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PROGNOSTIC VALUE OF CARDIOPULMONARY EXERCISE TESTING AND EXERCISE ECHOCARDIOGRAPHY IN SUSPECTED HEART FAILURE WITH PRESERVED EJECTION FRACTION

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ABSTRACT

Heart Failure with preserved Ejection Fraction (HFpEF) is a complex syndrome with a rising prevalence due to the aging population and a reserved prognosis. Early pathological changes may not be noticeable at rest but can be identified through exercise stress testing. The combination of CPET and exercise stress echocardiography (ESE) could provide important insights for early diagnosis and risk stratification. Sixty-six patients with chronic exertional dyspnea and suspected HFpEF were included in the study. They underwent symptom-limited combined CPET with ESE and were monitored for cardiac decompensation for 12 to 18 months. Twenty-six patients (39% of the cohort) experienced cardiac decompensation during this period. Several resting and ESE parameters, along with most CPET parameters, demonstrated predictive value, for identifying cardiac decompensations in the studied population, as determined by linear regression analysis. Due to the high number of predictors and their correlations, Lasso regression was applied to address multicollinearity. After Lasso analysis, only three parameters remained significantly associated with cardiac decompensation: exercise E/e' ratio, exercise left atrial (LA) strain, and maximum work rate. The model, including all three key predictors, achieved 87.87% accuracy, 63.63% sensitivity, and 100% specificity. ESE is a useful tool in evaluating prognosis and risk stratification of patients with chronic exertional dyspnea and suspected HFpEF. The addition of the novel parameter, exercise LA strain, enhanced the predictive value of the classic echocardiographic parameter, E/e' ratio at effort. Although CPET parameters showed some predictive potential, the added benefit of incorporating CPET remains limited in the early stages of HFpEF.

Keywords: cardiopulmonary exercise testing, exercise echocardiography, heart failure

INTRODUCTION

Heart Failure with preserved Ejection Fraction (HFpEF) is a complex and heterogeneous syndrome, whose prevalence is increasing due to an aging population (1–3). Despite a preserved left ventricular ejection fraction (LVEF), HFpEF patients experience significant morbidity and mortality, with prognoses comparable to heart failure with reduced ejection fraction (HFrEF), particularly regarding hospitalizations and mortality (4–6). A key characteristic, exercise intolerance, is strongly associated with poor outcomes, with reduced exercise capacity linked to higher rates of hospitalization and cardiovascular events (7).

Pathological changes in early-stage HFpEF may be inapparent at rest but become evident during

physical exertion, thus underscoring the value of exercise stress testing (8–11). A recent study by Saito et al. reinforced this observation, demonstrating that exercise stress testing- particularly combining cardiopulmonary exercise testing (CPET) and exercise stress echocardiography (CPET-ESE) can effectively identify HFpEF patients, enabling risk stratification in those with chronic exertional dyspnea, and revealing comparable risk profiles to those diagnosed using resting evaluations (12).

This combined CPET-ESE approach provides a comprehensive assessment of exercise capacity, ventilatory efficiency, and cardiac function, offering valuable prognostic information for patients suspected of having HFpEF (12–15).

Our study aimed was to identify echocardiographic (at rest and during exercise) and CPET predictors of cardiac decompensations in patients with chronic exertional dyspnea, suspected of having HFpEF.

MATERIAL AND METHODS

We conducted a prospective, observational, non-randomized study between 2018-2020 and 2022-2024, involving patients suspected of having HFpEF, based on clinical symptoms and transthoracic echocardiography (TTE), who were either hospitalized or admitted for day hospitalization at the Emergency Clinical Hospital Bucharest .The inclusion criteria were patients over 18 years of age who presented with exertional dyspnea and showed an indeterminate or normal pattern after diastolic dysfunction assessment, according to the 2016 guidelines for LV diastolic function by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).(16) Additionally, all enrolled patients provided written informed consent, had a preserved left ventricular ejection fraction (LVEF ≥50%) and were able to perform a maximal exercise test with gas exchange analysis. Exclusion criteria were: prior diagnosis of HF, NT-proBNP ≥125 pg/mL, significant valvular disease (defined as at least moderate to severe regurgitation or mild stenosis), significant coronary artery disease, arrhythmia other than sinus rhythm (SR) at the time of study enrollment, recent pulmonary embolism, known aortic dissection or aneurysm >50 mm, severe chronic kidney disease [glomerular filtration rate (GFR) <30 mL/min/1.73 m²], or other conditions contributing to dyspnea [including at least moderate respiratory conditions or significant anemia with hemoglobin (Hb) <10 g/dL].

