

Prognostic Utility and Clinical Significance of Cardiac Mechanics in Heart Failure With Preserved Ejection Fraction

Importance of Left Atrial Strain

Benjamin H. Freed, MD; Vistasp Daruwalla, MD; Jeanette Y. Cheng, MHS;
Frank G. Aguilar, MPH; Lauren Beussink, RDCS, MHS; Andrew Choi, BS;
David A. Klein, MS; Debra Dixon, BS; Abigail Baldrige, MS;
Laura J. Rasmussen-Torvik, PhD, MPH; Kameswari Maganti, MD; Sanjiv J. Shah, MD

Background—Left atrial (LA) enlargement is associated with adverse events in heart failure with preserved ejection fraction (HFpEF). However, the role of LA mechanics (ie, LA strain measures) in HFpEF has not been well studied. We hypothesized that in HFpEF, reduced (worse) LA strain is a key pathophysiologic abnormality and is a stronger correlate of adverse events than left ventricular or right ventricular longitudinal strain.

Methods and Results—We evaluated baseline LA function in 308 patients with HFpEF who were followed up longitudinally for adverse outcomes. All patients underwent speckle-tracking echocardiography for measurement of left ventricular longitudinal strain, right ventricular free wall strain, and LA booster, conduit, and reservoir strains. The clinical and prognostic significance of left ventricular, right ventricular, and LA strain measures was assessed by regression analyses. The mean age was 65±13 years, 64% were women, 26% had atrial fibrillation, and LA enlargement was present in the majority of patients (67%). Decreased LA reservoir strain was associated with increased pulmonary vascular resistance ($P<0.0001$) and decreased peak oxygen consumption ($P=0.0001$). Of the left ventricular, right ventricular, and LA strain measures, LA reservoir strain was the strongest correlate of adverse events and was independently associated with the composite outcome of cardiovascular hospitalization or death (adjusted hazard ratio per 1-SD decrease in LA strain, 1.54; 95% CI, 1.15–2.07; $P=0.006$).

Conclusions—Abnormal indices of LA mechanics (particularly LA reservoir strain) are powerful clinical and prognostic factors in HFpEF. Unloading the LA and augmentation of LA function may be important future therapeutic targets in HFpEF.

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The left atrium (LA) plays an integral role in the pathophysiology and prognosis of heart failure with preserved ejection fraction (HFpEF).¹ As diastolic function worsens because of vascular and left ventricular (LV) stiffening, LV filling pressures increase, leading to LA pressure overload and enlargement.

See Editorial by Jellis and Klein See Clinical Perspective

More recently, LA mechanical dysfunction (above and beyond LA size) has gained a considerable amount of attention because of technological advances in noninvasive imaging and

a better understanding of the pathophysiology of the HFpEF syndrome. LA function is comprised of reservoir, conduit, and booster phases, all of which can be accurately measured with high feasibility and reproducibility by 2-dimensional (2D) speckle-tracking echocardiography analysis for the calculation of LA strain.²⁻⁴

With worsening LV diastolic function, both LA compliance and LA function decline.⁵⁻⁷ By exploiting this phenomenon with speckle-tracking strain analysis, investigators have found that indices of LA strain add incremental diagnostic value to conventional markers in HFpEF, above and beyond LA size.^{8,9} However, the clinical significance and prognostic

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From the Division of Cardiology, Department of Medicine (B.H.F., V.D., J.Y.C., F.G.A., L.B., A.C., D.A.K., D.D., K.M., S.J.S.) and the Department of Preventive Medicine (A.B., L.J.R.-T.), Northwestern University Feinberg School of Medicine, Chicago, IL.

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Correspondence to Sanjiv J. Shah, MD, Heart Failure with Preserved Ejection Fraction Program, Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, 676 N St Clair St, Suite 600, Chicago, IL 60611. E-mail sanjiv.shah@northwestern.edu

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value of LA strain in patients with HFpEF is not known. Furthermore, no previous studies have compared the prognostic utility of LA strain versus LV and right ventricular (RV) strain in HFpEF.

Therefore, we sought to (1) determine the clinical, invasive hemodynamic, and cardiopulmonary exercise testing (CPET) correlates of LA strain in HFpEF; and (2) evaluate the prognostic utility of LA strain in HFpEF and determine its significance when compared with conventional echocardiographic and clinical factors, and indices of LV and RV mechanics. We hypothesized that in HFpEF, decreased LA strain (indicative of worse LA function) is associated with worse hemodynamics and decreased peak oxygen consumption (VO_2); is associated with poor outcomes; and is a stronger correlate of adverse events than LV or RV strain.

Methods

Study Population

Between March 2008 and May 2011, consecutive patients were prospectively enrolled from the outpatient clinic of the Northwestern University HFpEF Program as a part of a systematic observational study of HFpEF (ClinicalTrials.gov; NCT01030991). All patients were enrolled into the study in the outpatient setting after a hospitalization for HF. Patients were initially identified by an automated daily query of the inpatient electronic medical record at Northwestern Memorial Hospital (at the time of hospitalization) using the following search criteria: (1) diagnosis of HF or the term HF in hospital notes, (2) B-type natriuretic peptide >100 pg/mL, or (3) administration of ≥ 2 doses of intravenous diuretics. Patients were offered postdischarge follow-up in a specialized HFpEF outpatient program if they met the following 3 inclusion criteria: age ≥ 21 years, LVEF $\geq 50\%$, and the presence of HF as defined by Framingham criteria.¹⁰

Post hospitalization, the HF diagnosis was confirmed in the outpatient HFpEF clinic. All patients met the European Society of Cardiology criteria for the diagnosis of HFpEF.¹¹ Patients were excluded if they had more than moderate valvular disease, previous cardiac transplantation, previous history of a reduced LVEF $<40\%$ (ie, recovered EF), severe LV dilation (LV end-diastolic volume >97 mL/ m^2), or constrictive pericarditis. All study participants gave written informed consent, and the Institutional Review Board at Northwestern University approved the study.

Clinical Characteristics

We collected the following data in all study participants: demographics, New York Heart Association (NYHA) functional class, comorbidities, medications, vital signs, body mass index, and laboratory data, including creatinine, hemoglobin, and B-type natriuretic peptide. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation. Definitions of each of the individual comorbidities are listed in the Data Supplement.

Conventional Echocardiography

All study participants underwent comprehensive 2D echocardiography with Doppler and tissue Doppler imaging using commercially available ultrasound systems with harmonic imaging (Philips iE33 or 7500; Philips Medical Systems, Andover, MA; or Vivid 7; GE Healthcare, General Electric Corp, Waukesha, WI), as detailed in the Data Supplement.

