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Left atrial dysfunction relates to symptom onset in patients with heart failure and preserved left ventricular ejection fraction

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Aims Pathophysiology of heart failure (HF) with preserved ejection fraction (HFPEF) remains unclear. Left atrial (LA) function has been related to HF symptoms. Our purpose is to analyse LA function in outpatients with new onset symptoms of HF.

Methods and results An observational study was performed including 138 consecutive outpatients with suspected HF referred to a one-stop clinic. Final diagnosis [HF with reduced EF (HFREF), HFPEF, or non-HF] was established according to current recommendations. Echocardiography was performed in all patients. LA function was analysed using strain derived from speckle tracking in sinus rhythm patients ($n = 83$). Results were analysed with ANOVA and Bonferroni statistical tests. Receiver operating characteristic (ROC) curves were constructed to investigate the predictive ability of LA parameters for the final diagnosis of HF. Patients were 75 $\pm$ 9 years and 63% women. Final diagnosis was 23.2% HFREF, 45.7% HFPEF, and 31.2% non-HF. Left ventricular strain rate showed no differences between non-HF and HFPEF groups, but both groups showed differences with the HFREF group. LA strain rate (A- and S-waves) was significantly reduced in both HF groups (without differences among them) when compared with the non-HF group. LA strain rate and indexed volume showed significant accuracy for HF diagnosis in ROC curves.

Conclusions In outpatients with new-onset symptoms of HF, LA dysfunction was observed. It might be the initial mechanism in the development of symptoms in HFPEF patients. These findings support the relationship of LA dysfunction with HFPEF, suggesting that the analysis of LA function may be useful in sinus rhythm patients with new-onset dyspnoea.

Keywords Outpatient • HFPEF • Speckle-tracking echocardiography • Atrial strain • Heart failure onset

Introduction

Heart failure (HF) with preserved left ventricular ejection fraction (HFPEF) is the most prevalent type of HF in the ambulatory setting.[1,2] Despite its high prevalence, it remains underdiagnosed and the corresponding mortality and morbidity are similar to HF with reduced EF (HFREF).[1,3]

In recent years, several mechanisms that could be related to the development of HFPEF have been proposed. Initial studies[4,5] reported left ventricular (LV) diastolic dysfunction and LV systolic longitudinal dysfunction, as shown by reduced longitudinal myocardial velocities and deformation, suggesting that HFPEF could be an HF stage preceding HFREF. However, the heterogeneity of the patient groups studied (ambulatory, in-hospital, recurrent HF, etc.) has produced somewhat contradictory results.[6–8] Left atrial (LA) dysfunction has also been associated with the development of HFPEF; initially, LA indexed volume was related to diastolic dysfunction,[9] exercise capacity,[10] and HFPEF syndrome.[11] In HFPEF patients, atrial fibrillation and loss of atrial function have been related to worse clinical outcomes,[12] and atrial strain analysis has been used to study LA function. Two studies have suggested that abnormal LA strain could be related to clinically overt HF and predictive symptoms. In a study of patient groups that did not differ by LA volume, LA strain was significantly decreased in HF patients (HFPEF and

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particularly HFREF) when compared with patients with diastolic dysfunction but without HF.[13] More recently, impaired LV and LA strain have been described in HFPEF patients, compared with non-HF patients with diastolic dysfunction.[14] In addition, atrial dysfunction as evaluated by LA strain has been related to exercise capacity[15–17] and cardiovascular outcome.[18]

We hypothesized that LA function could be already impaired in early stages of HFPEF, and that this impairment could be at least, in part, responsible for the development of clinical symptoms in these patients. Additionally, evaluation of LA function could be useful to improve the differential diagnosis of patients presenting with HF, namely differentiating HFPEF from non-HF. Accordingly, we sought to analyse if there were any differences in LA function among patients with dyspnoea, non-HF, HFPEF, and HFREF.

Methods

Study design and ethics

The study was observational and descriptive. Patients with new-onset HF symptoms were prospectively included. The study was approved by the Ethics Committee of our institution and complied with the Helsinki declaration. All participants provided written informed consent and all data were treated according to Spain's Organic Law 15/1999 of Personal Data Protection and Royal Decree 1720/2007.

