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Peak atrio-ventricular mechanics predicts exercise tolerance in heart failure patients

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Abstract

Purpose: Exercise intolerance is a cardinal symptom of patients with heart failure (HF). We hypothesized that patients with HF with preserved ejection fraction (HFpEF) in comparison with those with reduced ejection fraction (HFrEF) have disproportionate exercise-induced impairment of left atrial (LA) function that may explain the effort intolerance..

Methods: Total 40 HFpEF patients, 40 HFrEF patients, and 20 matched healthy controls underwent resting and exercise stress transthoracic echocardiography using modified Bruce protocol with speckle-tracking derived assessments of peak atrial longitudinal strain (PALS) and left ventricular global longitudinal strain (LVGLS).

Results: In comparison to controls, PALS and LVGLS were reduced in HFpEF and HFrEF patients (P<0.01); however, the strain magnitudes were significantly lower in HFrEF than in HFpEF (P<0.01). Both HFpEF and HFrEF showed a 28% and 30% reduction in exercise time in comparison with controls (HFpEF, 363±152, HFrEF 352±91, controls, 505±42 seconds, P<0.01) and exercise-related rise in E/E' in HFpEF patients. However, during exercise PALS reduced from resting values by 26% (resting 23.1±4.7 and peak 18.5±3.5, P<0.01) in HFpEF but only 8% in HFrEF (resting 11.5±1.4 and peak 10.5±1.5, P<0.01), and remained unchanged in controls (resting 34±1.9 and peak 34.4±1.2, P=0.4). Regression analysis of the combined data from the HF patients and controls revealed that PALS was independently associated with exercise time such that a 1% reduction in PALS was associated with a 10 seconds reduction in exercise duration (p<0.01). . PALS at baseline and peak exercise differentiated normal from HF patients. LVGLS at baseline and peak exercise differentiated HFpEF from HFrEF and patients of HFpEF showed abnormality of both PALS and LVGLS.

Conclusion: Although left ventricle and LA strain are lower in HFrEF than HFpEF at rest and exercise compared to healthy controls, patients with HFpEF show more profound deterioration of LA reservoir function with exercise which appears to contribute to exercise intolerance.

Keywords: Heart failure, left atrium, exercise intolerance

Heart failure (HF) is a clinical syndrome characterized by the inability of the heart to meet the demands of the tissues, which results in symptoms of fatigue or dyspnea on exertion progressing to dyspnea at rest affecting quality of life. Approximately half of patients with signs and symptoms of heart failure have a normal left ventricular (LV) ejection fraction (EF) [1]. Accordingly, HF patients have been classified clinically and in trials using LV ejection fraction (EF) into HF with reduced LV EF<40% (HFrEF), HF with mid-range EF (40-50%), and HF with preserved EF >50% (HFpEF) [2]. In addition to structural and functional changes in the LV, left atrial (LA) remodeling and dysfunction are also common in this population[3, 4]. Specifically, for HFpEF, LA dilatation and LA dysfunction are independent risk factors for the development and progression of HF [5-8]. LA chamber dilation and dysfunction in HFpEF have been related to left ventricular (LV) diastolic dysfunction and elevated diastolic filling pressures [9, 10]. However, LA chamber enlargement and dysfunction may also occur due to a pattern of LA myopathy that develops concurrently with LV myopathy, or out of proportion to LV myopathy [11].

Exertional dyspnoea and fatigue are cardinal symptoms of both HFrEF and HFpEF. Despite the similar extent of exercise intolerance and prognosis seen in HFpEF and HFrEF, the contribution of LA along with LV mechanics towards the development of exercise intolerance have not been defined for the two HF syndromes [12-16]. Understanding the concurrent alterations in LV and LA mechanical function with stress may have pathophysiologic, therapeutic, and prognostic implications. Two-dimensional (2D) echocardiography combined with speckle tracking echocardiography (STE) offers the opportunity to study the left ventricular and atrial adaptations during exercise by analysing the specific role of the left atrium. [17] The coupled interactions of LV and LA and the cardiac-cycle phase-dependent adaptation of the LA reservoir and booster pump function may have relevance to the dyspnea sensation and exercise intolerance seen in HF. In this investigation we hypothesized that patients with HF with preserved ejection fraction (HFpEF) in comparison with those with reduced ejection fraction (HFrEF) have disproportionate exercise-related impairment of LA function that may explain the similar extent of dyspnea and effort intolerance observed in the two HF syndromes.

