The Left Atrial and Right Ventricular Strain by Speckle Tracking Echocardiography in Patients with HFpEF

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KEYWORDS

Heart failure; Heart failure, Ejection fraction; Longitudinal strain; Left atrial strain; Right ventricular strain; H2FPEF.

ABSTRACT

Background: Myocardial strain parameters are increasingly adopted in heart failure with preserved ejection fraction (HFpEF), a condition challenging to diagnose. Conventional echocardiographic measures are of limited value. GLS detects early myocardial dysfunction, while LAS correlates strongly with filling pressures and HFpEF complications. RV strain parameters also show prognostic value in HFpEF, independent of pulmonary hypertension-related afterload. However, methodological inconsistencies hinder clinical standardization.

Objective: This case-control study aims to evaluate LA and RV strain impairment in HFpEF using the H2FPEF score, and to correlate strain measures (LASr, LASct, RVFWSL) with traditional echocardiographic indices (LAVI, LVMI, E/e') to validate their diagnostic and prognostic utility.

Methods: This case-control study was carried out at Beni-Suef University Hospital (January—July 2023) to compare LA and RV strain parameters between 30 HFpEF cases and 30 controls, excluding subjects with significant VHD, atrial fibrillation, or isolated right heart disease. Patients underwent clinical evaluations, ECG, and echocardiography, including STE for strain measures. Statistical analysis included t-tests, χ^2, Pearson correlations, and regression models to identify predictors. Ethical approval was obtained, and informed consent ensured confidentiality. Strain parameters were measured in different cardiac phases, following validated guidelines. Results were reported as mean and standard deviation, with $p<0.05$ representing significance.

Results: HFpEF patients had significantly higher H2FPEF scores, LAVI, RWT, and LVMI than the controls. Diastolic dysfunction (E/e') and worse myocardial strain markers (LASr, LASct, RVFWSL) were noted in cases. Strong correlations existed between BMI, E/e' ratio, EPASP, H2FPEF scores, and various cardiac parameters. Regression models revealed BMI and age as key predictors of myocardial strain deterioration.

Conclusion: Advanced echocardiographic parameters, LA and RV strain measures, as well as the H2FPEF score aid HFpEF diagnosis, revealing diastolic dysfunction, atrial, and ventricular remodeling. Future integration of these tools may streamline the diagnosis, facilitate patient stratification, and introduce tailored therapies to improve outcomes.

INTRODUCTION

Measurement of myocardial strain parameters are becoming increasingly recognized as invaluable in the understanding of cardiovascular pathology, especially enigmatic phenotypes, such as heart failure with preserved ejection fraction (HFpEF). Certain phenotypic undercurrents should be considered for heart failure—which usually requires clinical manifestations of cardiac compromise along with abnormalities in natriuretic peptides and/or pulmonary or systemic congestion **(1)**, as these features are not clear cut in HFpEF **(2)**.

Being noninvasive, echocardiography is central to the workup of suspected HFpEF. However, conventional echocardiographic measures of LV filling pressures, such as the E/e' ratio, are not always reliable in establishing a diagnosis of HFpEF as they can be altered by conditions such as mitral calcification, conduction abnormalities, constrictive pericarditis, RWM abnormalities, or high output states **(3, 4)**. This limited value led to the introduction of global longitudinal strain (GLS) and left atrial strain (LAS) measures as promising tools for diagnosing HFpEF **(5)**.

Animal models have shown that GLS predicts cardiac failure before cardiac fibrosis occurs, with evidence of intracellular alterations in excitation-contraction coupling ultimately leading to abnormal myocardial mechanics **(6)**. This was similarly shown in diabetic humans who exhibited strain impairments that corresponded to a heightened risk of heart failure **(7)**. Moreover, LAS is a noninvasive marker of LV filling pressures, which has been postulated to be not only useful in the diagnosis of HFpEF, but also a valuable prognostic tool as it displayed significant associations with major adverse cardiovascular events, as well as atrial fibrillation (AF) **(5, 8)**. Bearing in mind that elevated filling pressures represent the essence of HFpEF, the utility of LAS stands out, especially LAS of the reservoir phase (LASr). Evidence shows that LAS measures have a significant capacity to distinguish between HFpEF and noncardiac causes of dyspnea, as well as being more predictive of complications of HFpEF than the LV parameters **(9, 10)**. Accordingly, it has been suggested that LASr can substitute the left atrial volume index (LAVI) as a measure of increased filling pressures in forthcoming guidelines **(3)**.

Due to LV diastolic dysfunction in HFpEF, the burden of maintaining forward cardiac output is cast on the right ventricle **(11)**, thus, RV dysfunction is detrimental in patients with HFpEF; however, the underlying mechanisms and the prognostic impact of RV affection remain unclear **(12)**. Despite efforts to elucidate the extent of RV dysfunction in HFpEF using measures of RV shortening and systolic velocities **(13-15)**, these measures are confounded by the elevated afterload in HFpEF due to pulmonary hypertension (**16, 17)**, offering little to no delineation between RV dysfunction and afterload mismatch **(18)**. Studies have shown that measures of RV strain such as RV GLS and RVFWSL were highly useful in the prognostication of HFpEF, as they could reliably predict all-cause mortality due to HFpEF **(12)**. Therefore, it is undeniable that myocardial strain measures when encompassing those of the left atrium and the right ventricle, offer more comprehensive input regarding the diagnosis and prognosis of HFpEF **(5)**.

