Impaired Systolic Function by Strain Imaging in Heart Failure With Preserved Ejection Fraction

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Objectives
This study sought to determine the frequency and magnitude of impaired systolic deformation in heart failure with preserved ejection fraction (HFpEF).

Background
Although diastolic dysfunction is widely considered a key pathophysiologic mediator of HFpEF, the prevalence of concomitant systolic dysfunction has not been clearly defined.

Methods
We assessed myocardial systolic and diastolic function in 219 HFpEF patients from a contemporary HFpEF clinical trial. Myocardial deformation was assessed using a vendor-independent 2-dimensional speckle-tracking software. The frequency and severity of impaired deformation was assessed in HFpEF, and compared to 50 normal controls free of cardiovascular disease and to 44 age- and sex-matched hypertensive patients with diastolic dysfunction (hypertensive heart disease) but no HF. Among HFpEF patients, clinical, echocardiographic, and biomarker correlates of left ventricular strain were determined.

Results
The HFpEF patients had preserved left ventricular ejection fraction and evidence of diastolic dysfunction. Compared to both normal controls and hypertensive heart disease patients, the HFpEF patients demonstrated significantly lower longitudinal strain (LS) (−20.0 ± 2.1 and −17.07 ± 2.04 vs. −14.6 ± 3.3, respectively, p < 0.0001 for both) and circumferential strain (CS) (−27.1 ± 3.1 and −30.1 ± 3.5 vs. −22.9 ± 5.9, respectively; p < 0.0001 for both). In HFpEF, both LS and CS were related to LVEF (LS, R = −0.46; p < 0.0001; CS, R = −0.51; p < 0.0001) but not to standard echocardiographic measures of diastolic function (E’ or E/E’). Lower LS was modestly associated with higher NT-proBNP, even after adjustment for 10 baseline covariates including LVEF, measures of diastolic function, and LV filling pressure (multivariable adjusted p = 0.001).

Conclusions
Strain imaging detects impaired systolic function despite preserved global LVEF in HFpEF that may contribute to the pathophysiology of the HFpEF syndrome. (LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction; NCT00887588) (J Am Coll Cardiol 2014;63:447–56 © 2014 by the American College of Cardiology Foundation)
strategies by defining subphenotypes in this heterogeneous population. Indeed, prior studies suggest that LV longitudinal function assessed by tissue Doppler imaging may be impaired in HFP EF (6–11). However, tissue Doppler-based assessment of LV longitudinal function is angle dependent and typically assesses only mitral annular motion.

More recently, B-mode speckle tracking has allowed for quantitative assessment of LV deformation, and abnormalities of strain and strain rate have been described in HFpEF in several single-center studies (12–15). We employed myocardial deformation imaging to determine the frequency, severity, and correlates of impaired systolic function among patients with HFpEF enrolled in a contemporary multicenter clinical trial. Specifically, we hypothesized that despite preserved LVEF, abnormal strain would be prevalent in HFpEF, differentiate HFpEF from asymptomatic hypertensive heart disease (HHD), and would relate to levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a soluble biomarker of myocardial wall stress with prognostic relevance in HFpEF, independent of measures of diastolic function.

Methods

Patient population. The PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction Trial) study enrolled patients with signs and symptoms of heart failure (HF), New York Heart Association class II to IV symptoms, LVEF ≥45%, and NT-proBNP level >400 pg/ml. Patients were randomly allocated to receive either the angiotensin-receptor neprilysin inhibitor (ARNI) LCZ696 or valsartan over a period of 12 weeks. The study protocol was approved by all individual site institutional review boards and ethics committees, and all recruited patients gave written informed consent. Details of the inclusion and exclusion criteria, study design, and primary findings have been previously published (18,19). Briefly, the EXCEED trial was a multicenter, open-label study of patients ≥45 years of age with a history of uncontrolled systolic hypertension, preserved LVEF (≥50%), and echocardiographic evidence of diastolic dysfunction. Patients with HF symptoms, secondary hypertension, diabetes, atrial fibrillation, a vascular event within the prior 6 months, serum creatinine >2.0 mg/dl, or nephrotic syndrome were excluded. All participants underwent echocardiography at enrollment, which was analyzed centrally by the same core laboratory as the PARAMOUNT study (Brigham and Women’s Hospital, Boston, Massachusetts).