METHODS

Study population

The prospective cross-sectional study was conducted between May 2019 to Jan 2021. 109 stable subjects were initially screened of which 49 were of HFpEF, 40 of HFrEF and 20 age and sex-matched controls. 9 patients of HFpEF were excluded as 7 had atrial fibrillation and 2 had history of myocardial infarction in last 3 months. Subsequently 40 HFrEF, 40 HFpEF, and 20 age and sex-matched controls were finally enrolled in the study (Supplement Figure 1). Stable heart failure was defined as a patient being clinically stable for at least 6 weeks before enrolment and on optimal medical management. Patients were diagnosed as HFrEF who had signs and symptoms of heart failure with reduced LV ejection fraction (EF) $\leq$ 40% and as HFpEF, who had signs and symptoms of heart failure with structural and/ or functional cardiac abnormality and with raised N-terminal pro-b-type natriuretic peptide (NT pro-BNP).[18] Patients with valvular heart disease, severe arrhythmias including atrial fibrillation (AF), history of a recent acute coronary syndrome in the last 3 months, idiopathic pulmonary arterial hypertension, implanted LV assist device, pregnancy, active malignancy or inability to provide informed consent were excluded from the study. Patients with AF were excluded from the study as two-dimensional strain analysis for LA is difficult and is not standardized in patients with AF.[19] The clinical variables included demographics, New York Heart Association (NYHA) functional class, comorbidities, medications, vital signs, body mass index, and laboratory data, including hemoglobin, serum creatinine, and N-terminal pro-hormone beta natriuretic peptide (NT pro-BNP). All study participants provided written informed consent and the study was approved by the institutional ethics committee. All study procedures were performed in accordance with the declaration of Helsinki.

Transthoracic Echocardiography

All subjects underwent transthoracic echocardiography examinations with all procedures performed as per the recommendations provided by the American Society of Echocardiography (ASE) [7]. The echocardiography examination was performed in the left lateral decubitus position using a Vivid E95 system (GE Ultrasound, Horten, Norway) equipped with a 2.5 MHz matrix array transducer in keeping with current guidelines. 2-D gray-scale images were acquired over 3 heart cycles and analysed off-line (EchoPAC PC, version 2.0.2 GE Ultrasound, Wisconsin) by a single echocardiographer blinded to the data. All the images were acquired during end-expiratory breath-hold at a frame rate of 50-80 frames/sec. LV end-diastolic, end-systolic volume, and ejection fraction (EF) were measured using the Simpsons biplane method.

Stroke volume and cardiac measurements were made at the level of the LV outflow tract. For LA volumes, the 'method of disk' was used, which was then indexed to body surface area to derive LA volume index (LAVi). The early (E) and late (A) mitral flow velocities were recorded using a 5mm pulsed wave (PW) sample volume. Tricuspid regurgitation peak velocity (TRVmax) was recorded employing continuous-wave Doppler. Spectral tissue velocities were recorded in the septal and lateral mitral annulus using a 5mm PW sample volume and the early myocardial relaxation velocity (e´) was recorded. The E/e´ ratio was calculated from the average of septal and lateral myocardial velocities. LV mass was measured using the standard recommended guidelines. LV stiffness index was calculated by the ratio of E/e' to LV end-diastolic dimension in diastole. [13]

Myocardial deformation was analyzed by 2-D speckle tracking. LV global longitudinal strain (LV-GLS) was calculated as the average value of 12 segments obtained from the apical 4-,3- and 2-chamber views. LV endocardial border was traced in the end-systolic frame. The software automatically divides the entire circumference of the LV into equal segments and generates myocardial strain curves. It generates frame-by-frame tracking of the natural acoustic markers throughout the entire duration of the cardiac cycle. From these curves, subsequent peak-systolic strain curves were recorded for each of the myocardial segments and averaged to derive a global value which was used for the analysis.

