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Original Article

Determinants of exercise capacity in patients with heart failure without left ventricular hypertrophy

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ABSTRACT

Background: Determinants of exercise intolerance in a phenotype of heart failure with preserved ejection fraction (HFpEF) with normal left ventricular (LV) structure have not been fully elucidated.
Methods: Cardiopulmonary exercise testing and exercise-stress echocardiography were performed in 44 HFpEF patients without LV hypertrophy. Exercise capacity was determined by peak oxygen consumption (peak VO_2). Doppler-derived cardiac output (CO), transmitral E velocity, systolic (LV-s′) and early diastolic mitral annular velocities (e′), systolic pulmonary artery (PA) pressure (SPAP), tricuspid annular plane systolic excursion (TAPSE), and peak systolic right ventricular (RV) free wall velocity (RV-s′) were measured at rest and exercise. E/e′ and TAPSE/SPAP were used as an LV filling pressure parameter and RV-PA coupling, respectively.
Results: During exercise, CO, LV-s′, RV-s′, e′, and SPAP were significantly increased ($p < 0.05$ for all), whereas E/e′ remained unchanged and TAPSE/SPAP was significantly reduced ($p < 0.001$). SPAP was higher and TAPSE/SPAP was lower at peak exercise in patients showing lower-half peak VO_2. In univariable analyses, LV-s′ ($R = 0.35$, $p = 0.022$), SPAP ($R = -0.40$, $p = 0.008$), RV-s′ ($R = 0.47$, $p = 0.002$), and TAPSE/SPAP ($R = 0.42$, $p = 0.005$) were significantly correlated with peak VO_2. In multivariable analyses, not only SPAP, but also TAPSE/SPAP independently determined peak VO_2 even after the adjustment for clinically relevant parameters.
Conclusions: In HFpEF patients without LV hypertrophy, altered RV-PA coupling by exercise could be associated with exercise intolerance, which might not be caused by elevated LV filling pressure.
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Introduction

Limited exercise capacity is a major symptom in patients with chronic heart failure (HF) regardless of the left ventricular (LV) ejection fraction (EF) [1]. Over the past decade, contributors to the reduced exercise capacity are being gradually elucidated in HF with preserved LV EF (HFpEF), that is, abnormal increase in LV filling pressure, blunted heart

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rate response, peripheral factors, and impaired right ventricular (RV) to pulmonary artery (PA) coupling during exercise [2–5]. Among the contributing factors, elevated LV filling pressure caused by increased LV stiffness manifests the characteristics of HFpEF patients [5–7]. And in general, the changes in LV properties are assumed to result from LV hypertrophy or concentric remodeling [6]. On the other hand, a substantial proportion of HFpEF patients are reported to lack abnormal cardiac morphology [8,9]. They are considered a subset of patients with minor cardiac loads and degeneration, but little is known what leads to impaired exercise tolerance in LV properties. We thought that by focusing on this specific subset, we might approach the mechanisms that lead to impaired exercise capacity in HFpEF without LV hypertrophy.

Methods

Study population and protocol

This study was designed as a prospective observational study of adult HF patients in a single tertiary hospital from September 2019 to July 2021. Patients were included according to echocardiographic criteria: I) normal LV mass index (≤115 g/m^2 in men, ≤95 g/m^2 in women) and II) preserved LV ejection fraction ≥50 % and met at least one of the following clinical criteria: 1) history of HF hospitalization, 2) presenting any HF symptoms, 3) signs of LV diastolic dysfunction according to the guidelines [10], 4) elevated plasma N-terminal brain natriuretic peptide (NT-proBNP) levels (≥125 pg/mL), and 5) those with history of atrial fibrillation (AF). To avoid including AF patients without HFpEF, we excluded AF patients who lacked objective evidence of HFpEF; i.e. HFA-PEFF score < 5 [11]. Other exclusion criteria were set at known cardiomyopathy or myocardial diseases, significant left-sided valvular heart disease (≥moderate regurgitation, ≥mild stenosis), prior cardiac surgery, congenital heart disease, left-to-right shunt, unstable coronary artery disease, and constrictive pericarditis. Also, patients with lung disease were carefully excluded based on the findings of chest X-rays and spirometry. Accordingly, 52 patients were included in the final analysis. After written informed consent was obtained, blood samples were stored, and exercise-stress echocardiography (ESE), cardiopulmonary exercise testing (CPET), and cardiac magnetic resonance (CMR) were examined within 7 days. When the patient was given a β blocker, exercise testing was done under its continuation. The study was performed in accordance with the declaration of Helsinki, and our institutional review board approved the protocol.

Data collection

We collected the following data from all study participants: body mass index, vital signs, comorbidities, medications, New York Heart Association (NYHA) functional class, clinical frailty scale (CFS), HFA-PEFF score, and laboratory analysis. Systemic hypertension was defined as elevated resting blood pressure (systolic blood pressure ≥ 140 mm Hg) or taking medication including calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), or beta-blockers. HFA-PEFF score was calculated using the recently proposed algorithm using Step 2 [11], accounting for e′, E/e′, TR peak velocity, LAVI, LVMI, and serum NT-proBNP level. In addition, serum levels of procollagen-III-peptide (P-III-P) were measured on the immunoradiometric assay (BML, Tokyo, Japan) to obtain a marker of myocardial fibrosis.

Cardiopulmonary exercise testing

A symptom-limited CPET was performed using an upright electromechanical bicycle ergometer (Aerobike 75XLII; Combi Wellness, Tokyo, Japan) using a ramp protocol. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured using simultaneous respiratory gas analysis with a breathing apparatus (Aeromonitor AE-300S; Minato Medical Science, Osaka, Japan). Exercise capacity was assessed by the highest value of maximum VO_2 (peak VO_2). The maximum work and anaerobic threshold (AT) determined by the V-slope method were also measured [12]. Ventilatory efficiency was expressed by the slope of VE/VCO_2.