Speckle-Tracking Echocardiography

All images used for speckle-tracking echocardiographic analysis were obtained at a frame rate of 50 to 70 fps. Strain was analyzed by a single investigator using a customized software package (2D Cardiac Performance Analysis, TomTec v4.5, Munich, Germany). Three

consecutive cardiac cycles were recorded and averaged. Speckle-tracking analysis was not performed in patients with unacceptable image quality, defined as >1 segment dropout, missing view, or significant foreshortening of the LV, RV, or LA.

We used the ventricular cycle as the reference point (ie, zero baseline) to calculate LA strain.² Therefore, the onset of the QRS complex is the zero reference, and all longitudinal LA strain values are positive. We defined the following components of LA function (strain): LA reservoir strain=peak (maximal) longitudinal LA strain; LA booster strain=longitudinal LA strain measured between onset of the P wave and onset of the QRS complex; and LA conduit strain=LA reservoir strain-LA booster strain. In patients who were in atrial fibrillation at the time of echocardiography, there is no LA booster function because of the loss of coordinated LA contraction; in these cases, LA conduit strain=LA reservoir strain.

To generate LA strain curves, the LA endocardial border was manually traced in the apical 4- and 2-chamber views. The region of interest generated was subsequently adjusted to include the full thickness of the LA myocardium. In each patient, the software divided the LA into 6 separate segments, longitudinal strain curves were generated, and tracking was evaluated. Any segment that did not sufficiently track well was excluded from final analysis, and the remaining segments were averaged for each view. LA reservoir, booster, and conduit strains were calculated by averaging the apical 4- and 2-chamber strain values. In patients with atrial fibrillation at the time of echocardiography, speckle-tracking of the apical 4- and 2-chamber views was performed on 3 different beats, and LA strain values from the 3 beats were averaged in each view. LA stiffness index was calculated as the ratio of E/e' to LA reservoir strain as previously defined.⁵

In addition to LA strain, LV longitudinal strain and longitudinal RV free wall strain were also measured. The LV endocardial border was manually traced in the apical 4- and 2-chamber views, and the RV endocardial border traced in the apical 4-chamber RV-focused view. Similar to the LA, the software divided the LV and RV into 6 segments and regions with insufficient tracking were excluded. LV longitudinal strain was calculated by averaging the remaining segments for each view, and RV free wall strain was calculated by averaging the 3 RV free wall segments.

For ease of reporting and interpretation, all strain values were reported as absolute values (lower absolute strain values correspond to worse cardiac mechanics).

Invasive Hemodynamic Testing and Cardiopulmonary Exercise Testing

In subsets of the study participants, right-sided heart catheterization and symptom-limited CPET were performed as described in the Data Supplement.

Outcomes

After enrollment, study participants were evaluated in the Northwestern HFpEF Program at least every 6 months. At each visit, intercurrent hospitalizations were documented, reviewed, and categorized because of cardiovascular or noncardiovascular causes. Every 6 months, participants (or their proxy) who were not able to come into clinic were contacted to determine vital status with verification of deaths through query of the Social Security Death Index. Enrollment date was defined as the first visit to the outpatient HFpEF clinic. Date of last follow-up was defined as the date of death or last HFpEF clinic visit. Follow-up was complete in all patients. The primary end point was a combined outcome of cardiovascular hospitalization and death, which included hospitalization for any cardiovascular cause (including HF) and death from any cause.

Statistical Analysis

Intraobserver variability for LA strain was assessed in 15 randomly selected patients by having the same observer repeat the analysis 1 month apart. Interobserver variability for LA strain was assessed in 30 randomly selected patients by having the same observer and

another experienced observer repeat the analysis. Reproducibility data were reported using intraclass correlation coefficients and coefficient of variation.

Clinical characteristics, laboratory data, echocardiographic measures, invasive hemodynamics, and CPET data were summarized for the entire cohort, and univariable Cox regression analyses were used to determine the association between these variables and adverse outcomes (cardiovascular hospitalization [which included HF hospitalization] or death). Next, we examined the correlation between indices of cardiac mechanics (LV, RV, and LA strain measures) and both invasive hemodynamics and CPET variables. These analyses were performed using a Pearson pairwise correlation. For the dependent variables, pulmonary artery (PA) systolic pressure, thermodilution cardiac output, pulmonary vascular resistance (PVR), and peak $\dot{V}O_2$, we used unadjusted and multivariable-adjusted linear regression analyses with LA reservoir strain as the independent variable. Covariates included age, sex, obesity, atrial fibrillation, LA volume, LV mass, and E/e' ratio. Formal interaction testing with multiplicative interaction terms and the likelihood ratio test was used to determine whether clinical characteristics (age, sex, and comorbidities) modified the associations between LA reservoir strain and the aforementioned hemodynamic and CPET indices.

For survival analyses, we used Cox proportional hazards regression to evaluate the unadjusted relationship between the measures of LA function and outcomes. Models were then adjusted for covariates chosen based on a combination of clinical relevance and association with adverse outcomes in HFpEF. We used a series of models for our Cox regression analyses. After performing unadjusted analyses, we performed the following multivariable-adjusted analyses: model 1 included sex, atrial fibrillation, the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, LV mass, and LA volume; model 2 included model 1 covariates+E/e' ratio; and model 3 included model 2 covariates+LV longitudinal strain and RV free wall strain. The MAGGIC risk score¹² is a mortality risk score for patients with HF, including those with HFpEF, and includes age, LVEF, creatinine, diabetes mellitus, chronic obstructive pulmonary disease, systolic blood pressure, body mass index, heart rate, NYHA functional class, angiotensin-converting enzyme inhibitor use, β -blocker use, HF duration, and current smoking.

To determine the relative utility of strain measures beyond conventional risk predictors, and to compare the prognostic and discriminative utility across strain measures, we used a combination of tests, including Harrell C-statistic, integrated discrimination improvement, net reclassification improvement, the likelihood ratio test, and Bayes information criterion.

In sensitivity analyses, we repeated linear and Cox regression analyses after excluding participants who had atrial fibrillation or moderate mitral regurgitation at the time of echocardiography. A 2-sided $P < 0.05$ was considered to indicate statistical significance. All analyses were performed using Stata version 12 (StataCorp, College Station, TX).

Results

Baseline Clinical Characteristics

Of the 419 enrolled patients, echocardiographic images could not be retrieved in 56 patients. An additional 55 patients were excluded from the final analysis because of poor image quality for speckle-tracking strain analysis (feasibility=85%). Table 1 summarizes the clinical characteristics and the association of these characteristics with adverse events for the remaining 308 patients. The majority of patients were women, nearly half of the study sample was nonwhite (48%), and most patients (84%) had NYHA functional class II or III symptoms.