Although plenty of evidence exists regarding the utility of LA and RV strain measures in HFpEF, the available literature comes short of optimizing their use in clinical practice due to significant methodological variability. We noted several gaps in the current available literature, such as heterogenous inclusion criteria, which did not strictly involve patients with HFpEF, thus limiting the generalizability of their results **(19, 20)**. Moreover, echocardiographic data were sometimes analyzed by more than one operator, leading to potential interobserver variability, which diluted the significance of such evidence **(19)**.

Often, studies did not holistically assess all LA strain parameters, with a notable absence of data regarding RV strain in HFpEF and its correlation with other measures of strain, leaving parts of the echocardiographic spectrum unexamined **(2, 21, 22)**.

In this case-control study, we aim to bridge this gap by evaluating the extent of LA and RV strain impairment in patients diagnosed with HFpEF, using the H2FPEF scoring system. In addition, we seek to determine the correlation between strain parameters, such as LASr, LASct, RVFWSL and other echocardiographic measures (e.g., LAVI, LVMI, E/e' ratio), to further confirm their capacity in predicting HFpEF.

METHODS

The reporting process of this manuscript adhered to the items of the STROBE checklist **(23)**. This case-control study was carried out at the Cardiology Department, Beni-Suef University Hospital between January 2023 and July 2023, following the approval of the scientific and ethics committee. It included 60 patients divided into two groups: 30 cases with HFpEF and 30 age- and sex-matched controls. Twenty-two of our overall sample were males, whereas 38 were females. The cases had a mean age of 62.13 years, while the controls were 59.40 years. Recruitment was undertaken from the cardiology outpatient clinic at Beni-Suef University Hospital and informed consent acquisition was ensured prior to enrollment.

We included patients with manifestations of heart failure and an LVEF >50%, in the absence of other causes of dyspnea, and categorized them as HFpEF patients according to the H2FPEF score. We excluded subjects with significant VHD, atrial fibrillation, as well as those with isolated right heart disease.

All patients were subjected to a complete cardiac evaluation. Demographic and clinical data were documented with full history taking, clinical examination, and a standard 12-lead ECG. Two-dimensional echocardiography (2D-Echo) was performed followed by Speckle-tracking Echocardiography (STE) to measure LA and RV strain parameters. A diagnosis of HFpEF was subsequently established according to the H2FPEF score.

An experienced cardiologist performed transthoracic echocardiographic assessments for all participants using the Philips Epiq device (Philips Medical Systems). Left atrial strain parameters were obtained using a 3.5-MHz transducer at a 16 cm depth from the apical 4-chamber view, while right ventricular (RV) strain parameters were measured in an RV-focused view. Cine loops of three consecutive beats were recorded and stored for analysis. Conventional measurements adhered to the guidelines of the American Society of Echocardiography **(24)**. Speckles were detected and tracked via standard 2D grayscale imaging, and myocardial strain was calculated by analyzing their positional changes within myocardial segments during the cardiac cycle. For RV global longitudinal strain (GLS) assessment, 2D-STE is applied to the apical 4-chamber view. The endocardial borders of the RV free wall segments (basal, mid, and apical) were examined at end-systole, with RV GLS derived by averaging peak systolic longitudinal strains from these three segments. Measurement of LV strain, in the apical 4C or 2C view, was done during three different phases: reservoir, conduit, and contraction **(25)**.

Definitions of different LA strain parameters (25):

- Reservoir strain (LASr): this phase spans from the end of ventricular diastole to mitral valve opening, covering isovolumic contraction, ejection, and isovolumic relaxation. LASr is the difference between strain at mitral valve opening and at ventricular end-diastole (positive value).

- Conduit strain (LAScd): This phase begins at mitral valve opening and lasts until the onset of left atrial (LA) contraction in sinus rhythm patients. LAScd is calculated as the strain at the start of atrial contraction minus the strain at mitral valve opening (negative value).
- Contraction strain (LASc): This phase begins with LA contraction and ends at ventricular diastole in patients with sinus rhythm. LASct is calculated, only in sinus rhythm, as the strain at ventricular end-diastole minus the strain at the start of atrial contraction (negative value).

Following the approval of the Ethical Committee of the Faculty of Medicine, Beni-Suef University, informed written consent from all participants was acquired and the objectives of the work were explained before the beginning of the study. Confidentiality was guaranteed when handling databases and patient information was concealed and coded by an identification number to maintain anonymity. All individuals included in the study were informed about the related procedures and were made aware of their rights to refuse participation or withdraw from the study.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) was utilized for all statistical analyses in this study. Normal distribution of continuous-variables was ensured by the Kolmogorov–Smirnov test and presented as mean and standard deviation, and categorical variables were expressed as frequencies and percentages. The $\chi 2$ test as deployed for comparison of categorical variables, whereas the t-test or Mann–Whitney U test were utilized for quantitative data, such as LAVI, LASr, and RVFWSL. To assess relationships between clinical and echocardiographic parameters, Pearson correlation coefficients were calculated. Significance levels were determined at p-value <0.05 for statistical significance and p-value <0.01 for high significance. Multiple linear regression models were developed to identify predictors of dependent variables. Predictor variables were analyzed for their contributions to the variance in these outcomes. The models reported R^2 values, indicating the proportion of variance explained, and standardized beta coefficients (β), reflecting the strength and direction of the associations. All statistical tests were two-tailed, and a significance threshold of p-value <0.05 was applied throughout the analyses.