Exercise stress echocardiography

ESE was performed by using a supine bicycle ergometer (Angio V2; Lode BV, Groningen, Netherlands) and an iE33 ultrasound system with an S5-1 transducer (Philips Ultrasound, Bothell WA, USA). To adjust the workload among the patients, we defined submaximal workload as the level of AT and the peak workload as 80 % of the peak load (AT and peak load were adapted from the result of CPET) [13]. The workload was increased to the level of AT in a minute and two-dimensional, Doppler, and color M-mode Doppler (CMMD) echocardiographic images at submaximal exercise were acquired within 3 min. After that, the workload was further increased to the peak level in the following 2 min, and images at peak exercise were obtained. Standard measurements of the LV and left atrial (LA) chambers were obtained in accordance with current recommendations [14]. Stroke volume (SV) was calculated from the time velocity integral of the LV ejection flow and the diameter of the LV outflow tract. Cardiac output was calculated as SV times heart rate. Transmitral Doppler flow was recorded, and peak early-diastolic velocity (E) was measured. Peak systolic (s′) and early-diastolic (e′) septal mitral annular velocities were measured from the apical 4-chamber view and the ratio of E to septal e′ (E/e′) was calculated. CMMD images were recorded with the cursor parallel to LV inflow in the apical 4-chamber view to analyze intraventricular pressure difference (IVPD). Tricuspid regurgitation pressure gradient (TRPG) was estimated by continuous Doppler image and systolic pulmonary artery pressure (SPAP) was estimated by adding right atrial pressure of 10 mm Hg [15]. In 5 patients whose TRPG was not available, SPAP was assumed to be 20 mm Hg [16]. Mean pulmonary artery pressure was estimated by using the following formula: Mean pulmonary artery pressure = 0.61 × SPAP + 2 mm Hg [17]. Total pulmonary resistance (TPR) was calculated as mean pulmonary artery pressure divided by cardiac output. RV functional indices including tricuspid annular plane systolic excursion (TAPSE), peak systolic RV free wall velocity (RV-s′), and RV fractional area change (RVFAC) were measured according to the current guideline [14]. RV-PA coupling was assessed by TAPSE/SPAP [3]. In patients with AF at the time of evaluation, all measurements were repeated at least three times and averaged.

Speckle tracking method

LV global longitudinal strain (GLS) were assessed using the speckle tracking method. Two-dimensional echocardiographic images were analyzed offline by using vendor-independent software (2D Strain Analysis software version TTA2.4, TomTec Imaging Systems, Unterschleissheim, Germany) as previously reported [18]. LV endocardial border was manually traced in the apical four-, two-, and three-chamber views to determine LV global longitudinal strain (GLS). GLS was then averaged and expressed as an absolute value.

Analysis of the IVPD with the use of CMMD images

For the estimation of early-diastolic IVPD, CMMD images were analyzed using an automated analysis algorithm based on Matlab (The Mathworks, Natick, MA, USA). Briefly, the temporal profile of the IVPD from the mitral annulus to the LV apex was determined to integrate the Euler equation, and the early-diastolic peak of the IVPD was measured [13,19]. This method has been validated by comparison with direct measurements with micromanometers [20].

Cardiac magnetic resonance imaging

CMR was performed using a 3T whole-body scanner (Ingenia Elision X or Achieva TX; Philips Medical Systems, Best, the Netherlands) with dS Torso/dS Posterior coil or a 32-channel phased-array receiver torso-cardiac coil with a breath-holding expiration. Gadolinium-enhanced CMR was performed with intravenous gadobutrol administration (0.1 mmol/kg, Gadovist; Bayer Yakuhin, Osaka, Japan). Ten minutes after the contrast injection, inversion recovery-prepared, three-dimensional turbo field echo pulse sequence with electrocardiogram gating was performed to obtain a delayed-enhancement image with fat saturation. The imaging parameters were as follows: slice thickness = 10 mm; FOV = 380 mm; matrix size = 212 × 160 or 256 × 167; TR/TE = 3.6/1.7 or 3.7/2.3 ms; flip angle = 15° or 10°. Look–Locker sequence was performed prior to myocardial delayed-enhancement imaging to null the signal intensity of normal myocardium. Hyper-enhanced (late gadolinium enhancement; LGE) lesions were visually evaluated in the whole LV wall by an experienced radiologist (S.T.). For pre- and post-contrast T_1-mapping, LV short-axis image at midventricular level was obtained using a modified Look-Locker inversion recovery sequence with the following parameters: slice thickness = 10 mm; FOV = 300 mm; matrix size = 152 × 150 or 160 × 158; TR/TE = 2.3 ms/1.0 ms; flip angle = 20°. Pre- (native) and post-contrast T_1 values were measured by setting oval region of interest (ROI) (larger than 10 mm^2) in the septum of mid-LV using a standard DICOM viewer (XTREK view, J-MAC SYSTEM Inc., Sapporo, Japan). Areas of LGE lesions were visually excluded from the ROI to avoid artificially elevated values. These measurements were performed by an experienced radiologist (S.T.). Extracellular volume fraction (ECV) was calculated using pre- and post-contrast T1 values of myocardium and blood pool ($T_{1\ myo\ pre}$, $T_{1\ myo\ post}$, $T_{1\ blood\ pre}$, and $T_{1\ blood\ post}$, respectively) as follows: ECV (%) = (100 − hematocrit (%)) × $(1/T_{1\ myo\ post} - 1/T_{1\ myo\ pre})/(1/T_{1\ blood\ post} - 1/T_{1\ blood\ pre})$ [21]. Venous blood samples for hematocrit were measured on the same day as the CMR study.