The median follow-up time was 13.8 months (25th–75th percentile, 4.5–23.9 months). During the follow-up period, 94 patients (31%) were hospitalized for a cardiovascular reason, 66 (21%) were hospitalized for HF, 37 (12%) died, and 115

(37%) experienced the composite end point of cardiovascular hospitalization (including HF hospitalization) or death.

Several clinical and laboratory characteristics were associated with adverse outcomes on univariable Cox regression analyses. Older age; worse NYHA functional class, systemic hypertension, chronic kidney disease, certain medications (loop diuretics, β -blockers, and nitrates); higher B-type natriuretic peptide; and lower hemoglobin were associated with adverse outcomes. In addition, a higher MAGGIC risk score was associated with adverse events.

Baseline Echocardiographic Characteristics, Including Speckle-Tracking LV and RV Longitudinal Strain Measures

Table 2 summarizes the conventional echocardiographic, tissue Doppler, and speckle-tracking measures of the study cohort and their association with adverse events. Overall, patients had evidence of structural heart disease with high prevalence of LV hypertrophy (43%) or concentric remodeling (38%) and moderate or greater LV diastolic dysfunction (75%). Although LVEF was preserved overall ($\geq 50\%$ in all patients, with a mean value of $61 \pm 6\%$), tissue Doppler imaging s' velocity and LV longitudinal strain were decreased in the study cohort.¹³ Of the 308 study patients, 230 (75%) had abnormal absolute LV longitudinal strain (defined as absolute LV longitudinal strain $< 20\%$ ¹⁴). The prevalence of RV systolic dysfunction was relatively low when defined by conventional echocardiographic measures (19% of patients had an RV fractional area change $< 35\%$; 26% of patients had a tricuspid annular plane systolic excursion < 1.6 cm). However, when defined by RV free wall strain (absolute RV free wall strain, $< 20\%$ ¹⁴), the prevalence of RV systolic dysfunction was higher (48% of patients).

A higher LV mass index and increased E/e' ratio, consistent with pathological LV hypertrophy and elevated LV filling pressures, respectively, were associated with adverse outcomes. Lower tissue Doppler imaging s' velocities, decreased (worse) LV longitudinal strain, and decreased (worse) RV free wall strain were also associated with adverse outcomes (Table 2).

Baseline LA Size and Function, Including Speckle-Tracking LA Strain Measures

On average, LA size, as measured by LV volume index, was dilated in the study population, and 67% of the study patients had evidence of LA enlargement (using a cutoff of > 28 mL/ m^2). Figure 1 displays examples of LA strain curves in HFpEF patients with and without atrial fibrillation. Table I in the Data Supplement displays the intra- and interobserver variability of LA strain measures. The normal range for LA reservoir strain using TomTec strain software is not defined. However, based on published normal values for LA reservoir strain¹⁵ using GE strain software, 26% of the patients had LA reservoir strain values $< 22.7\%$, which is 2 SDs below the mean in healthy controls (44.1%), and 56% of patients had LA reservoir strain values $< 34.1\%$, which is 1 SD below the mean in healthy controls.

Beat-to-beat variability was evaluated in patients with atrial fibrillation. The mean value for LA reservoir strain in

Table 1. Summary of Clinical Characteristics of the Study Cohort and Association of Clinical Characteristics With Cardiovascular Hospitalization or Death on Cox Regression Analysis

Clinical Characteristic	Total Cohort (n=308)	Hazard Ratio (95% CI)	P Value
Age, y*	65±13.0	1.27 (1.10–1.47)	0.001
Women, n (%)	197(64)	1.02 (0.69–1.49)	0.94
Race, n (%)			0.29
White	159 (52)	1.00 (referent)	
Black	118 (38)	1.26 (0.86–1.84)	
Other	31 (10)	0.78 (0.37–1.64)	
NYHA class, n (%)			<0.001
I	44 (14)	1.00 (referent)	
II	118 (38)	1.15 (0.61–2.18)	
III	141 (46)	2.40 (1.32–4.38)	
IV	4 (1)	2.78 (0.63–12.33)	
Comorbidities, n (%)			
Atrial fibrillation	79 (26)	1.24 (0.83–1.86)	0.30
Coronary artery disease	153 (50)	1.32 (0.92–1.91)	0.14
Hypertension	232 (75)	1.61 (1.00–2.58)	0.05
Diabetes mellitus	91 (30)	1.46 (1.00–2.14)	0.05
Cigarette smoker	125 (41)	1.00 (0.69–1.45)	0.99
Hyperlipidemia	161 (52)	0.89 (0.62–1.29)	0.54
Obesity	154 (50)	1.02 (0.70–1.46)	0.94
Chronic kidney disease	94 (31)	1.89 (1.29–2.78)	0.001
COPD	106 (34)	1.33 (0.92–1.94)	0.13
Obstructive sleep apnea	105 (34)	1.40 (0.96–2.03)	0.08
Vital signs and laboratory data			
Systolic blood pressure, mm Hg†	125±13	0.88 (0.73–1.06)	0.19
Diastolic blood pressure, mm Hg†	70±12	0.73 (0.59–0.89)	0.002
Body mass index, kg/m ² ‡	31.5±8.6	1.02 (0.85–1.23)	0.82
Hemoglobin, g/dL‡	11.9±1.8	1.26 (1.06–1.52)	0.009
Estimated GFR, mL/min per 1.73 m ² ‡	60±28	1.45 (1.20–1.77)	<0.001
BNP, pg/mL (median, 25th to 75th percentile)†	230 (69–474)	1.25 (1.10–1.41)	0.001
Medications, n (%)			
ACE-inhibitor or ARB	166 (54)	0.90 (0.62–1.30)	0.58
β-blocker	206 (67)	1.55 (1.01–2.36)	0.04
Calcium channel blocker	101 (33)	1.39 (0.96–2.02)	0.08
Nitrate	40 (13)	2.84 (1.78–4.52)	<0.001
Loop diuretic	168 (55)	2.28 (1.54–3.37)	<0.001
Thiazide diuretic	67 (22)	1.05 (0.68–1.64)	0.81

(Continued)

Table 1. Continued

Clinical Characteristic	Total Cohort (n=308)	Hazard Ratio (95% CI)	P Value
Mineralocorticoid receptor antagonist	38 (12)	1.24 (0.74–2.09)	0.41
Statin	148 (48)	1.43 (0.99–2.06)	0.06
Aspirin	138 (45)	1.37 (0.95–1.98)	0.09
Warfarin	70 (23)	1.26 (0.83–1.93)	0.28
MAGGIC risk score†	19.3±7.3	1.07 (1.04–1.10)	<0.001

Categorical variables are presented as counts and percentages; continuous variables are presented as mean±SD unless otherwise specified. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; and NYHA, New York Heart Association.

*Hazard ratio is per 10-year increase.

