



## Correlation between left atrial strain and left ventricular filling pressure in patients suspected of heart failure with a preserved left ventricular ejection fraction

### Corrélation du strain atrial gauche avec les pressions de remplissage du ventricule gauche chez les patients suspects d'avoir une insuffisance cardiaque ayant une fraction d'éjection préservée

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#### ABSTRACT

**Introduction:** Despite different ultrasound parameters, left ventricular filling pressures (LVFP) assessment remains inconclusive in some cases.

**Aim:** To determine the contribution of left atrial strain (LAS) in estimating LVFP in patients with exertional symptoms and preserved left ventricular ejection fraction.

**Methods:** This was a monocentric study, carried out in the cardiology department of the Interior Security Forces Hospital, La Marsa, between October 2021 and March 2022. Patients with exertional symptoms had a physical examination, a biological assessment and an ultrasound examination at rest and, if necessary, during exercise. We investigated the performance of LAS components (Peak atrial longitudinal strain (PALS), peak atrial contraction strain (PACS) and conduit function (FnC) in predicting LVFP rising. Patients were categorized into two final groups according to LVFP: Group A= high LVFP at rest or during exercise (25 patients) and Group B= not-high LVFP at rest and during exercise (48 patients).

**Results:** Seventy-three patients were enrolled in the study, with a mean age of 61±12 years and a majority being female (57%). The median PALS was 29.3% [21.4-32.4]. The mean PACS and FnC values were 13.4%±4.9 and 13.7%±4.7, respectively. Patients with high LVFP demonstrated lower LAS parameters and elevated NT-Pro BNP levels. LAS showed negative correlations with the E/e' ratio and NT-Pro BNP. PALS emerged as an independent predictor of LVFP elevation (HR=0.71; 95% CI: 0.513-0.986; p=0.041).

**Conclusion:** This study highlights that LAS, as a simple ultrasound parameter, can effectively predict high LVFP.

**Key words:** Echocardiography, left atrial strain, Left ventricular filling pressure.

#### RÉSUMÉ

**Introduction:** Malgré les différents paramètres échographiques et Doppler, l'évaluation des pressions de remplissage du ventricule gauche (PRVG) reste non concluante dans certains cas. Objectif : Déterminer l'apport du strain de l'oreillette gauche (SOG) dans l'estimation des PRVG chez des patients symptomatiques à l'effort et ayant une fraction d'éjection préservée.

**Méthodes:** Il s'agissait d'une étude prospective monocentrique, évaluative et transversale, réalisée au service de cardiologie de l'hôpital des Forces de Sécurité Intérieure de la Marsa, menée entre Octobre 2021 et Mars 2022. Tous les patients avec des symptômes à l'effort ont eu un examen clinique, un bilan biologique ainsi qu'une exploration échographique au repos et, si besoin, à l'effort. Nous avons étudié les performances des trois composants du strain de l'OG (la fonction réservoir (PALS), la fonction pompe (PACS) et la fonction conduit (FnC)) dans la prédiction d'élévation des PRVG. Les patients ont été classés en deux groupes en fonction des PRVG : groupe A = PRVG élevées au repos ou pendant l'exercice (25 patients) et groupe B = PRVG non élevées au repos et pendant l'exercice (48 patients).

**Résultats:** Au total, 73 patients ont été recrutés. L'âge moyen de notre population était de 61±12 ans avec une prédominance féminine (57,5%). Le PALS médian était de 29,3% [21,4-32,4]. Les valeurs moyennes de PACS et de FnC étaient de 13,4%±4,9 et 13,7%±4,7, respectivement. Les patients avec PRVG élevées avaient des paramètres du SOG plus abaissés et des niveaux de NT-Pro BNP plus élevés. Le SOG avait des corrélations négatives avec le rapport E/e' et NT-Pro BNP. Le PALS était un prédicteur indépendant de l'élévation des PRVG (HR=0,711 ; IC à 95 % : 0,513-0,986 ; p=0,041).

**Conclusion:** Le strain de l'OG est un paramètre échographique simple, reproductible et sensible pour prédire l'élévation des PRVG.

