Left atrial function in heart failure with mid-range ejection fraction differs from that of heart failure with preserved ejection fraction: a 2D speckle-tracking echocardiographic study

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Abstract

Aims Heart failure (HF) with mid-range ejection fraction (HFmrEF) shares similar diagnostic criteria to HF with preserved ejection fraction (HFpEF). Whether left atrial (LA) function differs between HFmrEF and HFpEF is unknown. We, therefore, used 2D-speckle-tracking echocardiography (2D-STE) to assess LA phasic function in patients with HFpEF and HFmrEF.

Methods and results Consecutive outpatients diagnosed with HF according to current European recommendations were prospectively enrolled. There were 110 HFpEF and 61 HFmrEF patients with sinus rhythm, and 37 controls matched by age. LA phasic function was analysed using 2D-STE. Peak-atrial longitudinal strain (PALS), peak-atrial contraction strain (PACS), and PALS−PACS were measured reflecting LA reservoir, pump, and conduit function, respectively. Among HF groups, most of left ventricular (LV) diastolic function measures, and LA volume were similar. Both HF groups had abnormal LA phasic function compared with controls. HFmrEF patients had worse LA phasic function than HFpEF patients even among patients with LA enlargement. Among patients with normal LA size, LA reservoir, and pump function remained worse in HFmrEF. Differences in LA phasic function between HF groups remained significant after adjustment for confounders. Global PALS and PACS were inversely correlated with brain natriuretic peptide, LA volume, *E*/*A*, *E*/*e*′, pulmonary artery systolic pressure, and diastolic dysfunction grade in both HF groups.

Conclusion LA phasic function was worse in HFmrEF patients compared with those with HFpEF regardless of LA size, and independent of potential confounders. These differences could be attributed to intrinsic LA myocardial dysfunction perhaps in relation to altered LV function.

Keywords atrial strain, HFmrEF, HFpEF, speckle-tracking echocardiography

Introduction

Heart failure (HF) is a clinical syndrome characterized by non-specific symptoms and signs.[1] Left ventricular ejection fraction (LVEF) is typically used by most clinical trials, as defined by clinical guidelines, to classify HF patients into HF with reduced LVEF <40% (HFrEF) and preserved LVEF ≥50% (HFpEF).[1,2] Despite the lack of robust prognostic or pathophysiological data advocating a suitable cut-off for HFpEF (50% vs. 40%), LVEF 50% has been used to clearly differentiate HFpEF from HFrEF.[3] This has left a void of LVEF 40–49% between both HF categories. Recently, the European Society of Cardiology has defined a new distinct category with LVEF 40–49% as HF with mid-range LVEF (HFmrEF).[1] Patients with HFmrEF account for approximately 10–20% of the HF population, and tend to be predominantly male, younger, and are more likely to have a history of ischaemic heart disease (IHD), hypertension (HTN), and diabetes mellitus (DM).[3] Conversely, HFpEF patients constitute approximately more than half of the HF population.[4,5] Most are female, elderly, and hypertensive with multiple comorbidities.[4–7]

The proposed diagnostic criteria of HFmrEF are parallel to those for HFpEF including elevated natriuretic peptides, evidence of diastolic dysfunction (DD), and structural changes such as left atrial (LA) enlargement and/or left ventricular (LV) hypertrophy (LVH).[1] LV DD is considered the primary pathology in HFpEF patients and perhaps HFmrEF determined by current conventional echocardiographic measures.[1,8] LA function has a close interconnection with LV function and is divided into three phases, LA reservoir, conduit, and pump function, all of which contribute to LV filling.[9,10] Conversely, LV function influences LA function. LA reservoir function is affected by LV contraction as LV base descends during systole, as well as LA compliance, and the transmission of right ventricular systolic pressure via the pulmonary circulation.[9] LA pump function is influenced by LV end-diastolic pressure, LV compliance, and LA contractile properties, while LA conduit function is dependent on LV diastolic properties.[9] As LV dysfunction progresses, the LA contribution to LV filling decreases, which may be attributed to intrinsic LA dysfunction caused by increased workload of the LA myocardium.[11] Indeed, previous studies comparing HFrEF and HFpEF phenotypes found greater impairment in LA phasic function in HFrEF.[12,13]

In clinical practice, LA function can be assessed by 2D-echocardiography, analysis of pulmonary venous and transmitral flows by Doppler echocardiography, and LA myocardial velocities by tissue-Doppler echocardiography. However, its comprehensive quantification remains a challenge.[10] Assessment of LA phasic function using 2D-speckle-tracking echocardiography (2D-STE) has gained considerable attention due to its high feasibility and reproducibility[14–16] and has led to the early detection of LA impairment in a number of conditions including HF.[10] Recently, it has been proposed that LA dysfunction assessed by 2D-STE may play an important role in the pathophysiology of HFpEF[17–21] and that LA deformation using 2D-STE predicts adverse events in the general population,[22] and in HFpEF.[23,24] In contrast, LA function in HFmrEF has not been previously investigated, and whether LA phasic function differs between HFmrEF and HFpEF is unknown. We, therefore, hypothesized that LA function is abnormal in HF patients and worse in HFmrEF patients than in those with HFpEF. To test this hypothesis, we evaluated LA phasic function using 2D-STE in consecutive HFmrEF and HFpEF patients.

Methods

Study population

Consecutive outpatients from HF clinics fulfilling current HF recommendations[1] were prospectively enrolled between January and May 2017. All patients were in optimal medical treatment and were haemodynamically stable. Inclusion criteria were patients with sinus rhythm who met the clinical and echocardiographic criteria of HFpEF and HFmrEF (LVEF ≥50% for HFpEF, and 40–49% for HFmrEF[1] including features of DD,[8] and/or evidence of structural changes such as LVH and LA enlargement). Out of 253-screened patients, 171 (67.5%) were included in the analysis: 110 (64.3%) with HFpEF, and 61(35.7%) with HFmrEF [excluded patients: 11 in atrial fibrillation; four had significant valvular heart disease; four had implantable pacemaker; 41 had suboptimal echocardiographic image quality; 13 had >2 non-visible LA segments (unsuitable for LA speckle-tracking analysis); nine HFrEF].

A control group of 37 normal individuals of similar age to the HF groups with no previous medical history and normal echocardiogram were recruited for comparison. The study protocol was approved by the local Research Ethics Committee.

