LAScd	− 19.81 ± 4.84	− 12.99 ± 4.61	***<0.001***	− 18.55 ± 5.03	− 12.19 ± 3.79	***<0.001***
LASct	− 19.91 ± 4.19	− 13.64 ± 4.14	***<0.001***	− 19.26 ± 4.34	− 11.93 ± 2.82	***<0.001***

DT deceleration time, *FAC* fractional area change, *GLS* global longitudinal strain, *IVRT* isovolumic relaxation time, *LAS cd* conduit left atrial strain, *LASct* contractile left atrial strain. *LASr* reservoir left atrial strain, *LAVI* left atrial volume indexed, *LVH* left ventricle hypertrophy, *RV* right ventricle, *TR* tricuspid regurgitation

Correlation of LAS and traditional echocardiographic variables with LVFP

LASr and LASct revealed a moderate to strong correlation with LVEDP and LV pre-A (Table 3). The scatter diagrams of LAS are exhibited in Fig. 4. E/e′ average, TR peak velocity, and LAVI were also correlated with LVFP. TR peak evaluation was not feasible (none/trace) in 18 (22%) cases.

A binary logistic regression analysis was performed to study the variables LAVI > 34 ml/m², LASr < 26%, and E/e′ average > 14 as predictors of LVEDP and LV pre-A VE. The model containing these 3 variables was significant for predicting LVEDP [X² (3) = 24.99; p < 0.001; Nagelkerke R² = 0.35] and LV pre-A [X² (3) = 39.87; p < 0.001; Nagelkerke R² = 0.54]. In this model, LASr was the only significant predictor for LVEDP (OR 7.1; 95% CI 1.7–29.3; p = 0.007) and LV pre-A (OR 18.2; 95% CI 4.5–73.4; p < 0.001).

Diagnostic accuracy of traditional echocardiographic parameters to predict elevated LVFP

E/e′ average, TR peak velocity, and LAVI, as single variables, demonstrated high specificity and lower sensitivity (Table 4). On ROC analysis, these parameters revealed a

Table 3 Correlation values of LAS and other echocardiographic parameters to LVEDP and LV pre-A

Variable	r (LVEDP)	p-value	r (LV pre-A)	p-value
LASr	−0.67	<0.001	−0.65	<0.001
LAScd	0.37	<0.001	0.44	<0.001
LASct	0.62	<0.001	0.63	<0.001
LA SRs	−0.57	<0.001	−0.55	<0.001
LA SRe	0.36	0.001	0.36	0.001
LA SRa	0.59	<0.001	0.56	<0.001
E/e′ average	0.51	<0.001	0.56	<0.001
TR velocity	0.49	<0.001	0.50	<0.001
LAVI	0.33	0.003	0.30	0.006

LAScd conduit left atrial strain, *LASct* contractile left atrial strain, *LASr* reservoir left atrial strain, *LAVI* left atrial volume indexed, *SRs* systolic strain rate, *SRe* early diastolic strain rate, *SRa* late diastolic strain rate, *TR* tricuspid regurgitation

good ability to identify high LVEDP (E/e′: area under the curve—AUC 0.78; TR peak velocity: AUC 0.77, for feasible evaluations; LAVI: AUC 0.71) and LV pre-A (E/e′: AUC 0.83; TR peak velocity: AUC 0.75 for feasible evaluations; LAVI: 0.70).

Based on the 2016 ASE/EACVI guidelines, the multiparametric algorithm classified 14 patients with normal diastolic function, 55 with grade I DD, and 11 with grade II DD. No case was defined as grade III DD. In one case, the grade of DD was classified as indeterminate. Excluding the indeterminate case, sensitivity, specificity, PPV, NPV, and accuracy for elevated LVEDP were 26.3%, 97.6%, 90.9%, 59.4% and 63.8%, respectively; for high LV pre-A, 37.5%, 96.4%, 81.8%, 78.3% and 78.8%, respectively.