LA global strain (LA-GS) was assessed using images obtained in apical 4- and 2-chamber views at a frame rate of 50-80 Hz. The ventricular cycle was used as the reference point (i.e. zero baselines) to calculate LA strain. The onset of the QRS complex was the zero reference, and all longitudinal LA strain values were positive. For generating LA strain curves, the LA endocardial border was manually traced in the apical 4- and 2- chamber views. The region of interest generated was subsequently adjusted to include the full thickness of the LA myocardium. In every patient, the software divided the LA into six separate segments, longitudinal strain curves were generated, and tracking was evaluated. Segments that failed to track were excluded from the final analysis; the remaining segments were averaged for each view. The following components of LA function (strain) were defined: LA reservoir strain = peak atrial longitudinal strain (PALS) and LA booster strain = peak atrial contraction strain (PACS) measured between the onset of the P wave and onset of the QRS complex (Figure 1); both the strains values were calculated by averaging the apical 4- and 2-chamber strain values. [8] LA stiffness index was calculated as the ratio of E/e' to LA reservoir strain with higher

values indicating greater LA stiffness and correlating with severe diastolic dysfunction. [12]

Exercise protocol

All patients enrolled in the study underwent a symptom-limited, graded exercise test using a modified Bruce protocol on a treadmill. Symptom limitation was defined uniformly by Borg rating of perceived exertion scale.[20] Heart rate data, blood pressure (BP), and echocardiographic data were obtained at rest (baseline i.e. before exercise) and 2-3 minutes of the exercise termination as diastolic abnormalities persists even after cessation of exercise.[21] All the standard echocardiographic images were again acquired post exercise on the same machine as described earlier.

Statistical analysis

All continuous variables were represented by mean and standard deviation. Categorical variables were expressed as percentages and distribution. P values less than 0.05 were considered to be statistically significant. The comparison of each echo parameter across groups was performed using one-way analysis of variance, while the pair-wise comparison was done using Tukey's post hoc test. The analyses were performed between data obtained at baseline and following peak exercise.. The change in the echo parameters between baseline and peak exercise state between the three groups were compared by using ANOVA test. The correlation between exercise time and baseline clinical and echocardiography variables (differences between peak exercise and baseline – resting values) were studied using Pearson's correlation coefficient. Variables of statistically significant relationship ($p<0.05$) were entered into a multivariable regression model analysis. The inter and intra-observer variability of echo parameters was assessed on 20 randomly selected patients and analyzed using an intraclass correlation coefficient. All analyses were performed using SPSS version 20.0 (IBM Corp.,USA). A $p<0.05$ was considered as significant.

Results

Demographics

The demographics and clinical characteristics are presented in Table 1. There were 40 patients in the HFpEF group with a mean age of 59 ± 7 years (15 males) and the mean BSA was

1.68±0.18 m^2. The average duration of heart failure symptoms was 2.00 ± 1.52 years. In the HFrEF category, the mean age was 57±6 years (25 males) and the mean BSA was 1.7±0.21 m^2. The average duration of heart failure symptoms was 2.58 ± 1.34 years. The mean NTproBNP was greater in HFrEF patients as compared to HFpEF and controls (2043± 1046 vs 1291 ± 1404 vs 207± 78 pg/ml, $p < 0.01$).

Baseline Structure and Haemodynamics

Patients with HFpEF were characterized by concentric remodeling with a normal EDV of 83±17 mL, increased LV mass of 115±23 g, and increased relative wall thickness of 0.43±0.07. Patients with HFrEF were characterized by eccentric remodeling with an increased end diastolic volume (EDV) of 100±27 mL and LV mass of 135±19 g and decreased relative wall thickness of 0.37±0.05 compared with control values. Compared to HFrEF, patients with HFpEF had a smaller volume and LV mass ($p<0.001$ for both). Heart rate (HR) and mean arterial pressure (MAP) were normal and not significantly different in both patients with HFrEF and HFpEF as compared to controls. (Table 2).

The mean cardiac output at rest was significantly higher in HFpEF as compared to HFrEF ($p< 0.01$). However, the mean systemic vascular resistance (SVR) at baseline was lower in HFpEF as compared to HFrEF ($p<0.01$). At rest, the mean LV ejection fraction, stroke volume, and cardiac power output were significantly higher in HFpEF than in HFrEF, ($p < 0.01$). The mean right ventricular systolic parameters were significantly higher in HFpEF than HFrEF at baseline ($p<0.01$).