Patients

Consecutive outpatients with new-onset HF symptoms referred by primary healthcare centres to our one-stop HF clinic for examination between March 2009 and July 2012 were included. Clinical evaluation, determination of natriuretic peptide B-type (BNP) plasma levels, and echocardiography were performed as reported elsewhere.[2] In accordance with current recommendations,[19] patients were diagnosed as HFREF, HFPEF, or non-HF. Exclusion criteria were age <18 years, life expectancy <1 year, and/or inability to complete the diagnostic circuit.

Echocardiography acquisition and analysis

A comprehensive two-dimensional echocardiography study with conventional Doppler and tissue Doppler was performed using a commercially available system (Vivid 7, GE Healthcare, Milwaukee, WI, USA). LV and LA dimensions were determined according to the current recommendations[20] and indexed by body surface area (Du Bois method). Evaluation of LV diastolic function was based on three factors: (i) LV filling, determining maximum early (E-wave) and late (A-wave) diastolic velocities and the relationship between both (E/A) and the deceleration time of the E-wave; (ii) the peak velocity of systolic and diastolic flow in the pulmonary veins; and (iii) tissue Doppler peak diastolic velocities of the lateral mitral annulus (E′ and A′).[21]

Two-dimensional echocardiography using the dedicated software (2D strain, EchoPAC^{TM}, GE Healthcare) was used to assess LA and LV myocardial deformation. The analysis was performed by a reader blinded to clinical status. The frame rate was set between 60 and 80 frames per second, and three beats in sinus rhythm and five beats in atrial fibrillation patients were averaged to measure the strain and strain rate. Global longitudinal LV strain was quantified and the values for six myocardial LV segments in the apical four-chamber view were averaged. The LA longitudinal deformation was quantified and averaged for six LA segments from the apical four-chamber view with initial onset in the ECG P-wave. Most previous authors have used the QRS as the time reference for the onset of LA strain analysis.[14,16–18] We selected P-wave of the ECG signal as our starting point in order to isolate LA contractile function, assuming that the LV is completely relaxed at that time; this should guarantee that all the LA shortening was produced by atrial contraction. We are confident that this assumption is valid because none of our patients showed EA waves fusion in the LV inflow, which would indicate incomplete LV relaxation at the time of the P-wave onset. Using the P-wave as the onset for deformation analysis, we determined LA peak systolic strain rate (S-wave; LASRs) as a surrogate of LA reservoir function and LA peak strain rate after contraction (A-wave; LASRa) as a surrogate of LA contractile function (*Figure 1*). An extreme value (minimum of longitudinal strain) was taken into account for the analysis. Adequate reproducibility for LA deformation analysis in our Laboratory has been previously reported.[22]

Statistical analysis

Quantitative variables are shown as mean $\pm$ standard deviation. Qualitative variables are shown as total number and percentage. Descriptive and comparative analyses of the different diagnostic groups were performed. Normal distribution of quantitative variables was assessed using the Kolmogorov–Smirnov test. Intergroup differences (unpaired data) were assessed by the χ^2 test or Fisher test for categorical variables and Student's *t*-test for quantitative variables.

ANOVA and Bonferroni statistical tests were used to compare quantitative variables between more than two groups. The receiver operating characteristic (ROC) curve was assessed to identify correlation of echocardiographic parameters with diagnosis and to determine cut-off values. Pearson test was used to correlate quantitative variables. A *P*-value of <0.05 (two-sided) was considered statistically significant. Data were processed with SPSS version 18 (IBM, Armonk, NY, USA).

Results

Demographics and clinical data

A total of 138 elderly patients (mean age 75 $\pm$ 9 years) with complete echocardiography studies were included. Participants were mainly hypertensive (77.5%) and women (65.2%). The mean time from onset of symptoms to the outpatient visit was 131 $\pm$ 124 days. The final diagnosis, determined according to the current guidelines,[19] was HFPEF in 45.7% ($n = 63$), HFREF in 23.2% ($n = 32$), and non-HF in 31.2% ($n = 43$) of the studied patients.