A complete TTE, focused on diastolic dysfunction (DD) evaluation in accordance with ASE/EACVI guidelines, was performed on all subjects upon enrollment. The following parameters with the corresponding cut-off values were assessed: average E/e' > 14, septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s, peak tricuspid regurgitation velocity (TRV) > 2.8 m/s, and left atrium volume index (LAVI) > 34 mL/m². (16) Patients with an indeterminate-normal pattern (50% of parameters abnormal or <50% of parameters abnormal) were included.

The patient's age, weight, height, and medical history (including comorbidities and medications) were recorded. Complete blood tests, as recommended in the HF guidelines, including NT-proBNP, and an electrocardiogram were performed at enrollment.

Echocardiography:

The Vivid E95 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) was used at rest and during exercise, with data stored digitally (5 consecutive cardiac cycles in cine-loop format) and analyzed using EchoPAC software, version 112 (GE Vingmed Ultrasound). Echocardiographic parameters were measured according to current guidelines (16–18).

Left atrial (LA) strain - reservoir function was assessed both at rest and during exercise according to the EACVI/ASE guidelines (18). It was calculated from apical 4- and 2-chamber views as the average peak positive longitudinal strain during LA relaxation across all 12 segments. Apical views were optimized to avoid foreshortening, with a frame rate >50 fps, and the QRS onset was used as the time reference point. During exercise LA-strain was analyzed at 50% of peak oxygen uptake (peak VO2).

Additionally, echocardiographic parameters measured at rest and during exercise included: early (E) and late (A) diastolic transmitral flow velocities, deceleration time (Doppler echocardiography), peak early mitral annulus velocities (e'- averaged from septal and lateral e', tissue Doppler measurements) , LVEF (2D biplane Simpson method), systolic tricuspid lateral annular velocity (S'T- tissue Doppler), peak TRV (continuous Doppler), and estimated pulmonary artery systolic pressure (PASP, calculated as 4 × TRV + right atrial (RA) pressure). Exercise RA pressure was assumed to be 10 mm Hg, as suggested by previous studies (19). E/e' and S'T/PASP ratios were calculated at rest and peak.

The intraobserver and interobserver variability for echocardiographic measurements were both < 10%, based on a sample size of 20 subjects.

Cardiopulmonary exercise test

A symptom-limited cardiopulmonary exercise test (CPET), performed simultaneously with exercise echocardiography, was conducted on a tiltable cycle

ergometer for all participants. An individualized ramp protocols designed to achieve the patient's estimated peak oxygen consumption (peak VO2) in 8–12 min was used. This included 2 minutes of unloaded pedaling, followed by 8-15 W/min load increments, and a recovery period of 5 minutes. Expiratory gases were collected on a breath-by-breath basis and analyzed using a Cortex Metalyzer 3B metabolic device (Cortex Biophysik GmbH, Germany). Spirometry was conducted for all patients prior to the test, and all exhibited results within normal limits or minimal changes without clinical significance.

Peak VO2 and the peak respiratory exchange ratio (RER) were expressed as the highest 10 second averaged sample obtained during the final 30 seconds of effort. An RER ≥ 1.05 at the end of the test was considered to indicate the achievement of maximal effort. The ventilatory anaerobic threshold (VAT) was determined using the V-slope analysis on VO2 versus carbon dioxide production (VCO2), and further verified using ventilatory equivalents and end-tidal partial pressure methods, VAT was expressed in l/min. Peak VO2 values were expressed in ml/kg/min or as a percentage of the predicted peak VO2 based on age, sex, and body dimensions, according to the equations proposed by Wasserman and Hansen (20). O2 pulse was determined, as the ratio of VO2 to heart rate (HR). The slope of the relationship between minute ventilation (VE) and carbon dioxide production (VCO2)- VE/VCO2 slope, was calculated using linear regression, based on all exercise data (initiation to peak effort). The oxygen uptake efficiency slope (OUES) was determined as the slope of the regression line between the logarithmically transformed ventilatory equivalent for oxygen (VE) on the x-axis and oxygen consumption (VO2) on the y-axis during exercise. The HR reserve was calculated as the difference between the maximum predicted HR (220-age) and the peak HR. Circulatory power (CP), a surrogate for cardiac power (cardiac output × mean arterial pressure- invasive assessment), was determined as the product of peak VO2 and peak systolic blood pressure, as previously proposed by other researchers (21).