## Diagnostic accuracy of LAS to predict high LVFP

LAS presented powerful diagnostic performance for predicting high LVFP (Fig. 5). On ROC analysis, AUC for LASr was superior compared with E/e′ (difference AUC of 0.13

Table 4 Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for echocardiographic variables to predict elevated LV pre-A

Variable	Sensitivity (%) LVEDP/LV pre-A	Specificity (%) LVEDP/LV pre-A	PPV (%) LVEDP/LV pre-A	NPV (%) LVEDP/LV pre-A	Accuracy (%) LVEDP/LV pre-A
E/e′ average > 14	22.5/29.6	97.6/96.3	90/80	56.3/73.2	60.5/74.1
LAVI > 34 ml/m²	50/63	90.2/87	83.3/70.8	64.9/82.5	70.4/79
TR velocity > 2.8 m/s	10.3/16.7	97.1/97.8	75/75	55.9/74.6	57.1/74.6
LASr < 26%	46.3/73.1	92.5/92.6	86.4/82.6	62.7/86.2	62.7/85.2
LASr < 23%	31.7/48.1	100/98.1	100/92.9	58.8/77.9	65.4/81.5
LASr < 18%	7.3/7.4	100/98.1	100/66.7	51.3/67.9	53.1/66.7
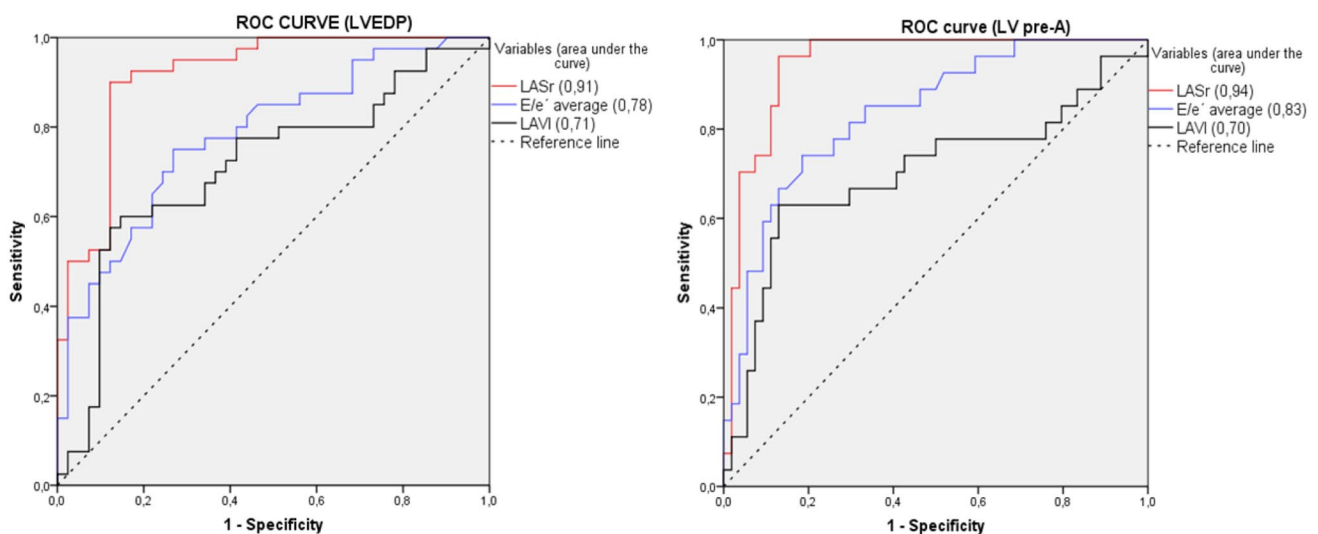
Fig. 5 ROC curves for ability of LASr, E/e′ average, and LAVI to predict high LVFP
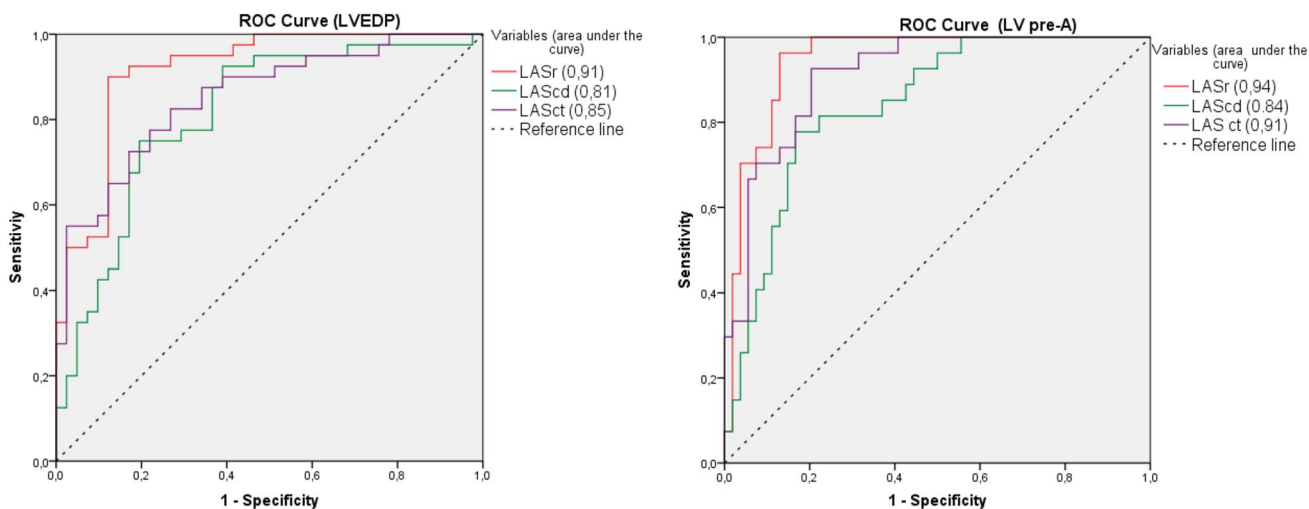
Fig. 6 ROC curves for ability of LASr, LAScd, and LASct to predict high LVFP