†Hazard ratio is per 1-SD increase.

‡Hazard ratio is per 1-SD decrease.

patients with atrial fibrillation at the time of echocardiography was 16.9%. The SD of LA reservoir strain measured across multiple beats was 1.7 units. The coefficient of variation for LA reservoir strain measured across multiple beats was 9.2%.

LA volume index was not associated with adverse outcomes during follow-up. However, lower septal and lateral tissue Doppler imaging a' velocities (markers of the LA contribution to mitral annular motion at end-diastole) were associated with adverse events. In addition, as shown in Table 2, decreased (worse) LA booster, conduit, and reservoir strain were all associated with adverse events. Increased LA stiffness was also associated with poor outcomes in the study sample.

Comparison of the Clinical and Prognostic Utility of LV, RV, and LA Strain

Table II in the Data Supplement displays the demographic, clinical, laboratory, and echocardiographic measures that were associated with LA booster, conduit, and reservoir strain. Several factors, including atrial fibrillation; increased B-type natriuretic peptide, MAGGIC risk score, LV mass, LA volume, and E/ e' ratio; and decreased glomerular filtration rate, tissue velocities were each associated with associated with worse LA strain values. LV longitudinal strain and RV free wall strain were associated with decreased (worse) LA strain, particularly LA reservoir strain. To determine the clinical utility of LV, RV, and LA strain measures, we also examined the association between strain measures and (1) invasive hemodynamics and (2) CPET variables. Several invasive hemodynamic and CPET variables, including right atrial pressure, PA pressure, and peak VO_2 , known to carry prognostic value in HF, were also associated with adverse events in our study (Table III in the Data Supplement).

As shown Table III in the Data Supplement, LV longitudinal strain was only marginally associated with PA pressure, cardiac index, exercise workload, and ventilatory efficiency. RV free wall strain was associated with cardiac index and PVR, but was not associated with any CPET variables. However, LA reservoir strain was significantly associated with several

Table 2. Summary of Echocardiographic, Invasive Hemodynamic, and Cardiopulmonary Exercise Test Characteristics of the Study Cohort, and Association of These Characteristics With Cardiovascular Hospitalization or Death on Cox Regression Analysis

Parameter	Total Cohort (n=308)	Hazard Ratio (95% CI)	P Value
Echocardiography			
Septal wall thickness, cm*	1.20±0.30	1.28 (1.11–1.48)	0.001
Posterior wall thickness, cm*	1.15±0.28	1.27 (1.11–1.46)	<0.001
Relative wall thickness*	0.51±0.16	1.25 (1.09–1.43)	0.001
LV mass index, g/m ² *	104.5±39.7	1.26 (1.10–1.44)	0.001
LV end-diastolic volume index, mL/m ² *	41.6±12.3	0.92 (0.74–1.13)	0.43
LV end-systolic volume index, mL/m ² *	16.7±7.5	0.93 (0.76–1.15)	0.52
LV ejection fraction, %†	61.0±6.4	0.94 (0.79–1.14)	0.56
LA volume index, mL/m ² *	34.4±13.7	1.16 (0.99–1.35)	0.06
E velocity, cm/s*	104.6±35.8	1.27 (1.07–1.50)	0.006
A velocity, cm/s*	85.9±30.3	1.12 (0.90–1.40)	0.30
E/A ratio*	1.3±0.7	1.13 (0.94–1.36)	0.19
RV fractional area change, %†	44±7	1.20 (1.01–1.42)	0.04
TAPSE, cm†	2.0±0.6	1.19 (0.99–1.43)	0.06
PA systolic pressure, mm Hg*	43.7±15.5	1.21 (0.98–1.49)	0.08
Tissue Doppler measures‡			
s' velocity, cm/s†	7.2±2.1	1.42 (1.13–1.77)	0.002
e' velocity, cm/s†	7.0±2.7	1.19 (0.96–1.46)	0.10
a' velocity, cm/s†	8.4±3.1	1.61 (1.31–1.98)	<0.001
E/e' ratio†	15.0±8.1	1.31 (1.14–1.50)	<0.001
Aortic stenosis, n (%)			
Mild	1 (0.3)
Moderate	3 (1)	0.97 (0.14–6.96)	0.98
Aortic regurgitation, n (%)			
Mild	5 (1.6)	1.81 (0.57–5.69)	0.31
Moderate	2 (0.6)
Moderate mitral regurgitation, n (%)	44 (14)	1.66 (1.01–2.73)	0.04
Speckle-tracking echocardiography§			
LV longitudinal strain, %†	17.5±4.1	1.25 (1.03–1.52)	0.02
RV free wall strain, %†	21.1±8.1	1.30 (1.07–1.58)	0.009
LA conduit strain, %†	19.8±8.5	1.58 (1.25–2.00)	<0.001
LA booster strain, %†	18.3±7.7	1.56 (1.23–1.99)	<0.001
LA reservoir strain, %†	36.2±14.9	1.72 (1.37–2.15)	<0.001
LA stiffness index*	0.49±0.43	1.44 (1.27–1.62)	<0.001
Invasive hemodynamics (n=177)			
Right atrial pressure, mm Hg*	13±6	1.43 (1.14–1.80)	0.002
Mean PA pressure, mm Hg*	33±10	1.37 (1.08–1.72)	0.008
PCWP, mm Hg*	23±8	1.27 (1.00–1.62)	0.05
Cardiac output, L/min†	6.0±2.2	1.14 (0.87–1.50)	0.35

(Continued)

Table 2. Continued

Parameter	Total Cohort (n=308)	Hazard Ratio (95% CI)	P Value
Pulmonary vascular resistance, WU*	1.9±1.4	1.22 (1.02–1.46)	0.03
Cardiopulmonary exercise testing (n=117)			
Respiratory exchange ratio†	1.11±0.13	1.13 (0.82–1.56)	0.44
Workload, watts†	60.1±31.7	1.96 (1.29–2.98)	0.002
Exercise time, seconds†	391±252	2.06 (1.34–3.18)	0.001
Anaerobic threshold†	11.0±3.6	3.78 (1.72–8.30)	0.001
Peak VO ₂ , mL/kg per min†	13.9±5.4	2.33 (1.44–3.76)	0.001
Oxygen pulse, mL/beat†	10.8±3.85	1.59 (1.10–2.30)	0.01
V _E /VCO ₂ ratio at anaerobic threshold*	32.7±4.8	1.14 (0.81–1.59)	0.46

Summary values represent mean±SD. There were too few events to calculate hazard ratios for mild aortic stenosis or moderate aortic regurgitation. A indicates late (atrial) mitral inflow; CI, confidence interval; E, early mitral inflow; LA, left atrial; LV, left ventricular; RV, right ventricular; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure; TAPSE, tricuspid annular plane systolic excursion; WU, Wood units; V_E/VCO₂, ventilatory efficiency; and VO₂, oxygen consumption.