RESULTS

Table (I): Baseline Demographic Characteristics of Cases and Controls:

The demographic characteristics of participants are presented in Table I. The mean age of the cases was 62.13 ± 6.49 years. The mean age of the control group was 59.40 ± 5.02. In terms of gender distribution, 45.5% of the cases were males, and 52.6% were females. Similarly, 54.5% of the controls were males, whereas the remaining 47.4% were females.

Table (I): Baseline Demographic Characteristics of Cases and Controls:

Demographics	Case (Mean ± SD)	Control (Mean ± SD)
Age	62.13 ± 6.49	59.40 ± 5.02
Sex (Male) Count (%)	10 (45.5%)	12 (54.5%)
Sex (Female) Count (%)	20 (52.6%)	18 (47.4%)

Table (II): The probability of HFPEF and H2FPEF Scores Between Cases and Controls:

Based on a mean H2FPEF score of 5.40 ± 0.81 in the cases, and 0.50 ± 0.73 in the controls (p=0.001; Table II), the probability of HFpEF among the cases was calculated to be 83.67 ±

7.65 as opposed to 25.00 ± 7.31 in the control group, both with robust statistical significance (p=0.001; Table II).

Table (II): The probability of HFPEF and H2FPEF Scores Between Cases and Controls:

Variable	Case (Mean ± SD)	Control (Mean ± SD)	P-Value
Probability of having HFPEF	83.67 ± 7.65	25.00 ± 7.31	0.001
H2FPEF Score	5.40 ± 0.81	0.50 ± 0.73	0.001

HFPEF: Heart Failure with Preserved Ejection Fraction, H2FPEF Score: A clinical scoring system used to estimate the probability of HFPEF based on specific clinical and echocardiographic parameters.

Table (III): Comparing LAVI, RWT, and LVMI Between Cases and Controls:

The LAVI was significantly higher in the cases when compared to the controls (33.20 vs. 25.77; p=0.001; Table III). Moreover, the cases demonstrated considerably greater RWT as opposed to the controls (0.431 vs. 0.391; p=0.001; Table III). Lastly, substantially greater LVMI was observed in the cases when compared to the controls (126.93 vs. 98.37; p=0.001; Table III).

Table (III): Comparing LAVI, RWT, and LVMI Between Cases and Controls:

Variable	Case (Mean ± SD)	Control (Mean ± SD)	P-Value
LAVI	33.20 ± 3.21	25.77 ± 2.56	0.001
RWT	0.431 ± 0.046	0.391 ± 0.018	0.001
LVMI	126.93 ± 17.36	98.37 ± 9.32	0.001

LAVI: Left Atrial Volume Index, RWT: Relative Wall Thickness, LVMI: Left Ventricular Mass Index

Table (IV): Diastolic Function (E/e') Between Cases and Controls:

The mean E/e’ ratio, a marker of diastolic dysfunction, was noted to be exceedingly higher in the HFpEF group when contrasted with the controls (12.23 vs. 7.40; p=0.001; Table IV), highlighting significantly higher LV filling pressures.

Table (IV): Diastolic Function (E/e') Between Cases and Controls:

Variable	Case (Mean ± SD)	Control (Mean ± SD)	P-Value
E/e’	12.23 ± 1.92	7.40 ± 1.25	0.001

E/e’: The ratio of early mitral inflow velocity (E) to mitral annular early diastolic velocity (e’)

Table (V): Comparing Measures of Myocardial Strain (LASr, LASct, and RVFWSL) Between Cases and Controls:

Significant impairments were observed among the cases in terms of all measures of myocardial strain, suggested by significantly lower LASr (0.224 vs. 0.369; p=0.001; Table V), LASct (13.30 vs. 18.33; p=0.001; Table V), and RVFWSL (22.03 vs. 27.27; p=0.001; Table V), among patients with HFpEF unlike their healthy counterparts.

Table (V): Comparing Measures of Myocardial Strain (LASr, LASct, and RVFWSL) Between Cases and Controls:

Variable	Case (Mean ± SD)	Control (Mean ± SD)	P-value
LASr	0.224 ± 0.064	0.369 ± 0.034	0.001
LASct	13.30 ± 4.23	18.33 ± 2.89	0.001
RVFWSL	22.03 ± 6.22	27.27 ± 3.74	0.001

LASr: Left Atrial Strain Reservoir, LASct: Left Atrial Strain Contractile, RVFWSL: Right Ventricular Free Wall Strain

Table (VI): Gender-Based Differences in LVMI and LAVI Between Male and Female Participants:

Gender-based analysis demonstrated significantly higher LVMI among all male subjects in contrast to female subjects (122.14 vs. 107.16; p=0.004; Table VI). However, the difference in terms of the LAVI was not statistically significant (29.45 vs. 29.50; p=0.097; Table VI).