Echocardiographic acquisition and analyses

All patients underwent a comprehensive transthoracic-echocardiographic examination in the left-lateral decubitus position using commercially available equipment (Phillips iE33, GE Vivid-7 or Vivid-E9 ultrasound systems). Images and loops were stored electronically (ProSolv cardiovascular, Fujifilm, Indianapolis, IN, USA) for offline analysis. Standard 2D- and Doppler-echocardiographic measurements were performed following ASE/EACVI guidelines.[8,25] LV volumes and LVEF was calculated using the modified biplane Simpson's rule.[25] LV dimensions and wall thicknesses were measured during diastole from which LV mass index (LVMi) was calculated and indexed to body surface area (BSA).[25] Relative wall thickness (RWT) and LV geometry were defined according to standardized methodologies.[25] Maximum LA volume indexed (LAVi) to BSA was calculated by the biplane method of discs at end-systole with LA remodelling (enlargement) defined as LAVi >34 mL/m^2.[25] Minimum LA volume at QRS complex and pre-A LA volume preceding the P-wave were also calculated to assess LA phasic function by the volumetric method as follows[26]:

$$\text{LA total emptying fraction (reservoir function)} = [(\text{LA volume}_{max} - \text{LA volume}_{min})/\text{LA volume}_{max}] \times 100,$$

$$\text{LA passive emptying fraction (conduit function)} = [(\text{LA volume}_{max} - \text{LA volume}_{pre\text{-}A})/\text{LA volume}_{max}] \times 100,$$

$$\text{LA active emptying fraction (pump function)} = [(\text{LA volume}_{pre\text{-}A} - \text{LA volume}_{min})/\text{LA volume}_{pre\text{-}A}] \times 100.$$

LV diastolic function was evaluated in accordance with the current ASE/EACVI guidelines.[8] This included mitral inflow [early (E-wave) and late (A-wave) diastolic filling velocities, *E*/*A* ratio, and deceleration time (DT)], tissue-Doppler analysis of lateral mitral annular velocities (e′, a′, and s′) from which *E*/*e*′ ratio was calculated, and Doppler derived-pulmonary artery systolic pressure (PASP) was estimated from the peak tricuspid regurgitation (TR) velocity

jet. The following parameters were used to determine the DD grade in HF patients as recommended: mitral inflow velocities, TR velocity jet >2.8 m/s, LAVi >34 mL/m^2, lateral mitral annular *e′* velocity <10 cm/s, and lateral *E*/*e′* ratio >13.[8]

LA phasic function was also assessed using 2D-STE.[10,14–16,27–29] The analysis was performed by a single investigator using vendor-independent acoustic-tracking software (TomTec Imaging Systems GMBH, Munich, Germany). LA endocardial borders were manually traced in non-foreshortened apical four- and two-chamber views with a frame rate of 60–80 frames per second[14] taking the onset of QRS as a reference point.[29] The software divided the LA into six segments to generate the LA strain curves and a total of 12-LA segments were obtained. The resulting tracking quality was evaluated in both views and manual adjustment was performed when necessary. Participants with significant foreshortened images of LA cavity or >2 non-visible LA segments were excluded as being unsuitable for LA 2D-STE analysis. LA strain measures were as follows (*Figure 1*): (i) peak-atrial longitudinal strain (PALS) measured during ventricular systole reflecting LA reservoir function, (ii) peak-atrial contraction strain (PACS) measured from the onset of P-wave prior to atrial contraction reflecting LA pump function, and (iii) the difference between PALS and PACS (PALS−PACS) reflecting LA conduit function.[14,15,30] Global PALS and PACS were calculated by averaging the strain values of all LA segments.[14,15,30]

Intraobserver and interobserver variability were assessed for LA strain measures. The coefficient of variation (CV), intraclass correlation coefficient (ICC), and Bland–Altman limits of agreement showed overall good agreement [intraobserver variability, the CV was 7.6% for PALS, 13.3% for PACS, and 10.5% for PLAS−PACS, the ICC was 0.97 (0.95–1.0) for PALS, 0.91 (0.83–0.99) for PACS, and 0.97 (0.95–1.0) for PALS−PACS, and the mean difference was 0.39 (−4.2 to 4.9) for PALS, 0.35 (−3.2 to 3.9) for PACS, and 0.74 (−2.8 to 4.3) for PALS−PACS; interobserver variability, the CV was 12.0% for PALS, 15.1% for PACS, and 12.3% for PALS−PACS, the ICC was 0.86 (0.69–1.0) for PALS, 0.89 (0.76–1.0) for PACS, and 0.93 (0.85–1.0) for PALS−PACS, and the mean difference was 0.23 (−5.2 to 5.7) for PALS, 0.81 (−2.7 to 4.3) for PACS, and 1.0 (−1.7 to 3.7) for PALS−PACS].

Statistical methods

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range) as appropriate. Categorical variables are presented as counts and percentages. Differences between groups were assessed using two-sample *t*-test with unequal variance or Mann–Whitney test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. One way analysis of variance (ANOVA) with a *post hoc* test (pairwise comparison) was used for comparisons between more than two groups and the robust sandwich variance estimator was used when variance was heterogeneous between groups.

Pearson or Spearman's rank tests were used for correlation analysis as appropriate. Multiple linear regression analysis was performed to compare LA strain measures between HF groups after adjustment for potential confounders (Model 1) or confounders plus possible mediators (Model 2) selected on *a priori* clinical-grounds [Model 1: age, sex, body mass index (BMI), heart rate, systolic blood pressure (SBP), DM, HTN, and IHD; Model 2: Model 1 plus LV end-diastolic volume index (LVEDVi), LVMi, LAVi, *E*/*A*, DT, *E*/*e′*, and *S′*]. Regression diagnostics were performed to ensure the assumptions for multiple linear regression were satisfied.

We considered the possibility that LA function between HF groups might be modified by the DD grades and hence two-way ANOVA was performed. There was no evidence of a significant interaction between DD grades and HF groups for all LA strain measures ($P > 0.05$), so we concluded that DD grades did not modify the relationship between HF groups and LA strain measures (LA phasic function by DD grade are shown in **Supplementary data online, *Table S1***). We also tested the possibility that LA function might be modified by remodelled LA (LAVi >34 mL/m^2). There was a significant interaction between LAVi >34 mL/m^2 and HF groups, and hence results were presented stratified by LA size. A two-tailed *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA software version 12.0 (StataCorp LLC, USA).

