ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 4751–4759
Published online 2 November 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13654

ORIGINAL ARTICLE

Left atrial structural and mechanical remodelling in heart failure with reduced ejection fraction

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Abstract

Aims In patients with heart failure with reduced ejection fraction (HFrEF), an association between left atrial (LA) dilatation and dysfunction is expected, but the degree of coexistence of the two abnormalities and their relative prognostic role is not known.

Methods and results A total of 626 HFrEF patients formed the study population. All of them underwent a comprehensive echocardiographic evaluation. LA maximal volume was indexed to body surface area (LAVi); LA function was assessed using strain analysis during the reservoir phase: peak atrial longitudinal strain (PALS) analysis. Study primary endpoint was overall mortality or hospitalization for worsening heart failure. Four groups of patients were included in this study according to LAVi ($\leq$34 or $>$34 mL/m^2) and PALS ($\leq$23% or $>$23%); 61 (10%) patients had normal LA volume and function (Group 1), 58 (9%) had LA dilatation but normal function (Group 2), 100 (16%) had normal volume but abnormal function (Group 3), and 407 (65%) had enlarged left atrium and abnormal function (Group 4). PALS was associated with primary endpoint in patients with both normal-size [Groups 1 and 3: hazard ratio (HR) 0.92, 95% confidence interval (CI) 0.88–0.96; P = 0.0006] and dilated left atria (Groups 2 and 4: HR 0.93, 95% CI 0.91–0.96; $P < 0.0001$). In contrast, LAVi was associated with the primary endpoint in patients with abnormal LA function (Groups 3 and 4: HR 1.018, 95% CI 1.011–1.024; $P < 0.00001$) but not in those with normal PALS (Groups 1 and 2: HR 1.023, 95% CI 0.99–1.057; P = 0.1).

Conclusions Left atrial dilatation and dysfunction frequently but not invariably coexist. PALS emerged as a significant prognostic parameter in HFrEF even in the absence of LA dilation.

Keywords Left atrial remodelling; Left atrial function; Heart failure; Prognosis

Received: 1 March 2021; Revised: 13 August 2021; Accepted: 1 October 2021
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Introduction

In patients with heart failure (HF), remodelling of the LA cavity is very common, regardless of the disease phenotype.[1,2] In patients with HF with reduced ejection fraction (HFrEF) or preserved ejection fraction (EF) and in those with mitral valve regurgitation, left atrial (LA) dilatation frequently occurs and is associated with increased disease severity.[3–5] Evaluation of LA volume and cavity remodelling, in daily practice, is achieved by echocardiography using reproducible measurements.

Nevertheless, the LA remodelling process is a complex phenomenon that encompasses changes at molecular, cellular, tissue, and chamber levels,[6] thus making determination of the LA chamber volume alone an oversimplification of such complex pathophysiology. Recent echocardiological technological advances allowed accurate evaluation of LA myocardial deformation, measured by strain and strain rate.[7] LA

strain measurements during the reservoir phase, defined as peak atrial longitudinal strain (PALS) analysis, describe myocardial stretch during cavity filling, a fundamental property of LA function. Reduced PALS has been shown to be associated with important clinical outcomes.[8–10] It has also been proposed to be used as an integral measure of LA remodelling in different cardiac diseases.[11]

The aim of the present study was to evaluate whether LA structural remodelling (increased LA volume) and mechanical remodelling (reduced PALS) necessarily coexist and if their combination may have a better predictive value of clinical outcome in a homogeneous group of heart failure with EF $<$ 40% (HFrEF) patients.

Methods

Our data, methods, and study materials will be made available to other researchers on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Heart failure with reduced ejection fraction (defined as EF $<$ 40%) patients followed in the HF clinic of three Italian centres were prospectively included in the study database between 2010 and 2019. Exclusion criteria were as follows: (i) presence of atrial fibrillation at the time of the echocardiogram; (ii) previous surgical or percutaneous treatment of mitral regurgitation or previous heart transplantation; (iii) more than moderate organic mitral and aortic valve disease; (iv) hospitalization for worsening HF, myocardial infarction, and coronary revascularization in the previous 6 months; and (v) malignancies or other non-cardiac diseases that could affect short-term outcome.

The present study complied with the Declaration of Helsinki, the locally appointed ethics committee had approved the research protocol, and an informed consent was obtained from all included subjects.

Clinical evaluation

Clinical data were obtained from medical records. Age, gender, clinical symptoms [New York Heart Association (NYHA) class], and disease aetiology were recorded. Patients were classified as having HF of ischaemic aetiology on the basis of a history of myocardial infarction, prior coronary revascularization, or objective evidence of significant ($>$70%) stenosis in at least one epicardial coronary artery as assessed by coronary angiography. Hypertension and diabetes mellitus were considered to be present when there was a history or corresponding medical therapy, or patients were on respective treatment. A modified congestion score was calculated as previously described.[12] Venous blood samples for brain natriuretic peptide (BNP) and creatinine assessment were drawn on the day of index echocardiogram. Chilled EDTA tubes were centrifuged immediately at 4000 *g* (48°C) for 15 min. Plasma samples were processed by immunofluorescence assay. For BNP, the lower assay detection limit was 1 pg/mL.