Echocardiographic analyses. All sonographers at participating sites underwent central training in the details of the echocardiographic views and techniques at study investigator meetings. Echocardiograms were performed at study enrollment and were sent on digital storage media to the echocardiography core laboratory at Brigham and Women’s Hospital. Conventional echocardiographic analysis including 2-dimensional, Doppler, and tissue Doppler were performed by technicians blinded to clinical information and treatment assignment using an offline analysis work station, as previously described in detail (20). Ventricular volumes were calculated by the modified Simpson’s method using the apical 4- and 2-chamber views, and LVEF was derived from volumes in the standard manner (17). The LV mass was calculated from LV linear dimensions and indexed to body surface area as recommended by American Society of Echocardiography guidelines. Left ventricular hypertrophy was defined as LV mass indexed to body surface area (LVMi) >115 g/m² in men or >95 g/m² in women. The relative wall thickness (RWT) was calculated from LV end-diastolic dimension and posterior wall thickness. The left atrial (LA) volume was measured by the biplane
area-length method using apical 4- and 2-chamber views at
the end-systolic frame preceding mitral valve opening, and
was indexed to body surface area to derive LAVi. Early
transmitral velocity (E wave) was measured by pulsed wave
Doppler from the apical 4-chamber view with the sample
volume positioned at the tip of the mitral leaflets. Tissue
Doppler derived peak longitudinal systolic shortening
velocity (S') was obtained in the apical 4-chamber view at
the lateral and septal mitral annulus and averaged. Peak left
ventricular relaxation velocity (E') was obtained from the
lateral and septal mitral annulus and averaged. The E/E'
ratio was calculated as E wave divided by E' velocities.
Diastolic dysfunction grade was derived from mitral inflow
E/A ratio, tissue Doppler septal E', and deceleration time
(21). All measurements were performed in triplicate.

Digitally acquired baseline echocardiography images
in Digital Imaging and Communications in Medicine
(DICOM) format with acceptable image quality were
uploaded to the TomTec system (Munich, Germany) for
further deformational analyses (Cardiac Performance
Analysis software, TomTec). These methods have been validated
against magnetic resonance imaging and sonomicrometry
(22,23), and we have previously reported excellent repro-
ducibility (24–26). A total of 219 patients of the total
PARAMOUNT patient population of 301 participants
(73% of total enrolled) had adequate echocardiographic
image quality for deformational analysis by B-mode speckle
tracking. Unacceptable image quality was defined as lack of
a full cardiac cycle, >1 segment dropout, digital format other
than DICOM, missing view, or significant foreshortening
of the left ventricle. As compared to the 219 patients with
image quality adequate for strain analysis, the 82 excluded
patients were less frequently female (45% vs. 61%), had
a lower prevalence of chronic obstructive pulmonary disease
(6% vs. 16%), a higher prevalence of diabetes (49% vs. 34%),
and a lower LVEF (56% vs. 59%, p = 0.006). No significant
differences were noted in other clinical or echocardiographic
measures, including age, NT-proBNP level, LV mass index,
LAVi, E', and E/E'. (Detailed information on included
and excluded patients are given in Online Table S1.)

For deformation analysis, endocardial borders were traced
at the end-diastolic frame in apical views and at an end-
systolic frame in short-axis views. End diastole was
defined by the QRS complex or as the frame after mitral
valve closure. The software tracks speckles along the endo-
cardial border throughout the cardiac cycle. Peak longitu-
dinal strain (LS) and peak circumferential strain (CS) were
computed automatically generating regional data from 6
segments and an average value for each view. For patients
in sinus rhythm, analyses were performed on a single cardiac
cycle; and for patients in atrial fibrillation, strain values were
calculated as the average of 3 cardiac cycles. Peak average LS
was measured in the apical 4-chamber and apical 2-chamber
views (in 6 segments from each view) and averaged, and
peak average CS was obtained from 6 segments measured in
the short-axis view at the midpapillary level.