Results

Baseline clinical and echocardiographic characteristics

Baseline characteristics of the study population are summarized in *Table 1*. All groups were similar in age, heart rate, and BMI. Females were more prevalent in the HFpEF group and controls. Brain natriuretic peptide (BNP) was similar in both HF groups and blood pressure was well controlled. Comorbidities characterized by history of HTN, DM, hypercholesterolaemia, renal, and IHD were similar in both HF groups except that HFpEF patients had a higher prevalence of renal disease.

Of both HF groups, HFmrEF had higher LV volumes, mass and size, lower RWT, and more eccentric hypertrophy (19.5% vs. 8%), but less concentric remodelling or hypertrophy (34.5% vs. 62%) compared with HFpEF (*Table 1*). HFpEF patients had higher LV volumes, mass, and RWT when compared with controls. Compared to controls, maximal, and pre-A LA volumes were higher in both HF groups with no difference between them, whereas minimal LA volume was higher in HFmrEF than in HFpEF patients. LA enlargement (>34 mL/m^2) was noted in 61% of HFmrEF and in 62% of HFpEF. Compared to controls, *E*/*e*′, TR velocity, and PASP were higher, and *S*′, *e*′, and *a*′ were lower in both HF groups with no difference between them. The HFpEF group had higher transmitral flow velocities and DT compared with other groups, but *E*/*A* ratio and LV DD grades were similar in both HF groups.

LA function

LA reservoir function (global PALS and LA total emptying fraction), pump function (global PACS and LA active emptying fraction), and conduit function (global PALS−PACS and LA passive emptying fraction) were impaired in both HF groups compared with controls, and were worse in HFmrEF patients than in HFpEF patients (*Figures 2* and *3*). LA conduit function determined by LA passive emptying fraction was lower in the HFmrEF group than in the HFpEF group although the difference was not statistically significant. Among patients with LA enlargement, LA phasic function by 2D-STE remained lower in HFmrEF *(Figure 4A*). Even among patients with normal LA size (LAVi ≤34 mL/m^2), LA reservoir and pump function were worse in HFmrEF (*Figure 4B*). Of HFpEF patients with normal LA size, LA reservoir and conduit, but not pump function were lower compared to controls.

Differences in LA reservoir, pump, and conduit function between HF groups were hardly altered and remained significant after adjustment for confounders including age, sex, BMI, heart rate, SBP, DM, HTN, and IHD. Further adjustment for LVEDVi, LVMi, LAVi, *E*/*A*,

DT, *E*/*e*′, and *S*′ also had negligible effects on differences ($P \leq 0.001$ for all) (*Table 2*). Features of normal and HF (HFpEF and HFmrEF) hearts are summarized in *Table 3*.

Correlates of LA strain measures

Worse global PALS and PACS were associated with higher BNP levels, LAVi, *E*/*A* ratio, LV filling pressure (*E*/*e*′), and PASP, as well as worse DD grade in both HF groups (*Table 4*, *Figure 5*). Worse global PALS−PACS was only associated with higher LAVi and *E*/*e*′ and greater DD grade in patients with HFpEF (**Supplementary data online, *Table S2***).

Discussion

In this study, we looked at LA phasic function using 2D-STE in patients with HFmrEF in relation to those with HFpEF. We found that although both HF groups showed abnormal LA size and function overall, patients with HFmrEF had worse LA reservoir, conduit, and pump function than those with HFpEF while conventional echocardiographic measures of LA size and LV diastolic function were relatively similar. LA phasic function remained lower in HFmrEF patients regardless of LA size and after adjustment for multiple confounders or possible LV mediators. Further, differences in LA phasic function between both HF groups as assessed by 2D-STE were consistent with these obtained by the volumetric analysis. These findings indicate differences between the two HF categories, which could possibly be attributed to intrinsic LA myocardial dysfunction perhaps in relation to altered LV function.

Previous studies have shown lower LA deformation indices assessed by tissue-Doppler imaging[13] and different LA remodelling by volumetric indices[12] in patients with HFrEF compared with those with HFpEF supporting that each of these HF categories represents distinct pathophysiological entities.[31] In our study, using 2D-STE, we extend those findings by showing that LA function assessed by 2D-STE as well as by volumetric indices remodelled differently in patients with HFmrEF compared with those with HFpEF supporting the hypothesis that HFmrEF and HFpEF represent different pathophysiological entities. Further, HFmrEF patients had greater degree of adverse LV remodelling as determined by lower LVEF, and higher LV volumes and mass highly indicating the close connection between LA and LV function.[11,32]

LA dysfunction in HFpEF has previously been described and it has been suggested that it may contribute to its pathophysiology.[12,17–21] Santos *et al*.[18] found that impaired LA reservoir function determined by lower LA systolic strain was independent of LA size or remodelling secondary to atrial fibrillation in HFpEF patients. Likewise, we showed that all LA phasic functions were impaired in HF patients with a normal LA size except for LA pump function in HFpEF. This could be explained by a biphasic response: during the early stages of HF, LA pump function is increased to compensate for impaired LV filling in early diastole, but with more prolonged or severe HF LA contraction gradually deteriorates.[10,28,33] In contrast, LA pump and reservoir function were more impaired in HFmrEF patients, both in those with a normal LA size, and in the subset with a structurally remodelled LA (LAVi >34 mL/m^2). The reason why this is the case is unclear, and the cross-sectional nature of our data limits our ability to draw firm conclusions on this. Further LV dysfunction leads to increased LA afterload, which may lead to intrinsic LA myocardial dysfunction.[11,13] However, LV filling pressure determined by *E*/*e*′ was not different between the two HF groups. Additionally, increased LA wall tension through pressure overload caused by greater LVH may also contribute to LA dysfunction at least in part.[18]

LA dysfunction varies according to the grade of LV DD.[34] Otani *et al*.[34] reported a progressive declined in LA reservoir and conduit function assessed by 2D-STE at advanced grades of DD, with initial augmentation of LA pump function in mild DD to allow adequate LV filling before being declined progressively in moderate to severe DD. In our study, we found a similar pattern that LA strains decreased progressively with higher grades of DD in both HF groups. Further, differences in LA phasic function between both HF groups was most prominent in the subset of patients with mild DD and decreased with advanced grades of DD.