Patients were monitored for 12–18 months. Cardiac decompensation events prompted comprehensive clinical, biological, ECG, and echocardiographic evaluations. Patients without decompensation also underwent a final evaluation at the end of the follow-up period.

Cardiac decompensation was defined as the occurrence of any of the following events: worsening HF symptoms requiring medications adjustment (including loop diuretics), with confirmation of HFpEF; hospitalization for HF; new-onset atrial fibrillation or flutter (EHRA II–IV classification); or cardiovascular death.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the local ethics committee. All patients provided informed consent prior to participation in the study.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and were compared using Welch's t-test. Categorical variables are presented as absolute and relative frequencies and were compared using Pearson's chi-squared test or Fisher's exact test, as appropriate.

The significance level (α) was established at 0.05, with p-values below this value considered statistically significant.

Univariate binary logistic regression was used to determine the association between cardiac decompensation and demographic, anthropometric, laboratory, echocardiographic, and CPET-derived parameters.

Variables with $p < 0.05$ from univariate analysis were selected for a multiple regression model. Due to multicollinearity among the numerous predictors, Lasso regression was employed using the glmnet package in R to determine the optimal model (22,23). The analysis involved standardizing the regressors to prevent scale-related biases. The patient cohort was randomly split into training and test sets. Five-fold cross-validation was used to identify the optimal lambda value, which was then used to obtain the final model coefficients. The model's predictive accuracy was subsequently evaluated on the unseen test set.

Statistical analysis was performed using R software, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria; URL: https://www.R-project.org)

RESULTS

The final study group included 66 patients with exertional dyspnea, suspected of HFpEF, with a median age of 57 years (mean ± standard deviation: 57 ± 15 years), 65% of whom were male. All patients presented with dyspnea (NYHA class I-III) and had the following risk factors: obesity (38%), hypertension (79 %), a history of atrial fibrillation (AF) (11%), and diabetes (11%).

Among the 26 patients (39%) experiencing cardiac decompensation, 10 (15%) required HF medication adjustments (including loop diuretics) and had confirmed HFpEF, 9 (14%) were hospitalized for HFpEF, and 7 (11%) developed atrial fibrillation/flutter (EHRA II-IV). No deaths were reported.

Patients with cardiac decompensation were older, female, had a higher body mass index (BMI) and a greater prevalence of hypertension and history of AF, compared to those without. Diabetes prevalence did not differ significantly. As expected, NT-proBNP was higher in the group with cardiac decompensation (Table 1).

Variable	Overall N = 66	Without cardiac decompensation N = 40	Cardiac decompensation N = 26	p-value[1]
Age, Mean (SD)	57 (15)	52 (16)	65 (10)	<0.001
Sex, n (%)				<0.001
F	23 (35)	5 (13)	18 (69)	
M	43 (65)	35 (88)	8 (31)	
Body mass index, kg/m², Mean (SD)	27.7 (4.6)	26.9 (4.7)	29.1 (4.1)	0.049
Comorbidities				
Hypertension, n (%)				0.005
Yes	52 (79)	27 (68)	25 (96)	
No	14 (21)	13 (33)	1 (4)	
Diabetes, n (%)				0.42
Yes	7 (11)	3 (7)	4 (15)	
No	59 (89)	37 (93)	22 (85)	
History of AF, n (%)				0.013
Yes	7 (11)	1 (2)	6 (23)	
No	59 (89)	39 (98)	20 (77)	
NT pro BNP, pg/ml, Mean (SD)	76 (33)	66 (34)	91 (25)	0.001
Medication				
Loop diuretics, n (%)				0.057
Yes	3 (5)	0 (0)	3 (12)	
No	63 (95)	40 (100)	23 (88)	
MRA, n (%)				0.42
Yes	7 (11)	3 (7)	4 (15)	
No	59 (89)	37 (93)	22 (85)	
Indapamide, n (%)				0.044
Yes	21 (32)	9 (23)	12 (46)	
No	45 (68)	31 (78)	14 (54)	
Beta blockers, n (%)				0.007
Yes	43 (65)	21 (53)	22 (85)	
No	23 (35)	19 (48)	4 (15)	
Calcium channel blockers, n (%)				0.050
Yes	19 (29)	8 (20)	11 (42)	
No	47 (71)	32 (80)	15 (58)	
ACE inhibitors/ARB, n (%)				0.22
Yes	45 (68)	25 (63)	20 (77)	
No	21 (32)	15 (38)	6 (23)	
Statin, n (%)				0.070
Yes	42 (64)	22 (55)	20 (77)	
No	24 (36)	18 (45)	6 (23)	
Antiplatelet therapies, n (%)				0.42
Yes	34 (52)	19 (48)	15 (58)	
No	32 (48)	21 (53)	11 (42)	