The baseline patient characteristics are summarized in *Table 1*. The three diagnostic groups were similar in age, diabetes status, and previous occurrence of atrial fibrillation. Women were more prevalent in the HFPEF and non-HF groups; there were fewer patients with hypertension in the non-HF group. Patients in the HFREF group had higher prevalence of tobacco use and lower body mass index. The group of sinus rhythm patients ($n = 93$) had similar baseline characteristics (74.2 $\pm$ 9.4 years, 69% women, 79.3% hypertension, 29.3% diabetics, 31.7% smokers, and body mass index 30.6 $\pm$ 5 kg/m^2).

Echocardiographic findings

Table 2 presents LV dimensions, diastolic and systolic function, and LA dimensions in the three groups of patients. The LV was enlarged in the HFREF group, compared with the HFPEF and non-HF groups. According to the diagnostic criteria, the LVEF was normal in non-HF and HFPEF patients (no differences between groups) and significantly lower in the HFREF group. LV strain could be measured in

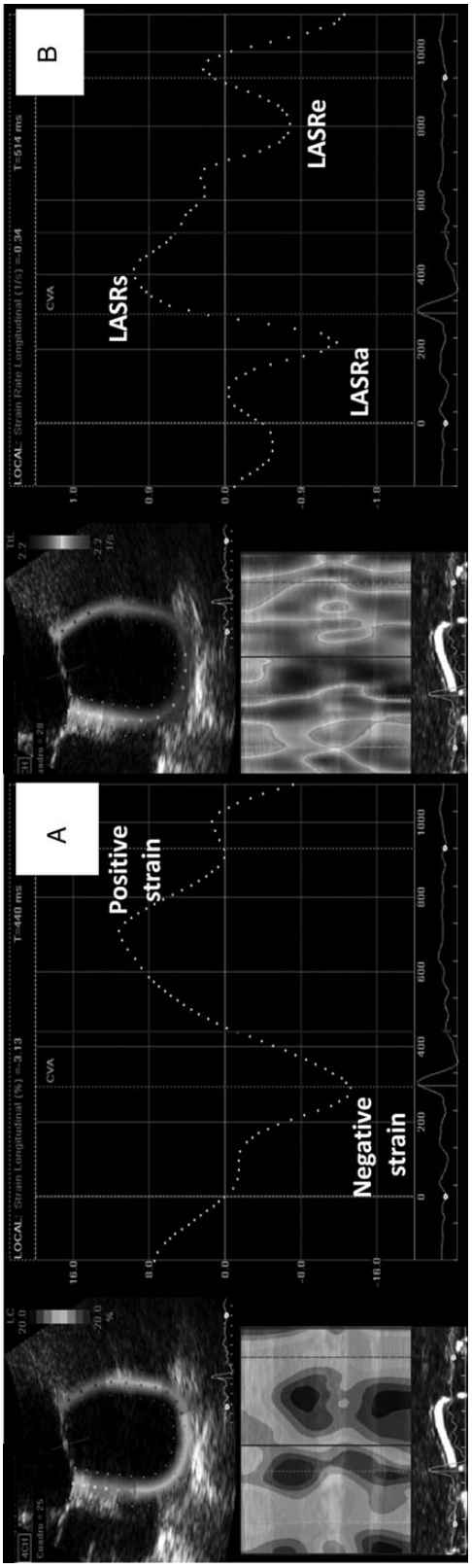

Figure 1: Left atrial strain waves (speckle-tracking echocardiography). (*A*) Left atrial longitudinal strain waves. (*B*) Left atrial longitudinal strain-rate waves. LASRa, left atrial strain-rate A-wave; LASRs, left atrial strain-rate S-wave; LASRe, left atrial strain-rate E-wave.

121 patients (87.7%). Impairment of LV longitudinal deformation (strain and strain rate) was observed in the HFREF group when compared with the HFPEF and non-HF groups, with no differences between the latter two. Compared with the non-HF group, LA was significantly enlarged in both HF groups (with no statistically significant differences between them). Regarding diastolic function, E/e′ and E/A index showed no differences between HF groups, but significant differences with the non-HF group. E-wave deceleration time was also significantly shorter in the HFREF group when compared with the HFPEF patients.