All strain analysis on HFpEF, HHD, and normal control
subjects were performed by a single investigator. Intra-
observer variability for LS and CS was assessed in a sample
of 30 randomly selected patients. Coefficient of variation
was 6.8% and 8.1% for LS and CS, respectively. Intraclass
correlation coefficients were 0.95 for LS (95% confidence
interval: 0.91 to 0.98) and 0.94 for CS (95% confidence
interval: 0.91 to 0.98).

Statistical analyses. Descriptive statistics for continuous
variables are expressed as mean and standard deviation for
normally distributed variables and median and interquartile
range for non-normally distributed data. Categorical variables
are presented as percentages. Comparison of echocardiographic
measures between HFpEF versus HHD and normal controls
was performed using Student t tests, Wilcoxon rank-sum tests,
or chi-square tests, as appropriate. The relationship between
average LS and CS and clinical characteristics, echocardi-
ographic measures, electrocardiographic parameters, and
NT-proBNP was assessed using linear regression or non-
parametric trend tests. Abnormal LS and CS was defined as
>1 SD or ≥2 SD below the mean value of normal controls.

The NT-proBNP was log-transformed due to its skewed
distribution. Pearson correlation coefficient was used to
assess the relationships between log-transformed NT-
proBNP and strain measures. Multivariable linear regression
was used to determine the relationship between strain
measures and NT-proBNP after adjustment for potential
confounders. All p values were 2-sided, with p < 0.05 used
to define statistical significance. Statistical analyses were
performed using STATA version 11.2 (Stata Corp., College
Station, Texas).

Results

Of 301 patients randomized in the PARAMOUNT study,
219 (73%) had echocardiographic images in appropriate
format and of adequate quality for speckle-tracking analysis
(Online Table S1). Baseline patient characteristics of the
219 included patients are summarized in Table 1. The
average age was 71 ± 9 years, and the majority of patients
were female, white, and had a history of hypertension. Half
had a history of prior HF hospitalization. In addition
to diuretic use (100%), which was a required inclusion
criterion, rates of therapy with an angiotensin-converting
enzyme inhibitor or angiotensin-receptor blocker (92%)
and beta-blockers (80%) were high. The median NT-
proBNP level was markedly elevated (894 pg/ml, inter-
quartile range: 526 to 1,457 pg/ml).

Among the normal control group (n = 50), the mean age
was 69 ± 7 years, 68% were female, the majority was
white, and their mean body mass index was 25.9 ± 3.9 kg/m².
All patients in the control group were free of hypertension,
diabetes, hyperlipidemia, smoking, coronary artery disease,
and structural or valvular heart disease, and were not taking
any cardiovascular medication. Echocardiographic analysis
showed normal-sized ventricles, wall thickness, and left
among the 44 age- and sex-matched HHD patients, the average age was 71 ± 8, 61% were female, the majority was white, and their mean body mass index was 28.5 ± 4.8 kg/m². Mean blood pressure was 165/85 mm Hg. Echocardiographic analysis showed normal-sized ventricles (mean left ventricular end-diastolic volume 100 ± 17 ml) with preserved LVEF (mean 56 ± 3%). The LV mass index was 73.5 ± 16.1 g/m². By definition, all patients had evidence of diastolic dysfunction with a mean E/E' of 9.4 ± 2.2 and LAVi of 26.6 ± 3.7 ml/m². (A comprehensive summary of clinical and echocardiographic characteristics of the normal control, the HHD, and the HFPpEF group is provided in Online Table S2.)
Conventional 2-dimensional and Doppler echocardiographic findings in the overall HFpEF cohort are shown in Table 1. Diastolic dysfunction was present in 95% of patients, with 66% having grade II or III diastolic dysfunction. Median septal E/E' was 14.7 (11.5–18.8) and two-thirds presented with enlarged left atria using a cutoff of 29 ml/m² (median LAVi 33.9 (26.8–43.0) ml/m²) (19). Despite the high prevalence of diastolic abnormalities and signs of increased LV filling pressure, LV volumes, mass, and geometry were normal in most subjects, with only 15% demonstrating LV hypertrophy and 21% demonstrating concentric remodeling or hypertrophy.