**Mots clés:** Echocardiographie, strain atrial gauche, pressions de remplissage du ventricule gauche.

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## INTRODUCTION

Heart failure (HF) diagnosis is based on clinical, electrocardiographic, biological (natriuretic peptides) and echocardiographic data. It is simple in the case of reduced left ventricular ejection fraction (LVEF) but more complex in the case of preserved one ( $\geq 50\%$ ). Symptoms and signs of HF are neither sensitive nor specific especially in the case of HF with preserved ejection fraction (HFpEF) in which even natriuretic peptides may be negative or moderately increased due to other comorbidities (such as old age, atrial fibrillation, renal failure...). The ultrasound is the key test to distinguish between the different phenotypes of HF and to identify structural and functional abnormalities that leads to the diagnosis of HFpEF, such as diastolic dysfunction and high left ventricular filling pressures (LVFP) [1]. Assessment of LVFP is an important step for both the diagnosis and management of patients with HFpEF [2,3]. Although invasive procedures are considered the «gold standard» for the measurement of these pressures, conventional echocardiography is commonly used as a noninvasive alternative. Since none of the ultrasound methods used can measure them directly, several parameters and algorithms have been proposed by American and European associations initially in 2009 and then simplified in 2016 [4]. However, in some cases, the assessment of LVFP remains undetermined because of the absence of one of the required ultrasound parameters. Recently, the analysis of the longitudinal deformation of the left atrial by speckle tracking or LA strain (LAS), a new method developed to study atrial function, has been used to assess left diastolic ventricular function in several heart diseases [5–8].

Thus, we aimed to assess the contribution of LA strain in the estimation of LVFP in patients suffering from exertional symptoms and with preserved LVEF.

## METHODS

### Patients and study design

This was a prospective mono-centric cross-sectional study, conducted from October 2021 to March 2022 in the Cardiology Department of the Internal Security Forces Hospital of Marsa Tunisia. The study was approved by the hospital's ethics committee. Informed verbal consent was obtained by all patients before participation in the study.

We included consecutive patients presenting exertional symptoms and without known structural heart diseases (significant valvular heart disease, prior valve replacement or repair, LVEF < 50%, infiltrative or hypertrophic cardiomyopathy, constrictive pericarditis, congenital heart disease, idiopathic pulmonary hypertension).

Patients with acute heart failure or with rhythm other than sinus at the time of the ultrasound examination, or with severe anemia and patients in whom one of the above-mentioned heart diseases was discovered on resting transthoracic echocardiography (TTE) or unable to perform exercise stress echocardiography (ESE) if indicated, were excluded from our study.

Patient demographic and anthropometric data, cardiovascular risk factors and comorbidities were collected. Symptoms (dyspnea, asthenia, reduced exercise tolerance) leading to the diagnosis of HF were noted. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) at rest and during exercise were measured.

All patients performed a biological examination including hemoglobin (Hb), N terminal pro brain natriuretic peptide

(NT-Pro BNP), and creatinine levels with the calculation of creatinine clearance by the MDRD formula [9].

### Echocardiographic examination

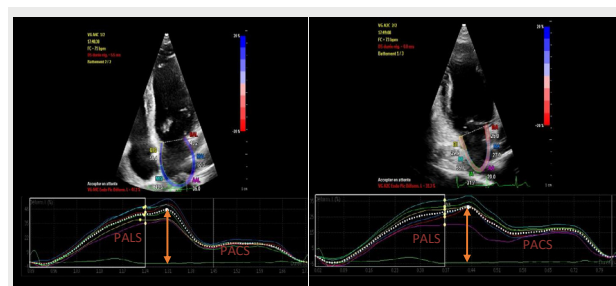
All patients underwent an ultrasound examination at rest using a Philips EPIQ 7C echocardiography with simultaneous and continuous electrocardiographic tracing. All measurements were performed according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) [10].