Table 3 summarizes LV and LA dimensions and function only for patients with sinus rhythm ($n = 93$); LA strain could be measured in 82 of these patients (88.2%). LASRa and LASRs were significantly impaired and the LA significantly dilated in both HF groups when compared with non-HF patients, with no differences between HF groups. In addition, there were no differences in the parameters of LV dimensions and systolic function between the non-HF and HFPEF groups.

The comparison of indexed LV and LA volumes, LV mass, and LVEF between patients with ($n = 45$) or without AF ($n = 93$) at the moment of inclusion was not significantly different (*P*-values = 0.746, 0.111, 0.520, and 0.744, respectively)

LA parameters for HF diagnosis

LA volume, LASRa, and LASRs were significantly correlated with BNP levels (Pearson correlation 0.326, −0.421, and −0.462, respectively; all $P < 0.001$). Higher LA volumes and lower levels of LA strain rate were related to higher BNP levels. These parameters were also related to the degree of LV diastolic dysfunction (Pearson correlation with LA volume: 0.417; LASRa: 0.498; LASRs: −0.462; $P < 0.001$ in all cases).

Figure 2 shows the ROC curve for the final HF diagnosis, comparing the diagnostic values of LA dimension and function in patients with sinus rhythm. LASRa, LASRs, and LA volume predicted HF diagnosis with an area under the curve (AUC) of 0.801, 0.847, and 0.852, respectively (all with *P*-value <0.001). The ratio of LASRs/LA volume index (normalization of LA deformation with LA volume, as both being determinants of LA stroke volume) had an AUC of 0.902 for HF diagnosis. *Table 4* reports the cut-off values for each parameter; the LASRs/LA volume index ratio with a cut-off value of 0.025 had the best specificity, sensitivity, and positive-negative-predictive values.

Discussion

In this study, LA function (LASRa and LASRs) was significantly impaired and LA volumes were significantly larger in both groups with HF (HFPEF and HFREF) and sinus rhythm, when compared with the non-HF group; there were no differences in LV systolic function between non-HF and HFPEF groups. In patients with sinus rhythm, LA function (strain rate) and dimensions (LA volume) were highly predictive for the final diagnosis of HF; particularly, the greatest predictive value was achieved by combining atrial deformation and size (LASRs/LA volume index).

Previous studies have reported that LA volume helps to identify HFPEF[11] with a sensitivity and specificity similar to our results (close to 80%). In HFPEF patients, LA volume[10] and function[15,17]

Table 1 Baseline characteristics

	HFPEF ($n = 63$)	HFREF ($n = 32$)	Non-heart failure ($n = 43$)	Total ($n = 138$)	*P*-value
Age (years)	76 ± 8	74 ± 12	73 ± 8	75 ± 9	0.155
Female	45 (71.4%)	**12 (37.5%)**	33 (76.7%)	90 (65.2%)	**<0.001**
Hypertension	54 (85.7%)	25 (78.1%)	**28 (65.1%)**	107 (77.5%)	**0.024**
Diabetes	15 (23.8%)	14 (43.8%)	8 (18.6%)	37 (26.8%)	0.082
Smoker	19 (30.2%)	**18 (56.3%)**	14 (32.6%)	51 (37%)	**0.002**
Previous known AF	25 (39.7%)	16 (50%)	4 (9.3%)	49 (35.5%)	**<0.001**
Degree of LV diastolic dysfunction	1.61 ± 0.07	2.02 ± 0.12	0.89 ± 04	1.47 ± 0.06	**<0.001**
Body mass index (kg/m^2)	29.62 ± 4.94	28.08 ± 5.6	**31.66 ± 4.36**	29.93 ± 5.09	**0.002**
Class of dyspnoea (NYHA) >2	27 (42.9%)	16 (50%)	**7 (16.3%)**	50 (36.2%)	**0.005**
BNP (ng/mL)	160.20 ± 124.30	300.40 ± 252.89	40.19 ± 26.41	153.00 ± 175.89	**<0.001**

AF, atrial fibrillation; BNP, natriuretic peptide B-type; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; LV, left ventricle; NYHA, New York Heart Association.
Bold values refers to statistically significant values.

