Research Article

Investigating Gait Speed as the Index of Exercise Tolerance in Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Introduction: As an essential factor affecting life prognosis and rehospitalization in patients with chronic heart failure, exercise tolerance is a significant outcome of cardiac rehabilitation. Heart failure with preserved ejection fraction (HFpEF) from reduced diastolic capacity has recently increased among patients with chronic heart failure. This study evaluates the factors indicating exercise tolerance in patients with HFpEF from various perspectives, including cardiac and skeletal muscle functions.

Materials and Methods: The subjects were 31 patients with HFpEF who underwent cardiac rehabilitation. The exercise tolerance was assessed using a 6-min walking test. Physical function, physical activity, body composition test, baseline characteristics, blood data, and echocardiography results were extracted from medical records to identify the indicators of exercise tolerance.

Results: Gait speed significantly differed in exercise tolerance for HFpEF patients (β=0.75, P<0.01). Unlike heart failure with reduced ejection fraction (HFrEF), HFpEF was not significantly different in brain natriuretic peptide levels and cardiac function.

Conclusion: Gait speed indicates exercise tolerance in HFpEF patients; however, its pathological course differs from heart failure with reduced ejection fraction, suggesting that it is poorly related to brain natriuretic peptide, a biomarker for heart failure and cardiac function.

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Introduction

Cardiac rehabilitation for patients with chronic heart failure is recommended as a Class I treatment in international guidelines. It improves the quality of life (QoL) and life prognosis and prevents rehospitalization [1, 2]. In heart failure, exercise tolerance is an important indicator that strongly influences rehospitalization and life prognosis [3-5]. Although it is impaired in heart failure due to the disruption of the compensatory mechanism of the cardiac pump function, peripheral skeletal muscle function, and not cardiac function, defines exercise tolerance [6-8]. Accordingly, exercise tolerance in patients with chronic heart failure is widely used as a simple indicator in clinical practice because it correlates with physical functions, such as grip strength and lower limb muscle strength [9, 10]. Significant correlations have also been reported with muscle mass and physical activity [11, 12].

In recent years, heart failure with preserved ejection fraction (HFpEF), in which the left ventricular ejection fraction is preserved and diastolic failure is the leading cause of heart failure, has been increasing. HFpEF is the most common heart failure in the elderly, and its prevalence and life prognosis are comparable to heart failure with reduced ejection fraction (HFrEF), in which the left ventricular ejection fraction is reduced [13]. However, unlike HFrEF, there is no established standardized treatment for improving life prognosis in patients with HFpEF. Exercise training for HFpEF has been reported to improve cardiorespiratory fitness and QoL [14]. Furthermore, outpatient cardiac rehabilitation intervention with a comprehensive multi-professional rehabilitation team has been reported to enhance life prognosis and rehospitalization rates [15]. Studies on exercise tolerance in HFpEF have reported that decreased skeletal muscle oxygen utilization and anatomical quality of muscle (decreased slow-twitch muscle fibers and capillary density) were associated with decreased exercise tolerance, in contrast to cardiac function [16, 17]. In the future, cardiac rehabilitation focusing on exercise therapy may be an effective treatment for HFpEF.

Nevertheless, it is difficult to routinely perform cardiopulmonary exercise testing and assess the anatomical quality of the muscles for exercise tolerance assessment in clinical practice. Moreover, no previous studies have examined the factors that served as indicators of exercise tolerance in patients with HFpEF from various perspectives, including cardiac and skeletal muscle function, physical activity, and muscle mass. Hence, this study evaluates these factors based on clinically available data.

Materials and Methods

The subjects were 31 patients with HFpEF who underwent cardiac rehabilitation at Kumamoto University Hospital between March 2020 and March 2021. The control group was 27 patients with HFrEF. The classification of chronic heart failure was based on the European Society of Cardiology guidelines. HFpEF was defined as having heart failure symptoms and a left ventricular ejection fraction of 50% or higher. The diagnosis of diastolic dysfunction was evaluated based on a report by Nagueh et al. [18]. Meanwhile, the severity was classified based on a report by Anderson et al. [19]. HFrEF was then defined as a left ventricular ejection fraction below 40%.

The exclusion criteria were having severe valvular disease, unstable angina, poorly controlled arrhythmia, which caused subjective symptoms or hemodynamic abnormalities, poorly controlled symptomatic heart failure, and inability to provide consent for participation in this study.

Baseline characteristics

Sex, age, body mass index (BMI), underlying cardiac disease, comorbidities, New York Heart Association (NYHA) class, blood biochemistry, echocardiography, and body composition test results were extracted from medical records. Left ventricular ejection fraction (LVEF) was used as an index of contractility. The indices of diastolic capacity were the mean ratio of early diastolic filling velocity to early diastolic minimal annular velocity (E/e'), the ratio of early diastolic left ventricle filling velocity to atrial filling velocity ratio (E/A) (only in sinus rhythm), septal and lateral wall e,' left atrial volume index (LAVI), deceleration time (Dct), and tricuspid regurgitation velocity (TRV).