The following ultrasound parameters were collected at resting TTE: LVEF, left ventricular end-diastolic diameter (LVED), left ventricular mass index (LVMI), left ventricular end-diastolic volume index (LVEDV), maximum velocities of the E wave (E) and the A wave (A), E/A ratio, Septal  $e'$  velocity, Lateral  $e'$  velocity, tricuspid regurgitation (TR) velocity, left atrial volume index (LAVI), Average E/ $e'$  ratio and left ventricular global longitudinal strain (SLG).

LAS was done using LV dedicated and not LA dedicated strain software. It was measured as follow: Two loops of the left atrial were obtained in apical four and two-chamber views after moving the focus to the left atrial and reducing the size of the sector and emphasizing the distinction between the myocardium and extracardiac structures, during a brief apnea and with a stable electrocardiogram recording and frame rate between 60 and 80 frames per second. Atrial strain curves were generated after semi-automatic tracing of the endocardial limits.

Peak atrial longitudinal strain (PALS) is defined by the first peak of the positive atrial longitudinal strain at the beginning of the QRS complex. Peak atrial contraction strain (PACS) is defined by the second positive peak, lower than the first, which corresponds to the period before the atrial contraction (after the onset of the P wave on the electrocardiogram). The PALS and PACS values analyzed were averaged on apical four and two-chambers views (Figure 1). The conduit function (FnC) is the difference between PALS and PACS.

The normal values of PALS, PACS and FnC were 39.4% (27.6 to 59.8%), 17.4% (14 to 25%) and 23%  $\pm 2$ , respectively [11].



**Figure 1.** Left atrial strain measurement in four and two-chambers views. FnC: conduit function, PALS: peak atrial longitudinal strain; PACS: peak atrial contraction strain

The LVFP at rest was assessed by applying the decision algorithm published by ASE/EACVI in 2016 [4] with three possible profiles: normal, high, or indeterminate. Those with normal or indeterminate LVFP at rest underwent ESE, according to the recommendations of the European Society of Cardiology [12] and the following protocol:

On a semi-supine bicycle, the patient should pedal with a speed of 60 rpm starting with a low workload at 15W and with a gradual increase of 5W every minute, until a submaximal target heart rate of 100-110/min (before the fusion of the E and A waves) or until the patient develops limiting symptoms. In both cases, the effort was considered maximal and at this time the E wave, A wave, lateral  $e'$  velocity,

septal e' velocity, and the ratio average E/e' ratio were measured.

Exercise LVFP was considered elevated if the average E/e' ratio at peak stress increases to  $\geq 15$ .

At the end of this assessment (at rest and during exercise), patients were classified, firstly, into three groups according to the estimated LVFP: Group 1 (high LVFP at rest), Group 2 (normal or indeterminate LVFP at rest but raised during exercise) and Group 3 (normal or indeterminate LVFP at rest and normal during exercise). Then, patients were categorized into two final groups according to LVFP: Group A= high LVFP at rest or during exercise and Group B= not-high LVFP at rest and during exercise.

### Statistical analysis

Data were recorded and analyzed using IBM SPSS Statistics 23 software.

The baseline characteristics were summarized using mean  $\pm$  standard deviation (SD) or median  $\pm$  25-75 percentile levels, where appropriate, for continuous data, and counts with percentages for categorical data. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal.

Comparisons of means on independent series were performed by Student's t-test for independent series. Comparisons of percentages on independent series were made by the Pearson chi-square test. The links between two quantitative variables were assessed by Pearson's correlation coefficient (r). A correlation was considered as very weak, weak, moderate, strong, and very strong if r was between 0-0.19, 0.2-0.39, 0.40-0.59, 0.6-0.79 and 0.8-1, respectively. The determination of threshold values of the studied parameters was done by analyzing their receiver operating characteristic (ROC) curves with a comparison of the areas under the curve (AUC) using the Delong method.

Binary logistic regression analysis was performed for the multivariate study. Except for the ultrasound parameters used in the 2016 decision algorithm, all the other parameters for which the univariate analysis had p values  $< 0.05$  were included in the multivariate analysis.

In all statistical tests, the significance level was set at 0.05.