The mean LVGLS at baseline was significantly lower in both HFpEF and HFrEF as compared to controls, and significantly lower in HFrEF as compared to HFpEF (-15.9±2.7 % vs -11.1±3.4 % vs -20.3±0.9 %, $p <0.01$). The mean peak atrial longitudinal strain (PALS) at rest was significantly lower in HFpEF and HFrEF as compared to controls with the lowest in HFrEF (23.1±4.7 vs 11.5±1.4 vs 34.03±1.85, $p<0.01$). The mean peak atrial contraction strain (PACS) at rest was significantly lower in HFpEF and HFrEF as compared to controls with the lowest in HFrEF (8.5±1.6 vs 2.6±0.8 vs 9.8±1.8, $p< 0.01$). There was no significant difference in the mean E/E' at rest between the two groups. At rest, the mean LA stiffness index was significantly lower in HFpEF as compared to HFrEF (0.57 ± 0.22 vs 1.19 ± 0.63 mm Hg/ml, $p<0.01$). However, the mean LV stiffness index was similar in HFpEF to HFrEF.

Response to Exercise

The mean exercise time for HFpEF and HFrEF were similar and were significantly lower by 28% and 30% in HFpEF and HFrEF compared with controls (363±152 vs. 352±91 vs. 505±42, p<0.01). Similarly, the resting and exercise-related changes in heart rate, mean arterial pressure, cardiac power output, and RV systolic pressure were similar both in HFpEF and HFrEF. Although the mean LVEF was maintained in both HFpEF and HFrEF after exercise as compared to baseline, the mean stroke volume increased significantly in HFpEF (p<0.01). There was no significant change in LVGLS and RV free wall strain in HFpEF and HFrEF after exercise. In regards to atrial mechanics, there was a significant decrease in PALS in HFpEF after exercise (23.1±4.7 vs 18.5±3.5, p< 0.0001), which was not seen in HFrEF (Figure 2). There were no significant differences in the exercise changes in peak atrial contraction strain for both groups (PACS). Similarly, both HF groups demonstrated a significant increase in LA stiffness index (p<0.01) after exercise. However, a significant increase in LV stiffness index was only seen in HFpEF (0.16 ± 0.05 vs 0.18 ± 0.07 ml^{-1}, p<0.01). There was a significant rise in E/E' in HFpEF patients after exercise (12.57±3.3 vs 14.44±5.1, p<0.01), which was not seen in HFrEF patients.

Multivariate Regression:

On univariate regression analysis, exercise time significantly correlated with mean arterial pressure, NTproBNP, serum creatinine, septal e' velocity, baseline PALS and baseline LVGLS (p<0.01 for all) (Supplement Table 1). Table 3 shows the correlation between exercise time and baseline clinical variables and the change in magnitude of echocardiography variable expressed as a difference of the peak and baseline (resting) values for the data combined from both heart failure groups and controls. Exercise time was independently associated with a change in cardiac output (p=0.02), mean arterial pressure (p=0.01), PALS (p<0.01), and end-diastolic RV size (p=0.05) with delta PALs having the highest standardised coefficient of all the variables (Supplement table 1). A reduction in exercise related magnitude of PALS was seen in 82.5% HFpEF cases, 67.5% HFrEF cases and 35% controls. Conversely, an improvement in exercise related magnitude of PALS was seen in 17.5% HFpEF cases, 32.5% HFrEF cases and 65% controls. Regression analysis of the combined data revealed that a 1% reduction in PALS was associated with 10 seconds reduction in exercise time respectively. On sub-group analysis PALs change showed significant effect on exercise time. In HFpEF group, MAP also showed significant relationship with time in addition to PALs change. In HFrEF

group, serum creatinine showed significant relation with exercise time in addition to PALs change (Supplement Table 2). We assessed correlations between PALS and E/E' and TR V max and no collinearity was detected. However, there was significant correlations of baseline and peak PALS with LAVi, CO, E' both at baseline and peak and also with change in CO ($p<0.001$) (Supplement Table 3).

Reproducibility

Intraclass correlation coefficients for intra- and inter-observer variability for key echocardiography variables are presented in Supplement Table 4.

DISCUSSION

In this prospective study, we compared left atrial and ventricular longitudinal strain patterns at rest and after peak exercise in a stable cohort encompassing HFrEF, HFpEF, and controls. The principal findings were: 1) compared to controls, both HFpEF and HFrEF demonstrated significantly lower PALS and LVGLS at rest and after exercise, although the magnitude of strains was lower in HFrEF than HFpEF; 2) in response to exercise, the PALS was substantially decreased in HFpEF by 26%, with no significant difference noted in other groups; 3) a multivariable regression model revealed a change in PALS as an independent predictor of exercise time. This suggests that progressive LA remodeling leads to attenuation of LA reservoir capacity which contributes to exercise intolerance in HFpEF.