**HFpEF versus controls.** Although global systolic pump function (LVEF) did not differ significantly between the PARAMOUNT study patients and normal controls (59 ± 8% versus 61 ± 3%, respectively; p = 0.09), HFpEF patients demonstrated significantly lower LS and CS (LS, p < 0.0001; CS, p < 0.0001) (Fig. 1, Table 2). We observed a relationship between LVEF and both LS (Pearson correlation = −0.46, p < 0.001) and CS (Pearson correlation = −0.51, p < 0.001). However, both LS and CS remained significantly lower among HFpEF patients compared to controls after adjusting for LVEF (p < 0.001 for both LS and CS) (Fig. 1, Table 2) and after excluding subjects with LVEF <55% (p < 0.0001 for LS, p = 0.0002 for CS). Patients with evidence of ischemic heart disease had worse LS and CS as compared to those HFpEF patients without ischemic heart disease.

To further investigate the role of ischemic heart disease in the observed differences in LV deformation, we performed a sensitivity analysis excluding all patients with a history of myocardial infarction, coronary artery disease, revascularization procedures, and anginal symptoms, and all patients with an LVEF <55%. In the remaining 91 patients without any evidence of myocardial ischemia and an LVEF ≥55%, both LS and CS remained significantly lower as compared to controls (HFpEF vs. controls: LS, −15.7 [−18.0 to −13.8] vs. −19.9 [−21.3 to −18.3], p < 0.0001; CS, −24.2 [−29.0 to −20.4] vs. −26.9 [−28.5 to −25.0], p = 0.0007).

**HFpEF versus HHD.** Compared to HHD, the HFpEF group demonstrated significantly lower LS (p < 0.0001) and CS (p < 0.0001) (Fig. 1, Table 2). Interestingly, when compared to controls, the HHD group demonstrated significantly lower LS (p < 0.0001) but higher CS (p < 0.0001).

**Prevalence of abnormal strain in HFpEF.** Abnormal LS and CS was present in 66.7% and 40.4% of HFpEF patients, respectively, when abnormal was defined as >2 SD below the mean value of controls (Table 2). In analyses stratified by LVEF (<50%, 50% to 55%, and >55%), the proportion of patients with abnormal LS and CS was greatest in the lowest LVEF category. The LS was more frequently abnormal than the CS, a pattern that held across all LVEF categories (Table 2). The magnitude of...
Impaired Systolic Strain in HFpEF

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Kraigher-Krainer

Table 2 Percentage of Patients With Abnormal Strain*

<table>
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<td>27.1 ± 6.0</td>
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Longitudinal strain in HFpEF. Worse LS was significantly associated with nonwhite race, a history of HF hospitalization, higher heart rate, ischemic etiologic, and lower LVEF (Table 1). No significant association was noted between LS and sex, cardiovascular comorbidities, or pharmacotherapy. Importantly, LS was not associated with systolic or diastolic blood pressure, and 70% of patients with normal blood pressure at the time of echocardiography had abnormal LS. Worse LS was significantly associated with lower LVEF (p < 0.001), stroke volume (p = 0.003), and S' (p = 0.009). The association with LVEF remained significant when LVEF was stratified into categories (LVEF <50%, p < 0.001; LVEF 50% to 55%, p = 0.005; LVEF >55%, p < 0.001) (Table 1). Worse LS was also associated with higher LV end-systolic volume index (p < 0.001), LV end-diastolic volume index (p = 0.03), and LV mass index (p = 0.04). There was no association between LS and echocardiographic measures of diastolic function (Table 1).