*Hazard ratio is per 1-SD increase.

†Hazard ratio is per 1-SD decrease.

‡All tissue Doppler values represent average of septal and lateral indices.

§All speckle-tracking measures are presented as absolute values.

invasive hemodynamic indices and CPET variables. LA reservoir strain correlated with elevated PA pressures and PVR, decreased PA compliance, and decreased resting thermodilution cardiac output, exercise workload, peak VO₂, and ventilatory efficiency.

On linear regression analyses, LA reservoir strain remained associated with PA systolic pressure and PVR after multivariable adjustment (Table 3). We did not identify any interactions between clinical characteristics (eg, comorbidities) and LA reservoir strain for the association with PA systolic pressure or PVR. Figure 2 displays the relationship between quartiles of LA reservoir strain and PVR.

On multivariable-adjusted linear regression analyses, LA reservoir strain also remained associated with thermodilution cardiac output (measured invasively) and peak VO₂ (Table 3). We found multiple significant interactions (P<0.05) for the association between LA reservoir strain and peak VO₂. The association between LA reservoir strain and peak VO₂ was much stronger in those who were younger and in the absence of chronic obstructive pulmonary disease, obesity, chronic kidney disease, and diabetes mellitus. Figure 3 displays examples of the aforementioned interactions: Figure 3A shows the relationship between LA strain and peak VO₂, stratified by median age (65 years); Figure 3B shows the same relationship stratified by the presence or absence of obesity.

Table IV in the Data Supplement shows that exclusion of patients with either atrial fibrillation (n=39) or moderate mitral regurgitation (n=36) at the time of echocardiography did not eliminate most of the associations between LA reservoir strain and invasive hemodynamic and CPET measures. LA reservoir strain was still associated with cardiac index, PVR, and peak VO₂ after multivariable adjustment.

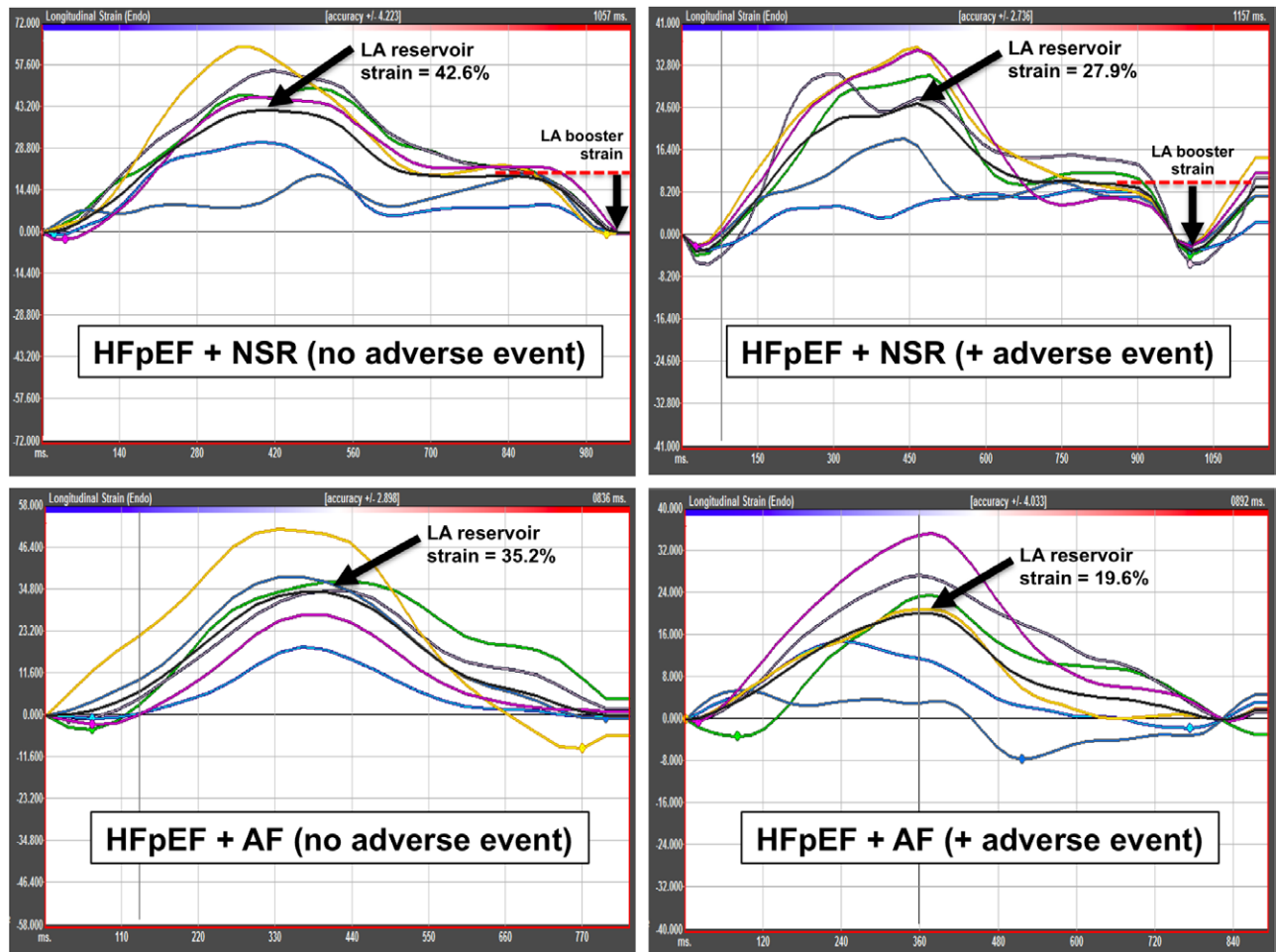


Figure 1. Representative left atrial strain images. X axis is time (ms) and Y axis is longitudinal strain (%). Note: each graph has different range for the Y axis. Left atrial (LA) booster strain is not present in the setting of atrial fibrillation (AF). LA conduit strain=LA reservoir strain–LA booster strain. In AF, LA reservoir strain=LA conduit strain. HFpEF indicates heart failure with preserved ejection fraction; and NSR, normal sinus rhythm.

Association of Indices of Cardiac Mechanics With Outcomes on Cox Regression Analysis

In unadjusted Cox proportional hazards models, all indices of cardiac mechanics were associated with adverse outcomes (Table 4). On the basis of hazard ratios per 1-SD worsening of indices of cardiac mechanics, LA reservoir strain was most closely associated with adverse events, followed by LA conduit and booster strains. After multivariable adjustment for several demographic, clinical, and echocardiographic variables (including LV and RV longitudinal strain), both LA reservoir and booster strains still remained associated with adverse outcomes. Further adjustment for the presence and severity of mitral regurgitation did not attenuate the association between LA strain and outcomes.