Chronotropic incompetence is noted in patients of HFpEF.[22] Whether HFpEF causes this or is the result of exercise intolerance has been debated. Our cohort of patients were characterised by absence of chronotropic incompetence. The physiologic determinants of heart response to exercise are alteration in autonomic tone during different stages of exercise, responsiveness of sinoatrial node to neurohumoral stimuli and the amount and intensity of exercise performed.[23] Studies have reported that chronotropic response to exercise is a surrogate of maximal exercise capacity.[24]

In the present study, the pulmonary artery systolic pressure (PASP) derived from tricuspid jet peak velocity was higher in HFpEF and HFrEF at baseline as compared to controls. It increased significantly after peak exercise and more so in HFrEF. In individual subjects, assessment of PASP by transthoracic echocardiographic doppler assessment of tricuspid regurgitation (TR) accurately predicts the PASP observed by invasive measurements and now has become non-invasive method of choice.[25, 26] Sometimes, estimated PASP by echo can have reduced

accuracy due to poor quality of TR jet, difficulty in acquiring TR velocity or when right atrial pressure assessment if difficult.[27]

Two-dimensional (2D) echocardiography by speckle tracking echocardiography (STE) is used for HF patients to assess LV function and deformation. It provides quantification of both regional and global functions. [28, 29] Many studies have looked at the exercise response to LV systolic properties in HFpEF patients. Some have reported blunted responses to LV systolic functions, while others have shown no difference in systolic response of HFpEF to exercise. [30, 31]. In the present study, no significant exercise-related changes were seen in either LV systolic function as measured using either EF or GLS. However, HFpEF patients demonstrated significant improvement in their stroke volume after physiological exercise which was not seen in HFrEF patients. Groepenhoff et al reported similar findings [32]. A significant rise in cardiac output and cardiac power output was seen in both HFpEF and HFrEF patients.

While LV GLS quantifies the systolic deformation of the LV as the base descends toward the apex, PALS measures the maximum ability of the LA in elongating and as a reservoir during LV systole. The LA-reservoir function assessment plays an important role in disease progression in various clinical states including HF and is influenced both by the LV performance and the intrinsic LA compliance. [33] Reduced LA reservoir strain has been associated with progression of HFpEF and shown to have a strong prognostic value [4-6]. More specifically, reduced LA reservoir strain has been associated with increased pulmonary capillary wedge pressure as a mechanistic explanation of exercise intolerance seen in HFpEF. [14-16, 34]. In a pre-clinical setting under physiological conditions and in humans with mild LV diastolic dysfunction, LA reservoir strain increased during exercise, which may be due to increased speed of LV filling and rise in LA preload.[35, 36] Very few studies have looked at the exercise response to LA deformation in various cardiovascular conditions. Sugimoto et al. showed that exercise LA reservoir and pump function were impaired in patients of mitral regurgitations.[37] Sugimoto et al in another study in heart failure patients showed that LA strains are blunted during exercise and are associated with a worse cardiopulmonary performance.[38] However, the LA with LV function have a coupled behavior such that peak LV shortening strains that results into mitral annular decent in systole has correlation with peak left atrial expansion and reservoir function. This results in complexities in uncovering the causal relationships between LA versus LV mechanical contributions to exercise related symptoms since a modest correlation between LA and LV strain is also observed in HFpEF.[9]

This has resulted in a suggestion that the relationship between LA reservoir strain and adverse outcomes may simply represent LV dysfunction, as measured by reduced LV strain.[6, 10] Our data also suggests that characterization of exercise-related changes in atrial and ventricular mechanics helps uncover the underlying pathophysiological abnormalities in cardiac function that can differentiate HFpEF from HFrEF. Although both GLS and PALS are interrelated, the multivariable regression analysis showed only the change in PALS to be associated with exercise time after adjusting for other clinical and echocardiographic variables. This is consistent with recent studies that have suggested a important role of the LA, [39] although HFpEF is a disease where the cumulative burden of LV and LA mechanical dysfunction results. For example, a recent analysis of the PARAGON-HF trial patients with HFpEF demonstrated a pattern of LV mechanical dysfunction as seen in HFrEF. [40] Thus, a detailed assessment of LV and LA function during rest and exercise may have further incremental value to differentiate the subsets of HFpEF patients for more individualized therapeutic interventions.