Table (VI): Gender-Based Differences in LVMI and LAVI Between Male and Female Participants:

Variable	Male (Mean ± SD)	Female (Mean ± SD)	p-value
LVMI	122.14 ± 21.91	107.16 ± 16.68	0.004
LAVI	29.45 ± 4.51	29.50 ± 4.90	0.097

LAVI: Left Atrial Volume Index , LVMI: Left Ventricular Mass Index

Table (VII): Pearson Correlation Between Key Independent and Dependent Variables:

Table (7) details the correlations among independent variables such as age, BMI, EPASP, E/e' ratio, H2FPEF score, and HFpEF probability—and dependent variables such as measures of strain (LASr, LASct, and RVFWSL), LAVI, and LVMI. We found strong positive correlations between EPASP and LAVI, RWT, as well as LVMI (r=0.832, r=0.556, r=0.673, respectively; p=0.000; Table VII). Additionally, strong negative correlations were noted between EPASP and LASr (r=-0.748, p=0.000; Table VII), and between EPASP and RVFWSL (r=-0.581, p=0.000; Table VII). A modest negative correlation was spotted between EPASP and LASct (r=-0.428, p=0.001; Table VII).

The LAVI, RWT, and LVMI, were positively correlated with the BMI, and the correlation was strong (r=0.678, r=0.508, r=0.701, respectively; p=0.000; Table VII). Similarly, LASr and LASct demonstrated strong negative correlations with the BMI (r=-0.740, r=-0.500, respectively; p=0.000; Table VII). The BMI and RVFWSL were very weakly correlated (r=-0.390, p=0.002; Table VII).

Almost all the dependent variables strongly correlated with the E/e' ratio. Positive correlations were found with the LAVI, RWT, and LVMI (r=0.821, r=0.548, r=0.640, respectively; p=0.000; Table VII). Negative correlations existed with LASR, LASct, and RVFWSL (r=-0.699, r=-0.459, r=-0.550, respectively; p=0.000; Table VII).

The H2FPEF score showed appreciable strong correlations with all the dependent variables. This was illustrated in strong positive correlations with the LAVI, RWT, and LVMI (r=0.837, r=0.578, r=0.759, respectively; p=0.000; Table VII), and strong negative correlations with LASr, LASct, and RVFWSL (r=-0.823, r=-0.580, r=-0.537, respectively; p=0.000; Table VII). Accordingly, the probability of having HFpEF showed similar correlations with all the dependent variables (r=0.832, r=0.568, r=0.759, r=-0.830, r=-0.580, r=-0.527, respectively; p=0.000; Table VII).

Table (VII): Pearson Correlation Between Key Independent and Dependent Variables:

		LAVI	RWT	LVMI	LASr	LASct	RVFWSL
Age	(r) coefficient	.329*	.248	.197	-.371-**	-.261-*	-.367-**
	P-value	.010	.056	.131	.004	.044	.004
EPASP	(r) coefficient	.832**	.556**	.673**	-.748-**	-.428-**	-.581-**
	P-value	.000	.000	.000	.000	.001	.000
BMI	(r) coefficient	.678**	.508**	.701**	-.740-**	-.500-**	-.390-**
	P-value	.000	.000	.000	.000	.000	.002
E\ e '	(r) coefficient	.821**	.548**	.640**	-.699-**	-.459-**	-.550-**
	P-value	.000	.000	.000	.000	.000	.000
H2FPEF score	(r) coefficient	.837**	.578**	.759**	-.823-**	-.580-**	-.537-**

	P-value	.000	.000	.000	.000	.000	.000
HFPEF	(r) coefficient	.832**	.568**	.759**	-.830-**	-.580-**	-.527-**
	P-value	.000	.000	.000	.000	.000	.000

EPASP: Estimated Pulmonary Artery Systolic Pressure, HFPEF: Heart Failure with Preserved Ejection Fraction, BMI: Body Mass Index, E/e': The ratio of early mitral inflow velocity (E) to mitral annular early diastolic velocity (e'), HFPEF: Heart Failure with Preserved Ejection Fraction, H2FPEF Score: A clinical scoring system used to estimate the probability of HFPEF based on specific clinical and echocardiographic parameters.

Table (VIII): Correlation Matrix of Cardiovascular Parameters Among Cases:

According to the correlation matrix, significant positive correlations were noted between LAVI and RWT (r=0.414, p=0.023; Table VIII), LVMI and RWT (r=0.750, p<0.001; Table VIII), LASr and LASct (r=0.639, p<0.001; Table VIII), and LASr and RVFWSL (r=0.450, p=0.013; Table VIII). The only notable negative correlation was seen between RVFWSL and LAVI (r=-0.534, p=0.002; Table VIII).

Table (VIII): Correlation Matrix of Cardiovascular Parameters Among Cases:

Variables	LAVI	RWT	LVMI	LASr	LASct	RVFWSL
LAVI	1.000-	0.414*	0.302-	-0.292-	-0.274-	-0.534**
RWT	0.414*	1.000-	0.750**	0.147-	-0.067-	-0.328-
LVMI	0.302-	0.750**	1.000-	-0.047-	-0.180-	-0.250-
LASr	-0.292-	0.147-	-0.047-	1.000-	0.639**	0.450*
LASct	-0.274-	-0.067-	-0.180-	0.639**	1.000-	0.301-
RVFWSL	-0.534**	-0.328-	-0.250-	0.450*	0.301-	1.000-

LAVI (Left Atrial Volume Index), RWT (Relative Wall Thickness), LVMI (Left Ventricular Mass Index), LASr (Left Atrial Strain during Reservoir Phase), LASct (Left Atrial Strain during Contraction Phase), RVFWSL (Right Ventricular Free Wall Strain Longitudinal).
*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

Table (IX): Assessment of Myocardial Strain Parameters (LASr, LASct, and RVFWSL) Between Normal and Abnormal LAVI Groups:

Notably reduced mean LASr between the abnormal and the normal LAVI groups were highlighted (0.238 vs. 0.363; p=0.001; Table IX), as well as lower LASct in the abnormal group (13.59 vs. 18.36; p=0.001; Table IX), and similarly for the mean RVFWSL in the abnormal group (22.06 vs. 27.61; p=0.001; Table IX).