## RESULTS

### General characteristics

A total of 73 patients were eligible for the study. Patient characteristics are summarized in Table 1. The mean age was  $61 \pm 12$  years old. A female predominance was noted: 42 female patients (57.5%). Hypertension and diabetes were the most common cardiovascular risk factors, being found in 81% (n=59) and 51% (n=37) of patients, respectively. Ten patients (14%) had coronary artery disease and 92% (n=67) were either overweight or obese. Exertional dyspnea (86%, n=63) and poor exercise capacity (26%, n=19) were the two most frequent complaints.

The mean hemoglobin value was  $12.9 \pm 1.4$  g/dl, whereas median NT-Pro BNP and creatinine values were 85 [50-195] pg/ml and 66 [56-86]  $\mu\text{mol/l}$ , respectively. Ten patients had creatinine clearance  $< 60$  ml/min.

At echocardiography, the mean LVEF was  $65 \pm 6.3\%$ . The median GLS was  $-22\%$  [-24, -21], the median PALS was  $29.3\%$  [21.4-32.4]. The mean PACS and FnC values were  $13.4\% \pm 4.9$  and  $13.7\% \pm 4.7$ , respectively.

Assessment of rest LVFP classified 17 patients (23%) as having high LVFP, 51 patients (70%) as having normal pressures and 5 patients (7%) as having indeterminate pressures. Among the 56 patients (77%) who had not high LVFP at rest, only eight (11%) had raised filling pressures on ESE. (Figure 2)

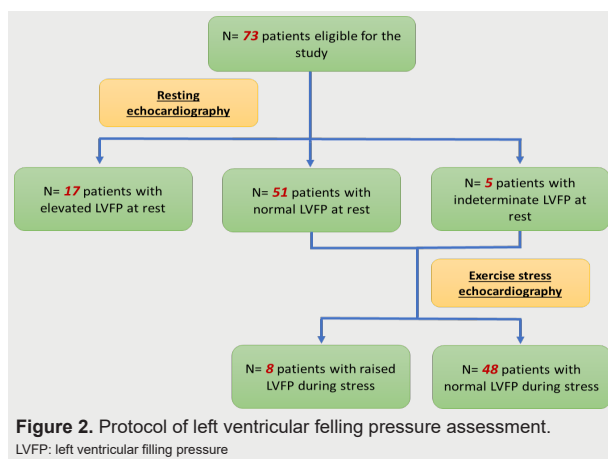


Figure 2. Protocol of left ventricular filling pressure assessment. LVFP: left ventricular filling pressure

### Correlation between left atrial strain and left ventricular filling pressure

Based on these findings, patients were categorized into two final groups according to LVFP: Group A= high LVFP at rest or during exercise (25=34%) and Group B= not-high LVFP at rest and during exercise (48=66%)

The comparison of clinical, biological, and ultrasonographic characteristics between these groups is reported in Table 1.