Table 1
Patients' characteristics.

Variables ($n = 44$)	
Age, years	69 ± 10
Male	27 (61)
Body mass index, kg/m^2	24.4 ± 3.9
Systolic blood pressure, mm Hg	121 ± 20
Heart rate, bpm	68 ± 13
Comorbidity	
Hypertension	39 (89)
Dyslipidemia	11 (25)
Diabetes mellitus	5 (11)
CKD ≥ stage 3 (eGFR ≤ 60 mL/min/1.73 m^2)	25 (57)
Atrial fibrillation	6 (14)
Medications	
ACEI or ARB, n (%)	19 (43)
Beta-blocker, n (%)	23 (52)
Diuretics, n (%)	10 (23)
NYHA	
I	21 (48)
II	23 (52)
CFS	
1	23 (52)
2	18 (41)
3	3 (7)
HFA-PEFF score	
Definite HFpEF (≥5 points)	20 (45)
Intermediate score (2–4 points)	20 (45)
HFpEF unlikely (≤1 point)	4 (9)
Laboratory data	
Hemoglobin, g/dL	13.2 ± 1.6
Albumin, g/dL	4.1 ± 0.3
Creatinine, mg/dL	0.9 (0.8–1.1)
eGFR, mL/min/1.73 m^2	58.3 ± 15.1
NT-proBNP level, pg/mL	179 (67–485)
P-III-P, U/mL	0.6 (0.5–0.9)
Echocardiographic data	
LV end-diastolic volume, mL	81.1 ± 22.6
LV end-systolic volume, mL	37.5 ± 15.8
LV ejection fraction, %	63 ± 6
LV mass index, g/m^2	79.1 (65.4–90.1)
Relative wall thickness	0.36 ± 0.06
LA volume index, mL/m^2	43.6 ± 24.8
E wave velocity, cm/s	69.7 ± 20.8
Deceleration time, ms	210 ± 62
E/A ($n = 38$)	1 ± 0.5
Medial e′, cm/s	6.4 ± 2.2
Lateral e′, cm/s	8.7 ± 3.3
E/e′	10.9 ± 6.9
TAPSE, mm	20 ± 4
RV-s′, cm/s	11.3 ± 1.8
RVFAC, %	42 ± 6.4
TRPG, mm Hg ($n = 36$)	24 ± 5
Moderate tricuspid regurgitation	2 (5)
CPET data	
Peak RER	1.2 ± 0.1
AT Load, watts	61 ± 20
AT, mL/min/kg	12.1 ± 2.7
Peak Load, watts	95 ± 29
Peak VO_2, mL/min/kg	17.5 ± 4.4
VE/VCO_2 slope	32.7 ± 5.2
CMR data	
LGE ($n = 34$)	17 (50)
Native T1, ms (n = 36)	1286 ± 43.4
ECV, % (n = 34)	29.1 ± 3.1

Notes to Table 1:
Data are expressed as mean ± SD, median (IQR), or n (%).CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; NYHA, New York Heart Association; CFS, clinical frailty scale; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; P-III-P, procollagen III propeptide; LV, left ventricular; LA, left atrial; E, early-diastolic transmitral flow velocity; e′, early-diastolic mitral annular velocity; E/e′, ratio of E to e′; TAPSE, tricuspid annular plane systolic excursion; RV-s′, peak systolic right ventricular free wall velocity; RVFAC, RV fractional area change; CPET, cardiopulmonary exercise test; RER, respiratory exchange ratio; AT, anaerobic threshold; VO_2, oxygen consumption; VE/VCO_2, minute ventilation/carbon dioxide production; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; ECV, extracellular volume fraction.

Statistical analysis

Continuous data were expressed as mean ± standard deviation or median (interquartile range) as appropriate. Paired *t*-test was used to compare continuous variables between the two groups. Categorical variables were presented as numbers (%) and compared between different groups by using chi-square test. ESE indices were summarized according to peak VO_2 upper or lower than median value (17.4 mL/min/kg), and unpaired t-test was performed. Pearson's or Spearman's correlation analyses were used to examine the relationship between them. Multivariable regression analysis was used to identify the independent determinant of peak VO_2 in which variables showing a significant correlation in univariable analyses were incorporated as explanatory variables. For all tests, values of $p < 0.05$ were considered significant. All statistical analyses were performed using JMP version 16.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics

Of the 52 patients, 3 patients were excluded because of inadequate workload based on low peak respiratory exchange ratio (RER) ≤1.05, and 5 AF patients were also excluded due to HFA-PEFF score lower than 5. Accordingly, the final study population consisted of 44 patients. The baseline characteristics of the studied patients are summarized in

Table 1. Roughly half of the cases were complicated by hypertension or chronic kidney disease along with mild HF symptoms. LV mass index was distributed within the normal range because LV hypertrophy was excluded. Besides, 6 patients (14 %) showed concentric LV remodeling defined by relative wall thickness ≥ 0.42, whereas no patients showed enlarged LV defined by indexed LV end-diastolic diameter > 36 mm/m^2 (male) or >37 mm/m^2 (female) [22]. There were two patients with moderate functional tricuspid regurgitation, whereas no patient showed severe tricuspid regurgitation. LA volume index was increased. There were 6 patients with history of AF, and all of them presented AF rhythm at the time of the echocardiographic evaluation.