Table (IX): Assessment of Myocardial Strain Parameters (LASr, LASct, and RVFWSL) Between Normal and Abnormal LAVI Groups:

	LAVI category	N	Mean	Std. Deviation	p-value
LASr	Normal	28	.36357	.045478	0.001
	Abnormal	32	.23844	.075684	
LASct	Normal	28	18.36	3.129	0.001
	Abnormal	32	13.59	4.165	
RVFWSL	Normal	28	27.61	4.149	0.001
	Abnormal	32	22.06	5.719	

Table (X): Comparing LASr, LASct, and RVFWSL Between Normal and Abnormal RWT Categories:

Among patients with abnormal RWT, LASr (0.237 vs. 0.314, p=0.001; Table X), LASct (12.86 vs. 16.72, p=0.002; Table X), and RVFWSL (20.79 vs. 25.83, p=0.004; Table X) were all reduced compared to the normal RWT group.

Table (X): Comparing LASr, LASct, and RVFWSL Between Normal and Abnormal RWT Categories:

	RWT category	N	Mean	Std. Deviation	p-value
LASr	Normal	46	.31489	.086772	0.001
	Abnormal	14	.23750	.070240	
LASct	Normal	46	16.72	4.324	0.002
	Abnormal	14	12.86	3.278	
RVFWSL	Normal	46	25.83	5.666	0.004
	Abnormal	14	20.79	4.117	

Table (XI): Regression Model Predicting LASr:

BMI, Age, and DM were significant predictors of LASr, collectively explaining 65.8% of the variance (R^2=0.658, R^2=0.658, R^2=0.658, respectively; p<0.001; Table XI). BMI was the strongest predictor (β=−0.617), followed by Age (β=−0.249) and DM (β=−0.235). Higher BMI, older age, and the presence of diabetes were associated with a significant decrease in LASr. The model explained 64.0% of the variance in LASct (R^2= 0.640; Table XI).

Table (XI): Regression Model Predicting LASr:

Predictor	**Unstandardized Coefficient (B)**	**Standard Error**	**Standardized Coefficient (Beta)**	**t**	**Sig.**
Constant	0.732	0.073	—	10.065	<0.001
BMI	-0.008	0.001	-0.617	-7.326	<0.001
Age	-0.004	0.001	-0.249	-3.14	0.003
DM	-0.039	0.014	-0.235	-2.831	0.006

R^2= 0.640

Table (XII): Regression Model Predicting LASct:

In this regression model, BMI was found to significantly predict LASct (B=−0.308, p<0.001; Table XII). The negative coefficient for BMI suggested that higher BMI is associated with lower LASct values. The model explained 25.0% of the variance in LASct (R^2= 0.25; Table XII).

Table (XII): Regression Model Predicting LASct:

Predictor	**Unstandardized Coefficient (B)**	**Standard Error**	**Standardized Coefficient (Beta)**	**t**	**Sig.**
Constant	23.385	1.791	—	13.059	<0.001
BMI	-0.308	0.07	-0.5	-4.398	<0.001

R^2= 0.25

Table (XIII): Regression Model Predicting RVFWSL:

BMI and age were significant predictors of RVFWSL, collectively explaining 24.5% of the variance in RVFWSL ($p<0.001$; Table XIII). Higher BMI ($B=-0.271$, $p=0.006$; Table XIII) and older age ($B=-0.300$, $p=0.011$; Table XIII) were associated with reduced RVFWSL ($R^2=0.245$; Table XIII).

Table (XIII): Regression Model Predicting RVFWSL:

Predictor	Unstandardized Coefficient (B)	Std. Error	Standardized Coefficient (Beta)	t	Sig.
Constant	49.494	6.9	—	7.173	<0.001
BMI	-0.271	0.094	-0.337	-2.88	0.006
Age	-0.3	0.113	-0.309	-2.64	0.011

$R^2=.245$

DISCUSSION

Heart failure with preserved ejection fraction (HFpEF) is a clinical entity depicted by exertional dyspnea and fatigue, suggestive of heart failure, yet with an EF ≥50 **(26, 27)**. Around 50% of patients with HF have an EF above 50, yet challenges delay the diagnosis **(28)**. Certain factors have been identified in relation to HFpEF such as advanced age, obesity, hypertension, coronary artery disease, atrial fibrillation, diabetes, and chronic kidney disease **(29)**. Nevertheless, with the morbidity and mortality associated with HFpEF being comparable to those seen with HF with reduced EF (HFrEF), noninvasive modalities are mandated to streamline the diagnostic process **(30)**.

Central to the diagnostic process, echocardiography can identify diastolic dysfunction noninvasively along with the HF2FPEF score, providing insights regarding the preserved EF (which is mandatory for diagnosis), elevated pulmonary artery systolic pressure (PASP)>35mmHg, and other functional measures that postulate diastolic dysfunction such as the E/e' ratio, which is usually above 9 **(31, 32)**.