The relationship between LA strain measures with the composite outcome of HF hospitalization, cardiovascular hospitalization, or death was relatively linear (Figure I in the Data Supplement), especially for LA reservoir strain. Figure 4A displays the Kaplan–Meier curves for LA reservoir strain, stratified by the median value (31.2%). Figure 4B demonstrates that the Kaplan–Meier curves appeared similar when considering only patients without atrial fibrillation. Table V in the Data Supplement displays results from Cox regression analyses

after excluding patients with either atrial fibrillation or moderate mitral regurgitation at the time of echocardiography.

Incremental Prognostic Utility of Indices of Cardiac Mechanics

As shown in Table VI in the Data Supplement, LA reservoir strain outperformed LV longitudinal strain and RV free wall strain in its prognostic and discriminative utility above and beyond traditional risk markers such as the MAGGIC risk score and LA volume. LA reservoir strain had the highest relative integrated discrimination improvement and increase in the C-statistic.

Discussion

In this study of a large, contemporary cohort of patients with HFpEF, we found that all components of LA strain (LA conduit, LA booster, and LA reservoir), as determined by speckle-tracking 2D echocardiography, were predictive of cardiovascular hospitalizations (including HF hospitalization) and death. In addition, LA reservoir strain remained strongly prognostic after adjustment for atrial fibrillation, LA volume, LV mass, and the MAGGIC risk score. Even after further adjustment for LV longitudinal strain and RV free wall

Table 3. Association of Left Atrial Reservoir Strain With Selected Invasive Hemodynamic and Cardiopulmonary Exercise Testing Measures on Linear Regression Analysis

Measure (Dependent Variable)	Unadjusted		Adjusted*	
	β -Coefficient† (95% CI)	P Value	β -Coefficient† (95% CI)	P Value
PA systolic pressure, mm Hg	4.0 (1.6 to 6.4)	0.001	3.3 (0.5 to 6.0)	0.019
Cardiac output, L/min	-0.64 (-0.99, -0.29)	<0.001	-0.55 (-0.93 to -0.17)	0.005
Pulmonary vascular resistance, WU	0.47 (0.27 to 0.67)	<0.001	0.41 (0.18 to 0.64)	<0.001
Peak VO_2 , ml/kg/min	-1.9 (-2.8 to -0.9)	<0.001	-1.8 (-2.8 to -0.8)	0.001

CI indicates confidence interval; PA, pulmonary artery; VO_2 , oxygen consumption; and WU, Wood units.

*Adjusted for age, sex, obesity, atrial fibrillation, left atrial volume, left ventricular mass, and E/e' ratio.

†Per 1-SD decrease (worsening) in left atrial reservoir strain.

strain, LA reservoir strain still retained its prognostic value. In addition, LA reservoir strain was more closely associated with PVR and VO_2 than LV and RV strain. To our knowledge, our study is the first to clearly demonstrate the central clinical and prognostic importance of LA strain in HFpEF, above and beyond LV or LA structure, LV strain, and RV strain.

Prognostic Value of LA Function Compared With LA Size in HFpEF

Although multiple studies have provided evidence of the value of LA function for the diagnosis of HFpEF^{5,9} and the role LA function plays in the pathophysiology of HFpEF,^{16,17} our study is the first to show the powerful prognostic role of LA strain in this patient population. Earlier publications showed that indexed LA volume is a robust correlate of adverse events including incident HF in patients with normal LVEF¹⁸ and incident atrial arrhythmia in people aged ≥ 65 years.¹⁹ However, these studies did not measure LA function using speckle-tracking analysis.

Our data are consistent with these recent publications and build on it by showing the improved ability of LA strain to predict adverse outcomes in patients with HFpEF when compared with LA size. This result underscores the idea that indexed LA volume is simply a surrogate of LV filling pressures and more accurately reflects an adaptive change to the increased pressure rather than the intrinsic LA myocardial abnormalities that occur with HFpEF. This is particularly true in our patient population in which the overall severity of symptoms (46% NYHA class III) and enlarged LA in the majority of patients (67%) makes LA size alone a relatively poor marker for predicting adverse events.

Prognostic Value of LA Function Compared With Other Strain Measures

We also found that in patients with HFpEF, speckle-tracking strain of the LA is a more powerful correlate of adverse outcomes than LV and RV longitudinal strain. Using a variety of metrics, we show convincingly that of the speckle-tracking indices of longitudinal cardiac mechanics, LA strain is most associated with future risk of adverse events. Although exclusion of patients with moderate mitral regurgitation and atrial fibrillation attenuated the significant association between LA strain and adverse outcomes in the fully adjusted multivariable analysis (model 3), LA booster and reservoir strains were still associated with adverse outcomes after adjustment for all variables except LV and RV longitudinal strains (model

2) in this subgroup. Furthermore, LA reservoir strain in this subgroup retained significance in a model including only LA reservoir strain, LV longitudinal strain, and RV free wall strain ($P < 0.001$ on Cox regression analyses).

Only 1 previous study compared the prognostic roles of LA and LV strain using speckle-tracking echocardiography.²⁰ This study demonstrated that LV longitudinal strain was a better correlate of death and cardiovascular hospitalization than LA function in patients with acute myocardial infarction. The different patient populations studied most likely explain the discrepancy in these results as ischemia affects LV longitudinal strain to a greater extent in patients with acute myocardial infarction than in patients with HFpEF.

The finding that LA strain is a more powerful correlate of outcomes than LV and RV longitudinal strain is meaningful because multiple pathophysiologic factors contribute to the HFpEF syndrome.²¹ LA reservoir function is considerably influenced by LA relaxation and compliance. In HFpEF, myocardial fibrosis of the LA likely plays a significant role in disease progression as it does in patients with atrial fibrillation²² and severe mitral regurgitation.²³ This is evident in our study by the significantly higher LA stiffness index in patients who experienced adverse events during follow-up. The subsequent remodeling of the LA myocardium decreases LA compliance and blunts LA reservoir function in response to increases in preload.⁹

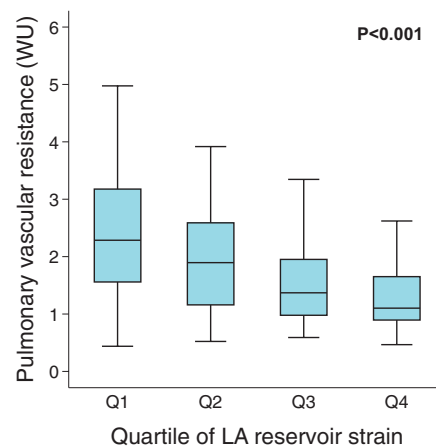


Figure 2. Box-and-whisker plots of pulmonary vascular resistance by quartiles of left atrial (LA) reservoir strain. Quartiles of LA reservoir strain correspond to the following values: Q1 < 22.2%, Q2 = 22.2% to 31.1%, Q3 = 31.2% to 42.8%, and Q4 > 42.9%. WU indicates Wood units.