Responses to exercise during ESE

Changes in hemodynamic and echocardiographic parameters during ESE are summarized according to peak VO_2 upper or lower than median value (17.4 mL/min/kg) in Table 2. Overall, there were trends for an increase in LV end-diastolic volume and ejection fraction, increasing SV. In relation to those, the exercise significantly increased LV-s′, GLS, e′, and IVPD. In contrast, E/e′ did not increase during the exercise despite the increase in SPAP. Although TAPSE and RV-s′ were also increased, TAPSE/SPAP was reduced by the exercise (Fig. 1). Precisely, 4 patients (9 %) reached the cut-off value to detect exercise-induced pulmonary hypertension (SPAP ≥60 mm Hg), meanwhile there were another 15 patients (34 %) with unusual elevation of TRPG during exercise (>38 mm Hg) [23]. Of these, 8 patients (18 %) represented the unusual elevation of SPAP without an increase in E/e′ (≥15) during peak exercise.

When these parameters at peak exercise were compared between patients showing upper half and lower half of peak VO_2, the differences between these groups were striking in higher SPAP and lower TAPSE/SPAP in patients with lower peak VO_2, whereas markers of LV systolic function, LV diastolic function, and filling pressure were comparable between the groups. Interestingly, TPR reduced during exercise only in patients showing upper half of peak VO_2 (Table 2).

Determinants of exercise capacity peak VO_2

Results of linear regression analyses to determine peak VO_2 are summarized in Table 3. As expected, higher age, lower serum albumin, and lower estimated glomerular filtration rate (eGFR) were associated with lower peak VO_2. Additionally, lower peak heart rate and lower peak CO were associated with lower peak VO_2. Surprisingly, any parameters of LV systolic and diastolic parameters except for LV-s′ did not determine peak VO_2. In contrast, SPAP was negatively, and RV-s′ was positively correlated with peak VO_2. Finally, TAPSE/SPAP was positively correlated with peak VO_2, suggesting a negative impact of impaired RV-PA coupling during exercise in the studied population (Fig. 2).

In multivariable analyses, not only SPAP but also TAPSE/SPAP was selected as an independent determinant of peak VO_2 whereas heart rate, LV end-diastolic volume, CO, LV-s′, and E/e′ were not after the adjustment of clinically relevant parameters (Table 4).

Correlation between LV myocardial fibrosis and exercise capacity

Among 36 patients who underwent CMR, ECV was slightly elevated (29.1 %) compared to the previously reported normal range [24]. The mean of native T1 value was about the upper limit of a normal range (1286 ms, reference value: 1180–1300 ms). Notably, 12 of the 18 patients (67 %) in lower-half of peak VO_2 showed elevated ECV (higher than the institution's normal value), which was more frequent than in patients in upper-half of peak VO_2 [5 of 16 (31 %), $p = 0.012$]. Both ECV and native T1 values were negatively correlated with peak VO_2. In contrast, no associations were observed between these parameters and echocardiographic parameters or P-III-P (Online Tables 1, 2).

Discussion

In our study, determinants of exercise capacity were tested in HFpEF patients without abnormal LV structure. The findings can be summarized as 1) IVPD, a measure of LV suction, was increased and E/e′ was not increased, whereas SPAP was substantially increased by the exercise, 2) parameters of LV diastolic function during exercise were not associated with exercise capacity, and 3) TAPSE/SPAP at peak exercise was a determinant of exercise capacity independent of clinically relevant factors of exercise capacity. Our result suggests that RV-PA uncoupling induced by pulmonary hypertension, which was not caused by elevated LV filling pressure, might be responsible for reducing exercise capacity in HFpEF patients without a noticeable change in LV morphology.

The abnormal LV structure as represented by LV hypertrophy has been described as a typical finding in HFpEF patients. The abnormal LV geometry and subsequent LV diastolic dysfunction are found to be associated with increased morbidity and mortality [7,9], and as well as a reduction in exercise capacity in HFpEF patients [25]. At the same time, a substantial number of patients in the HFpEF population has shown normal cardiac geometry. The most extensive study done on HFpEF patients demonstrated that 46 % of the HFpEF lacked the findings of LV hypertrophy or LV concentric remodeling [9]. Another seminal study found normal LV geometry in 31 % of the HFpEF population [8]. As well, a recent study from Japan reported that 56 % of elderly HFpEF patients presented normal range of relative wall thickness, and the proportion was similar to the healthy elderly subjects (54 %) [26]. Taken together with the longitudinal alteration of LV structure, which contain disappearance of LV hypertrophy over time, reported from the CHART-2 study [22], presence of LV hypertrophy could not necessarily express the early stage of Japanese HFpEF. Although cardiomyocyte cellular hypertrophy and subsequent diastolic dysfunction can occur even when LV hypertrophy is not present [9], and increase in LV filling pressure by exercise is the crucial hemodynamic characteristic of HFpEF [5], non-cardiac factors were also suggested to contribute the exercise intolerance in this population [4,27–29]. Haykowsky and coworkers investigated the determinants of aerobic capacity in HFpEF patients and found that arterial-venous oxygen content difference was the strongest predictor of peak aerobic capacity in HFpEF patients, suggesting that peripheral non-cardiac factors are essential contributors to exercise intolerance [4]. In addition, Gorter and coworkers demonstrated the inability to increase cardiac output associated with RV-PA uncoupling limited exercise capacity of HFpEF patients with combined pre- and post-capillary pulmonary hypertension by using exercise-stress hemodynamic monitoring [28]. In line with these observations, we found that exercise-induced pulmonary hypertension and RV-PA uncoupling were independent determinants of exercise capacity in HFpEF patients. Our results underline the importance of non-cardiac factors in maintaining exercise capacity in HFpEF patients.