Standard echocardiography

All patients underwent a comprehensive transthoracic echocardiogram using a Vivid 7 or Vivid S6 ultrasound system (GE Vingmed Healthcare, GE Medical system, Milwaukee, USA) or iE33 X-matrix (Philips, Eindhoven, the Netherlands). Left ventricular (LV) end-diastolic and end-systolic volumes and EF were measured as recommended.[13] Pulsed-wave peak early (E) and atrial (A) LV filling velocities, E/A ratio, and E-wave deceleration time were also measured. Pulsed-wave tissue Doppler imaging was used to detect lateral and septal mitral annular early diastolic velocities (E′), which were averaged. The ratio of early transmitral flow velocity (E wave) to the tissue Doppler imaging mitral annular averaged E′ velocity (E/E′) was then calculated. Right ventricular function was assessed by measuring tricuspid annular plane systolic excursion (TAPSE). Systolic pulmonary arterial pressure (SPAP) was estimated by combining the tricuspid regurgitation jet velocity with an estimate of right atrial pressure based on diameter and collapsibility of the inferior vena cava. The ratio between TAPSE and SPAP was then calculated.[14] Severity of mitral regurgitation (Grades I–IV) was determined by measuring the effective regurgitant orifice area or vena contracta width, as suggested.[15]

Left atrial remodelling

A special emphasis was applied for the evaluation of LA structure and function. The degree of LA structural remodelling was defined by the value of LA maximal volume measured at the time of end LV systole. LA volume was measured from apical four-chamber and two-chamber views (biplane Simpson) and was indexed for body surface area. According to the recommendations of the American and European Societies of Echocardiography, LA enlargement was defined as an LA maximal volume index (LAVi) higher than 34 mL/m^2. LA functional remodelling was determined by the evaluation of PALS, using speckle tracking echocardiography technology. Digital cine loops of two-dimensional greyscale images of three consecutive beats, during breathhold and stable electrocardiogram recordings, were acquired in standard four-chamber and two-chamber views and stored for offline analysis. Frame rate was set between 60 and 80 frames per second. The recordings were processed using an acoustic tracking dedicated software (EchoPAC or QLab), which allowed semi-automated analysis of LA strain. In order to

measure LA strain during the reservoir phase, we used the QRS onset on the superimposed electrocardiogram as reference. A normal value for PALS was considered >23% in a large multicentre study.[16]

Clinical follow-up

Follow-up information was obtained during clinical visits and by phone call interviews with the patients or their relatives. The composite primary endpoint of the study was all-cause mortality or hospitalization for worsening HF. Secondary endpoints were cardiac mortality and HF worsening hospitalization as a single endpoint. For patients without events, the date of last contact was considered the end of follow-up for the purpose of survival analysis.

Statistical analysis

Data for continuous variables are presented as mean ± standard deviation or as median with inter-quartile range in case of skewed distribution. Categorical variables are expressed as percentage. Graphic association between PALS and LAVi was assessed using restricted cubic spline analysis, and linearity was defined with the lowest Akaike information criterion. For the purpose of statistical analysis, patients were divided into four groups according to LA volume and function. Group 1 was defined as normal volume (LAVi $\leq$ 34 mL/m^2) and normal function (PALS > 23%); Group 2: increased volume but normal function; Group 3: normal volume but decreased function; and Group 4: abnormal volume and function. Clinical and echocardiographic variables were described in the overall population and in the pre-specified groups. Differences among groups were analysed by ANOVA or χ^2 test as appropriate. The association between clinical and echocardiographic variables and cardiovascular events during follow-up was calculated using unadjusted and multivariable adjusted Cox proportional hazards regression models. Kaplan–Meier curves were used to illustrate outcomes, and curves were compared using the log-rank test. The flexible continuous relationship between PALS and the composite outcome was displayed using restricted cubic spline models with three knots and resulted in the lowest model Akaike information criterion (three to six knots were assessed). Effect of modification of LA enlargement on the relationship between PALS and the composite endpoint was also tested using an interaction test. *P* values <0.05 were considered to indicate differences of statistical significance. All analyses were performed using Stata Version 14 (StataCorp LLC, College Station, TX, USA) and SPSS 23.0 software (Statistical Package for Social Sciences, Chicago, IL, USA).

Results

The study population was formed of 626 patients (mean age 65 ± 11 years; 25% female). *Table 1* (left column) shows the

Table 1 Clinical characteristics of patients divided according LA volume and function (Group 1: normal LA volume and function; Group 2: LA dilatation but normal function; Group 3: normal LA volume but abnormal function; and Group 4: enlarged LA and abnormal function)