Circumferential strain in HFpEF. Patients with worse CS were more likely to have a history of HF hospitalization, coronary heart disease, and prior myocardial infarction. Worse CS was also associated with lower systolic blood pressure but not with age, race, or heart rate. Like LS, lower CS was associated with lower LVEF, lower stroke volume, and higher LV end-systolic volume index. The association with LVEF remained significant after stratification by LVEF category (LVEF <50%, p < 0.001; LVEF 50% to 55%, p = 0.012; LVEF >55%, p < 0.001) (Table 3). There was no association between CS and S' (p = 0.40). Similar to LS, there was no association between CS and measures of diastolic function. The CS was related to LV geometry, with worse CS being significantly related to lower RWT (Table 3). Similarly, in a multivariable model accounting for clinical covariates and echocardiographic measures of cardiac structure and function, LV mass index was significantly associated with CS (p = 0.02).

Association of strain and NT-proBNP. Worse LS (modeled both as categorical variable in quartiles and continuously) was associated with higher NT-proBNP levels, both when modeled continuously (Pearson correlation 0.20, p = 0.005) (Fig. 2) and categorically (as quartiles; p for trend = 0.005). The inverse relationship between LS and NT-proBNP remained significant after adjusting for age, sex, systolic and diastolic blood pressure, body mass index, LVEF, LAVi, E/E', atrial fibrillation, and estimated glomerular filtration rate (adjusted p = 0.001). This robust relationship also remained significant when adjusting for E' instead of E/E' (p = 0.001) or when adding E' (p = 0.001) or S' (p = 0.002) to the model. In contrast to LS, contemporary measures of diastolic function (E' and LAVi) were not independently associated with NT-proBNP, nor...
was a history of ischemic heart disease or presence of EF <55%. The inverse association of LS with NT-proBNP, however, remained significant in the subgroup of patients without ischemic heart disease and with EF ≥55%. The CS was not associated with NT-proBNP.

**Discussion**

**Principal findings.** This study of 219 patients with HFpEF enrolled in a contemporary international multicenter clinical trial has 3 major findings. First, LV LS and CS are significantly reduced in HFpEF compared to normal controls and to age- and sex-matched hypertensive patients with diastolic dysfunction. Second, the prevalence of reduced LS and CS in HFpEF is high. Although LS and CS are significantly related to LVEF, the impairment in LS and CS in HFpEF persists even when restricted to patients with EF >55% or to patients without coronary heart disease. More than half of HFpEF patients with an LVEF ≥55% had reduced LS. Neither LS nor CS were significantly related to LVEF, the impairment in LS and CS in HFpEF persists even when restricted to patients with EF >55% or to patients without coronary heart disease. More than half of HFpEF patients with an LVEF ≥55% had reduced LS. Neither LS nor CS were significantly related to LVEF, the impairment in LS and CS in HFpEF persists even when restricted to patients with EF >55% or to patients without coronary heart disease. More than half of HFpEF patients with an LVEF ≥55% had reduced LS. Neither LS nor CS were significantly related to LVEF, the impairment in LS and CS in HFpEF persists even when restricted to patients with EF >55% or to patients without coronary heart disease. More than half of HFpEF patients with an LVEF ≥55% had reduced LS.
related to standard echocardiographic measures of diastolic function (E' or E/E'). Third, LS is significantly and independently associated with NT-proBNP level, a prognostically relevant biomarker in HFpEF.

Systolic dysfunction in HFpEF. Although LVEF is the most commonly used and accepted measure of systolic function, it is highly load dependent and relatively insensitive to subtle abnormalities of LV function (8,27). Indeed, some studies involving select HFpEF patients have failed to demonstrate abnormalities in systolic performance, reflected in stroke work, preload recruitable stroke work, and peak (+)dP/dt (28). In contrast, several other studies evaluating multiple noninvasive measures of LV systolic function by standard echocardiographic techniques, such as LV midwall fractional shortening or mitral annular plane systolic displacement, indicate that systolic function may not be uniformly normal in HFpEF (11,29). The reason for these discrepancies are unclear but may be related to the systolic measures evaluated and differences in the HFpEF patients studied. Early data employing tissue Doppler suggest that longitudinal systolic function may be abnormal despite preserved LVEF in conditions predisposing to HF and in HFpEF (6,11). However, tissue Doppler imaging faces technical limitations including preload and afterload dependence and is limited in its ability to assesses different planes of LV deformation other than longitudinal (30). In addition, prior studies in HFpEF have been largely limited to single-center experiences with small series of select patients (12–15).