Surprisingly, pulmonary hypertension was not associated with exercise-induced elevation of LV filling pressure in our population. This result suggests that pulmonary hypertension might have been driven by diminished distensibility of the pulmonary vessels themselves. During exercise, increased volumes of pulmonary blood flow are recruited to the pulmonary vessels [30] and thin-walled pulmonary vessels are distended to accommodate this increased blood flow without excessive increase in pulmonary artery pressure. Previous studies reported that pulmonary vascular distensibility was reduced in the circumstances of chronic hypoxia and aging [31,32]. Consistently, we observed the reduction of TPR only in patients showing upper-half of peak VO_2. Although the absolute value of non-invasively obtained TPR itself might be somewhat inaccurate, these data would confirm the consideration in which insufficient adaptation of pulmonary vasculature during exercise is associated with reduced exercise capacity. Therefore, some part of the population in clinically diagnosed HFpEF patients without LV hypertrophy might be suffering from abnormal pulmonary vascular response during exercise, which reduces exercise capacity independently of LV diastolic dysfunction. In this study, 8 patients

Table 2
Changes in hemodynamic and echocardiographic data during exercise-stress echocardiography.

Variables	Overall	Peak VO_2 < 17.4 (mL/min/kg) ($n = 22$)	Peak VO_2 ≥ 17.4 (mL/min/kg) (n = 22)	*P* value
Heart rate, bpm				
Baseline	71 ± 13	70 ± 13	72 ± 13	NS
Submaximum	102 ± 17*	99 ± 16*	106 ± 18*	NS
Peak exercise	115 ± 18*	110 ± 19*	120 ± 17*	NS
Systolic blood pressure, mm Hg				
Baseline	131 ± 18	128 ± 18	134 ± 18	NS
Submaximum	156 ± 30*	157 ± 32*	156 ± 29*	NS
Peak exercise	174 ± 30*	173 ± 31*	175 ± 30*	NS
LV end-diastolic volume, mL				
Baseline	69.9 ± 22.1	66.5 ± 25.2	73.3 ± 18.4	NS
Submaximum	72.4 ± 15.7	69.5 ± 15.9	75.3 ± 15.2	NS
Peak exercise	71.4 ± 18.3	66.8 ± 17.2	76.0 ± 18.5	NS
LV end-systolic volume, mL				
Baseline	25.7 ± 9.7	23.2 ± 8.6	28.2 ± 10.4	NS
Submaximum	24.0 ± 8.1	21.9 ± 5.4	26.2 ± 9.8	NS
Peak exercise	22.7 ± 7.8*	20.5 ± 6.2*	24.9 ± 8.8	NS
LV ejection fraction, %				
Baseline	64 ± 6	65 ± 6	62 ± 6	NS
Submaximum	67 ± 7*	68 ± 6*	66 ± 8*	NS
Peak exercise	68 ± 7*	69 ± 6*	67 ± 7*	NS
Stroke volume, mL				
Baseline	62.3 ± 15.4	64.9 ± 16.1	59.8 ± 14.6	NS
Submaximum	64.9 ± 14.8	64.4 ± 15.6	65.4 ± 14.3*	NS
Peak exercise	64.0 ± 18.2	64.4 ± 17.2	63.6 ± 19.5	NS
Cardiac output, L/min				
Baseline	4.3 ± 0.9	4.5 ± 1.0	4.2 ± 0.9	NS
Submaximum	6.6 ± 1.5*	6.3 ± 1.5*	6.8 ± 1.5*	NS
Peak exercise	7.2 ± 1.8*	7.0 ± 1.8*	7.5 ± 1.8*	NS
LV-s′, cm/s				
Baseline	7.5 ± 1.7	7.2 ± 1.3	7.9 ± 2.1	NS
Submaximum	9.0 ± 1.9*	8.8 ± 1.8*	9.2 ± 2.0*	NS
Peak exercise	9.8 ± 2.0*	9.4 ± 1.4*	10.2 ± 2.4*	NS
GLS, |%|				
Baseline ($n = 48$)	17.4 ± 3.9	17.4 ± 4.6	17.4 ± 3.3	NS
Submaximum ($n = 46$)	20.1 ± 3.5*	20.4 ± 4.4*	19.7 ± 2.3*	NS
Peak exercise ($n = 45$)	19.5 ± 4.8*	20.1 ± 5.0*	18.7 ± 4.6	NS
E, cm/s				
Baseline	73.0 ± 18.1	76.9 ± 18.5	69.1 ± 17.2	NS
Submaximum	104.9 ± 23*	106.7 ± 20.3*	103.2 ± 25.7*	NS
Peak exercise	112.6 ± 24.1*	117.2 ± 26.7*	107.9 ± 20.8*	NS
e′, cm/s				
Baseline	6.1 ± 1.8	5.8 ± 1.7	6.4 ± 1.8	NS
Submaximum	8.5 ± 2.5*	8.3 ± 2.7*	8.6 ± 2.3*	NS
Peak exercise	9.6 ± 2.8*	9.7 ± 3.3*	9.6 ± 2.1*	NS
E/e′				
Baseline	13.0 ± 5.3	14.3 ± 5.7	11.7 ± 4.5	NS
Submaximum	13.5 ± 5.2	14.4 ± 6.1	12.6 ± 4.3	NS
Peak exercise	12.8 ± 5.5	13.7 ± 6.5	11.9 ± 4.1	NS
IVPD, mm Hg				
Baseline (n = 44)	3.0 ± 1.0	3.0 ± 1.0	2.9 ± 1.0	NS
Submaximum ($n = 39$)	4.6 ± 1.7*	5.1 ± 1.5*	4.0 ± 1.8*	0.049
Peak exercise (n = 39)	5.4 ± 1.6*	5.2 ± 1.5*	5.6 ± 1.7*	NS
RV-s′, cm/s				
Baseline	11.2 ± 2.0	11 ± 2.1	11.5 ± 1.9	NS
Submaximum	13.4 ± 2.5*	13.3 ± 2.4*	13.6 ± 2.7*	NS
Peak exercise	15.2 ± 3.0*	14.1 ± 2.8*	16.3 ± 2.9*	NS
TAPSE, mm				
Baseline	20.3 ± 3.8	19.8 ± 4.0	20.8 ± 3.6	NS
Submaximum	22.1 ± 4.9*	21.5 ± 4.2	22.7 ± 5.6	NS
Peak exercise	22.9 ± 4.6*	22.6 ± 4.7*	23.2 ± 4.6*	NS
SPAP, mm Hg				
Baseline	29 ± 6	30 ± 5	27 ± 7	NS
Submaximum	38 ± 11*	40 ± 9*	36 ± 13*	NS
Peak exercise	43 ± 13*	47 ± 11*	38 ± 13*	0.016