In this case-control study, our purpose was to evaluate patients diagnosed with HFpEF, based on the H2FPEF score, for the extent of LA and RV strain affection and the significance of these parameters in predicting HFpEF.

In our study, we assessed the probability of HFpEF according to the H2FPEF scoring system, based on which we found that the probability of HFpEF was significantly higher for the cases than the controls (83.67 vs. 25; p=0.001). Correspondingly, a higher mean H2FPEF score in the cases, as opposed to the controls, was appreciated (5.40 vs. 0.50; p=0.001). Amanai et al. deduced that the H2FPEF score could identify HFpEF with reasonable plausibility as it did not require the addition of natriuretic peptide levels such as the HFAPEFF scorer. Moreover, they demonstrated the shared capacity of both scores to predict systolic and diastolic functions as well as left filling pressures; however, HF2FPEF was superior for patients presenting with exertional dyspnea as it was capable of delineating poor exercise capacity **(33)**.

Reddy et al. further emphasized the superiority of HF2PEFF in detecting HFpEF and stated that their analysis yielded that the H2FPEF and HFAPEFF scores were both able to distinguish patients with HFpEF from controls. However, the H2FPEF score demonstrated a higher AUC of 0.845 (95% CI: 0.810-0.875) compared to the HFAPEFF score, which had an AUC of 0.710 (95% CI: 0.659-0.756). The difference in AUC between the two scores was -0.134 (95% CI: -0.177:-0.094; p<0.001). Both scores showed strong specificity, but the HFA-

PEFF score had lower sensitivity, with a 55% rate of false-negative for low-probability scores, compared to 25% for the H2FPEF score **(34)**.

The echocardiographic parameters of both groups were investigated and notably, the mean LAVI was prominently higher in the cases than the controls (33.20 vs. 25.77; p=0.001). Moreover, the mean RWT in the cases was greater than that observed in the controls (0.431 vs. 0.391; p=0.001). In addition, the mean LVMI was exceedingly higher in the cases when compared to the controls (126.93 vs. 98.37; p=0.001). Among their cohort, Venkateshvaran et al. included participants who presented with unexplained breathlessness and EF>50%, who were found to have a PCWP of >15mmHg, and compared them to those with a PCWP<15mmHg. They found that the high PCWP group had significantly higher LAVI as opposed to the other group (39 vs. 28mL/m^2; p<0.001), as well as a greater mean LVMI (101 vs. 83g/m^2; p=0.007) **(19)**.

Comparing a group of patients with HFpEF their healthy controls, Zhang et al. emphasized appreciably higher LAVI in the HFpEF group (32.7 vs. 24.7; p<0.001). Moreover, the LVMI was also notably greater in the HFpEF group as opposed to the controls (119 vs. 98.5g/m^2; p<0.001), which endorsed our findings **(35)**. Dang et al. put forth results that were largely in line with ours, showing that patients with HFpEF had a mean LAVI that was significantly greater than the controls (24 vs. 18.30 mL/m^2; p=0.002). This was also the case regarding LVMI (130.45 vs. 96.75g/m^2; p<0.001). However, the reported RWT in their study did not vary between the two groups (0.403 vs. 0.400; p=0.891), which opposed our results. We attempted to explain this disparity by pointing out their relatively large sample size (118 vs. 60), which might have influenced the significance of their outcomes **(36)**.

Concerning the E/e' ratio, measured to assess the diastolic function, it was shown to be remarkably higher in the cases (12.23 vs. 7.40; p=0.001). This was suggestive of a rather elevated left ventricular filling pressure causing pronounced diastolic dysfunction in the cases. In alignment with our findings, Venkateshvaran et al. inferred that the mean E/e' ratio for patients who fit the picture of HFpEF was substantially higher than those who had a preserved EF with PCWP<15mmHg (16 vs. 10; p<0.001) **(19)**. Zhang et al. supported our data by showing that the E/e' ratio in HFpEF exceeded that of the healthy controls (10.6 vs. 6.7; p<0.001), demonstrating a significant increase in filling pressures which showcased diastolic dysfunction in the cases **(35)**. Dang et al. found that the average E/e' ratio was appreciably higher in the HFpEF group when compared to their healthy counterparts (13.15 vs. 7.96; p=0.002), which firmly matched our results **(36)**.

Furthermore, we touched upon the measures of myocardial longitudinal strain of LA and RV. The mean LASr was notably lower in the cases, consistent with reduced atrial functions in heart failure (0.224 vs. 0.369; p=0.001). Additionally, the mean LASct showed similarly reduced values in cases when compared with the controls (13.30 vs. 18.33; p=0.001), indicating impaired atrial contraction in the cases. In terms of the right ventricle, we observed RV free wall dysfunction in the cases, attested by significantly diminished mean RVFWSL values when compared to the controls (22.03 vs. 27.27; p=0.001). Consistent with our results, Venkateshvaran et al. observed considerably lower mean LASr for their group who presented with manifestations matching the criteria for HFpEF, as opposed to those with normal PCWP (16 vs. 24; p<0.001) **(19)**. According to the work of Zhang et al., left atrial strain parameters exhibited significant decline in patients with HFpEF unlike the controls, namely the LASr (17 vs. 26; p<0.001) and the LASct (10 vs. 13; p<0.001). They also compared the LASr of patients with HFpEF associated with hypertension to those who had hypertension without HFpEF and noted that there were obviously worse LA reservoir measures in those with HFpEF (17 vs. 23; p<0.001), highlighting the additional value of LASr as a prognostic measure of cardiovascular risk **(35)**. In accordance with our findings, Dang et al. indicated that the left atrial strain measures were undoubtedly lower in HFpEF patients as opposed to healthy controls, evidenced by LASr (19.97 vs. 34.70; p<0.001) as well as LASct (9.08 vs. 17.33; p<0.001). These measurements robustly affirm ours **(36)**.