Table 1 - Patients' characteristics ([1] Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test)

Beta blockers, calcium channel blockers, and indapamide were more frequently prescribed in the cardiac decompensation group, however, no significant difference was observed in the use of loop

diuretics, mineralocorticoid receptor (MR) antagonists, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), statins, or antiplatelet therapies (Table1).

Echocardiographic evaluation revealed significantly higher values for LAVI (p = 0.040) and resting and exercise E/e' ratio (p = 0.016, p < 0.001) in patients with cardiac decompensation. Conversely, this group showed significantly lower exercise LVEF (p = 0.030), resting and exercise LA strain (p = 0.002, p < 0.001), exercise S'T (p = 0.004), and exercise S'/PASP (p = 0.029) compared to those without decompensation. No significant differences were observed between groups in left ventricle mass index (LVMI), resting LVEF, tricuspid annular plane systolic excursion (TAPSE), TAPSE/PASP ratio, S'T, S'T/PASP ration or PASP at rest or during effort (Table 2).

Echocardiography Variable	Overall N = 66	Without cardiac decompensation N = 40	Cardiac decompensation N = 26	p-value[1]
LVMI, g/m2, Mean (SD)	88 (21)	89 (21)	86 (22)	0.66
LAVI, ml/m2, Mean (SD)	30 (8)	29 (7)	33 (9)	0.040
E/e' rest, Mean (SD)	8.24 (2.13)	7.72 (1.91)	9.05 (2.23)	0.016
E/e' effort, Mean (SD)	12.5 (5.3)	10.0 (3.0)	16.3 (5.9)	<0.001
LVEF rest, %, Mean (SD)	57.7 (4.3)	58.2 (4.2)	56.8 (4.4)	0.19
LVEF effort, %, Mean (SD)	64.2 (8.8)	66.3 (5.6)	60.8 (11.6)	0.030
LA strain rest, %, Mean (SD)	28 (9)	30 (7)	23 (9)	0.002
LA strain effort, %, Mean (SD)	27 (9)	30 (8)	21 (8)	<0.001
PASP rest, mmHg, Mean (SD)	18 (8)	17 (7)	20 (9)	0.17
PASP effort, mmHg, Mean (SD)	34 (13)	32 (12)	36 (14)	0.20
TAPSE rest, mm, Mean (SD)	22.53 (3.29)	22.65 (3.50)	22.35 (2.98)	0.71
TAPSE/ PASP rest, mm/mmHg, Mean (SD)	1.46 (0.62)	1.52 (0.60)	1.35 (0.64)	0.28
S'T rest, cm/s, Mean (SD)	13.02 (1.91)	13.30 (1.83)	12.58 (1.98)	0.14
S'T effort, cm/s, Mean (SD)	16.4 (3.2)	17.3 (3.0)	15.0 (3.0)	0.004
S'T/PASP rest, cm/s per mmHg, Mean (SD)	0.84 (0.37)	0.89 (0.34)	0.77 (0.41)	0.21
S'T/PASP effort, cm/s per mmHg, Mean (SD)	0.55 (0.22)	0.60 (0.21)	0.48 (0.21)	0.029

[1] Welch Two Sample t-test

Table 2 - Echocardiographic variables of patients with and without cardiac decompensation

CPET demonstrated significant differences between groups. Patients with cardiac decompensation showed significantly lower values for VO2 at VAT (p < 0.001), peak VO2 (p < 0.001) and O2 pulse (peak VO2/HR, p=0.002); but significantly higher values for VE/VCO2 slope (p = 0.002), and resting and exercise partial pressure of end-tidal carbon dioxide (Pet CO2) (p = 0.043, p = 0.034). No significant difference was found in % peak predicted VO2 (p= 0.31) and HR reserve (p= 0.073). Additionally, patients with cardiac decompensation demonstrated significantly lower values for OUES, maximum work rate, and circulatory power (p < 0.001 for all) (Table 3).