Speckle-tracking echocardiography is a relatively new technique, largely independent of angle of incidence, tethering, and cardiac translation, which allows for quantification of myocardial deformation in multiple planes. During systole, the components of LV deformation include longitudinal shortening, radial thickening, and circumferential shortening (31). These planes of deformation are thought to be related to LV myocardial fiber orientation, which is primarily in the longitudinal direction subendocardially and primarily in an oblique orientation subepicardially (32). Our findings demonstrate a high prevalence of impaired LV longitudinal function in HFpEF, even among patients with LVEF >55%, with worse LS significantly related to higher NT-proBNP levels even after adjusting for LVEF and diastolic measures. NT-proBNP is a powerful prognostic discriminator in HFpEF (33). Longitudinal strain predicts outcome in low LVEF patients independent of LVEF (24,25). Whether impaired longitudinal deformation has prognostic significance in HFpEF remains to be determined.

Our data further suggest impairment in LV circumferential deformation in HFpEF. Conditions predisposing to HFpEF, such as hypertension or diabetes, are characterized by reduced longitudinal strain but an increase in circumferential function (34–36), which has been proposed as a compensatory mechanism to preserve LVEF (37). Our findings suggest that reduced LV CS partially distinguishes patients with HFpEF from asymptomatic persons with similar comorbidities. This hypothesis is also supported by prior studies demonstrating a progressive decrease of global CS from normal to HFpEF to HFrEF groups even after adjustment for LV end-systolic wall stress (12).

The underlying pathophysiology in patients with HFpEF has been commonly believed to involve impairment of diastolic function, with increased passive chamber stiffness (38,39). However, the marked phenotypic and pathophysiologic heterogeneity characterizing this syndrome is now well recognized. Traditional noninvasive markers of diastolic dysfunction are absent in approximately one-third of patients enrolled in large HFpEF trials (40,41). Indeed, in the PARAMOUNT trial, although the majority of patients demonstrated some echocardiographic findings of diastolic abnormalities at rest, frankly elevated filling pressure—based on an E/E' ratio $\geq$15—was present in only 49% of the patients. Similarly, the prevalence of concentric ventricular remodeling was very low. These observations suggest that abnormalities other than concentric hypertrophy and elevated filling pressure (assessed as E/E' $\geq$15 at rest) may contribute to the pathogenesis of HFpEF. Our findings of lower LV strain, a measure of LV systolic function that was not correlated with diastolic indices, and its independent association with NT-proBNP suggest a contribution of systolic dysfunction despite preserved LVEF in at least a subset of patients with HFpEF.

Study limitations. Strain analysis was not possible in all patients enrolled in the PARAMOUNT trial, although no significant systematic differences were noted between patients included or excluded from this analysis. Studies were
performed at 65 sites and on echocardiography machines from a variety of vendors. However, all studies were recorded digitally, and quantitative analysis was performed centrally at a blinded core laboratory. All echocardiograms were performed in a resting condition, which limits the ability to assess the relationship between LS and impaired functional capacity, an important hallmark of the HFpEF syndrome. Patients enrolled in this contemporary HFpEF clinical trial may not be representative of HFpEF patients in the community, because of specific clinical trial inclusion and exclusion criteria. Future studies with clinical outcomes will be essential to understand the clinical relevance of our findings.

Conclusions

Systolic impairment in LV longitudinal and circumferential deformation is prevalent in HFpEF. Worse LS, in particular, is associated with higher NT-proBNP. Our findings suggest that abnormalities of LV systolic function measured by strain imaging may contribute to the HFpEF syndrome. These findings may help inform future studies to identify pathophysiologically relevant subgroups of patients within this heterogeneous syndrome.

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For supplemental tables, please see the online version of this article.