and 0.11 for LVEDP and LV pre-A, respectively; p < 0.001) and LAVI (difference AUC of 0.20 and 0.24 for LVEDP and LV pre-A, respectively; p < 0.001).

For LASr, LAScd and LASct, AUC values were 0.91, 0.81, and 0.85 to identify high LVEDP and 0.94, 0.84 and 0.91 to diagnose high LV pre-A (Fig. 6). LASr < 35% demonstrated 87% sensitivity and 88% specificity for LVEDP > 16 mmHg. On the other hand, LASr < 26% displayed 73% sensitivity and 93% specificity for LV pre-A > 12 mmHg. For a different cutoff, LASr < 23% showed 48% sensitivity and 98% specificity. For LASct, the cut-off 14% displayed 74% sensitivity and 85% specificity to identify elevated LV pre-A. LASct cut-off 15.4% demonstrated 73% sensitivity and 83% specificity for high LVEDP.

Reproducibility of LAS measurements

Two observers analyzed LAS in 16 cases randomly selected. Interobserver ICCs were 0.94 (95% CI 0.84–0.97), 0.93 (95% CI 0.80–0.97), and 0.84 (95% CI 0.60–0.94) for LASr, LAScd, and LASct, respectively. The corresponding intraobserver ICCs were 0.98 (95% CI 0.94–0.99), 0.96 (CI 95% 0.90–0.99) and 0.85 (95% CI 0.63–0.95).

Potential added value of LAS to the 2016 ASE/EACVI diastolic function algorithm

Incorporating LASr into the 2016 ASE/EACVI recommendation to substitute any missing additional parameter [17] did not improve its accuracy. E/e′ and LAVI were feasible in all cases in our sample. In 17 of 18 cases of missing TR peak velocity, E/e′ average and LAVI were both normal
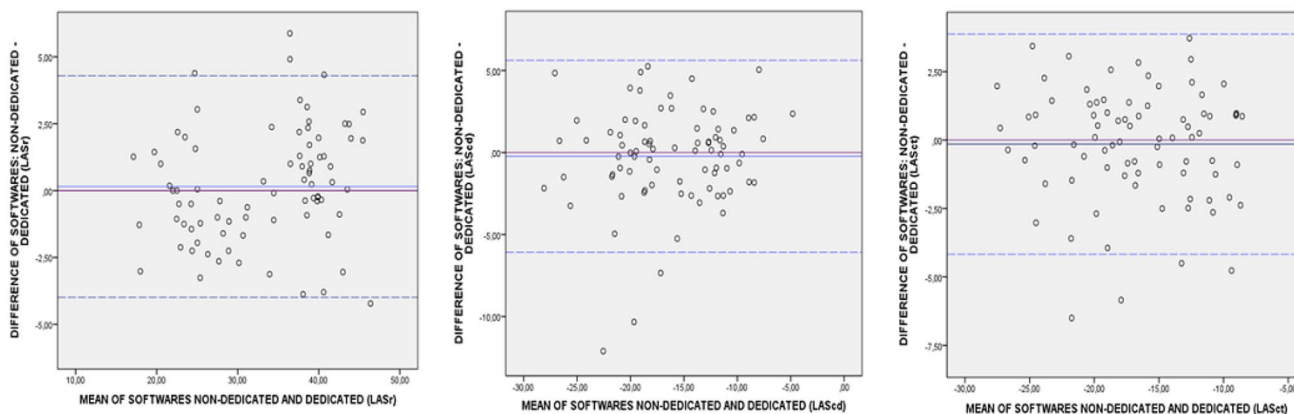
Fig. 7 Bland-Altman plots for agreement between nondedicated and dedicated software for LAS measurements