		Group 1	Group 2		Group 3	Group 4		*P* for
	Overall	61 (10%)	58 (9%)	*P* (1 vs. 2)	100 (16%)	407 (65%)	*P* (3 vs. 4)	trend
LAVi (mL/m^2)	48 ± 18	27 ± 5	46 ± 10	<0.0001	29 ± 4	57 ± 16	<0.0001	<0.0001
PALS (%)	17 ± 8	30 ± 7	29 ± 6	0.3	15 ± 4	13 ± 5	<0.0001	<0.0001
Age (years)	65 ± 11	64 ± 11	61 ± 13	0.2	66 ± 10	66 ± 11	0.9	0.04
Female gender (%)	22	32	33	0.9	23	18	0.2	0.005
NYHA	2.2 ± 0.7	1.7 ± 0.7	1.9 ± 0.6	0.2	2.0 ± 0.7	2.4 ± 0.6	<0.0001	<0.0001
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.6	1.9 ± 0.2	1.9 ± 0.2	0.1	0.5
BNP (log)	2.6 ± 0.5	2.2 ± 0.5	2.3 ± 0.5	0.1	2.3 ± 0.5	2.7 ± 0.4	<0.0001	<0.0001
Creatinine (mg/dL)	1.2 ± 0.7	1.00 ± 0.3	1.01 ± 0.4	0.9	1.17 ± 0.5	1.24 ± 0.5	0.2	0.006
Hypertension (%)	39	33	51	0.04	37	39	0.8	0.1
Diabetes (%)	49	33	46	0.2	45	55	0.1	0.009
CAD (%)	55	48	57	0.4	60	57	0.4	0.4
Furosemide (%)	82	71	75	0.7	91	94	0.5	0.0005
Furosemide (mg)	69 ± 76	24 ± 43	63 ± 93	0.01	52 ± 57	78 ± 76	0.01	0.003
Beta-blocker (%)	81	91	86	0.6	82	81	0.3	0.01
Spironolactone (%)	50	45	64	0.06	62	57	0.5	0.2
ACE/ARB (%)	85	91	86	0.8	87	85	0.4	0.4
Score congestion	0.6 ± 1.1	0.16 ± 0.5	0.20 ± 0.4	0.8	0.73 ± 1.02	0.73 ± 1.2	0.9	0.0001
All-cause death (%)	24	4	2	0.8	15	33	0.001	0.0005
Cardiac death (%)	23	1	2	0.5	15	30	0.004	0.0005
Hospitalization (%)	31	7	12	0.5	16	41	0.0005	<0.0001
Primary endpoint (%)	42	10	12	0.8	29	56	0.0005	<0.0001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; LA, left atrial; LAVi, left atrial maximal volume indexed by surface body area; NYHA, New York Heart Association functional class; PALS, peak atrial longitudinal strain.

clinical and echocardiographic characteristics of the overall population. The majority of patients (55%) had ischaemic LV dysfunction; 15% of patients were asymptomatic (NYHA I), 49% in NYHA Class II, 33% in NYHA Class III, and only 3% in NYHA Class IV. Based on inclusion criteria, all patients had reduced LV systolic function, and accordingly, mean EF was 30 ± 6 (range 10–39%); 275 (43%) patients had severe LV dysfunction, defined as EF $<$ 30%. In the overall population, the mean LAVi was 48 ± 18 mL/m^2, and 466 patients (75%) had dilated LAVi according to the American Society of Echocardiography/European Association of Echocardiography recommendations. Based on PALS as a marker of LA function, 508 (81%) patients had LA mechanical remodelling (defined as PALS $\leq$ 23%).

Although a close and negative association between LAVi and PALS was observed ($r = -0.41$; $P < 0.0001$) (*Figure 1*), when patients were grouped according LA structural and function remodelling, it was clear that the two aspects do not always coexist in the same patients. While 61 (10%) patients had completely normal left atrium (Group 1) and 407 (65%) had both enlarged and dysfunctional left atrium (Group 4), there were 158 patients (25%) with dissociated LA volume and function: in particular, 58 (9%) with LA dilatation but normal PALS (Group 2) and 100 (16%) with the opposite, that is, normal LAVi but abnormal PALS (Group 3).

In patients with normal PALS (Groups 1 and 2), the isolated LA dilatation was not associated with significant clinical outcomes: in terms of symptomatic impairment (P = 0.5), congestive score (P = 0.4), natriuretic production (P = 0.2), right ventricular pressure and function (SPAP and TAPSE/SPAP; P = 0.3 and 0.61, respectively), or primary and secondary endpoints ($P > 0.5$ for all). In contrast, in patients with normal LAVi (Groups 1 and 3), those with isolated reduced PALS were characterized by more symptomatic impairment (P = 0.006), higher congestive score (P = 0.003), higher natriuretic level (P = 0.08), worse pulmonary haemodynamics (SPAP and TAPSE/SPAP: P = 0.006 and P = 0.04, respectively), and worse clinical outcomes (P = 0.005 for primary; P = 0.07 and P = 0.01 for hospitalization and cardiac mortality, respectively) (*Table 2*).

Similarly, the coexistence of reduced PALS in the subgroups of patients with dilated left atrium (Groups 2 and 4) determined a significantly worse haemodynamic and clinical profiles ($P < 0.001$ for all). On Kaplan–Meier survival analysis, a significantly different prognosis was observed among groups (*Figure 2*). Group-to-group comparisons showed that there was no statistical difference between Groups 1 and 2 (log-rank Mantel–Cox 1.0; P = 0.3), a borderline significance between Groups 2 and 3 (log-rank Mantel–Cox 5.4; P = 0.05), and a significant difference between Groups 3 and 4 (log-rank Mantel–Cox 14.8; P = 0.008).

Cox survival analysis quantitated the risk associated with combined LA structural and function remodelling (Group 4) to be 5.5-fold higher [95% confidence interval (CI) 1.7–17.75; P = 0.004] than in patients with normal LA volume and function (Group 1) after adjusting for NYHA, age, gender, hypertension, EF, BNP, mitral regurgitation grading, TAPSE/SPAP, and E/E′. Analogously, Group 3 patients (normal LAVi and abnormal PALS) had a 4.4-fold increased risk (95% CI 1.3–14.7; P = 0.01) after adjusting for the same covariates. In contrast, the isolated LA dilatation (Group 2) was not independently associated with the primary endpoint (P = 0.2).

Peak atrial longitudinal strain was associated with primary endpoint in patients with both normal [Groups 1 and 3: hazard ratio (HR) 0.92, 95% CI 0.88–0.96; P = 0.0006] and dilated left atria (Groups 2 and 4: HR 0.93, 95% CI 0.91–0.95; $P < 0.0001$) (P for interaction 0.2) (*Figure 3*). In contrast, LAVi was associated with primary endpoint in patients with abnor-

Figure 1 Association between left atrial maximal volume index (LAVi) and peak atrial longitudinal strain (PALS); a significant non-linear association was observed. LA, left atrial.