(continued on next page)

Table 2 (*continued*)

Variables	Overall	Peak VO_2 < 17.4 (mL/min/kg) ($n = 22$)	Peak VO_2 ≥ 17.4 (mL/min/kg) (n = 22)	*P* value
TPR, mm Hg·min/L				
Baseline	4.7 ± 1.5	4.7 ± 1.3	4.6 ± 1.8	NS
Submaximum	4.1 ± 1.2*	4.2 ± 1.0*	4.0 ± 1.5*	NS
Peak exercise	4.1 ± 1.5*	4.5 ± 1.2	3.6 ± 1.7*	0.043
TAPSE/SPAP, mm/mm Hg				
Baseline	0.75 ± 0.23	0.68 ± 0.18	0.81 ± 0.25	0.044
Submaximum	0.65 ± 0.27*	0.56 ± 0.15*	0.73 ± 0.33*	0.036
Peak exercise	0.60 ± 0.28*	0.51 ± 0.17*	0.70 ± 0.33	0.019

p-values are for the comparisons between the 2 groups.
LV, left ventricular; LV-s′, systolic mitral annular velocity; GLS, global longitudinal strain; E, early-diastolic transmitral flow velocity; e′, early-diastolic mitral annular velocity; E/e′, ratio of E to e′; IVPD, intraventricular pressure difference; RV-s′, peak systolic right ventricular free wall velocity; TAPSE, tricuspid annular plane systolic excursion; SPAP, systolic pulmonary artery pressure; TPR, total pulmonary resistance; TAPSE/SPAP, ratio of TAPSE to SPAP.
* $p < 0.05$ versus baseline.

showed unusual elevation of SPAP without an increase in E/e′. Because the studied 44 patients were included from 159 screened HFpEF patients, the actual frequency of this manifestation was 5 % of HFpEF in our institution. Although it might be difficult to extrapolate this frequency to the real world data based on the characteristic of the university hospital, we may need to take into account for this type of hemodynamic characteristics when we manage HFpEF patients without LV hypertrophy.

On the other hand, we also found the relationship between exercise capacity and LV myocardial fibrosis assessed by ECV and native T1 value. Although elevated ECV and its association with LV stiffness have been observed in HFpEF [33], this was the first study to find its relationship to exercise capacity in HFpEF patients. Unexpectedly, however, we could not find any associations between ECV and parameters of LV diastolic function. Because ECV may represent the distinct domain of cardiac vulnerability from GLS [34], intercellular fibrosis might have been associated with exercise intolerance not through LV diastolic dysfunction, especially in patients showing normal LV geometry. Further studies are warranted to clarify the underlying mechanism of the relationship between myocardial fibrosis and exercise capacity in this population. In addition, we used TAPSE/SPAP as a simple index of RV-PA coupling that can be evaluated by echocardiography. Although it has been pointed out that TAPSE/SPAP may be more afterload-dependent than invasive measurement, it is well reproducible that can be used even in the evaluation during maximal exercise [32,35].

We need to acknowledge some limitations in the present study. First, this was a single-center study including a small population and thus more extensive studies are needed to confirm our results.

Second, although we strictly selected HFpEF patients based on clinical data, the exclusion of patients with LV hypertrophy might be associated with augmented e′ during exercise, therefore, one might have a concern about the diagnosis of HFpEF. In turn, clinically-diagnosed