Table 1. Patient characteristics according to left ventricular filling pressure

	General population (73=100%)	Groupe A (25=34%)	Groupe B (48=66%)	P value
Sex Male / Female (%)	31(42.5)/42 (57.5)	10(40)/15 (60)	21 (44)/27 (56)	0.807
Age (years)	61 $\pm$ 12	67 $\pm$ 12	57 $\pm$ 10	<b>&lt; 0.001</b>
Hypertension (n%)	59 (81)	24 (96)	35 (73)	<b>0.017</b>
Smoking (n %)	12 (16)	5 (20)	7 (15)	0.551
Dyslipidemia (n%)	31 (42.5)	8 (32)	23 (48)	0.192
Diabetes (n %)	37 (51)	16 (64)	21 (44)	0.140
CKD (n %)	9 (11)	8 (32)	1 (2)	<b>0.001</b>
overweigh/ obesity (n %)	67 (92)	21 (84)	46 (96)	0.172
Coronary artery disease (n %)	10 (14)	3 (12)	7 (15)	0.974
SBP (mmHg)	140 [130-145]	145 [138-150]	135 [125-140]	<b>0.008</b>
DBP (mmHg)	80 [77-90]	85 [80-92]	80 [75-84]	<b>0.005</b>
Heart ate (b/m)	80 [72-86]	81 [76-86]	77 [70-85]	0.474
creatinine level ( $\mu\text{mol/l}$ )	66 [56-86]	86 [62-101]	62 [55-77]	<b>0.002</b>
creatinine clearance (ml/min/1.73m <sup>2</sup> )	96 $\pm$ 33	79 $\pm$ 30	105 $\pm$ 31	<b>0.001</b>
Hemoglobin level (d/dl)	12.9 $\pm$ 1.4	12.5 $\pm$ 1.9	13 $\pm$ 1.1	0.247
NT Pro-BNP (pg/ml)	85 [50-195]	282 [108-480]	59 [35-101]	<b>&lt; 0.001</b>
LVFF (%)	65 $\pm$ 6	64 $\pm$ 6	66 $\pm$ 5	0.089
LVED (mm)	49 $\pm$ 5	50 $\pm$ 5	48 $\pm$ 5	0.134
LVEDV (ml/kg/m <sup>2</sup> )	39 [34-47]	38 [33-51]	39 [35-44]	0.919
LVMI (g/m <sup>2</sup> )	89 $\pm$ 23	102 $\pm$ 27	83 $\pm$ 19	<b>0.002</b>
LAVI (ml/m <sup>2</sup> )	35 $\pm$ 12	45 $\pm$ 12	30 $\pm$ 7.3	<b>&lt; 0.001</b>
Rest E/A ratio	1.01 $\pm$ 0.43	1.2 $\pm$ 0.58	0.93 $\pm$ 0.28	<b>0.002</b>
Rest average e' (cm/s)	8.8 $\pm$ 2.4	7.3 $\pm$ 1.7	9.6 $\pm$ 2.3	<b>0.001</b>
Average E/e' ratio at rest	9.5 $\pm$ 3.6	13 $\pm$ 3.3	7.7 $\pm$ 2	<b>&lt; 0.001</b>
TR velocity (cm/s)	2.3 [2-2.7]	2.9 [2.5-3.2]	2.1 [2-2.4]	<b>&lt; 0.001</b>
GLS (%)	-22 [-24, -21]	-21.5 [-23, -19]	-22 [-24, -21]	0.127
PALS %	29 [24-32]	20 [16-23]	31 [28-33]	<b>&lt; 0.001</b>
PACS (%)	13.4 $\pm$ 4.9	9.4 $\pm$ 4	15.5 $\pm$ 3.9	<b>&lt; 0.001</b>
FnC (%)	13.7 $\pm$ 4.7	10 $\pm$ 3	15.5 $\pm$ 4.2	<b>&lt; 0.001</b>
Average E/e' ratio at exercise	9.9 $\pm$ 3.3	16 $\pm$ 1	8.8 $\pm$ 2.1	<b>&lt; 0.001</b>

CKD: chronic kidney disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; LVED: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume index; LVMI: left ventricular mass index; LAVI: left ventricular atrial index; TR: tricuspid regurgitation; GLS: global longitudinal strain; PALS: peak atrial longitudinal strain; PACS: peak atrial contraction strain, FnC: conduit function.

Patients from group A were significantly older ( $p < 0.001$ ) with a significantly higher prevalence of hypertension ( $p = 0.017$ ) and chronic kidney disease ( $p = 0.001$ ). SBP ( $p = 0.008$ ) and DBP ( $p = 0.005$ ) were also significantly higher in those patients.

Patients from group A had higher creatinine levels ( $p = 0.002$ ) and lower clearance ( $p = 0.001$ ). The NT Pro-BNP level was significantly higher in this group ( $p < 0.001$ ). Given that the ASE/EACVI guidelines were followed for the evaluation of LVFP, the ultrasound parameters of diastolic function were significantly associated with LVFP including E/A ratio ( $p = 0.002$ ), average E/e' ratio at rest ( $p < 0.001$ ), TR velocity ( $p < 0.001$ ), rest average e' velocity ( $p = 0.001$ ), LAVI ( $p < 0.001$ ), and average E/e' ratio at stress ( $p < 0.001$ ). LVMI was significantly associated with higher LVFP ( $p = 0.002$ ).