Table 2 Echocardiographic parameters of all included patients ($n = 138$)

	Mean (*n*)			Statistical significance (*P*-value)		
	HFPEF ($n = 63$)	HFREF ($n = 32$)	Non-HF ($n = 43$)	Non-HF vs. HFPEF	Non-HF vs. HFREF	HFPEF vs. HFREF
LV end-diastolic volume (mL/m^2)	60 ± 15 (63)	102 ± 38 (32)	57 ± 15 (43)	1	**<0.001**	**<0.001**
LV end-diastolic diameter (mm)	50 ± 5 (63)	58 ± 9 (32)	48 ± 5 (43)	0.887	**<0.001**	**<0.001**
LV mass (g/m^2)	128.2 ± 27.6 (63)	148.8 ± 36.6 (32)	108.8 ± 21 (43)	**0.001**	**<0.001**	**0.010**
LVEF (%)	60 ± 5 (63)	34 ± 10 (32)	60 ± 4 (43)	1	**<0.001**	**<0.001**
LV longitudinal strain (%)	−16 ± 3.7 (54)	−9.5 ± 4.5 (30)	−17 ± 3.5 (37)	1	**<0.001**	**<0.001**
LV longitudinal strain rate (s^{-1})	−0.98 ± 0.26 (54)	−0.63 ± 0.23 (30)	−1.04 ± 0.26 (37)	0.951	**<0.001**	**<0.001**
LA volume (mL/m^2)	58.9 ± 23.3 (63)	57.8 ± 20.8 (32)	33.7 ± 13 (43)	**<0.001**	**<0.001**	0.129
LA anteroposterior diameter (mm)	42.7 ± 7.7 (63)	45.69 ± 6.7 (32)	36.2 ± 4.4 (43)	**<0.001**	**<0.001**	0.129
E/A	1.0 ± 0.6 (38)	1.7 ± 1.4 (16)	0.76 ± 0.2 (39)	**0.003**	**<0.001**	0.256
E-wave DT	218.7 ± 62.4 (63)	171.9 ± 45.7 (32)	239.1 ± 45.9 (43)	0.177	**<0.001**	**<0.001**
E/e′	11.3 ± 5.5 (63)	11.6 ± 7.6 (32)	7.4 ± 2.2 (43)	**0.001**	**0.003**	1.000
Pulmonary artery systolic pressure (Doppler derived)	40 ± 11 (46)	41 ± 11 (28)	33 ± 8 (14)	0.267	0.399	1.000

DT, deceleration time; LA, left atrial; LV, left ventricular; HFPEF, heart failure preserved ejection fraction; HFREF, heart failure reduced ejection fraction; Non-HF, non-heart failure; NYHA, New York Heart Association.
Bold values refers to statistically significant values.

have been related with exercise capacity. In our study, LA function (LASRa and LASRs) was related to HF diagnosis early after symptoms onset. Additionally, effort dyspnoea was the main symptom for referral to our clinic, supporting the relationship between atrial function and exercise capacity. The association of LA dysfunction or atrial fibrillation with worse clinical outcomes has been reported in previous studies;[12,18] however, our data also show that these abnormalities are already present in the early stages of the disease. Similar to the findings of previous studies,[13,14] we observed a significant impairment of LA deformation in both HF groups when compared with the non-HF group, with no differences between HF groups.

In our study, LA indexed volume, LASRa, and LASRs had similar AUC for HF diagnosis. Another study compared total LA strain with LA volume[18] to assess cardiovascular prognosis in a non-HF population at time of inclusion, reporting that LA strain was the more powerful predictor of cardiovascular events. Accordingly, in our study, LA deformation (LASRs, LASRa, and LASRs/LAvolume) were better correlated with BNP.