CPET Variable	**Overall N = 66**	**Without cardiac decompensation N = 40**	**Cardiac decompensation N = 26**	**p-value**
VO2 at VAT x10, (L/min) x10, Mean (SD)	7.78 (2.35)	8.61 (2.28)	6.49 (1.86)	<0.001
PeakVO2, ml/kg/min, Mean (SD)	19.6 (6.0)	21.9 (6.1)	16.0 (3.8)	<0.001
% predicted peak VO2, %, Mean (SD)	76 (16)	75 (16)	79 (15)	0.31
O2 pulse, ml O2/beat, Mean (SD)	11.64 (3.05)	12.58 (2.65)	10.19 (3.11)	0.002
HR Reserve, Mean (SD)	18 (12)	16 (11)	22 (12)	0.073
VE/VCO2 slope, Mean (SD)	30.3 (5.1)	28.7 (4.7)	32.6 (4.8)	0.002
Pet CO2 rest, mmHg, Mean (SD)	32.3 (3.7)	33.0 (3.7)	31.2 (3.5)	0.043
Pet CO2 effort, mmHg, Mean (SD)	38.2 (5.1)	39.2 (5.6)	36.7 (3.8)	0.034
OUES, (L/min), Mean (SD)	1.75 (0.49)	1.92 (0.45)	1.48 (0.43)	<0.001
Max Work rate (Watts), Mean (SD)	122 (42)	140 (40)	94 (28)	<0.001
Circulatory Power/10, (mmHg x ml/kg/min)/10, Mean (SD)	379 (141)	422 (145)	314 (107)	<0.001

Table 3. The cardiopulmonary variables of patients with and without cardiac decompensation

Linear regression identified age, female sex, and NT-proBNP as predictors of cardiac decompensation (Table 4). Also, it revealed that the echocardiographic variables showing statistically significant differences between groups were also predictive of cardiac decompensation.

Linear regression analysis revealed that lower values of VO2 at VAT, peak VO2, O2 pulse, OUES, maximum work rate, and circulatory power, and higher VE/VCO2 slope predicted cardiac decompensation. Resting PetCO2 showed a trend towards significance (Table 4).

Predictor	N	Cardiac decompensation N	OR (95% CI)[1]	p-value
Age	66	26	1.08 (1.03 to 1.13)	0.002
Sex				
F	23	18	—	
M	43	8	0.06 (0.02 to 0.21)	<0.001
Body mass index	66	26	1.12 (1.00 to 1.27)	0.061
NT pro BNP	66	26	1.03 (1.01 to 1.05)	0.005
Echocardiographic predictors				
LVMI	66	26	0.99 (0.97 to 1.02)	0.649
LAVI	66	26	1.08 (1.01 to 1.17)	0.040
E/e' rest	66	26	1.37 (1.07 to 1.81)	0.017
E/e' effort	66	26	1.53 (1.27 to 1.96)	<0.001
LVEF rest	66	26	0.92 (0.81 to 1.04)	0.182
LVEF effort	66	26	0.88 (0.79 to 0.97)	0.017
LA strain rest	66	26	0.90 (0.84 to 0.96)	0.003
LA strain effort	66	26	0.86 (0.78 to 0.93)	<0.001
PAPS rest	66	26	1.05 (0.98 to 1.12)	0.156
PAPS effort	66	26	1.03 (0.99 to 1.07)	0.184
TAPSE rest	66	26	0.97 (0.83 to 1.13)	0.712
TAPSE/PAPS rest	66	26	0.63 (0.26 to 1.42)	0.274
S'T rest	66	26	0.81 (0.59 to 1.06)	0.137
S'T effort	66	26	0.76 (0.62 to 0.92)	0.007
S'T/PAPS rest	66	26	0.38 (0.08 to 1.54)	0.194
S'T/PAPs effort	66	26	0.05 (0.00 to 0.68)	0.033
CPET predictors				
VO2 at VAT x 10	66	26	0.58 (0.40 to 0.78)	0.001
PeakVO2	66	26	0.79 (0.67 to 0.89)	<0.001
% predicted peak VO2	66	26	1.02 (0.98 to 1.05)	0.316
O2 pulse	66	26	0.70 (0.54 to 0.87)	0.004
HR Reserve	66	26	1.04 (1.00 to 1.09)	0.071
VE/VCO2 slope	66	26	1.18 (1.06 to 1.33)	0.004
Pet CO2 rest	66	26	0.86 (0.74 to 0.99)	0.050
Pet CO2 effort	66	26	0.90 (0.79 to 1.00)	0.056
OUES	66	26	0.07 (0.01 to 0.29)	0.001
Max Work Rate (Watts)	66	26	0.96 (0.94 to 0.98)	<0.001
Circulatory Power / 10	66	26	0.99 (0.99 to 1.00)	0.004