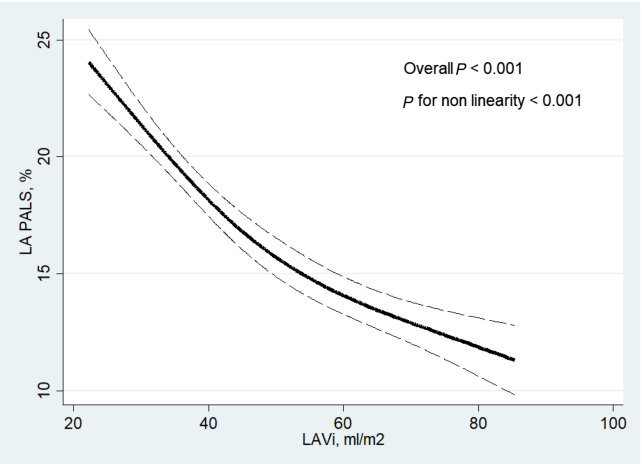
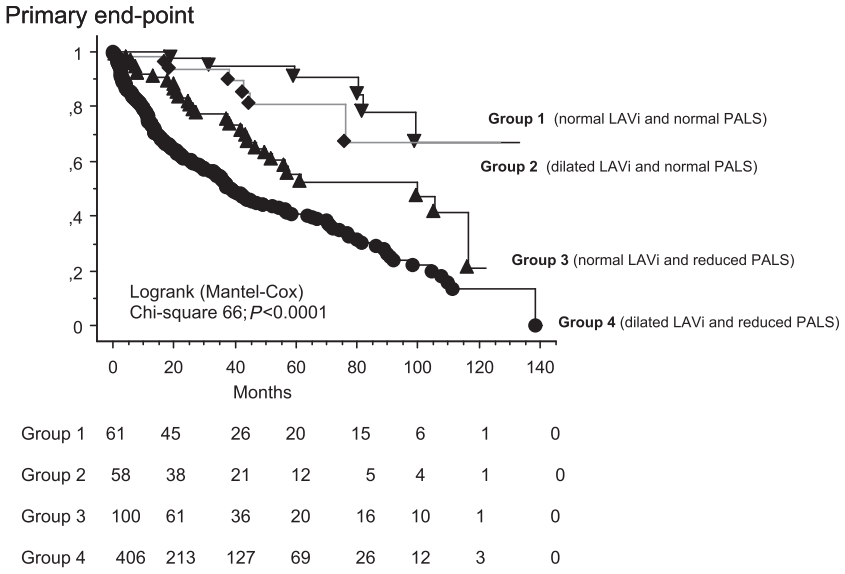


Table 2 Echocardiographic characteristics of patients divided according LA volume and function (Group 1: normal LA volume and function; Group 2: LA dilatation but normal function; Group 3: normal LA volume but abnormal function; and Group 4: enlarged LA and abnormal function)

	Overall	Group 1	Group 2		Group3	Group 4		*P* for
	626 pts	61 (10%)	58 (9%)	*P* (1 vs. 2)	100 (16%)	420 (65%)	*P* (3 vs. 4)	trend
LAV (mL)	92 ± 36	52 ± 12		<0.0001	55 ± 11	108 ± 33	<0.0001	<0.0001
LAVi (mL/m^2)	48 ± 18	27 ± 5	46 ± 10	<0.0001	29 ± 4	57 ± 16	<0.0001	<0.0001
PALS (%)	16 ± 8	30 ± 7	29 ± 6	0.3	15 ± 4	13 ± 5	<0.0001	<0.0001
LVD (mL)	200 ± 66	174 ± 45	188 ± 60	0.3	181 ± 18	212 ± 72	<0.0001	<0.0001
EF (%)	30 ± 7	32 ± 5	32 ± 5	0.5	32 ± 5	28 ± 6	<0.0001	<0.0001
ERO (mm^2)	13 ± 15	3.0 ± 8.0	10 ± 10	0.02	4.0 ± 9.0	20 ± 15	<0.0001	<0.0001
TAPSE (mm)	19 ± 4	20 ± 3	20 ± 3	0.9	20 ± 4	19 ± 4	0.008	0.0001
SPAP (mmHg)	36 ± 13	29 ± 6	31 ± 10	0.5	34 ± 10	39 ± 15	0.0005	<0.0001
TAPSE/SPAP	0.61 ± 0.35	0.73 ± 0.24	0.77 ± 0.4	0.6	0.66 ± 0.3	0.57 ± 0.3	0.03	<0.0001
E (cm/s)	65 ± 38	52 ± 28	62 ± 30	0.1	61 ± 30	69 ± 40	0.07	0.006
E/A	1.6 ± 1.2	1.0 ± 0.9	1.0 ± 0.6	0.9	1.2 ± 1.1	1.9 ± 1.1	<0.0001	<0.0001
DTE (ms)	173 ± 69	204 ± 75	190 ± 76	0.3	190 ± 66	162 ± 66	0.0004	<0.0001
E/E′	15 ± 8	10 ± 4	11 ± 4	0.5	13 ± 6	17 ± 8	<0.0001	<0.0001

DTE, E-wave deceleration time; EF, ejection fraction; ERO, mitral effective regurgitant orifice; LA, left atrial; LAV, left atrial maximal volume; LAVi, left atrial maximal volume indexed by surface body area; LVD, left ventricular diastolic volume; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

Figure 2 Kaplan–Meier survival curves of four patient groups, divided according left atrial maximal volume index (LAVi) and peak atrial longitudinal strain (PALS). Log-rank (Mantel–Cox) χ^2 84; $P < 0.0001$.



mal PALS (Groups 3 and 4: HR 1.018, 95% CI 1.011–1.024; $P < 0.00001$), but not in those with normal PALS (Groups 1 and 2: HR 1.023, 95% CI 0.99–1.057; $P = 0.1$).