Limitations

There are several limitations to our study. First, we did not perform an invasive assessment of left atrial filling pressures since this was not clinically indicated. However, the diagnosis of heart failure was clinically established in all patients with confirmation of elevated NT-ProBNP and abnormal echocardiography findings. Second, we did not perform a complete assessment of 3D LV mechanical deformation including assessment of LV twist mechanics since the assessment of circumferential, radial, and twist mechanics has marked variability and is not recommended for routine clinical application. Thirdly, cardio-pulmonary exercise testing was not used to understand anaerobic threshold. However symptom limitation was defined uniformly by Borg rating of perceived exertion scale.[20] In the present study we used treadmill test as a physiological stress test protocol. We did not use semi-supine bicycle stress test, which helps in continuous recording of images during exercise. Treadmill stress test allowed image acquisition before the test and after stopping the test and provided information regarding functional, structural, diastolic and systolic parameters.[41] Finally, the overall sample size was modest and powered for understanding the pathophysiological differences in two HF syndromes and not for deriving prognostic information on follow-up.

Conclusion

Left ventricle and left atrial strains are lower in HFrEF than HFpEF both rest and exercise. Patients with HFpEF show more profound deterioration of LA reservoir function with exercise. Thus, a unique pattern of LA abnormalities in HFpEF contributes to an equivalent degree of effort intolerance as seen in HFrEF.

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Figure Legends

Figure 1: Representative left atrial strain in at rest and after peak exercise in heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF) and normal control. X-axis= time in ms. Note each graph has different range for the Y-axis. PALS is peak atrial longitudinal strain.

Figure 2:Figure representing LVGLS and PALS at baseline and at peak exercise in the cohort

Tables Legend

Table 1: Demography and clinical characteristics

Table 2: Functional, structural, echocardiographic and hemodynamic characteristics at baseline and after peak exercise

Table 3: Multivariable regression model for prediction of exercise time

Supplementary File

Supplement Table 1: Univariate regression model for prediction of exercise time

Supplement Table 2: Subgroup analysis across 3 cohorts

Supplement Table 3: Pearson correlation between LA strain (PALS) and other variables

Supplement Table 4: Intraclass correlation coefficient of echocardiographic parameters at baseline and peak exercise.

Supplement Figure 1: Figure showing flow chart about study cohort inclusion

Table 1: Demography and clinical characteristics

Parameter	HFpEF (n=40)	HFrEF (n=40)	Healthy controls (n=20)
Age (years)	59 ± 7	57± 6	56 ± 6
Male	15	25	13
Height (cm)	155 ± 8	161± 9	163± 7
Weight (Kg)	69.5 ± 14.9	65.7± 10.5	62.7± 6.2
BSA (m^2)	1.68 ± 0.18	1.7 ± 0.21	1.68± 0.11
Duration of HF (years)	2.00 ± 1.52	2.58± 1.34	-
CAD	12	27	-
HT	36	23	-
DM	13	22	-
Smoker	6	14	
B-blocker	12	35	-
ACEI/ARB	34	12	-
ARNI	-	28	-
CCB	5	4	-
Hb (g%)	11.66 ± 1.7	11.64± 1.3	12.88± 0.9
TSH (IU/ml)	2.03 ± 1.27	2.19± 0.95	1.81± 0.49
NTproBNP (pg/ml)	1291 ± 1404*	2043± 1046*	207± 78
Serum sodium (meq/l)	138.2 ± 4.71	135.5± 4.87	138.3± 3.47
Serum potassium (meq/l)	4.09 ± 0.45	3.85± 0.5	4± 0.1
Serum creatinine (mg/dl)	0.95 ± 0.34	1.17± 0.23	0.95± 0.11
Total Cholesterol (mgld/l)	155.8 ± 20.9	177.7 ± 25.5	171.4 ± 24.8
LDL (mg/dl)	99.9 ± 27.2	114.5 ± 15.9	117.3 ± 12.5
HDL (mg/dl)	42.7 ± 7.9	37.1 ± 3.9	38.7 ± 3.7