LAS analysis showed that PALS ( $p < 0.001$ ), PACS ( $p < 0.001$ ), and Fnc ( $p < 0.001$ ) were significantly lower in group A compared with group B.

Data are presented as mean  $\pm$  SD, median (interquartile range), or count and percentage of patients. Bold values indicate  $p < 0.05$ .

To further explore the relation between LAS components and the other parameters of HFpEF, we performed a bivariate analysis, as shown in table 2.

Almost all of the LAS components were significantly correlated to the ultrasound and biological elements of HFpEF. There was a strong and negative correlation between PALS and average E/e' ratio at rest ( $r = -0.647$ ;  $P < 0.001$ ) and LAVI ( $r = -0.624$ ;  $P < 0.001$ ).

**Table 2.** Left atrial strain components and the other parameters of heart failure with preserved ejection fraction on bivariate analysis.

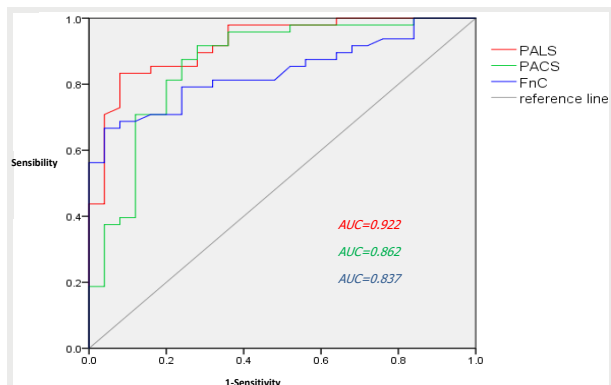
	PALS	PACS	Fnc
<b>Rest average e'R=</b>	<b>0.349; P= 0.002</b>	<b>0.154; P= 0.093</b>	<b>0.480; P&lt; 0.001</b>
<b>Average E/e' ratio at rest</b>	<b>R= -0.647; P&lt; 0.001</b>	<b>R= -0.539; P&lt; 0.001</b>	<b>R= -0.513; P&lt; 0.001</b>
<b>LAVI</b>	<b>R= -0.624; P&lt; 0.001</b>	<b>R= -0.476; P&lt; 0.001</b>	<b>R= -0.526; P&lt; 0.001</b>
<b>TR velocity</b>	<b>R= -0.523; P&lt; 0.001</b>	<b>R= -0.436; P&lt; 0.001</b>	<b>R= -0.405; P&lt; 0.001</b>
<b>NT Pro-BNP</b>	<b>R= -0.551; P&lt; 0.001</b>	<b>R= -0.440; P&lt; 0.001</b>	<b>R= -0.419; P&lt; 0.001</b>
<b>Average E/e' ratio at stress</b>	<b>R= -0.539; P&lt; 0.001</b>	<b>R= -0.373; P= 0.005</b>	<b>R= -0.428; P= 0.001</b>

LAVI: left ventricular atrial index; TR: tricuspid regurgitation.

We performed ROC curve analysis to assess the performance of LAS components in the prediction of high LVFP (group A) (Figure 3 and table 3).

All LAS components had a good performance to detect high LVFP (group A). PALS was the best predictor of group A, however this superiority was only significant compared to Fnc ( $p = 0.02$ ).

The ROC curves analyses were used to identify the cut-off values of LAS components predicting high LVFP.



**Figure 3.** Receiver operating characteristic curves of left atrial strain components to predict high left ventricular filling pressures

PALS: peak atrial longitudinal strain; PACS: peak contraction longitudinal strain; Fnc: conduit function.

Thus, PALS  $< 24$  (sensitivity of 82% and specificity of 85%) increased the likelihood of being from group A by 5.4 (RR = 5.4; 95% CI 2.21 – 13.5;  $p < 0.001$ ). PACS  $< 13$  (sensitivity of 80% and specificity of 78%) increased the likelihood of being from group A by 3.8 (RR = 3.8; 95% CI 1.73 – 8.56;  $p < 0.001$ ). For Fnc, a cut-off value  $< 14$  (sensitivity of 85% and specificity of 70%) increased the likelihood of being from group A by 8.5 (RR = 8.5; 95% IC 2.24 – 32.9;  $p < 0.001$ ).