In the overall population, independent correlates of PALS and LAVi were described in *Table 3*. Furthermore, limiting the multivariable adjusted analysis to patients with normal LAVi (Groups 1 and 3), E/E′ ($P = 0.009$) emerged as the only correlate of PALS. In contrast, limiting the analysis to patients with normal PALS (Groups 1 and 2), LV diastolic volume ($P = 0.001$), mitral regurgitation ($P = 0.0008$), and hypertension ($P = 0.02$) were independent correlates of LAVi, with a non-significant independent effect of E/E′.

Discussion

The main results of the present study are as follows: (i) there is close association between LA structural and mechanical remodelling, but the two pathological entities are not invariably linked; (ii) the coexistence of LA structural and mechanical remodelling identified a subgroup of patients with particular severe disease, as shown by symptoms, haemodynamic and hormonal disturbances, and poor prognosis; and (iii) the isolated LA mechanical remodelling (reduced PALS), but not cavity dilation, is associated with worse clinical condition.

DOI: 10.1002/ehf2.13654

Figure 3 Restricted cubic splines showing the continuous relationship between left atrial peak atrial longitudinal strain (LA PALS) and the composite of death or heart failure (HF), overall (left panel) and stratified by left atrial maximal volume index (LAVi) enlargement (right panel). The association between LA PALS and outcome was consistent regardless of LA enlargement (*P* for interaction = 0.49). *P* for non-linearity = 0.072 (>0.05) indicates a linear relationship between LA PALS and outcome.

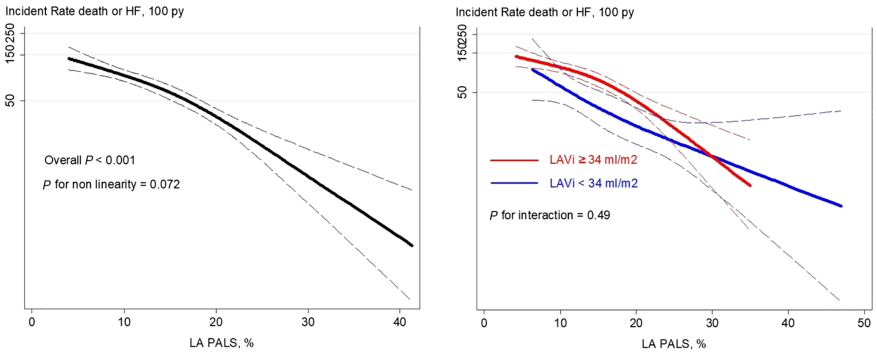


Table 3 Multivariable analysis showed the correlates of PALS and LAV in the overall population (coefficients and *P* values)

	PALS determinants	LAVi determinants
Age (years)	0.61; $P = 0.02$	0.03; $P = 0.04$
Female gender (%)	−2.6; $P < 0.0001$	1.7; P = NS
Hypertension (%)	0.18; P = NS	1.3; P = NS
Diabetes (%)	−0.23; P = NS	0.88; P = NS
Creatinine (mg/dL)	−1.3; $P = 0.008$	0.67; P = NS
LVD (mL)	0.05; $P = 0.009$	0.56; $P < 0.0001$
EF (%)	0.23; $P < 0.0001$	−0.02; P = NS
MR (grades)	−0.32; P = NS	4.7; $P < 0.0001$
E/E′	−0.23; $P < 0.0001$	0.3; $P = 0.0008$
LAVi (mL/m^2)	−0.08; $P < 0.0001$	N/A
PALS (%)	N/A	−0.3; $P < 0.0001$

EF, ejection fraction; LAV, left atrial maximal volume; LAVi, left atrial maximal volume indexed by surface body area; LVD, left ventricular diastolic volume; MR, mitral regurgitation; PALS, peak atrial longitudinal strain.

Left atrial structural and mechanical remodelling

In many clinical models, LA structure, expressed as increased cavity volume, and mechanical remodelling (reduced PALS) overlap, and accordingly, we examined such close relationship in our population. The question we were set to answer was whether such anatomical and function association is an established phenomenon in all patients with HFrEF or it varies in different conditions. LA cavity remodelling refers to adverse electrophysiological, cellular, and structural changes in myocardial tissue in response to pressure and volume overload or arrhythmic insults.[17] Non-cardiac conditions such as sleep apnoea syndrome, hypertension, diabetes, and obesity are important contributors to LA remodelling through haemodynamic and non-haemodynamic pathways.[18,19] In patients with mitral regurgitation, we have recently shown that LA remodelling is significant and multifaceted.[20] For the same degree of volume overload, the features of LA remodelling can be different according to the underlying mechanism for mitral regurgitation. In primary mitral regurgitation, there is a strong association between effective orifice area and LA volume (structural remodelling) but not with PALS (mechanical remodelling). In contrast, secondary mitral regurgitation is characterized by worse impaired mechanical than structural LA remodelling. These findings suggested that organic mitral leaflet disease causing regurgitation exerts a pure haemodynamic effect on the LA, leading to isolated dilatation, whereas tissue function impairment might be related to the chronic exposure to haemodynamic and non-haemodynamic atrial stressors.[21,22] A similar example of LA remodelling can be seen in athletes, likely due to increase in venous return and its impact on LA pressure.[23] When mitral regurgitation is determined by LV regional or global dysfunction (secondary regurgitation), it is likely that its impact on LA cavity changes is predominantly related to raised pressure, rather than volume effect, with its direct effect on myocardial intrinsic function. In the present study, therefore, we have observed similar differences, with structural and function remodelling not simultaneously occurring in all patients with HFrEF, and are also having different impact on clinical outcome. The exact underlying pathophysiological explanation of the link between LA structural and function abnormalities and adverse outcomes is not clear. There is increasing evidence that LA function abnormalities result from alterations in extracellular matrix that is reflected on pathophysiological changes in renin secretion, levels of angiotensin II, aldosterone, transforming growth factor-β1, sympathetic stimulation, and markers of systemic inflammation such as C-reactive protein, which are all well-known pathways in patients with HF.[24–28]