Body composition tests were conducted using dual-energy x-ray absorptiometry (Hologic Co., Ltd.: QDR-Discovery A). The muscle mass index was defined as the skeletal muscle mass index (SMI), and the fat mass index was expressed as the total fat percentage. Those with metal implants were excluded because the measurements would be overestimated [20].

Physical function

Exercise tolerance was assessed using the 6-min walk test, and the methods were based on the American Thoracic Society guidelines [21]. Muscle strength was evaluated by the grip strength (measuring equipment: Takei Scientific Instruments Co., T.K.K. 5401. JAPAN) and isometric knee extensor strength (measuring equipment: Hoggan Scientific LLC., microFET2). Grip strength was measured twice, alternately on the left and right side, with the arm in a standing posture and the arm naturally drooping. The average value of the better of the left and right recordings was adopted. Isometric knee extensor strength was performed sitting with the lower leg vertical and hanging down. The sensor pad was placed on the anterior aspect of the distal lower leg. Measurements were taken twice, alternating left and right. The average value of the better of the left and right recordings was calculated and corrected for the body weight. Balance ability was assessed by one-leg standing time, while frailty was assessed using the short physical performance battery (SPPB) and gait speed. The SPPB consisted of three sub-test scores (a five-times sit-to-stand test, gait speed, and standing balance performance), totaling 12 points (four points for each item). Gait speed was measured by measuring the time required for a 4-m section at normal walking speed; following the SPPB method, the value was converted to m/s. Muscle mass was assessed by upper arm and calf circumference, in addition to SMI. The average weekly high intensity (equivalent to 8.0 metabolic equivalent of tasks [METs]), moderate intensity (equivalent to 4.0 METs), walking (equivalent to 3.3 METs), and total physical activity were assessed by the international physical activity questionnaire (IPAQ), short version. The results were shown as the product of intensity/ METs and frequency (days/week). Based on the results of the body composition tests and physical function assessment, sarcopenia was classified according to the diagnostic criteria of the Asian working group for sarcopenia 2019 [22].

Statistics analyses

The statistical analyses were performed using R software, version 4.0.3 and SPSS software, version 20. The continuous variables were shown as Mean±SD, and categorical variables as numbers and percentages. A single regression analysis was performed with the 6-min walking distance as the objective variable to clarify the factors that were indicators of exercise tolerance with exercise tolerance. The items that showed statistically significant differences in the simple regression analysis were entered, and a multiple regression analysis was performed. The adjustment variables included sex, age, and BMI. In addition, an exploratory study comparing the two groups was conducted. Continuous variables were subjected to the student t-test and Mann-Whitney U test after confirming normality. The categorical variables were subjected to the Fisher exact test. The statistical significance was set at $P<0.05$.

Results

The baseline characteristics and results of the physical function assessment for both groups are shown in Table 1. The mean values and prevalence of the factor characteristics of the patients with HFpEF were 78.9±9.1 years; 54.8% were female; 19.4% were obese; 11.2±2 g/dL for anemia (hemoglobin value); 64.5% had hypertension, and 61.3% had atrial fibrillation [23, 24]. The mean value of the 6-min walking distance for the indicator of exercise tolerance was 235.5±122.3 m.

The results of the between-group comparison showed that age was significantly higher in the HFpEF group than in the HFrEF group. The blood data showed significantly higher values for sodium and creatinine while considerably lower values for albumin, hemoglobin, and estimated glomerular filtration rate (eGFR) in the HFpEF group. Echocardiography showed significantly higher LVEF, Dct, interventricular septal thickness at end-diastole (IVSTd), and posterior left ventricular wall thickness in diastole in the HFpEF group. In either group, there were no significant differences in the severity of NYHA class, brain natriuretic peptide (BNP) levels, and left ventricular diastolic capacity, representing the severity of heart failure.

The 6-min walking distance, SPPB, one-leg standing time, isometric knee extensor strength, and physical parameters related to gait were significantly lower in the HFpEF group compared to the HFrEF group. However, there were no significant differences in muscle mass and prevalence of sarcopenia.

Factors related to exercise tolerance

The results for factors related to exercise tolerance are illustrated in Table 2. The factors significantly correlated with exercise tolerance of HFpEF in the single regression analysis were sex ($\beta=0.38$, $P=0.04$), locomotor diseases ($\beta=-0.65$, $P<0.01$), hemoglobin ($\beta=0.38$, $P=0.04$), SPPB ($\beta=0.75$, $P<0.01$), gait speed ($\beta=0.89$, $P<0.01$), one-leg standing time ($\beta=0.66$, $P<0.01$), grip strength ($\beta=0.72$, $P<0.01$), isometric knee extensor strength ($\beta=0.70$, $P<0.01$), calf circumference ($\beta=0.37$, $P=0.04$),

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Table 1. The baseline characteristics and physical function assessment