Binary logistic regression analysis was performed for the multivariate study. Except for the ultrasound parameters used in the 2016 decision algorithm, all the other parameters for which the univariate analysis had  $p$  values  $< 0.05$  were included in the multivariate analysis. Only PALS (HR= 0.711; 95% CI: 0.513-0.986;  $p = 0.041$ ) was an independent predictor of high LVFP at rest or during exercise.

**Table 3.** Areas under curves of left atrial strain components to predict high left ventricular filling pressures with Delong test

	AUC	P value	95% IC		P value (Delong)
			IB	SB	
<b>PALS</b>	0.922	<b>&lt;0.001</b>	0.860	0.985	<b>PALS Vs PACS</b> 0.0807
<b>PACS</b>	0.862	<b>&lt;0.001</b>	0.766	0.959	<b>PALS Vs Fnc</b> <b>0.0209</b>
<b>Fnc</b>	0.837	<b>&lt;0.001</b>	0.748	0.926	<b>PACS Vs Fnc</b> 0.6907

PALS: peak atrial longitudinal strain; PACS: peak atrial contraction strain; Fnc: conduit function.

## DISCUSSION

This study revealed that LAS components showed mild to strong correlations with the parameters outlined in the 2016 decision algorithm. Cut-off values for predicting high LVFP (at rest or during exercise) were determined at 24, 13, and 14 for PALS, PACS, and Fnc, respectively. Importantly, the study found that among these LAS components, only PALS stood out as an independent predictor for high LVFP. Left atrial function is articulated in three phases during each cardiac cycle: a “reservoir” phase (PALS) during ventricular systole, a “conduit” phase (Fnc) during early diastole, and a “booster pump” phase (PACS) in late diastole. All phases are partially influenced by ventricular chamber spatial displacement of left ventricular systole with the downward movement of the mitral annulus and alongside with end-systolic volume, influence left atrial relaxation and compliance which determine PALS. The latter is pivotal for successively left ventricular filling since the energy stored by the left atrial during ventricular systole is then released after mitral valve opening, contributing to an adequate left ventricular stroke volume. Both left atrial and ventricular compliance influences Fnc which includes early left ventricular filling and diastasis. PACS is based on left atrial contractility, venous return, and left ventricular end-diastolic pressure [13–15].

The findings of the present study agree with the results of previously published reports. Gaun et al. found that PALS and PACS were significantly correlated with the E/e' ratio ( $r = -0.381$  and  $-0.467$ , respectively, all with  $P < 0.013$ ), in a population of 118 patients with HFpEF [16]. In a small cohort of 30 end-stage renal disease patients with HFpEF, Abid et al. found a negative correlation between PALS and E/e' ratio ( $r = -0.33$ ,  $p = 0.049$ ) and LAVI ( $r = -0.366$ ,  $p = 0.047$ ) and a positive correlation with average e' velocity ( $r = 0.557$ ,  $p = 0.001$ ) [17]. Lately, Fraydes et al. showed that PALS correlated with E/A ratio ( $r = -0.42$ ,  $p < 0.01$ ), LAVI ( $r = -0.35$ ,  $p < 0.01$ ), E/e' ratio ( $r = -0.42$ ,  $p < 0.01$ ), and TR velocity ( $r = -0.20$ ,  $p < 0.02$ ). In a cohort of 300 patients diagnosed with HFpEF [6]. With this sense, some studies have shown that PALS has a stronger correlation with invasive LVFP at rest than LAVI [18,19]. In other studies, PALS and PACS were more correlated with invasive pulmonary capillary pressures

measurement than the E/A ratio in patients with HFpEF [3,20]

In addition, many published reports assessed the relation between NT-Pro BNP and diastolic function and showed that it can be used to predict increased LVFP. Kurt et al. reported a negative and mild correlation between PALS and PACS on the one hand and NT-Pro BNP on the other ( $r=-0.42$ ,  $P=0.001$  and  $r=-0.37$ ,  $P=0.003$ , respectively) [18].