Table 5 Mean and mean absolute difference of LAS using nondedicated software and dedicated software

Variable	Nondedicated software	Dedicated software	p-value	Mean absolute difference
LASr	33.2 ± 8.4	33 ± 7.9	0.52	1.68 ± 1.28
LAScd	-16.4 ± 5.5	-16.2 ± 5.2	0.48	2.12 ± 2.10
LASct	-16.9 ± 5.1	-16.7 ± 5.3	0.51	1.58 ± 1.31

LAS cd conduit left atrial strain, *LASct* contractile left atrial strain, *LASr* reservoir left atrial strain

or both positive, so including a new parameter would not have changed algorithm conclusion.

Adding LASr to LAVI in the algorithm so that the parameter could be positive in case of LAVI > 34 ml/m² or LASr < 23% also did not change algorithm performance, due to the low rate of positivity of the other parameters. The isolated positive "LA criteria" was not sufficient to alter the algorithm conclusion.

Agreement of nondedicated and dedicated LA tracking tool for strain analysis

LAS measurements with both nondedicated (LV software) and dedicated (LA software) tools were similar (Table 5). Bland-Altman analysis plots are provided in Fig. 7.

Discussion

Our study could provide some insight into a challenging group, that has been studied across a heterogeneous spectrum of patients [7, 18].

Simultaneous analysis of both LVEDP and pre-A provides an incremental comprehension of diastolic function evolution. LVEDP data allow the analysis of the earliest pressure change in the initial stages of diastolic dysfunction. The isolated increase in LVEDP should not be assumed as diagnostic of HFPEF [19]. Although LVEDP is a metric of LV compliance, there is a pitfall in assuming this measurement to be synonym of mean pulmonary artery wedge pressure [20]. In addition, LV pre-A pressure includes a better surrogate parameter for LAP, which is a fundamental substrate for dyspnea in HFPEF. Of note, LVEDP was elevated in all patients with increased LV pre-A, but this pressure was normal in one third of the cases with high LVEDP in our study. The choice of the reference parameter for LVFP impacts the cutoff used to predict high pressures, as revealed by the lower value found when LV pre-A was the standard. The median value of LASr (34.4%) described for an isolated high LVEDP is near to a possible normal range and much higher to the one found for simultaneously high LVEDP and LV pre-A (23.7%). This reinforces that LV pre-A is a better surrogate of LAP and its increase is more related to a worse left atrial function. As previously reported by Braunwald et al. [10], in our sample, even when LVEDP is higher than 20 mmHg, the mean LAP (represented by LV pre-A) could be normal.

The near-simultaneous echocardiographic and hemodynamic data establish a potential better correlation of measurements, since variations in heart rate, blood pressure and volume status become insignificant. Hummel et al. [8] acquired echocardiographic data simultaneously with invasive study in supine position. Kasner et al. [21] performed an echocardiogram 3 to 5 h after invasive measurements. Reddy et al. [22] performed echocardiographic analysis at a median interval range of 6 days after hemodynamic study, with a possible limitation on parameter correlation.

Most patients presented reduced LV GLS (< 18% in absolute values), reinforcing that normal LVEF does not necessarily imply normal systolic function. However, no structural echocardiographic differences were found between the groups of normal or high LVFP in our study. Mean LV GLS also did not show any difference between these groups and the CAD profile was similar. Nonetheless, there was a higher prevalence of low LV GLS in the high LV pre-A group, although not statistically significant, which may can be related to sample size. The similar prevalence of cardiovascular risk factors in patients with normal or high LVFP does not imply a coincident evolutive stage, control, and magnitude of diseases, with a possible impact on diastolic function. Diabetes mellitus, for instance, independently predicts poorer LASr and LASct due to advanced glycated end products [23]. In addition, the grade of fibrosis in LA may be associated with a worsening of its function [24], although these data are not available for our sample.

Among the 27 patients with simultaneously high LVEDP and LV pre-A, only 3 patients had normal geometry, wall motion score index, and LV GLS. Some HFPEF trials [25, 26] have reported normal diastolic function in one-third of the sample. However, this classification was not based on the most recent guidelines, which include the essential concept of myocardial disease as indicative of DD.