*p<0.01, HFpEF- Heart failure with preserved ejection fraction, HFrEF- Heart failure with reduced ejection fraction, BSA- Body surface area, CAD- Coronary artery disease, HT- Hypertension, DM- Diabetes mellitus, ACEI- Angiotensin-converting enzyme inhibitor, ARB-Angiotensin receptor blocker, ARNI- Angiotensin receptor –neprilysin inhibitor, CCB- Calcium channel blocker, Hb- Haemoglobin, TSH- Thyroid-stimulating hormone, NTproBNP- N-terminal pro-b-type natriuretic peptide, LDL- Low-density lipoprotein, HDL – High-density lipoprotein

Table 2: Functional, structural, echocardiographic and hemodynamic characteristics at baseline and after peak exercise

Parameters	HFpEF (n=40)		HFrEF (n=40)		Control (n=20)	
	Baseline	Exercise	Baseline	Exercise	Baseline	Exercise
Functional						
Heart Rate (beats/min)	77±13.6	116.7± 11.5*	81.1±10.6	114.5±11.5*	72.1 ±6.9	116.2±5.2*
MAP (mm Hg)	93.2±6	112±6.5*	94.4±5.9	114.2±5.9*	93.6 ±4.9	113.5 ±3.4*
TR (m/sec)	0.13±0.33	1±0.23*	0.25±0.44	1.00*	-	-
PASP (mm Hg)	35.8±2.4	43.7±7**	38.4±4.8	49.1±3.7**	-	-
LVOT VTI (cm)	21.6±4.38	24.5±4.35*	14.3±2.63	14.23±3.14	23.5±2.19	26.2±2.41*
Structural						
LV mass (gm)	115±23.2	-	134.7±19.72	-	53.4±7.19	-
LV Mass index (g/m^2)	68.8±14.3	-	78.7±13.03		31.5±3.7	-
Relative wall thickness	0.43±0.07	-	0.37±0.05	-	0.32±0.04	-
LVOT (cm)	2.11±0.15	2.11±0.14	2.02±0.06	2.02±0.06	2.02±0.04	2.03±0.06
LVEDV 4C(ml)	83±17	81±17	100±27	98±25	88±9	85±7**
LVESV 4C(ml)	41±9	40±10	64±17	64±17	41±3	39±3
Diastolic						
E (m/sec)	0.91±0.24	1.08± 0.25*	0.7±0.23	0.81±0.22**	0.79±0.15	0.93±0.1**
A (m/sec)	0.83±0.18	0.92± 0.17**	0.68±0.2	0.74± 0.2	0.77±0.16	0.85±0.15**
E' septal (m/sec)	0.07±0.02	0.07±0.02	0.05±0.01	0.05±0.01	0.08±0.01	0.08±0.01
E' lateral (m/sec)	0.08±0.02	0.09±0.02	0.06±0.01	0.07±0.01	0.09±0.01	0.09±0.01
E/E'	12.6±3.3	14.4±5.1**	13.8±5.85	13.9±5.47	9.37±2.01	11.3±1.24*
dTE (msec)	198.3±40.7	159.7±41.8*	184.1±42.3	132.7±23.2*	197.4±20.5	135.8±17.1*
Systolic						
LVEF (%)	54.2±3.11	55.5±3.47	33.9±6.26	35.6±5.01	60.1±1.36	60.1±1.27
Stroke volume (ml/beat)	75.3±19.1	85.1±16.3**	45.6±9.19	46.7±12.1	75.±7.6	85±11.1*
Cardiac Power output (W)	1.14±0.30	2.47 ±0.59*	0.77±0.21	1.31±0.26*	1.17±1.38	2.47±0.28*
LVGLS (%)	-15.9±2.7	-15.5±3.2	-11.1±3.4	-11±2.6	-20.3±0.9	-19.9±0.8
TAPSE (cm)	2.18 ±0.27	2.23±0.37	1.99±0.19	1.95±0.12	2.07±0.13	2.03±0.2
RVS' (m/sec)	0.13±0.02	0.14±0.03	0.11±0.02	0.11±0.01	0.13±0.02	0.12±0.01