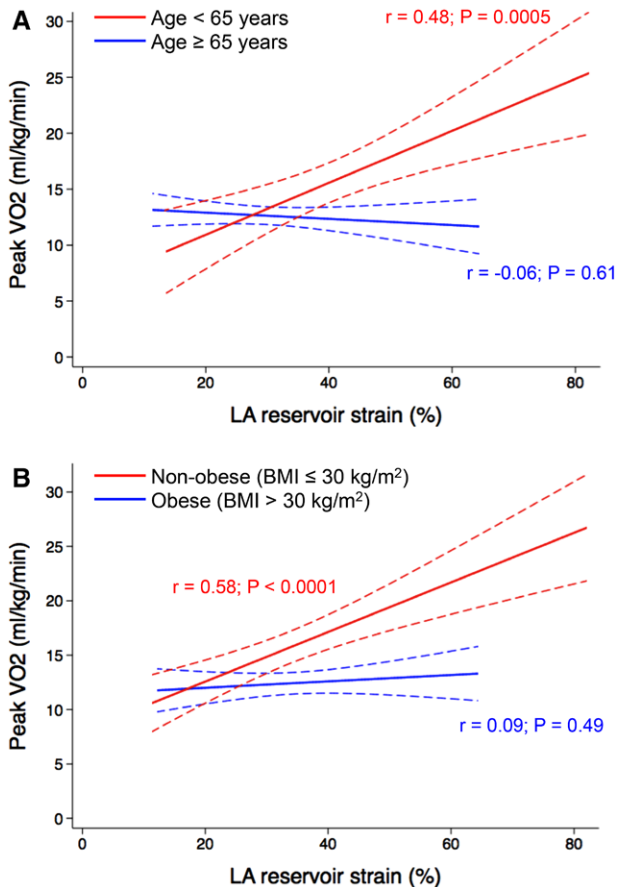


Figure 3. Relationship between left atrial (LA) reservoir strain and peak oxygen consumption (VO_2) stratified by (A) median age (65 y) and (B) presence or absence of obesity. Lines represent linear fit of the relationship between LA reservoir strain and peak oxygen consumption (dotted lines represent 95% confidence intervals). BMI indicates body mass index.

Abnormal LA Function: A Key Stimulus for Elevated PVR and Reduced Exercise Capacity in HFpEF

Several pathophysiologies exist in patients with HFpEF, and each of these may result in reduced exercise capacity and

worse outcomes. HFpEF patients with elevated PVR and right HF are particularly vulnerable to worse outcomes, and the factors that lead to these pathophysiologic abnormalities are unclear. Our study indicates that abnormal LA mechanics, more so than E/e' ratio or LA volume, may be indicative of significant chronic LA pressure and volume overload with subsequent chronic pulmonary venous congestion, ultimately resulting in pulmonary vasoconstriction and decreased PA compliance. In a smaller study ($n=101$) that examined LA EF in HFpEF, Melenovsky et al²⁴ also found an association between LA function and PVR; however, this study did not control for E/e' or LA volume, did not measure LA strain, and did not compare LA mechanics to LV mechanics in relationship to PVR. In addition, because of the smaller number of patients, this study was limited by an inability to perform multivariable adjustment for LA size or history of atrial fibrillation.

The association of LA reservoir strain and peak VO_2 suggests that worse LA mechanics leads to poor augmentation of cardiac output with exertion and decreased exercise tolerance. As shown in Figure 3, the results of our statistical interaction testing analysis demonstrate abnormal LA mechanics is especially important in younger patients with less comorbidities because these individuals are less likely to have extracardiac reasons for exercise intolerance (such as aging-related musculoskeletal problems or obesity).

Potential Therapeutic Implications of LA Dysfunction in HFpEF

The findings of our study point to a potential central role of abnormal LA mechanics in the HFpEF syndrome. Speckle-tracking LA strain measures, already known to be useful for the diagnosis of HFpEF, may also be useful in understanding responsiveness to pharmacological and device-based therapies. Indeed, in response to the growing recognition of the critical role the LA plays in the pathophysiology of HFpEF, new devices to unload and decompress the LA are increasingly becoming available. An interatrial shunt device to decrease LA pressure is currently being studied in controlled

Table 4. Association of Indices of Cardiac Mechanics With the Combined Outcome of Cardiovascular Hospitalization, Heart Failure Hospitalization, or Death in Heart Failure With Preserved Ejection Fraction

Independent Variable	Unadjusted		Adjusted (Model 1)		Adjusted (Model 2)		Adjusted (Model 3)	
	HR* (95% CI)	P Value	HR* (95% CI)	P Value	HR* (95% CI)	P Value	HR* (95% CI)	P Value
LV longitudinal strain	1.25 (1.03–1.52)	0.023	1.18 (0.97–1.45)	0.10	1.17 (0.95–1.43)	0.13
RV free wall strain	1.30 (1.07–1.58)	0.009	1.20 (0.98–1.02)	0.08	1.19 (0.97–1.47)	0.10
LA conduit strain	1.74 (1.35–2.24)	<0.001	1.42 (1.07–1.87)	0.013	1.33 (1.00–1.76)	0.05	1.22 (0.91–1.84)	0.18
LA booster strain	1.56 (1.23–1.99)	<0.001	1.45 (1.12–1.88)	0.004	1.40 (1.08–1.82)	0.01	1.33 (1.01–1.73)	0.04
LA reservoir strain	1.72 (1.37–2.15)	<0.001	1.63 (1.22–2.19)	0.001	1.54 (1.15–2.07)	0.006	1.43 (1.05–1.95)	0.02
LA stiffness index†	1.44 (1.27–1.63)	<0.001	1.44 (1.22–1.70)	<0.001	1.39 (1.17–1.66)	<0.001

Model 1 adjusts for sex; atrial fibrillation; Meta-Analysis Global Group in Chronic Heart Failure risk score (which includes the following variables: age, ejection fraction, creatinine, diabetes mellitus, chronic obstructive pulmonary disease, systolic blood pressure, body mass index, heart rate, New York Heart Association functional class, angiotensin-converting enzyme inhibitor use, β -blocker use, heart failure duration, and current smoker); LV mass; and LA volume. model 2 adjusts for model 1 variables+ E/e' ratio (average of septal and lateral E/e' ratios). model 3 adjusts for model 2 variables+LV longitudinal strain and RV free wall strain. CI indicates confidence interval; HR, hazard ratio; LA, left atrial; LV, left ventricular; and RV, right ventricular.