Clinical implications of atrial remodelling

In HF patients, several studies have shown that the increased LA volume is associated with higher mortality rate after

adjusting for well-recognized prognostic markers.[29–31] For many years, the most likely explanation for such association has been the underlying factors causing LA cavity enlargement. Therefore, the left atrium has been considered a simple marker unifying multiple factors, which individually affect prognosis. However, recently, the role of LA function itself emerged as an important predictor of clinical events.[4,8,9] Thanks to the new technologies, in particular speckle tracking echocardiography, which allows relatively fast evaluation of LA function during the whole cardiac cycle. LA strain during the reservoir phase of the cardiac cycle reflects the ability of LA myocardium to stretch during cavity filling and has proved to be an important parameter associated with clinical outcomes in different diseases.[32,33] It has been recently published that even in the general population, a subclinical LA dysfunction (expressed as PALS lower than 23%) was associated with a 111% increased higher adjusted risk for future adverse cardiac events.[34]

Although LA volume and function are strongly correlated, modification of LA function appears earlier than cavity remodelling and can be present even if LA volume is normal[35,36]; as our study showed, 16% of patients had LA mechanical remodelling but normal cavity volume. More importantly, PALS was clearly and independently associated with the primary outcome in patients with both dilated and normal LA volume. In contrast, LA volume was associated with prognosis, only in the presence of reduced PALS but not in patients with preserved PALS. Taken together, these findings underscore the clinical relevance of LA mechanical remodelling (PALS), which suggests that most of the predictive value of LA volume, documented in previous studies, might be hypothetically attributed to the associated reduced atrial function. The close association between PALS and degree of fibrosis in atrial tissue[21] underscores that this parameter reflects better than others, one of the main pathways leading to clinical impairment in HFrEF patients.

It might, then, be suggested that the evaluation of LA mechanical remodelling, through PALS assessment, should be incorporated as an integral evaluation of the LA in all cardiac patients irrespective of cavity size. The comprehensive LA evaluation provides relevant clinical information, which might enhance HFrEF patient care.

Limitations

A major limitation of the present study is the use of two different echocardiographic vendors and relative software for strain analysis with lack of inter-observer variability assessment. Another limitation is the definition of normality for PALS. We did not have a control group of normal people, so used a value of 23% to define normal PALS, as suggested in a large multicentre study[16] and in EACVI NORRE study.[37] We tried to overcome both limitations by redefining the cut-off value for PALS as a median, which were specific for populations studied with each vendor and accordingly regrouping patients. This trial did not change the results of the analysis (*Table 4*). Interestingly, a recent study proposed outcome-driven cut-off value for PALS and underscored that 23% was the PALS value, which better discriminated patients with adverse outcome in general population.[34] Another limitation might be the relatively small size of the population subgroups, particularly those characterized by structural remodelling and normal function (Group 2). However, with the reclassification of patients using median value of PALS, the size of the subgroup was larger and confirmed the results previously presented. Finally, the lack of information on atrial fibrillation because it might be associated with both LA structural and mechanical remodelling is a potential limitation. In order to avoid this confounding variable, we included only patients with sinus rhythm, but we are not certain about possible previous episodes of atrial fibrillation in some patients.

Table 4 Cox proportional multivariable hazard model

	HR (95% CI)	*P*-value
Group 4	3.4 (1.7–6.5)	0.0003
Group 3	2.7 (1.3–5.6)	0.01
Group 2	1.9 (0.9–3.6)	0.06
Age	1.02 (1.00–1.03)	0.009
Female gender	0.7 (0.5–1.0)	0.07
Hypertension	0.9 (0.7–1.2)	0.6
NYHA (%)	1.4 (1.1–1.8)	0.005
EF (%)	1.0 (0.97–1.02)	0.7
E/E′	0.99 (0.97–1.02)	0.3
MR	1.2 (1.1–1.3)	0.002
BNP (log)	2.1 (1.3 3.1)	0.0006
TAPSE/SPAP (mm/mmHg)	0.99 (0.49–1.36)	0.4

BNP, brain natriuretic peptide; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; MR, mitral regurgitation; NYHA, New York Heart Association functional class; PALS, peak atrial longitudinal strain; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.
Groups were redefined according to a cut-off value of PALS determined by the its median value specific for the population evaluated with different software.

Conclusions

Left atrial remodelling is a frequent phenomenon in patients with HFrEF, which is characterized by structural and mechanical chamber modifications. These two aspects are related but not invariably associated in HFrEF patients. The coexistence of LA structural and mechanical remodelling seems to exist in patients with worse symptoms, hormonal activation, and prognosis. However, our results highlight the LA mechanical impairment (reduced PALS) as the most important player in the disease burden, further supporting the hypothesis that LA remodelling is more than just LA enlargement.[38]

Conflict of interest

None declared.