Several studies suggest that DD and elevated filling pressure cannot completely account for LA dysfunction and that LA fibrosis may play an important role.[17,20,35] Indeed, global PALS and PACS showed only a moderate inverse correlation with diastolic function parameters presented in *Table 3* in both HF groups. These results match those observed in earlier studies of HFpEF and extend them to HFmrEF patients.[17,20,21,23,34] Morris *et al*.[20] suggested that LA dysfunction in HFpEF is likely to be related to the same fibrotic process, which influences the LV subendocardial layer secondary to several comorbidities such as DM, HTN, and coronary artery disease. Our study showed that a number of multiple comorbidities were prevalent in both HF groups. It is possible, therefore, that underlying LA fibrosis might further contribute to LA dysfunction and that LA dysfunction seen in our population may not be solely related to the DD, particularly in HFmrEF patients. Although detecting LA fibrosis by sophisticated magnetic resonance imaging (MRI) algorithms is difficult clinically due to poor reproducibility, future studies in this population may be needed to correlate LA strain measures to the extent of LA fibrosis assessed by MRI.[36]

BNP is a hormone secreted by atrial and ventricular myocytes in response to myocardial stress[37,38] and is included in the diagnostic algorithm for HFmrEF and HFpEF.[1] Kurt *et al*.[37] showed that LA strains were inversely correlated with N-terminal pro-BNP, and lower LA strains were noted in patients with LVEF <50% compared to those with normal LVEF. In this study, global PALS and PACS were lower in HFmrEF patients than in those with HFpEF, and worse global PALS and PACS correlated with higher BNP levels.

Limitations

A number of limitations of this study ought to be acknowledged. LA strain measurements require good delineation of LA endocardial borders. This resulted in the exclusion of a large number of patients from the analysis. Nevertheless, the reproducibility of measurements was good in the recruited patients. Although LA strain measures were obtained with the most widely used approach (onset of QRS complex),[29] some studies have used a different approach (onset of P-wave). Therefore, there is a need for standardizing methodology if this technique is to become clinically useful. The diagnosis of HFpEF and HFmrEF requires elevated natriuretic peptide levels; however, BNP measurements were not routinely performed in all patients, and were only available in 30% of HF patients. Despite that, we were able to show meaningful correlations between BNP and LA strain measures. Further, an invasive measurement of LV filling pressure was not obtained. Nevertheless, E/e' is an established non-invasive measure of LV filling pressure recommended by the ASE/EACVI guidelines.[8] An unresolved question is to what extent the observed difference in LA function is simply a consequence of worse LV systolic function in HFmrEF. Surprisingly, we observed no difference in S' between HFpEF and HFmrEF patients and adjustment for S' had minimal effects on differences between the two groups. LV global longitudinal strain might have provided more insight into this question but unfortunately it was not measured in this study.

Finally, the study was cross-sectional and lacked follow-up. Therefore, the clinical implications of our findings should be studied further.

Conclusion

In summary, LA phasic function determined by 2D-STE was worse in patients with HFmrEF compared to those with HFpEF while conventional echocardiographic measures of LA size and LV diastolic function were similar. The greater impairment in LA phasic function in HFmrEF patients was regardless of LA size and independent of potential confounders or possible LV mediators. These differences could possibly be attributed to intrinsic LA myocardial dysfunction perhaps in relation to altered LV function. The prognostic and clinical values of LA dysfunction in HFmrEF patients remain to be determined.

Acknowledgements

The authors acknowledge all Hammersmith Hospital echocardiographers for their professionalism and the performance of echocardiographic studies of the highest quality.

Funding

L.A. is supported by a scholarship grant from Imam Abdulrahman Bin Faisal University. A.H. receives support from the British Heart Foundation [PG/15/75/31748, CS/15/6/31468, and CS/13/1/30327], the National Institute for Health Research University College London Hospitals Biomedical Research Centre, and works in a unit that receives support from the UK Medical Research Council (Programme Code MC_UU_12019/1).

Conflict of interest: none declared.

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Table 1. Baseline characteristics of the study population

				Statistical significance (*P*-value)			
	HFpEF (*n* = 110)	**HFmrEF (*n* = 61)**	**Control (*n* = 37)**	***P*-value (Overall)**	**HFpEF vs. HFmrEF**	**HFmrEF vs. Control**	**HFpEF vs. Control**
Age (years)	63 ± 11	61 ± 14	59 ±10	0.13			
Female	42 (38.1)	12 (19.6)	15 (40.5)	**0.028**	**0.013**	**0.025**	0.79
Heart rate (bpm)	65 ± 12	69 ± 12	67 ± 12	0.17			
Systolic blood pressure (mmHg)	140 ± 22	139 ± 24	122 ± 15	**<0.001**	0.91	**<0.001**	**<0.001**
Diastolic blood pressure (mmHg)	75 ± 13	80 ± 16	73 ± 10	**0.026**	**0.025**	**0.017**	0.41
Body mass index (kg/m^2)	27.8 ± 5.4	26.4 ± 5.2	26.1 ± 4.4	0.11			
Body surface area (m^2)	1.85 ± 0.22	1.87 ± 0.21	1.80 ± 0.18	0.32			
Brain natriuretic peptide (ng/L)	174.6 (77.5–796.6) (*n* = 28)	267.5 (100–755.8) (*n* = 22)			0.96		
Hypertension	91 (82.7)	44 (72.1)			0.10		
Diabetes mellitus	53 (48.1)	20 (32.7)			0.051		
Hypercholesterolaemia	36 (36.7)	18 (36.7)			1.0		
History of ischaemic heart disease	66 (60)	41 (67.2)			0.35		
History of renal disease	50 (45.4)	13 (21.3)			**0.002**		
History of cardiomyopathy	3 (2.7)	11 (18)			**<0.001**		
Echocardiographic measures							
LVEF (%)	64.9 ± 7.7	44.9 ± 2.9	66.2 ± 5.7	**<0.001**	**<0.001**	**<0.001**	0.27
LV end-diastolic volume index (mL/m^2)	54.9 ±19.7	69.9 ± 17.7	47.4 ± 12.1	**<0.001**	**<0.001**	**<0.001**	**0.029**
LV end-systolic volume index (mL/m^2)	19.4 ± 8.6	38.4 ± 10.3	16.3 ± 5.8	**<0.001**	**<0.001**	**<0.001**	**0.013**