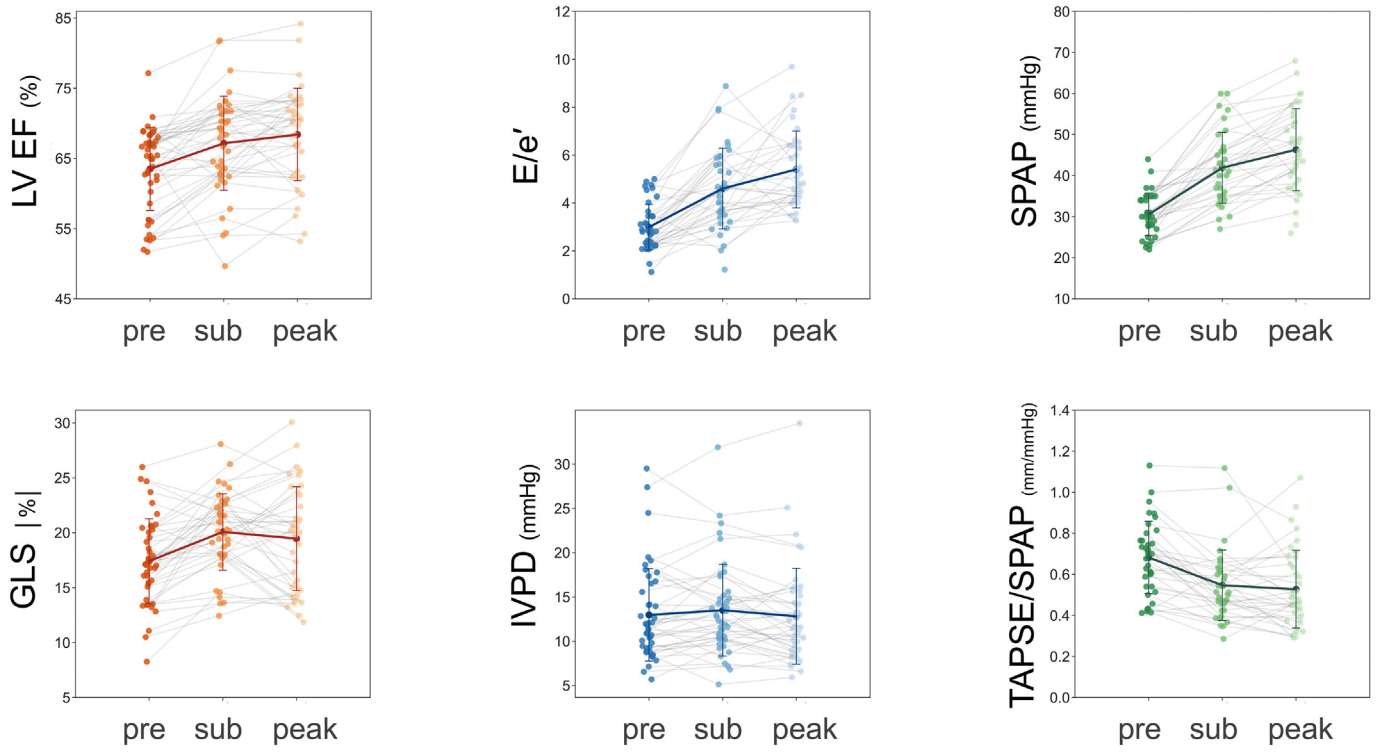

Fig. 1. Changes in exercise-stress echocardiography parameters during exercise. Changes in indices of left ventricular (LV) contraction, LV diastolic function, and right ventricle (RV)-pulmonary artery (PA) coupling at each stage of exercise. There was no change in E/e′ which reflects LV filling pressure. Note that SPAP plots the cases whose measurements were available.
pre, at baseline; sub, at submaximal exercise; peak, at peak exercise; LVEF, LV ejection fraction; GLS, global longitudinal strain; IVPD, intraventricular pressure difference; E, early-diastolic transmitral flow velocity; e′, early-diastolic mitral annular velocity; E/e′, ratio of E to e′; SPAP, systolic PA pressure; TAPSE, tricuspid annular plane systolic excursion.
*$p < 0.05$ versus baseline.

Table 3
Determinants of peak VO_2.

Variables	R	*p*-Value
Age	−0.36	0.017
Body mass index	−0.04	0.775
Albumin	0.29	0.052
eGFR	0.55	<0.001
P-III-P	(ρ) −0.269	0.089
EXE parameters (peak exercise)		
Heart rate	0.43	0.004
Stroke volume	0.02	0.886
Cardiac output	0.28	0.062
LV end-diastolic volume	0.36	0.017
LVEF	−0.18	0.256
GLS ($n = 41$)	−0.07	0.644
LV-s′	0.35	0.022
IVPD ($n = 35$)	0.14	0.425
e′	0.20	0.202
E/e′	−0.27	0.083
SPAP	−0.40	0.008
TAPSE	0.13	0.413
RV-s′	0.47	0.002
TAPSE/SPAP	0.42	0.005
CMR findings		
Native T1 (n = 36)	−0.27	0.118
ECV (n = 34)	−0.36	0.036

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; LV-s′, systolic mitral annular velocity; IVPD, intraventricular pressure difference; E, early-diastolic transmitral flow velocity; e′, early-diastolic mitral annular velocity; E/e′, ratio of E to e′; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; RV-s′, peak systolic right ventricular free wall velocity; TAPSE/SPAP, ratio of TAPSE to SPAP; ECV, extracellular volume fraction.

Table 4
Unadjusted and adjusted regression coefficients to determine peak VO_2.

Variables	R	*p*-Value	β	*p*-Value
Heart rate				
Unadjusted	0.43	0.004		
Adjusted[a]			0.23	0.092
LV end-diastolic volume				
Unadjusted	0.36	0.017		
Adjusted[a]			0.24	0.064
CO				
Unadjusted	0.28	0.062		
Adjusted[a]			0.16	0.220
LV-s′				
Unadjusted	0.35	0.022		
Adjusted[a]			0.08	0.226
E/e′				
Unadjusted	−0.27	0.083		
Adjusted[a]			−0.22	0.077
TAPSE				
Unadjusted	0.13	0.413		
Adjusted[a]			0.02	0.896
SPAP				
Unadjusted	−0.40	0.008		
Adjusted[a]			−0.31	0.014
TAPSE/SPAP				
Unadjusted	0.42	0.005		
Adjusted[a]			0.30	0.025

LV, left ventricular; CO, cardiac output; LV-s′, systolic mitral annular velocity; E, early-diastolic transmitral flow velocity; e′, early-diastolic mitral annular velocity; E/e′, ratio of E to e′; TAPSE, tricuspid annular plane systolic excursion; SPAP, systolic pulmonary artery pressure; TAPSE/SPAP, ratio of TAPSE to SPAP.
[a] Adjusted for age, albumin, eGFR.