References

1. Triposkiadis F, Pieske B, Butler J, Parissis J, Giamouzis G, Skoularigis J, Brutsaert D, Boudoulas H. Global left atrial failure in heart failure. *Eur J Heart Fail* 2016; **18**: 1307–1320.
2. Rossi A, Gheorghiade M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction: Structure, function and significance. *Circ Heart Fail* 2014; **7**: 1042–1049.
3. Rossi A, Cicoira M, Zanolla L, Sandrini R, Golia G, Zardini P, Enriquez-Sarano M. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2002; **40**: 1425–1430.
4. Khan MS, Memon MM, Murad MH, Vaduganethan M, Greene SJ, Hall M, Triposkiadis F, Lam CS, Shah AM, Butler J, Shan AJ. Left atrial function in heart failure with preserved ejection fraction: A systematic review and meta-analysis. *Eur J Heart Fail* 2020; **22**: 472–485.
5. Essayagh B, Antoine C, Benfari G, Messika-Zeitoun D, Michelena H, Le Tourneau T, Mankad S, Triboully CM, Thapa P, Enriquez-Sarano M. Prognostic implications of left atrial enlargement in degenerative mitral regurgitation. *J Am Coll Cardiol* 2019; **74**: 858–870.
6. Casaclang Verzosa G, Gersh BJ, Tsang TSM. Structural and functional remodeling of the left atrium. *J Am Coll Cardiol* 2008; **51**: 1–11.
7. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, Ballo P. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. *J Am Soc Echocardiogr* 2011; **24**: 898–908.
8. Carluccio E, Biagioli P, Mengoni A, Cerasa MF, Lauciello R, Zuchi C, Bardelli G, Alunni G, Coiro S, Gronda EG, Ambrosio G. Left atrial reservoir function and outcome in heart failure with reduced ejection fraction. *Circ Cardiovasc Imaging* 2018; **11**: e007696.
9. Pernigo M, Benfari G, Geremia G, Noni M, Borio G, Mazzali G, Zamboni M, Onorati F, Faggian G, Vassanelli C, Rossi A. Atrial function as an independent predictor of postoperative atrial fibrillation in patients undergoing aortic valve surgery for severe aortic stenosis. *J Am Soc Echocardiogr* 2017; **30**: 956–965.
10. Malagoli A, Rossi L, Bursi F, Zanni A, Sticozzi C, Piepoli MF, Villani GQ. Left atrial function predicts cardiovascular events in patients with chronic heart failure with reduced ejection fraction. *J Am Soc Echocardiogr.* 2019; **32**: 248–256.
11. Reddy YNV, Borlaug BA. Left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020; **22**: 486–488.
12. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M, EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J.* 2013; **34**: 835–843.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart JCardiovasc Imaging* 2015; **16**: 233–271.
14. Guazzi M, Naeije R, Ross A, Corrà U, Ghio S, Forfia P, Rossi A, Cahalin LP, Bandera F, Temporelli P. Echocardiography of right ventriculoarterial coupling combined with cardiopulmonary exercise testing to predict outcome in heart failure. *Chest* 2015; **148**: 226–234.
15. Lancellotti P, Moura L, Pierard L, Agricola E, Popescu BA, Tribouilloy C, Hagendorff A, Monin J-L, Badano L, Zamorano JL, European Association of Echocardiography. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr.* 2010; **11**: 307–332.
16. Morris DA, Takeuchi M, Krisper M, Kohncke C, Bekfani T, Carstensen T, Hassfeld S, Dorenkamp M, Otani K, Takigiku K, Izumi C, Yuda S, Sakata K, Ohte N, Tanabe K, Osmanoglou E, Kuhnle Y, Dungen HD, Nakatani S, Otsuji Y, Haverkamp W, Boldt L-H. Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: Multicentre study. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 364–372.
17. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tsang TSM. Left atrial size: Physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006; **47**: 2357–2363.
18. Oliver W, Matthews G, Ayers CR, Garg S, Gupta S, Neeland IJ, Drazner MH, Berry JD, Matulevicius S, de Lemon JA. Factors associated with left atrial remodeling in the general population. *Circ Cardiovasc Imaging* 2017; **10**: e005047.
19. Miller JD, Aronis KN, Chrispin J, Patil KD, Marine JE, Martin SS, Blaha MJ, Blumenthal RS, Calkins H. Obesity, exercise, obstructive sleep apnea, and modifiable atherosclerotic cardiovascular disease risk factors in atrial fibrillation. *J Am Coll Cardiol* 2015; **29**: 2899–2906.
20. Inciardi RM, Rossi A, Bergamini C, Benfari G, Maffeis C, Greco C, Drago A, Guazzi M, Ribichini FL, Cicoira M. Mitral regurgitation, left atrial structural and functional remodelling and the effect on pulmonary haemodynamics. *Eur J Heart Fail* 2020; **22**: 499–506.
21. Cameli M, Lisi M, Righini FM, Massoni A, Natali BN, Focardi M, Tacchini D, Geyer A, Curci V, Di Tommaso C, Lisi G, Maccherini M, Chiavarelli M, Massetti M, Tanganelli P, Mondillo S. Usefulness of atrial deformation analysis to predict left atrial fibrosis and endocardial thickness in patients undergoing mitral valve operations for severe mitral regurgitation secondary to mitral valve prolapse. *Am J Cardiol* 2013; **111**: 595–601.
22. Kihara Y, Sasayama S, Miyazaki S, Onodera T, Susawa T, Nakamura Y, Fujiwara H, Kawai C. Role of the left atrium in adaptation of the heart to chronic mitral regurgitation in dogs. *Cir Res* 1988; **62**: 543–553.
23. D'Ascenzi F, Pelliccia A, Natali BM, Zacà V, Cameli M, Alvino F, Malandrino A, Palmitesta P, Zorzi A, Corrado D, Bonifazi M, Mondillo S. Morphological and functional adaptation of left and right atria induced by training in highly trained female athletes. *Circ Cardiovasc Imaging* 2014; **7**: 222–229.
24. Xiao HD, Fuchs S, Campbell DJ, Lewis W, Dudley SC, Kasi VS, Kesheleva G, Zhao H, Capecchi MR, Bernstein KE. Mice with cardiac-restricted angiotensin-converting enzyme (ACE) have atrial enlargement, cardiac arrhythmia, and sudden death. *Am J Pathol* 2004; **165**: 1019–1032.