				Statistical significance (*P*-value)			
	HFpEF (*n* = 110)	**HFmrEF (*n* = 61)**	**Control (*n* = 37)**	***P*-value (Overall)**	**HFpEF vs. HFmrEF**	**HFmrEF vs. Control**	**HFpEF vs. Control**
LV mass (g)	179.4 ± 55	196.5 ± 47	117.2 ± 26.4	**<0.001**	**0.034**	**<0.001**	**<0.001**
LV mass index (g/m^2)	96.6 ± 27	105.1 ± 25	64.7 ± 12.5	**<0.001**	**0.040**	**<0.001**	**<0.001**
LVIDd index (cm/m^2)	2.5 ± 0.3	2.8 ± 0.3	2.4 ± 0.2	**<0.001**	**<0.001**	**<0.001**	0.90
IVS (cm)	1.0 ± 0.2	1.0 ± 0.1	0.83 ± 0.1	**<0.001**	0.09	**<0.001**	**<0.001**
PW (cm)	1.0 ± 0.1	0.9 ± 0.1	0.8 ± 0.07	**<0.001**	**0.032**	**<0.001**	**<0.001**
Relative wall thickness	0.45 ± 0.09	0.37 ± 0.08	0.36 ± 0.05	**<0.001**	**<0.001**	0.33	**<0.001**
LV geometry					**0.005**		
Normal	33 (30)	28 (46)					
Concentric remodelling	45 (41)	14 (23)					
Eccentric hypertrophy	9 (8)	12 (19.5)					
Concentric hypertrophy	23 (21)	7 (11.5)					
LA volume index (mL/m^2)	38.8 ± 12.7	39.5 ± 13	25.4 ± 5.1	**<0.001**	0.73	**<0.001**	**<0.001**
LA >34 mL/m^2	68 (62)	37 (61)			0.88		
LA volume$_{max}$ (mL)	71.6 ± 23.3	73.5 ± 24.1	45.6 ± 11.4	**<0.001**	0.63	**<0.001**	**<0.001**
LA volume$_{pre-A}$ (mL)	52.7 ± 18.3	56.3 ± 20.1	30.6 ± 8.6	**<0.001**	0.24	**<0.001**	**<0.001**
LA volume$_{min}$ (mL)	38.0 ± 16.5	44.7 ± 17.8	18.8 ± 5.6	**<0.001**	**0.016**	**<0.001**	**<0.001**
E-wave (cm/s)	78.6 ± 25.1	68.7 ± 22.8	67.1 ±16.5	**0.003**	**0.010**	0.69	**0.002**
A-wave (cm/s)	79 ± 22.1 (*n* = 108)	61.5 ± 20.7 (*n* = 58)	66.8 ±16	**<0.001**	**<0.001**	0.21	**0.002**
E/*A* ratio	0.89 (0.77–1.2)	0.92 (0.72–1.6) (*n* = 58)	0.97 (0.84–1.23)	0.10			

				Statistical significance (*P*-value)			
	HFpEF (*n* = 110)	**HFmrEF (*n* = 61)**	**Control (*n* = 37)**	***P*-value (Overall)**	**HFpEF vs. HFmrEF**	**HFmrEF vs. Control**	**HFpEF vs. Control**
	(*n* = 108)						
Deceleration time (ms)	225.3 ± 43.7	207.8 ± 56	200.2 ± 30.7	**<0.001**	**0.040**	0.39	**<0.001**
Lateral S′ (cm/s)	7.2 ± 1.8	7.2 ± 2.3	9.0 ± 2.3	**0.0001**	0.82	**<0.0001**	**<0.001**
Lateral e′ (cm/s)	7.1 ± 2.1	6.6 ± 2.5	10.3 ± 2.6	**<0.001**	0.15	**<0.001**	**<0.001**
Lateral a′ (cm/s)	8.7 ± 2.8	7.8 ± 2.6	9.8 ± 2.7	**0.002**	0.052	**0.001**	**0.028**
E/*e*′ ratio	11.7 ± 4.5	11.5 ± 5.2	6.6 ± 1.6	**<0.001**	0.80	**<0.001**	**<0.001**
Tricuspid regurgitation velocity (m/s)	2.6 ± 0.4 (*n* = 70)	2.7 ± 0.5 (*n* = 38)	2.3 ± 0.2 (*n* = 18)	**<0.001**	0.64	**<0.001**	**<0.001**
Pulmonary artery systolic pressure (mmHg)	35.6 ± 11.8 (*n* = 70)	36.7 ± 12.3 (*n* = 38)	27.7 ± 4.5 (*n* = 18)	**<0.001**	0.73	**<0.001**	**<0.001**
Diastolic dysfunction grade					0.12		
Grade 1	52 (51.5)	26 (46.4)					
Grade II	44 (43.5)	22 (39.3)					
Grade III	5 (5)	8 (14.3)					

Data are expressed as mean ± SD, median (interquartile range), or *n* (%). Bold values indicate statistically significant. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; IVS, inter-ventricular septum; LA, left atrial; LV, left ventricular; LVIDd, left ventricular internal diameter in diastole; PW, posterior wall.

Table 2. The difference in left atrial strain measures between HFmrEF and HFpEF with and without adjustment

	Global PALS (%)		Global PACS (%)		Global PALS−PACS (%)	
	β[a] (95% CI)	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Unadjusted	−5.6 (−7.6 to −3.5)	<0.001	−3.3 (−4.9 to −1.7)	<0.001	−2.3 (−3.7 to −0.88)	0.002
Model 1	−5.9 (−8.0 to −3.8)	<0.001	−3.6 (−5.3 to −1.9)	<0.001	−2.4 (−3.7 to −1.0)	0.001
Model 2	−5.5 (−7.4 to −3.6)	<0.001	−3.0 (−4.4 to −1.5)	<0.001	−2.4 (−3.9 to −1.0)	0.001

Model 1: adjusted for age, sex, heart rate, systolic blood pressure, body mass index, diabetes mellitus, hypertension, and previous ischaemic heart disease. Model 2: Model 1 + left ventricular (LV) end-diastolic volume index, LV mass index, left atrial volume index, early to late mitral inflow velocity ratio (*E*/*A*), deceleration time, *E*/*e*′ ratio of early lateral mitral annular velocity (e′) and S′. CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; PACS, peak-atrial contraction strain; PALS, peak-atrial longitudinal strain. [a] Regression coefficient.