RV free wall strain (%)	-22.6±2.43	-22.5±1.7	-20±1.26	-20±1.41	-22.2±1.36	-21.9±1.38
PALS (%)	23.1±4.7	18.5±3.5*	11.5±1.4	10.5±1.5	34±1.9	34.4±1.2
PACS (%)	8.5±1.6	8.1±2.2	2.6±0.8	2.5±0.7	9.8±1.8	10.8±1.2**
Hemodynamics						
Cardiac output (L/min)	5.51±1.35	9.93±2.23*	3.7±0.91	5.18±1.04**	5.38±0.6	9.84±1.04*
SVR (dynes/sec/cm^{-5})	1269.3±248.9	841.7±167.7*	1997.9±463.9	1644.9±291.4*	1408.4±185.1	924.5±88*
LA stiffness index (mm Hg/ml)	0.57 ± 0.22	0.83 ± 0.46*	1.19 ± 0.63	1.37 ± 0.61**	0.27 ± 0.06	0.33 ± 0.04*
LV stiffness index (ml^{-1})	0.16 ± 0.05	0.18 ± 0.07**	0.14 ± 0.07	0.15 ± 0.06	0.11 ± 0.02	0.13 ± 0.02*
Ventricular elastance (mm Hg/ml)	3.26 ± 0.74	3.97 ± 0.98**	2.06 ± 0.53	2.58 ± 0.75*	3.15 ± 0.34	3.89 ± 0.36**
Exercise time (sec)		363±152		352±91		505±42

* $p < 0.001$, **$p < 0.01$

HFpEF- Heart failure with preserved ejection fraction, HFrEF- Heart failure with reduced ejection fraction, MAP- mean arterial pressure, E- Early diastolic velocity, A-late diastolic velocity, E'- early tissue Doppler velocity, dTE- deceleration time, LVOT- left ventricular outflow tract, VTI- velocity-time integral, TR- tricuspid regurgitation, LV – left ventricular, EDV – end-diastolic volume, ESV- end-systolic volume, EF- ejection fraction, PASP- pulmonary artery systolic pressure, TAPSE- tricuspid annular peak systolic excursion, RVS'- right ventricular tissue systolic wave, GLS- global longitudinal strain, 4C- four-chamber, 3C- three-chamber, 2C- two-chamber, PALS – peak atrial longitudinal strain, PACS- peak atrial contraction strain, SVR – systemic vascular resistance

Table 3:Multivariable regression model for prediction of exercise time

Parameter	Unstandardized Coefficients		Standardized Coefficients	t	P-value	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Age	-0.532	1.796	-0.026	-0.296	0.77	-4.10	3.04
Sex	-11.549	22.471	-0.045	-0.514	0.61	-56.23	33.14
BMI	-1.203	2.513	-0.044	-0.479	0.63	-6.21	3.79
MAP	-5.646	2.064	-0.235	-2.735	0.01	-9.75	-1.54
NT Pro BNP	-0.003	0.011	-0.030	-0.278	0.78	-0.03	0.02
Serum Creatinine	-83.629	44.270	-0.186	-1.889	0.06	-171.67	4.41
PALS baseline	2.603	2.732	0.185	0.953	0.34	-2.830	8.037
Septal e' baseline	506.546	1020.540	0.071	0.496	0.62	-1522.91	2536.01
LVGLS baseline	-2.300	4.606	-0.080	-0.499	0.62	-11.461	6.860
CO change	0.006	0.008	0.090	0.697	0.49	-0.010	0.022
PALS change	13.087	3.838	0.399	3.410	0.001	5.454	20.720
TR change	23.877	33.166	0.090	0.720	0.47	-42.078	89.831
RVS change	-962.742	551.820	-0.181	-1.745	0.09	-2060.09	134.61
Septal E' change	-956.593	1052.961	-0.099	-0.908	0.37	-3050.52	1137.34
LV GLS change	4.457	6.010	0.076	0.741	0.46	-7.49	16.41

Multiple regression with exercise time as dependent variable and age, sex, body mass index (BMI), N-terminal pro-b-type natriuretic peptide (NTproBNP), serum creatinine, mean arterial pressure at peak exercise (MAP), and change in cardiac output (CO-change), peak left atrial strain (PALS-change), peak tricuspid regurgitation velocity (TR-change), right ventricular size in diastole (RVSd-change), and Septal E' (Septal-E'-change), left ventricular global longitudinal strain (LVGLS-change) as independent predictors of exercise time. The overall model R^2=0.45 and adjusted R^2=0.35

Author Statement

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Supplementary Material