25. Stockand JD, Meszaros JG. Aldosterone stimulates proliferation of cardiac fibroblasts by activating ki-RasA and MAPK1/2 signaling. *Am J Physiol Heart Circ Physiol* 2003; **284**: H176–H184.
26. Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. *Am J Cardiol* 2005; **95**: 764–767.
27. Thomas L, Abhayaratna WP. Left atrial reverse remodeling. Mechanisms, evaluation and clinical significance. *J Am Coll Cardiol* 2017; **10**: 65–77.
28. Reil JC, Tauchnitz M, Tian Q, Hohl M, Linz D, Oberhofer M, Kaestner L, Reil G-H, Thiele H, Steendijk P, Bohm M, Neuberger H-R, Lipp P. Hyperaldosteronism induces left atrial systolic and diastolic dysfunction. *Am J Physiol Heart Circ Physiol* 2016; **1**: 311–H1023.
29. Rossi A, Temporelli PL, Quintana M, Dini FL, Ghio S, Hillis G, Klein AL, Ajmone Marsan N, Prior DL, Yu CM, Poppe KK, Doughty RN, Whalley GA, MeRGE Heart Failure Collaborators. Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (MeRGE Heart Failure). *Eur J Heart Fail* 2009; **11**: 929–936.
30. Rossi A, Cicoira M, Bonapace S, Golia G, Zanolla L, Franceschini L, Vassanelli C. Left atrial volume provides independent and incremental information compared with exercise tolerance parameters in patients with heart failure and left ventricular systolic dysfunction. *Heart* 2007; **93**: 1420–1425.
31. Dini FL, Cortigiani L, Baldini U, Boni A, Nuti R, Barsotti L, Micheli G. Prognostic value of left atrial enlargement in patients with idiopathic dilated cardiomyopathy and ischemic cardiomyopathy. *Am J Cardiol* 2002; **89**: 518–523.
32. Habibi M, Zareian M, Ambale Venkatesh B, Samiei S, Imai M, Wu C, Launer LJ, Shea S, Gottesman RF, Heckbert SR, Bluemke DA, Lima JAC. Left atrial mechanical function and incident ischemic cerebrovascular events independent of AF: Insights from the MESA study. *JACC Cardiovasc Imaging* 2019; **12**: 2417–2427.
33. Vukomanovic V, Suzic-Lazic J, Celic V, Cuspidi C, Grassi G, Galderisi M, Djukic V, Tadic M. Is there association between left atrial function and functional capacity in patients with uncomplicated type 2 diabetes? *Int J Cardiovasc Imaging* 2020; **36**: 15–22.
34. Cauwenberghs N, Haddad F, Sabovcik F, Kobayashi Y, Amsallem M, Morris DA, Voigt J-U, Kuznetsova T. Subclinical left atrial dysfunction profiles for prediction of cardiac outcome in the general population. *J Hypertens* 2020; **38**: 2465–2474.
35. Cameli M, Mandoli GE, Lisi E, Ibrahim A, Incampo E, Buccoliero G, Rizzo C, Devito F, Ciccone MM, Mondillo S. Left atrial, ventricular and atrio-ventricular strain in patients with subclinical heart dysfunction. *Int J Cardiovasc Imaging* 2019; **35**: 249–258.
36. Henein MY, Suhr OB, Arvidsson S, Pilebro B, Westermark P, Hornsten R, Lindqvist P. Reduced left atrial myocardial deformation irrespective of cavity size: A potential cause for atrial arrhythmia in hereditary transthyretin amyloidosis. *Amyloid.* 2018; **25**: 46–53.
37. Sugimoto T, Robinet S, Dulgheru R, Bernard A, Ilardi F, Contu L, Addetia K, Caballero L, Kacharava G, Athanassopoulos GD, Barone D, Baroni M, Cardim N, Hagendorff A, Hristova K, Lopez T, de la Morena G, Popescu B, Penicka M, Ozyigit T, Carbonero JDR, van de Veire N, Von Bardeleben RS, Vinereanu D, Zamorano JL, Go YY, Marchetta S, Nchimi A, Rosca M, Calin A, Moonen M, Cimino S, Magne J, Cosyns B, Galli E, Donal E, Habib G, Esposito R, Galderisi M, Badano LP, Lang RM, Lancellotti P, NORRE Study. Echocardiographic reference ranges for normal left atrial function parameters: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging.* 2018; **19**: 630–638.
38. Hoit BD. Left atrial remodeling: More than just left atrial enlargement. *Circ Cardiovasc Imaging* 2017; **10**: e006036.