Correlation of LAS and LVFP

In a sample of patients with CAD and preserved LVEF, LASr and LASct provided a powerful diagnostic ability to predict LVFP based on hemodynamic data of LVEDP and LV pre-A.

LASr performance was superior to that of conventional parameters for diastolic function evaluation as previously reported. In patients with preserved LVEF, Hummel et al. [8] described AUCs to predict PCWP for E/e′ > 15, TR peak velocity > 2.8 m/s, LAVI > 34 ml/m² and multiparametric ASE/EACVI algorithm of 0.59, 0.69, 0.76 and 0.75, respectively. In multivariable linear regression analysis, only IVRT and LASr remained independently associated with this invasive measurement. Correlation of E/e′ with invasive measurement, mainly in preserved LVEF, has been described as weak to moderate [27, 28]. Our findings have corroborated lower sensitivity and higher specificity of the individual parameters E/e′, LAVI, and TR peak velocity in predicting LVFP [18]. Singh et al. [29] have previously reported the usefulness of LASr as a sole parameter for categorizing patients as having normal or high LFVP.

A potential contribution of adding LASr to the 2016 ASE/EACVI multiparametric algorithm is related to the sensitivity of the other parameters. The cutoff of E/e′ average > 14, for instance, has revealed better specificity than sensitivity in predicting high LVFP, mainly for patients with preserved LVEF [18]. Furthermore, many patients present intermediate E/e′ values and remain in the gray zone of 8–14 [27], as revealed by 70% of false negatives for E/e′ > 14 in patients with high LV pre-A in our sample.

Defining optimal cutoffs for key parameters demands an appropriate balance between sensitivity, specificity and prognostic value. Morris et al. described an association of LASr < 23% with dyspnea, worse functional class and PCWP > 15 mmHg, even for normal LAVI. In our sample, this value was similar to the median of the high LV pre-A group, but had low sensitivity and high specificity to predict LVFP. None of our patients were classified as having grade III diastolic dysfunction, which can be related to less advanced stages of LA dysfunction and less reduced LAS values [30]. Additionally, studies with higher LVFP have shown lower cutoffs for LAS, as revealed by Inoue et al. in a group in which 8% had PCWP > 30 mmHg. None of our patients presented LV pre-A > 30 mmHg and only 4 cases > 20 mmHg. Moreover, the exclusion of patients with atrial fibrillation and more than mild mitral regurgitation in our study may have influenced higher cutoffs. Inoue et al. [31] reported LASr < 20% in the subgroup of atrial fibrillation regardless of LVFP.

Notwithstanding the good correlation of LASr with LVFP, using it as a stand-alone index may be questionable. Since the normal range is wide, patients with diastolic function can have normal LARs and normal subjects can present decreased strain values due to loading conditions [32].

Echo software and technical aspects of strain analysis

Commercially available software was utilized in our analysis, which has been widely used to define the normal value range of LAS [33]. There has been good correlation demonstrated with other vendors, mainly after the technical standardization initiative [34]. However, the grade of correlation between LAS and invasive pressure measurements may still vary according to the software used [31].

Reproducibility of LAS measurements based on nondedicated and dedicated software

Specific tracking tools for LA provided interchangeable mean measurement results for strain compared to nondedicated software. A previous study [35] based on the same vendor also showed that the choice of software did not significantly impact strain values, but presented a better intra and interobserver correlation. It is reasonable to believe that automatized tools may favor the routine use of new techniques, mainly outside of a research setting.

Limitations

This was a single-center study with a relatively limited number of patients in a reference center with a profile of severe cardiovascular diseases. A single commercially available software was used to perform echo analysis, which may limit generalizability. Despite the use of two parameters for LVFP evaluation, PCWP data were not available, since right circulation was not studied invasively. Although fluid-filled transducers have often been used [16, 18], high-fidelity catheters could have provided better accuracy for pressure measurements. Ultrasound enhancing agents were not used in order to improve TR jet signal.

Conclusions

LAS revealed a moderate to strong correlation with invasive measurements of LVFP and may be a useful adjunct parameter to identify elevated pressures in patients with CAD and preserved LVEF. The choice of LVEDP or LV pre-A as the representative parameter of LVFP leads to different cutoffs to predict high pressures. The best strategy to add LASr to a multiparametric algorithm for the evaluation of LVFP demands further investigation.

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Declarations

Competing interests The authors declare no competing interests.

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