Table 4 - Linear Regression Analysis for Predictors of Cardiac Decompensation ([1] OR = Odds Ratio, CI = Confidence Interval)

Significant predictors (p-value < 0.05) from the univariate binary logistic regression were selected for the multiple regression model. Due to the high number of predictors and their correlations, Lasso regression was applied. The Lasso regression analysis identified three key predictors associated with cardiac decompensation: E/e' ratio at exercise, LA strain at exercise and Maximum Work Rate. LA strain at exercise and Maximum Work Rate (W) were negatively associated with the likelihood of cardiac decompensation, whereas exercise E/e' ratio showed a positive association.

•An increase of 1 unit on the LA strain effort scale was associated with a 1% decrease in the odds of decompensation (coefficient: -0.009, OR: 0.99).

•An increase of 1 unit on the Max Work Rate scale was associated with a 22% decrease in the odds of decompensation. (coefficient: -0.24, OR: 0.78)

•An increase of 1 unit on the E/e' effort scale was associated with twofold increase in the odds of decompensation (coefficient: 0.71, OR: 2.03).

The model's performance was evaluated based on the confusion matrix from Table 5

.

	Without cardiac decompensation Real	**With cardiac decompensation Real**
Without cardiac decompensation Model	**22**	**4**
With cardiac decompensation Model	**0**	**7**

Table 5 – Confusion matrix

The model's accuracy was 87.87%, with a sensitivity of 63.63% and a specificity of 100%.

Additionally, the ROC analysis yielded an AUC of 0.818, reflecting the model's efficacy in differentiating between patients with and without cardiac decompensation (Figure 1).

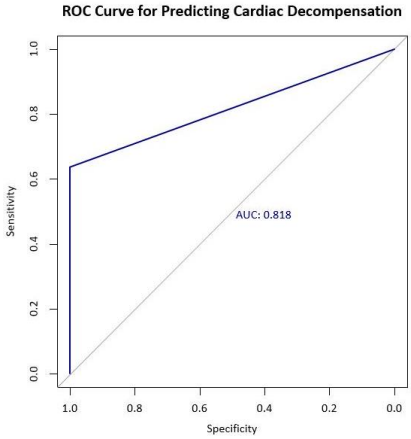

Figure 1 - ROC analysis

DISCUSSIONS

The diagnosis of HFpEF relies on the direct or indirect identification of elevated left ventricular (LV) filling pressures (9,16,24–26). In the early stages of HFpEF, these alterations may manifest only during exertion, with a significant number of patients exhibiting normal filling pressures at rest (27–29).

The E/e' ratio is the most established echocardiographic parameter used for the noninvasive estimation of LV filling pressures (6,9,25,30). However, previous studies have reported inconsistent findings regarding the accuracy of the E/e' ratio in estimating pulmonary capillary wedge pressure (PCWP). While some studies indicated a strong correlation between the E/e' ratio and elevated LV filling pressures (31–33) others reported only a moderate or no relationship between the E/e' ratio and invasive measurements (8,34–36).

Although the E/e' ratio has limitations in accurately estimating left ventricular (LV) filling pressures, it has been associated with outcomes such as mortality and composite endpoints in all 18 studies reviewed by Nauta and colleagues. Nonetheless, this association did not always reach statistical significance (37).