We extrapolated the possible correlations among multiple independent variables, including age, BMI, H2FPEF score, and echocardiographic measures such as the EPASP and the E/e' ratio, and dependent variables such as LAVI, LVMI, LASr, LASct, and RVFWSL. Firstly, we intended to validate the comparability of the EPASP with PCWP, which was utilized in many studies during their assessment of filling pressures. Mohan et al. analyzed the degree of correlation between invasively measured PCWP and the estimated echo-PCWP, using the formula (echo-PCWP = 0.5 echo-derived PASP), and they concluded that there was a robust positive correlation between the echo-PCWP and the invasive-PCWP—as measured by right heart catheterization (RHC; r=0.89, p<0.0001). Furthermore, this was assessed across a different PCWP values, revealing a mean difference between the echo-PCWP and invasive-PCWP of 3mmHg (±4mmHg). Additionally, the sensitivity of echo-PCWP (0.5 EPASP) in the prediction of invasive-PCWP was reported to be 100%, with a specificity of 91%. Lastly, this correlation was evaluated using subgroup analysis of patients with different ejection fractions, and intriguingly, there were remarkable correlations across the spectrum of EF. Relevant to our study on patients with HFpEF, they reported that this formula strongly correlated with the invasive-PCWP in those having preserved EF (EF>50%; r=0.87, p<0.0001) **(37)**.

Our correlation model revealed a strong positive correlation between EPASP and LAVI (r=0.832, p=0.000), RWT (r=0.556, p=0.000), as well as LVMI (0.673, p=0.000). Similarly, there is a strong negative correlation between EPASP and LASr (r=-0.748, p=0.000), in addition to EPASP and RVFWSL (r=-0.581, p=0.000). Venkateshvaran et al. inferred that in patients with a preserved EF, invasively measured PCWP correlated positively with LAVI (r=0.36, p<0.001) and LVMI (r=0.29, p=0.001). They also detected moderate negative correlations between PCWP and LASr (r=-0.37, p<0.001). While these correlations were not as strong as ours, they aligned with our data, and we owed this discrepancy in strength to the fact that their patients were not exclusively representative of HFpEF patients, since they were included based on 'unexplained breathlessness', not an established HFpEF diagnosis. Moreover, a core-lab approach was not followed in their study, raising the possibility of inter-operator variability. Additionally, a margin of error must be considered given the variance in modalities used to assess pulmonary artery pressures despite valid comparability. Nevertheless, these limitations do not necessarily negate the similarity with our findings **(19)**.

We noted strong positive correlations between BMI and LAVI (r=0.678, p=0.000), as well as between BMI and LVMI (r=0.701, p=0.000). Moreover, appreciable negative correlations were found between BMI and LASr (r=-0.740, p=0.000), as well as LASct (r=-0.500, p=0.000). In alignment with our outcomes, Steele et al. addressed the possible interplay between obesity and diastolic dysfunction in patients with an average BMI of 36.6kg/m^2 and compared them to those of normal weight. Interestingly, at baseline, both groups had comparable LA EF (63.3 vs. 63.1%; p=0.3); however, the LVMI was significantly greater in obese patients (151.5 vs. 117.6; p<0.0001), and the LASr was significantly lower compared to the controls (1.8 vs. 2; p=0.01). A discrepancy was noted in terms of LAVI as it was reported to be significantly lower in patients with a higher BMI (15.8 vs. 17.4mL/m^2; p<0.0001). Nonetheless, their patients were not included in the study based on a diagnosis of HFpEF, but rather a suspicion for diastolic dysfunction, and since the literature is almost devoid of data on this matter, we found their work suggestive of ours, although it must be examined with the underlined limitations in mind **(20)**.

The E/e' ratio correlated positively with LAVI (r=0.821, p=0.000), RWT (r=0.548, p=0.000), and LVMI (r=0.640, p=0.000). Negative correlation could be deduced from the model between E/e' ratio and LASr (r=-0.699, p=0.000), in addition to E/e' ratio and RVFWSL (r=-0.550, p=0.000). Kim et al. similarly reported a significant negative correlation between the E/e' ratio and LASr in a sample of patients with HFpEF (r=-0.43, p<0.001) **(38)**. Dang et al. reported a rather mild positive correlation between the E/e' ratio and LAVI (r=0.19, p<0.05). However, they reported a strong negative correlation with LASr (r=-0.540, p<0.001), which emphasized our findings **(36)**.