We found no differences in LV deformation between the non-HF and HFPEF groups. In previous studies, the isolated analysis of LV strain in patients with HFPEF has produced controversial results.[6–8] If patients were recruited mostly after a hospital admission,[6,8,14] LV strain was impaired in both HFPEF and HFREF patients, with worse values in HFREF patients. However, more advanced HF patients could have been included because some of these studies applied a cut-off point of 45% to define preserved LVEF.[7] Results might have

Table 3 Echocardiographic parameters of patients in sinus rhythm (ventricular and atrial measures) ($n = 93$)

	Mean (N)			Statistical significance (P-value)		
	HFPEF ($n = 38$)	HFREF ($n = 16$)	Non-HF ($n = 39$)	Non-HF vs. HFPEF	Non-HF vs. HFREF	HFPEF vs. HFREF
LV end-diastolic volume (mL/m^2)	63.7 ± 14.6 (38)	117.5 ± 44.7 (16)	57.6 ± 15.8 (39)	0.730	**<0.001**	**<0.001**
LV end-diastolic diameter (mm)	50.4 ± 5.9 (38)	61.1 ± 10.8 (16)	48.5 ± 5.2 (39)	0.672	**<0.001**	**<0.001**
LV mass (g/m^2)	136.5 ± 26.9 (38)	155.5 ± 48.3 (16)	108.3 ± 21.3 (39)	**<0.001**	**<0.001**	0.103
LVEF (%)	59.8 ± 5.3 (38)	30.1 ± 10.6 (16)	60.8 ± 3.9 (39)	1	**<0.001**	**<0.001**
LV longitudinal strain (%)	−16.7 ± 3.9 (32)	−9.8 ± 4.6 (14)	−17.1 ± 3.5 (34)	1	**<0.001**	**<0.001**
LV longitudinal strain rate (s^{-1})	−0.95 ± 0.25 (32)	−0.60 ± 0.24 (14)	−1.06 ± 0.26 (34)	0.311	**<0.001**	**<0.001**
LA volume (mL/m^2)	54.6 ± 16 (38)	54.5 ± 22.1 (16)	33.4 ± 13.1 (39)	**<0.001**	**<0.001**	1
LA positive strain (%)	8.9 ± 4.9 (36)	6.5 ± 5.4 (14)	9.9 ± 5.6 (32)	1.000	0.155	0.478
LA negative strain (%)	−10.8 ± 10.6 (36)	−11 ± 5.3 (14)	−15.2 ± 5 (32)	**0.016**	0.132	1.000
LASRa (s^{-1})	−1.22 ± 0.71 (36)	−1.10 ± 0.63 (14)	−1.97 ± 0.53 (32)	**<0.001**	**<0.001**	1
LASRs (s^{-1})	0.98 ± 0.35 (36)	0.73 ± 0.46 (14)	1.38 ± 0.40 (32)	**<0.001**	**<0.001**	0.157
LASRe (s^{-1})	−2.06 ± 8.58 (36)	−0.52 ± 0.55 (14)	−0.76 ± 0.58 (32)	1.000	1.000	1.000

HFPEF, heart failure preserved ejection fraction; HFREF, heart failure reduced ejection fraction; Non-HF, non-heart failure; LA, left atrial; LASRa, LA strain rate post A-wave; LASRs, LA systolic strain rate; LV, left ventricular; LASRe, left atrial strain-rate E-wave.
Bold values refers to statistically significant values.

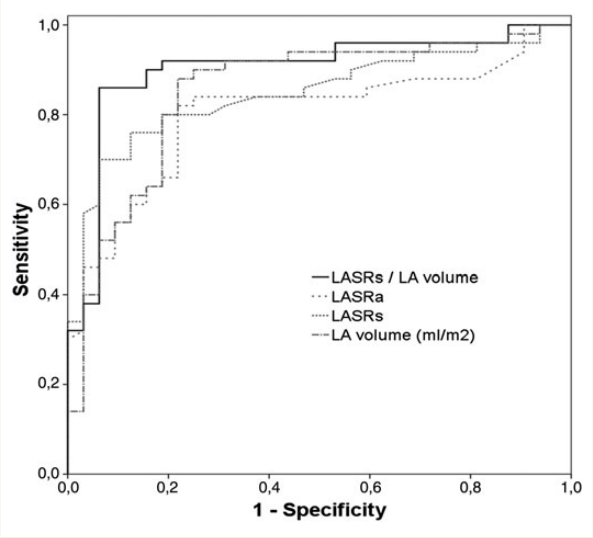

Figure 2: ROC curve for heart failure (preserved or reduced EF) diagnosis in patients in sinus rhythm. LA, left atrium; LASRa, LA strain-rate post-A-wave; LASRs, LA systolic strain rate.