The results of our study are consistent with those from previous research concerning the E/e' ratio. Significant differences were found between patients with cardiac decompensation and those without, for both resting E/e' ($p = 0.016$) and E/e' during exertion ($p < 0.001$). Furthermore, univariate logistic regression analysis indicated that both resting E/e' (OR = 1.37, 95% CI: 1.07–1.81, $p = 0.017$) and E/e' during exertion (OR = 1.53, 95% CI: 1.27–1.96, $p < 0.001$) were predictive of cardiac decompensation in our cohort. However, Lasso regression analysis revealed that only the E/e' ratio during exertion remained a significant prognostic factor (coefficient = 0.71, OR = 2.03). In our cohort, patients with cardiac decompensation had a resting E/e' ratio of 9.05 ± 2.23, compared to 7.72 ± 1.91 in those without decompensation. This finding suggests that a considerable number of patients likely maintained normal filling pressures at rest. Additionally, an E/e' ratio within the intermediate range has demonstrated reduced sensitivity in identifying elevated mean pulmonary capillary wedge pressure (mPCWP). (9,38) These observations could explain why the resting E/e' ratio did not retain its predictive ability in the Lasso analysis of our study.

In patients with HFpEF, elevated filling pressures contribute over time to LA remodeling, a process driven by atrioventricular uncoupling and systemic inflammation (39,40).

LA volume, commonly quantified as LAVI using the biplane Simpson method, reflects the cumulative impacts of increased left ventricular (LV) filling pressure over time (16,41). However, its ability to detect early alterations in left ventricular diastolic dysfunction (LVDD) was limited, as LAVI primarily indicates the chronic consequences of prolonged elevated LV filling pressures (16,41). Nonetheless, in HFpEF patients, an increased LAVI has been identified as an independent predictor of death, heart failure, atrial fibrillation (AF), and ischemic stroke (16).

In our study, LAVI was significantly elevated in patients with cardiac decompensation compared to those without (33 ± 5 vs. 29 ± 6, p = 0.04). Moreover, it demonstrated predictive value for cardiac decompensation in our linear regression analysis (OR = 1.08, 95% CI: 1.01–1.17, p < 0.04); however, this predictive capability did not persist in the Lasso analysis. The LAVI values for patients with cardiac decompensation in our study were 33± 5 ml/m². These values are lower than those reported in other studies where LAVI demonstrated prognostic significance. Additionaly, a considerable number of patients with cardiac decompensation had values below the cutoff limit of 34 mL/m² recommended by clinical guidelines (6,30). This may explain the limited prognostic value of LAVI in our research.

Recent studies have indicated that a new functional parameter of the LA, LA strain , exhibits a stronger correlation with invasive gold standard diastolic measurements and LV filling pressures, surpassing LAVI in this aspect.(42–45) Additionally, LA strain provides a thorough evaluation of atrial function, remodeling, and distensibility, all of which progressively deteriorate in patients with HFpEF.(42,46–48) This establishes LA strain a valuable tool in assessing the evolving pathophysiology of HFpEF.

Patients experiencing cardiac decompensation displayed significantly lower LA strain values compared to those without decompensation, both at rest (23 ± 9 vs. 30 ± 7, p = 0.02) and during exertion (21 ± 8 vs. 30 ± 8, p < 0.001), in the present study. Both resting and exertional LA strain demonstrated prognostic value in the linear regression analysis, with LA strain at rest yielding an odds ratio of 0.9 (95% CI: 0.84–0.94, p < 0.003) and exertional LA strain showing an odds ratio of 0.86 (95% CI: 0.78–0.93, p < 0.001). Notably, exertional LA strain retained its predictive ability even following Lasso analysis, with coefficients and odds ratio for exertional LA strain indicated as (coefficient = -0.009, OR = 0.99).

In our study, exertional LA strain demonstrated superior predictive capability for cardiac decompensation compared to both LAVI and resting LA strain in patients suspected of having HFpEF. This finding indicates that LA strain during exercise may be more effective in detecting early alterations in the LA associated with elevated LV filling pressures than LAVI and resting LA strain in this patient population. Previous researches support this hypothesis, finding a significant correlation between LA strain and the severity of LVDD (49–53). The results of our study are consistent with those of Morris et al., who observed that a substantial proportion of patients with LV diastolic alterations had a normal LAVI but an abnormal LA strain (52). Furthermore, their study indicated that incorporating LA strain into the evaluation of LVDD markedly improved the detection rate of LVDD, reinforcing the concept that LA strain offers advantages over LAVI for earlier identification of diastolic changes (52).

Another study that supports these findings is Sugimoto's research, which examined the role of dynamic LA function in limiting oxygen consumption and cardiac output during exercise in HF patients. It found that reduced resting and exertional LA strain were both associated with poorer prognosis in HFpEF patients (54). Additionally, reduced exertional LA strain demonstrated superior discriminatory ability compared to LA strain at rest (54).