The H2FPEF score showed considerable correlations with all the dependent variables, with evident strength across the board. Positive correlations were noted with LAVI (r=0.837, p=0.000), RWT (r=0.578, p=0.000), and LVMI (r=0.759, p=0.000). Negative correlations could be demonstrated with LASr (r=-0.823, p=0.000), LASct (r=-0.580, p=0.000), and RVMWSL (r=-0.537, p=0.000). This was also the case for the correlation between HFpEF and all the dependent variables, namely, LAVI (r=0.832, p=0.000), RWT (r=0.568, p=0.000), LVMI (r=0.759, p=0.000), LASr (r=-0.830, p=0.000), LASct (r=-0.580, p=0.000), and RVMWSL (r=-0.527, p=0.000). Reddy et al. showed that left atrial volume indices were all significantly higher in patients with HFpEF as opposed to those with dyspnea unattributable to H, evident by greater LA maximal volume index (32 vs. 23; p<0.0001) and LA minimal volume index (18 vs. 9; p<0.0001). This was also true for LVMI (92 vs. 85g/m^2; p=0.002), but not for RWT (0.42 vs. 0.41; p=0.1). In addition, they explored the strain parameters of the same two groups, and it was shown that the LASr was exceedingly lower in patients with HFpEF (29 vs. 40; p<0.0001). However, their data was insufficient on left atrial strain measures as they measured only the booster strain (16 vs. 17; p=0.1), and not the broader, more encompassing, LA contractile strain **(21)**. Aung et al. emphasized our findings, showing that LAVI (OR 1.59; 95% CI: 1.02-2.48; p<0.001), under both univariate and multivariate analyses, was a prominent predictor of HFpEF. They also elaborated on the correlation between HFpEF, LVMI and global LA strain, under a similar analytical framework, both of which proved to be associated with HFpEF (OR 1.04, 95% CI: 0.98-1.11; p<0.001, OR 0.71, 95% CI: 0.451-0.99; p<0.001, respectively). However, RVMWSL was not one of the addressed parameters in any of the highlighted works here, leaving a notable gap in the literature **(22)**.

As shown in our correlation matrix, LAVI exhibited a significant positive correlation with RWT (r=0.414, p=0.023), as well as a robust negative correlation with RVFWSL (r=-0.534, p=0.01). Another statistically meaningful correlation was noted between LVMI and RWT (r=0.750, p<0.001), and another between LASr and LASct (r=0.639, p=0.01), as well as a moderate correlation between LASr and RVFWSL (r=0.450, p=0.01). These results indicate that each measure of strain is closely linked to the other, with changes in each of the aforementioned parameters directly impacting their counterparts; for example, an increase in the RWT leads to an increase in the LVMI, and similarly for increases in LAVI leading to increases in the RWT. On the other hand, an increase in the LAVI subsequently leads to a decrease in the RVFWSL. Conversely, we deemed the correlation between LASr and LAVI, as well as the correlation between LASr and RWT lacking in statistical significance (r=-0.292, p>0.05; r=-0.147, p>0.05, respectively). Consistent with our data, Dang et al. reported a strong positive correlation between LASr and LASct (r=0.730, p<0.05), and refuted the significance of the correlation between LASr and LAVI (r=-0.24) **(36)**. Kim et al. contrasted our findings, reciting a moderate negative correlation between LASr and LAVI (r=-0.41, p<0.001), as well as a mild, yet significant, negative correlation between LASr and RWT (r=-0.26, p<0.001).We hypothesized that this discrepancy was largely caused by the use of the HFAPEFF score in their study, a more resource-intensive system, while our patients were diagnosed based on the HF2PEF score, and according to the work of Mert et al., these two scoring systems exhibited a low concordance rate, making the comparability here highly unreliable **(39)**. Additionally, differences in utilized technical equipment and echocardiography machine software updates could have contributed to more or less accurate measurements. As reported by Farsalinos et al., there was significant variability in longitudinal strain parameters as measured by echocardiographic machines from different manufacturers. Echocardiography software update was also shown to influence longitudinal strain calculations **(5, 40),** and since we analyzed our measurements using QLab v.10, and they used the EchoPAC v.204, disparities in reported measures are possible **(38)**.

Lastly, our regression model for LASr showed significant negative correlations with BMI (t=-7.326; p<0.001) as well as diabetes mellitus (t=-2.831; p=0.006). Steele et al. corroborated our findings, noting that strain analysis revealed significantly lower reservoir rates in obese patients as well as those with DM (p=0.01). Moreover, their correlation model indicated that in obese patients, the lateral e’ and LASr were interrelated negatively, with lower LASr being associated with significantly lower lateral e’ measures (r=0.20, p=0.03), which is indicative of diastolic dysfunction, such as seen in HFpEF **(20)**.

CONCLUSION

In conclusion, our findings emphasized the pivotal role of advanced echocardiographic measures and the H2FPEF scoring system in the accurate diagnosis and phenotyping of HFpEF. We highlighted significant correlations between echocardiographic parameters, such as LAVI, LVMI, strain measures (LASr, LASct, RVFWSL), and the EPASP, along with clinical markers such as the H2FPEF score. These correlations expound on the multifaceted pathophysiology of HFpEF, driven by diastolic dysfunction, atrial remodeling, and atrial and ventricular strain abnormalities. Moreover, the predictive value of the H2FPEF score further supported its utility over alternative scoring systems in providing insights into disease severity.

While limitations related to sample size, equipment variability, and lack of invasive validations persist, our results aligned closely with the available evidence. However, it is imperative that future research focuses on integrating these measures into clinical practice and exploring their role in stratifying patients for tailored therapeutic interventions, ultimately improving outcomes in this challenging phenotype.

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