In a cohort of 74 patients with acute coronary syndrome, Topal et al. found a negative correlation between PALS and BNP ( $p=0.001$ ,  $r=-0.440$ ) [21]. A similar finding was reported by other authors ( $r=-0.482$ ,  $p=0.007$ ) [17]. Identical to our results, Aung et al. found a strong negative correlation between PALS and BNP ( $r=-0.567$ ,  $p<0.001$ ) [22].

In the present study, LAS components were associated with high LVFP at rest. From perspective, two recent studies should be mentioned. Inoue et al. included more than 300 patients with a median LVEF of 55% and showed that both PALS and PACS were associated with LVFP. The optimal cut-off to differentiate between normal and high LVFP was 18% for PALS and 8% for PACS [23]. Recently, Milijkovic et al. showed that PALS was significantly associated with the severity of diastolic dysfunction in hypertensive patients with HFpEF [5]. They found that a PALS value  $<24.27\%$  could predict high LVFP at rest with a sensitivity of 78.9% and a specificity of 84.6%. These results were equal to ours.

It is known that patients with HFpEF can elevate their filling pressures during exercise, despite normal resting LVFP. In a similar study, Ye et al. also evaluated the diagnostic value of LAS in detecting exercise LVFP raising in 669 patients with dyspnea assessed by stress echocardiography. They found that PALS and FnC were significantly lower in the case of elevated LVFP during exercise, regardless of the grade of diastolic dysfunction at rest [7]. Telles et al. concluded that PALS and PACS were correlated with invasive pulmonary capillary pressures measured during exercise ( $r=-0.64$  and  $r=0.72$ ,  $P<0.001$ ) and these parameters remained independent predictors of HFpEF after multivariate analysis. A PALS value  $\leq 33\%$  predicted an invasively verified diagnosis of HFpEF with a sensitivity of 88% and specificity of 77% [24].

Left ventricular diastolic dysfunction is one of the major pathophysiological processes of HFpEF [25]. In the early stage, the left atrial enhances its pump function (PALS) to compensate for the obstruction of left ventricular filling caused by reduced left ventricular compliance. With prolonged and worse diastolic dysfunction, the compliance of the left atrial is gradually impaired, which results in a decrease in the reserve (PALS) of the left atrial, eventually leading to the enlargement and failure of the left atrial [26]. Therefore, left atrial strain reflects the cumulative adverse impact of chronically left ventricular diastolic dysfunction impaired on the left atrial [27].

The latest algorithms of EACVI guidelines for estimating diastolic dysfunction [23] are based on several standard parameters and describe a precise scoring to quantify its severity. The persistence of a «gray zone» of values in which quantification of diastolic dysfunction is not feasible, as well as an increase in the prevalence of HFpEF, has driven the research and the use of parameters with greater specificity and sensitivity: one of them is LAS. The anatomy and mechanics of the left atrial are crucial to preserve the left ventricular function and the asymptomatic state of the patient. LAS, easily measured, correlates with LVFP raising both at rest and during exercise and therefore can be used as an alternative parameter in the diagnosis of HFpEF.

## LIMITATION

Our study was monocentric and cross-sectional, used non-randomized observational data, and is therefore subject to selection bias. However, we were careful to include consecutive patients.

Secondly, we used echocardiographic variables to define high LVFP without hemodynamic validation. Besides, some degree of interobserver and intra-observer variability is known to be related to the analysis of the LAS. Also, LAS was done using LV dedicated and not LA dedicated strain software.

Finally, our study population was small compared with several larger-scale studies published in the literature. It is possible that the present study in some way is insufficient to accurately estimate the association between LAS and LVFP.

Further longitudinal studies with a larger population are needed to confirm our results.

## CONCLUSION

Our findings were concordant with studies that have recently underlined the predictive value of LAS components, essentially PALS, in predicting high LVFP, at rest or during exercise. Thus, this parameter may provide a simple, reproducible, and sensitive ultrasound parameter which can be used for the assessment of LVFP.

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