These findings suggest that exertional LA strain may have the potential to identify patients at greater risk for cardiac events in the early stages of HFpEF.

Other echocardiographic parameters in the present study that exhibited significant differences between the two groups and demonstrated predictive value for cardiac decompensation in linear regression analysis were LVEF, S'T, and S'T/PASP, all measured during exertion. However, these parameters lost their predictive value after Lasso analysis.

The ratio TAPSE/PASP has emerged as a reliable noninvasive index for assessing right ventricle (RV) to pulmonary circulation (PC) coupling and the overall RV performance in patients with HFpEF. (55–59) Additionally, recent studies have highlighted the utility of the S'T/PASP ratio for the same purpose.(60) However, Palazzuoli's study indicated that only S'/PASP had prognostic value in patients with acute HFpEF. In contrast, TAPSE/PASP was predictive in those with reduced EF, emphasizing the distinct patterns of RV adaptation and RV-PC coupling between the two groups (61).

The results of our study align with the aforementioned findings. Both TAPSE/PASP and S'T/PASP ratios at rest showed no statistically significant differences or predictive ability between the two groups. Notable differences were observed only

during exertion for parameters such as S'T and the S'T/PASP ratio. This may suggest an early stage of RV myocardial contractility impairment that becomes apparent during exercise, as indicated by the effort-related S'T measurements, especially since no significant differences were observed in PASP values at rest or during exertion between the groups.

Although most of the CPET variables were significant univariate predictors of cardiac decompensation among patients with suspicion of HFpEF in the present study (VO2 at VAT, Peak VO2, VO2 pulse, VE/VCO2 slope, OUES, Max Work Rate, and Circulatory Power), only maximum work rate retained predictive power for cardiac decompensation after Lasso analysis.

A significant number of studies have demonstrated the prognostic value of CPET in HF. Peak VO2 and VE/VCO2 slope are the parameters with the most substantial prognostic evidence in HFpEF, (15,62–64) with some studies showing an additional benefit for VE /VCO2 slope (62,65–67). The cut-off values used in these studies are lower for peak VO2 and higher for VE /VCO2 slope compared to the average values obtained in our study. This is likely the reason why these variables did not maintain their predictive value after the Lasso analysis.

A similar rationale likely applies to the other variables, including OUES and peak Circulatory Power, which lost their predictive value after Lasso regression. Even though Cohen's study identified peak Circulatory Power as the only independent predictor of outcome in patients with chronic HF, the findings in our study suggest a different context for early-stage HFpEF.(21) These results indicate a limited prognostic value of CPET variables in this patient population.

Our model, developed from the analysis of key predictors identified through Lasso regression (E/e' during effort, LA strain during effort, and maximum work rate), demonstrated high accuracy at 87.87%, alongside a sensitivity of 63.63% and a specificity of 100%. The ROC analysis further validated this, reporting an AUC of 0.818, which underscores the model's effectiveness in distinguishing between patients with and without cardiac decompensation. While the model exceled at correctly identifying patients without decompensation (true negatives), its ability to accurately detect all patients with decompensation (true positives) remained somewhat limited. These findings suggest that future studies, by incorporating refinements or additional predictors, could enhance the model's sensitivity and improve the identification of patients at risk for cardiac decompensation among those suspected of having HFpEF.

The small sample size may limit the generalizability of the findings, as a larger cohort could provide a more robust assessment of the prognostic value of CPET- ESE parameters in patients with suspected HFpEF.

CONCLUSIONS

Our study underscores the importance of integrating echocardiographic and cardiopulmonary exercise testing (CPET) parameters in the assessment of patients with suspected HFpEF. ESE proved to be a valuable tool for evaluating prognosis and risk stratification in patients with chronic exertional dyspnea and suspected HFpEF. The inclusion of LA strain at exercise significantly enhanced the predictive value of the classic echocardiographic parameter, the E/e' ratio at exercise. Additionally, adding maximum work rate further enhanced the prognostic accuracy of the model. While CPET parameters demonstrated some predictive potential, their added benefit for risk stratification in the early stages of HFpEF remains limited. However, the CPET test remains an important tool in evaluating patients with exertional dyspnea, allowing for the differentiation between various types of exertional dyspnea. This was not applicable in our study due to the exclusion of patients with known causes of dyspnea, such as pulmonary impairment.

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