*Per 1-SD decrease in each strain variable; all strain values are presented as absolute values (thus, a decrease in each independent variable indicates worse strain). For LA stiffness index, HRs are per 1-SD increase in the independent variable.

†LA stiffness index= $E/e' \div$ LA reservoir strain; thus, model 2 (which adjusts for E/e' ratio) does not apply to LA stiffness index because E/e' is used to calculate the LA stiffness index, and model 3 for the LA stiffness index includes LV longitudinal strain and RV free wall strain but does not include E/e' .

trials.²⁵ Another potential therapeutic strategy in advanced HFpEF patients is a LA assist device.²⁶ Additional study is necessary to determine whether improvement in LA mechanics could lead to decreased PVR, increased cardiac output, and increased exercise capacity.

Strengths and Limitations

The strengths of our study include the prospective and standardized recruitment of high-risk patients with HFpEF, the large number of patients included in the final analysis (with high feasibility of speckle-tracking echocardiography), and the prognostic comparison of LA strain with LV and RV strain measures. Furthermore, in relatively large subsets of patients, we were able to examine the associations between LA strain measures and invasive hemodynamics and CPET variables, thereby providing pathophysiological insight into the importance of LA strain in HFpEF. Finally, the sample size and number of events allowed us to perform comprehensive multivariable adjustment to clearly show the prognostic utility of LA mechanics in HFpEF.

Nevertheless, certain limitations should also be considered when interpreting our results. First, strain acquisition was not possible in 55 patients. However, we were able to perform

speckle-tracking analysis on the majority (85%) of the study participants and reproducibility was excellent. Strain analysis was also performed by averaging all 6 segments of the LA endocardium in only 2 imaging planes. Other studies have used 3 imaging planes, and some have consistently excluded the posterior LA. Currently, there is no standardization of LA strain acquisition. Three-dimensional speckle-tracking strain might have overcome some of the limitations in LA strain analysis, but this technique is not widely used, and there are limited data to support the use of this method. Second, the cutoff values for abnormal strain values—particularly for LA strain using TomTec software—are not well defined, and our study did not include a control group. Thus, the prevalences of abnormal LV, RV, and LA strain in our cohort should be interpreted with caution. Third, patients with either atrial fibrillation or moderate mitral regurgitation, both of which can affect LA mechanics, were included in our primary analyses. However, we adjusted for these factors in our multivariable analyses, and the associations of LA strain with PVR, peak VO_2 , and adverse outcomes persisted. In addition, we performed sensitivity analyses after excluding patients with atrial fibrillation or moderate mitral regurgitation at the time of echocardiography. Finally, the associations identified in the present study cannot prove causation given our study design and the possibility of unmeasured confounders in regression analyses.

Conclusions

In patients with HFpEF, indices of LA mechanics—particularly LA reservoir strain—are independently associated with adverse outcomes. LA reservoir strain is the speckle-tracking measure most associated with elevated PVR, decreased cardiac output, reduced exercise capacity, and the increased risk of the combined end point of cardiovascular hospitalization or death. Given these findings, novel therapeutic options for unloading the LA and augmenting its function may be beneficial in HFpEF.

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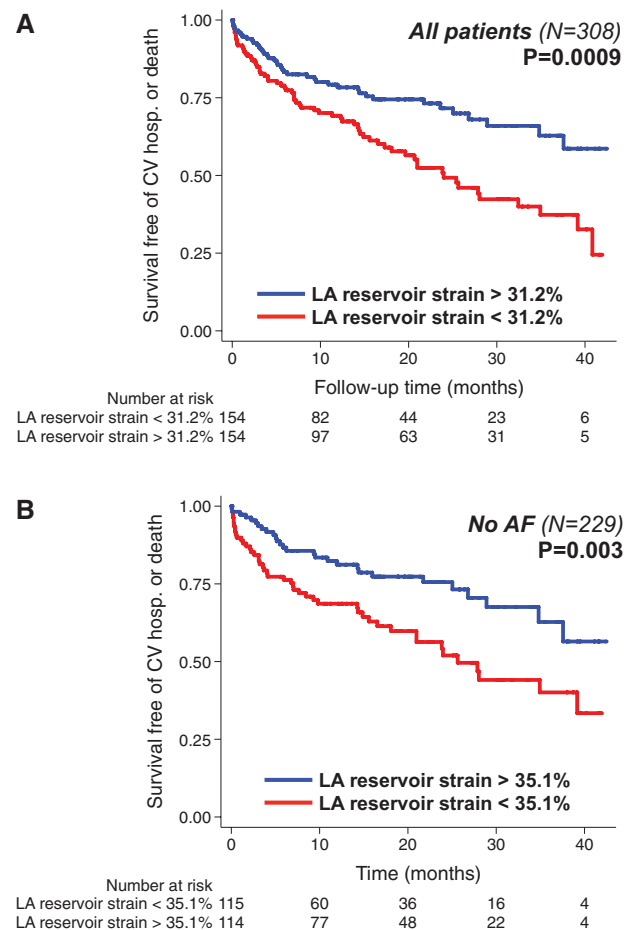


Figure 4. Kaplan–Meier curves for survival free of cardiovascular (CV) hospitalization (hosp.; including heart failure hospitalization or death), stratified by median left atrial (LA) reservoir strain (**A**) in all patients and (**B**) after excluding patients with a history of atrial fibrillation (AF).

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CLINICAL PERSPECTIVE

Effective treatment for patients with heart failure with preserved ejection fraction remains elusive, in part, because of the myriad pathophysiologies that define this syndrome. One common clinic characteristic is left atrial (LA) enlargement because of decreased left ventricular (LV) compliance and increased LV filling pressure. Although not required for the diagnosis of heart failure with preserved ejection fraction, previous studies have demonstrated the prognostic utility of LA size in this patient population. However, less is known about the role of LA mechanics (which may be more important than LA size) in heart failure with preserved ejection fraction. Using speckle-tracking echocardiography for the measurement of cardiac mechanics, our study shows that reduced LA strain (indicating worse LA mechanics) is a key pathophysiologic abnormality that is associated with a worse clinical profile, higher pulmonary vascular resistance, decreased peak oxygen consumption, and worse outcomes—above and beyond abnormalities in LV and right ventricular mechanics. These findings suggest that improving LA function may be an important therapeutic target in this challenging syndrome. Specifically, speckle-tracking LA strain parameters, already known to be useful for the diagnosis of heart failure with preserved ejection fraction, may also be useful in understanding responsiveness to therapies that unload and decompress the LA.