also varied according to the age of the participants. In our cohort, main LV global strain in patients with non-HF is −17.1%. This relative low value could be explained by considering the advanced age of our patients (73 ± 8 years) as an age-related decline in longitudinal left ventricular strain has also been previously observed.[23] The lack of differences in LV strain between the HFPEF and non-HF groups in our study could be related to the fact that our population consisted of outpatient subjects with new-onset HF symptoms. Therefore, we could hypothesize that the LA is the first to fail in the early stages of HFPEF, as LA dysfunction seems to be related to symptoms development. We observed a significant correlation between LA function (LASRa and LASRs) and LV diastolic function. If the disease progresses, LV systolic function could be more impaired, as shown in other studies with in-hospital HF diagnosis.[6,8]

If atrial dysfunction is the initial mechanism in HF development, assessing LA function and dimensions could be useful for improving HF diagnosis. Our results show that LASR and LA volume have similarly good predictive values for HF diagnosis, with LASRs providing the best correlation with BNP and HF diagnosis. The combination of LA function and size, using the LASRs/LA volume index, seems to be the best predictor for HF diagnosis.

Clinical implications

Our study demonstrates structural and functional changes in the LA, even in the early stages of HFPEF. If LA function could be preserved or even improved, symptoms might improve in patients with HFPEF. More studies are needed to determine whether structural LA changes are reversible, but pharmacological (antiarrhythmic drugs) or non-pharmacological (catheter or surgical ablation) therapies aimed at maintaining sinus rhythm could potentially help to preserve LA function.[24–25] Subclinical LA dysfunction can currently be identified with non-invasive imaging such as echocardiography; therefore, LA assessment should be mandatory in this type of patients with new-onset HF symptoms.

Given difficulties in the differential diagnosis of HFPEF, the analysis of LA could be useful in daily clinical practice. The presence of an enlarged LA with normal LVEF should make clinicians to consider the possibility of a HFPEF diagnosis. LA indexed volume could be a

Table 4 Cut-off values for HF diagnosis of left atrium derived parameters

	Area under the curve	Cut-off value	Sensitivity (%)	Specificity (%)	Positive-predictive value (%)	Negative-predictive value (%)
LASRa (s^{-1})	0.801	**−1.690**	80	78	78	79
LASRs (s^{-1})	0.847	**1.065**	81	80	85	81
LA volume (mL/m^2)	0.852	**43**	80	81	81	80
LASRs/LA volume	**0.902**	**0.025**	**87**	**86**	**86**	**87**

LA, left atrial; LASRa, LA strain rate post A-wave; LASRs, LA systolic strain rate.
Bold values refers to statistically significant values.

rapid and simple method to diagnose HF in ambulatory patients with new-onset HF symptoms. Additionally, LA strain analysis could add more evidence of atrial dysfunction and potentially identify those patients at a higher risk of presenting overt HF symptoms.

Potential limitations

This is a descriptive study with cases and controls obtained from the same cohort. The index-symptom is dyspnoea; therefore, other unknown diagnoses may exist in the non-HF group, and these could be confounding. The number of patients was limited, so these results must be confirmed by larger studies. The LA strain analysis was obtained with ECG P-wave onset; other studies were performed with initial onset on QRS.

Conclusions

In an outpatient population with new-onset HF symptoms and sinus rhythm, LA volume and function measured with deformation imaging are impaired in HFPEF patients when compared with a non-HF group (though LV deformation remains normal), with no differences between HFREF and HFPEF groups.

Atrial dysfunction could be one, among others, of the initial mechanisms in the development of symptoms in HFPEF patients.

Conflict of interest: none declared.

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