HFpEF patients without LV hypertrophy might include patients with relatively preserved LV relaxation. Furthermore, the inclusion criteria are at risk of including non-HF patients, although we found that all asymptomatic patients without AF showed objective evidence of HF such as elevated NT-pro BNP levels, reduced e′, or enlarged left atrium. Nevertheless, we need to confirm the observed results in a future study including HFpEF patients diagnosed by established criteria [36]. Third, CPET and ESE were performed separately with different protocols used. Fourth, we did not consider peripheral determinants of exercise

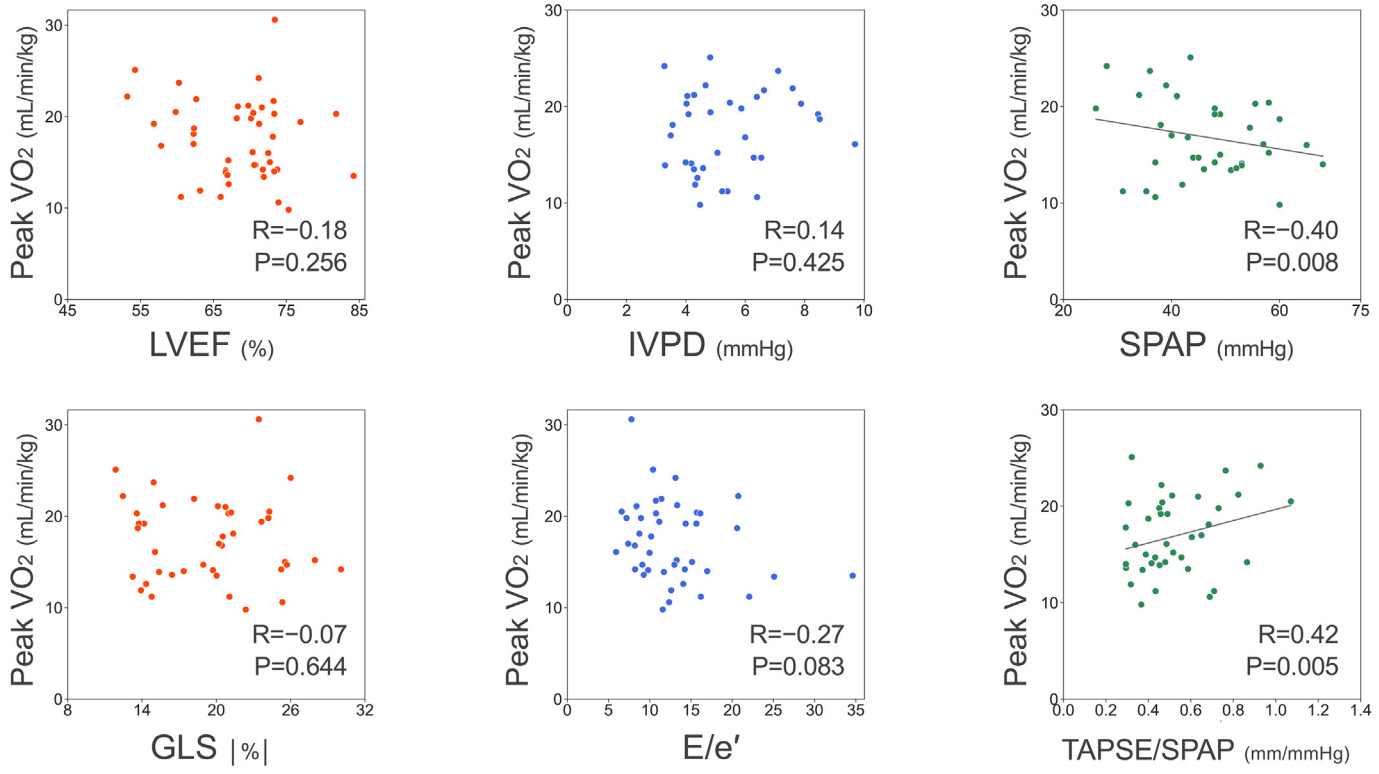

Fig. 2. Correlations between exercise-stress echocardiography parameters (at peak exercise) and peak VO_2.
LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; IVPD, intraventricular pressure difference; E, early-diastolic transmitral flow velocity; e′, early-diastolic mitral annular velocity; E/e′, ratio of E to e′; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

capacity, such as inactivity, skeletal muscle atrophy, and oxygen metabolism. However, the relationship between TAPSE/SPAP during exercise and peak VO_2 in the present results should be consistent regardless of the limiting factors of the exercise. Fifth, some cases might present with subclinical respiratory dysfunction because they did not perform specific evaluations such as spirometry. Sixth, substantial proportion of the enrolled patients used beta-blockers for hypertension and AF. In these patients, beta-blocker might affect their exercise intolerance through chronotropic incompetence [37]. However, there was no difference between the patients using beta-blockers and those without in terms of heart rate at peak exercise (117 ± 18 bpm vs 113 ± 19 bpm, $p = 0.43$) and peak VO_2. Finally, because of the evaluation during exercise, the image quality of CMMD of the LV inflow may have been somewhat inappropriate, weakening the relationship between IVPD and peak VO_2.

Conclusions

In HFpEF patients without LV hypertrophy, altered RV-PA coupling by exercise could be associated with exercise intolerance, which might not be caused by elevated LV filling pressure. The present results are needed to be confirmed in another population diagnosed by established HFpEF criteria.

Declaration of competing interest

There is no conflict of interest to disclose relating to the present study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.09.004.

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