Table 3. Features of normal vs. heart failure (HFpEF and HFmrEF) hearts

	Normal	**HFpEF**	**HFmrEF**
Age (years)	~60		
LVEF (%)	N	N	40–50%
LV end-diastolic volume (mL/m^2)	N	N	↑
Relative wall thickness	N	↑	N
LV mass (g)	N	N or ↑	N or ↑
LV geometry	N	Concentric LVH	Eccentric remodelling
LVDF	N	↓	↓
S′ (cm/s)	N	↓	↓
LA volume$_{max}$ (mL)	N	↑	↑
LA volume$_{min}$ (mL)	N	↑	↑↑
LA volume$_{Pre}$ (mL)	N	↑	↑
LA total emptying fraction (%)	N	↓	↓↓
LA passive emptying fraction (%)	N	↓	↓
LA active emptying fraction (%)	N	↓	↓↓
LA reservoir strain (%)	N	↓	↓↓
LA conduit strain (%)	N	↓	↓
LA pump strain (%)	N	N or ↓	↓
BNP	N	↑	↑↑

LA, left atrial; LV, left ventricular; LVDF, left ventricular diastolic function; LVH, left ventricular hypertrophy; N, normal.

Table 4. Correlates of global PALS and PACS in HFmrEF and HFpEF patients

	HFpEF (*n* = 110)				**HFmrEF (*n* = 61)**			
	Global PALS (%)		**Global PACS (%)**		**Global PALS (%)**		**Global PACS (%)**	
	***r*[a]**	***P*-value**	***r***	***P*-value**	***r***	***P*-value**	***r***	***P*-value**
BNP (ng/L)	−0.57	0.001	−0.53	0.003	−0.53	0.009	−0.44	0.04
Left atrial volume index (mL/m^2)	−0.58	<0.001	−0.50	<0.001	−0.42	<0.001	−0.33	0.01
E/*A* ratio	−0.47	<0.001	−0.54	<0.001	−0.32	0.01	−0.52	<0.001
E/*e*′ ratio	−0.52	<0.001	−0.50	<0.001	−0.44	<0.001	−0.40	0.001
Tricuspid regurgitation velocity (m/s)	−0.50	<0.001	−0.45	<0.001	−0.60	<0.001	−0.55	<0.001
Pulmonary artery systolic pressure (mmHg)	−0.49	<0.001	−0.45	<0.001	−0.63	<0.001	−0.59	<0.001
Diastolic dysfunction grade[b]	−0.66[b]	<0.001	−0.68[b]	<0.001	−0.34[b]	0.007	−0.48[b]	<0.001

BNP, brain natriuretic peptide; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; PACS, peak-atrial contraction strain; PALS, peak-atrial longitudinal strain. [a] Pearson correlation coefficient. [b] Spearman's rho (correlation coefficient).

Figure 1. LA function by 2D speckle-tracking echocardiography. (*A*) Tracing of LA endocardial borders in the apical-four chamber view. (*B*) LA strain measures [peak-atrial longitudinal strain (PALS) = LA reservoir function, peak-atrial contraction strain (PACS) = LA pump function and PALS−PACS = LA conduit function].

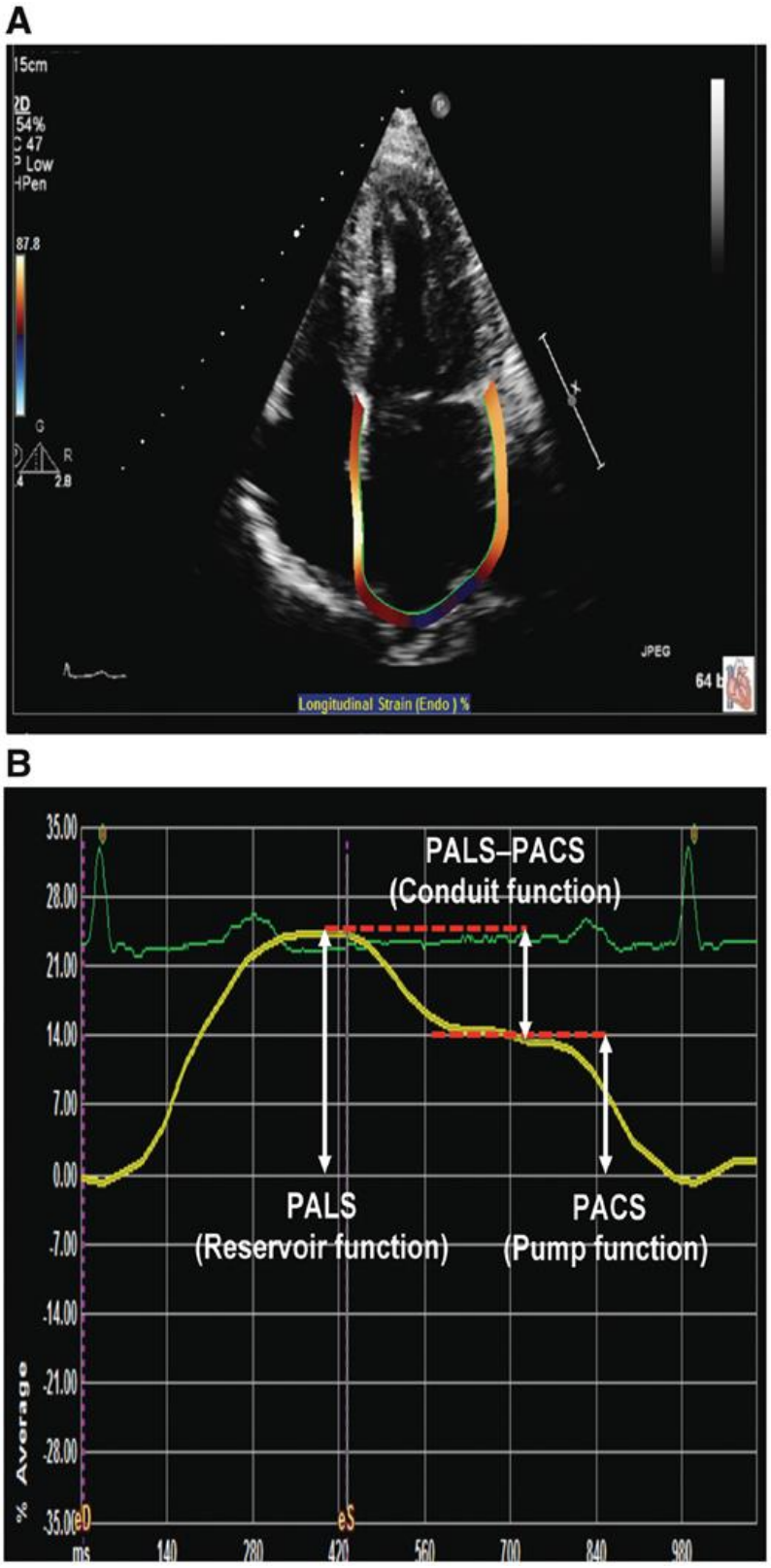

Figure 2. Comparison of LA phasic function between overall patients with HFmrEF, HFpEF, and controls assessed by volumetric method (A) and by 2D speckle-tracking echocardiography (B). Data are expressed as mean (95% confidence interval). HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; PACS, peak-atrial contraction strain; PALS, peak-atrial longitudinal strain.

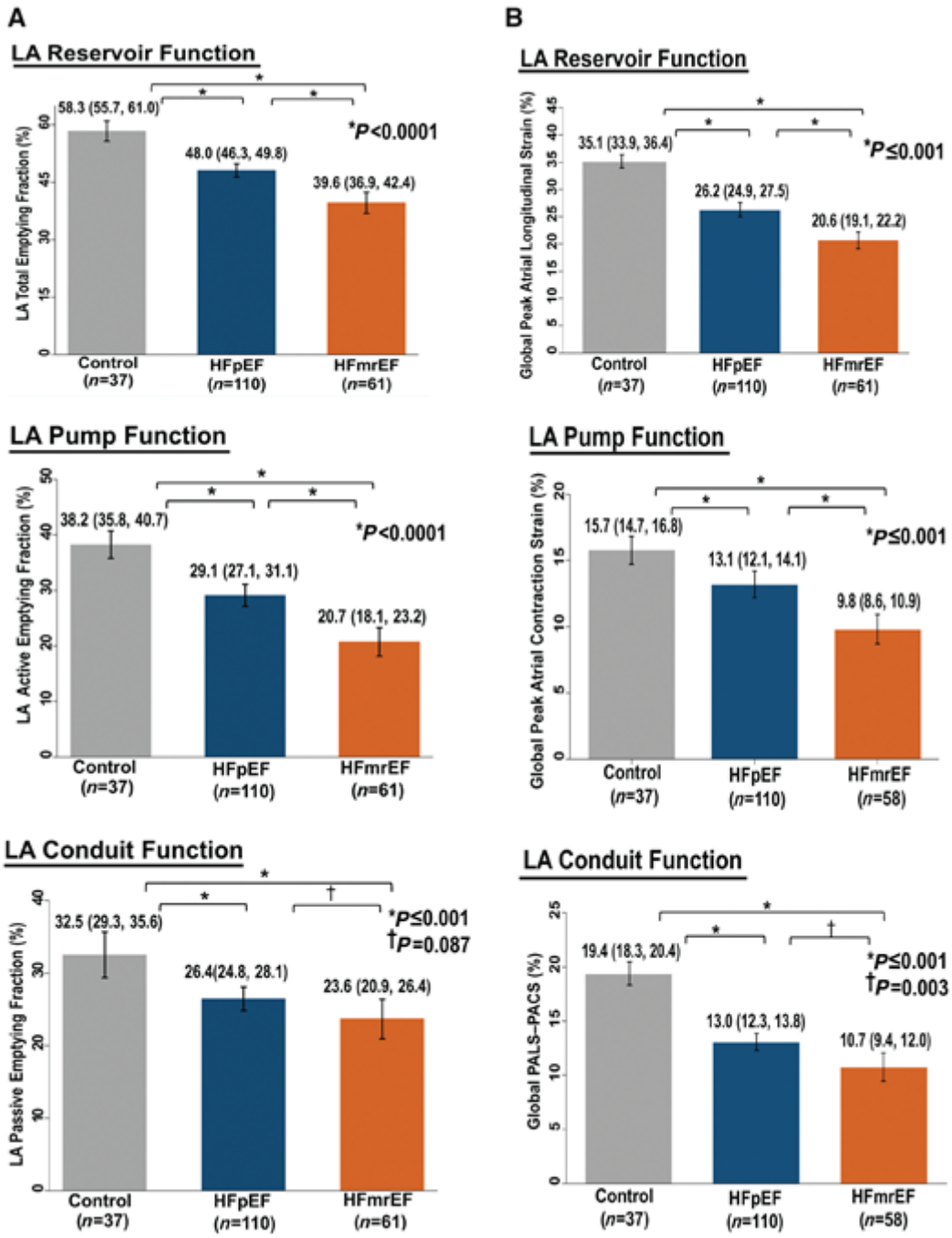

Figure 3. Representative images of LA strain curve in (A) a patient with HFmrEF, (B) a patient with HFpEF, and (C) a control. Global PALS = LA reservoir function, global PACS = LA pump function and global PALS–PACS = LA conduit function. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; PACS, peak-atrial contraction strain; PALS, peak-atrial longitudinal strain.

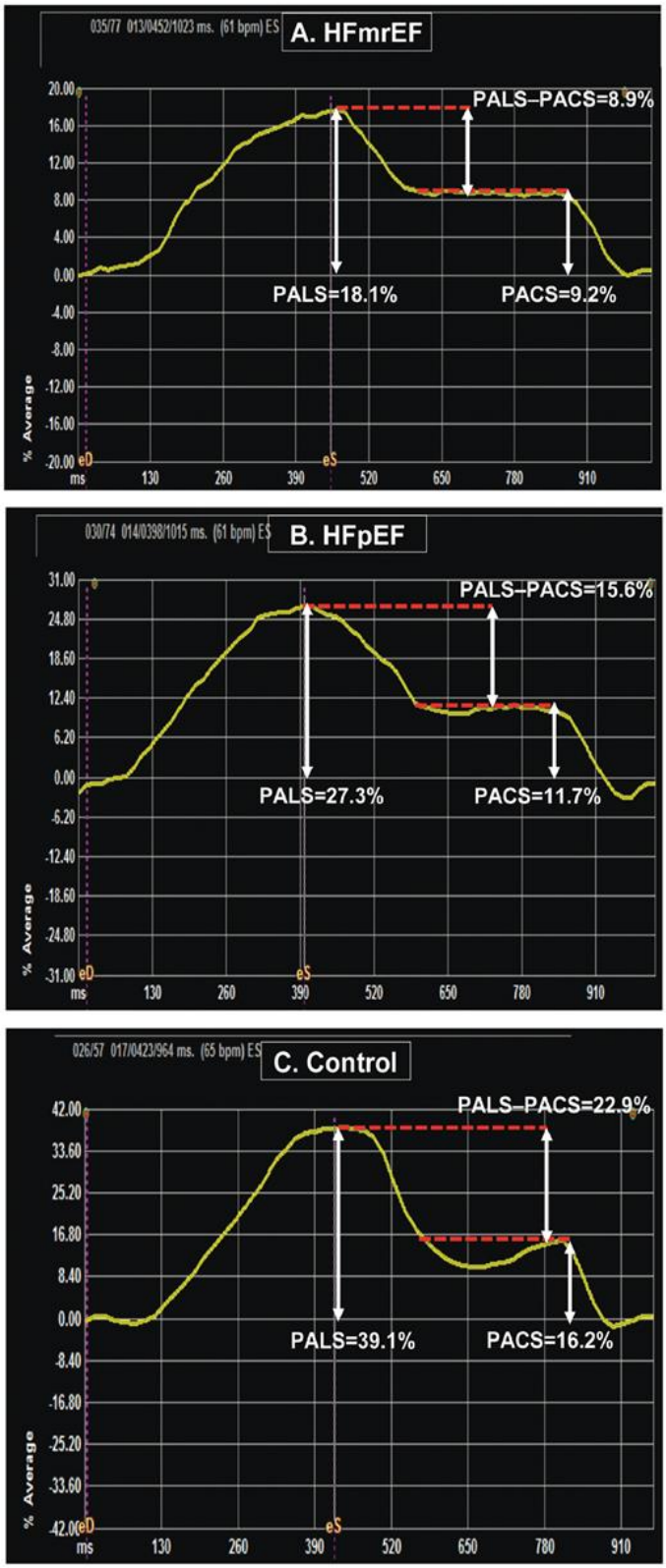

Figure 4. LA phasic function in HFmrEF and HFpEF by LA size. (A) Patients with LA enlargement (LA volume >34 mL/m2). (B) Patients with normal LA size (LA volume ≤34 mL/m2) compared with controls. Data are presented as mean (95% confidence interval). HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; PACS, peak-atrial contraction strain; PALS, peak-atrial longitudinal strain.

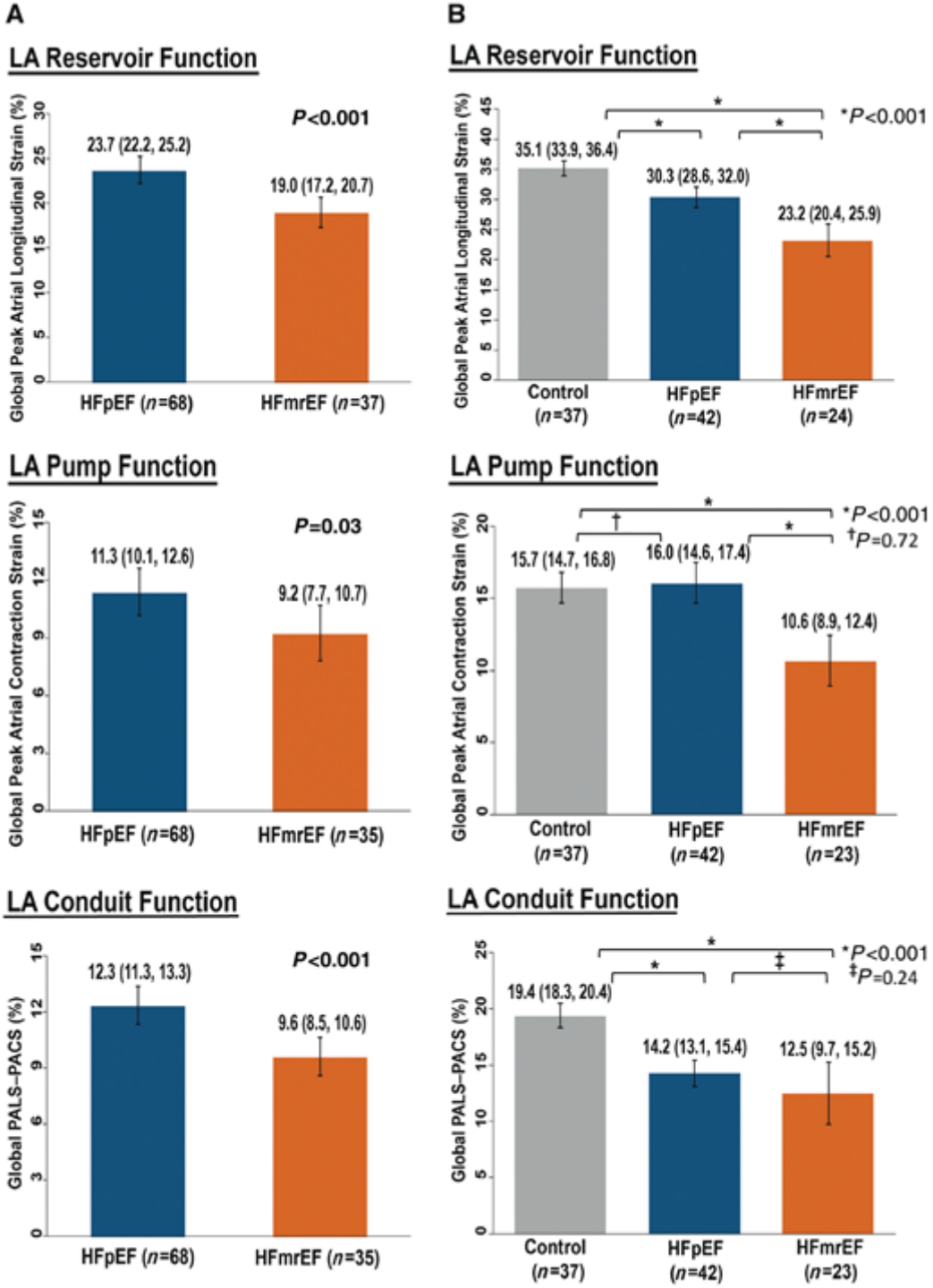

Figure 5. Scatter plots showing the inverse correlation of global PALS and PACS with pulmonary artery systolic pressure (*A*) and *E*/*e*′ (*B*) in HFmrEF and HFpEF patients. *r*, Pearson correlation coefficient.