Variables		No. (%)/Mean±SD		P
		HFpEF	HFrEF	
Male		14(45.2)	14(51.9)	0.79
Age (y)		78.9±9.1	69.4±14.4	0.01
BMI (kg/m²)		22.0±3.4	22.2±5.9	0.38
Etiolody	Isochemic	10(32.3)	10(37.0)	
	Cardiomyopathy	10(32.2)	13(48.1)	
	Hypertensive	4(12.9)	1(3.7)	
	Valvular	3(9.7)	1(3.7)	
	Arrhythmia	2(6.5)	2(7.4)	
	Other	2(6.5)	0(0)	
	NYHA class (I/II/III)	1(3.2)/10(32.3)/20(64.5)	0(0)/12(44.4)/15(55.6)	0.41
Comorbidities	Locomotor disorders	14(45.2)	9(33.3)	0.42
	Cerebrovascular disease	4(12.9)	7(25.9)	0.31
	Respiratory disease	6(19.4)	9(33.3)	0.24
	Kidney disease	19(61.3)	12(44.4)	0.29
	Diabetes mellitus	12(38.7)	7(25.9)	0.40
	Hypertension	20(64.5)	11(40.7)	0.11
	Atrial fibrillation	19(61.3)	15(55.6)	0.79
	Coronary artery disease	15(48.4)	8(29.6)	0.18
	Obesity (BMI >25)	6(19.4)	7(25.9)	0.75
Blood date	Sodium (mEq/L)	140.0±2.6	136.9±3.4	<0.01
	White blood cells (10³/µL)	5.9±1.9	6.4±2.4	0.42
	Hemoglobin (g/dL)	11.2±2.0	12.8±2.0	<0.01
	Total cholesterol (mg/dL)	157.3±35.4	170.3±51.2	0.54
	HDL cholesterol (mg/dL)	54.4±22.8	53.9±16.5	0.56
	LDL cholesterol (mg/dL)	82.6±30.5	96.1±38.9	0.36
	Triglyceride (mg/dL)	99.2±66.2	116.8±82.4	0.32
	Albumin (g/dL)	3.2±0.4	3.5±0.4	0.02
	Creatinine (mg/dL)	1.6±0.9	1.2±0.6	0.04
	eGFR (mL/min/1.73 m²)	36.3±16.2	47.1±21.2	0.03
	BNP (pg/mL)	255.9±203.0	307.5±255.7	0.55
	CRP (mg/dL)	0.23±0.2	0.28±0.4	0.99

Variables		No. (%)/Mean±SD		P
		HFpEF	HFrEF	
Echocardiography	IVSTd (mm)	11.9±2.0	9.2±2.0	<0.01
	PLVWd (mm)	11.3±2.0	8.8±1.8	<0.01
	LVEF (%)	58.8±5.0	30.2±9.5	<0.01
	E/e' ratio	16.9±7.4	16.1±5.6	0.77
	E/A ratio	1.3±0.8	1.3±0.9	0.77
	Septal e' (cm/s)	4.8±1.5	4.6±1.4	0.61
	Lateral e' (cm/s)	6.4±2.1	6.4±2.4	0.99
	Dct (ms)	210.4±85.1	168.0±74.2	0.02
	TRV (m/s)	2.5±0.5	2.5±0.4	0.95
	LAVI (mL/m^2)	61.1±36.2	62.6±23.5	0.38
	Diastolic dysfunction grade 1/2/3	10(32.3)/15(48.4)/6(19.4)	13(48.1)/11(40.7)/3(11.1)	0.46
Body composition	SMI (kg/cm^2)	5.9±1.7	6.2±1.3	0.61
	Total percentage fat (%)	21.0±8.2	22.2±5.8	0.60
	6 MWD (m)	235.5±122.3	302.9±106.1	0.02
	SPPB point	7.0±3.4	9.2±2.8	0.02
	Gait speed (m/s)	0.67±0.2	0.79±0.2	0.05
	One-leg standing time (s)	7.9±14.7	18.8±22.9	<0.01
	Grip strength (kg)	17.5±7.9	21.8±9.9	0.06
	Isometric knee extension muscle strength (kgf/kg)	0.33±0.1	0.39±0.1	<0.01
	Arm circumference (cm)	23.3±3.4	24.8±5.6	0.63
	Calf circumference (cm)	30.1±3.7	31.5±5.3	0.28
IPAQ METs*day/week	Vigorous physical activity	2.6±14.6	35.5±184.7	0.94
	Moderate physical activity	317.3±1191.8	26.8±101.6	1.00
	Walking physical activity	267.3±623.9	398.4±644.8	0.04
	Total physical activity	587.3±1515.1	460.8±876.0	0.07
	Sarcopenia/severe sarcopenia	2(8.7)/7(30.4)	4(20.0)/5(25.0)	0.68

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Abbreviations: HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; BMI: Body mass index; NYHA: New York heart association; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BNP: Brain natriuretic peptide; CRP: C-reactive protein; LVEF: Left ventricular ejection fraction; E: Early diastolic filling velocity; e': Early diastolic myocardial velocity; A: Atrial diastolic velocity; Dct: Deceleration time; TRV: Tricuspid regurgitation velocity; IVSTd: Interventricular septal thickness at end-diastole; PLVWd: The posterior left ventricular wall thickness in diastole; LAVI: Left atrial volume index; SMI: Skeletal muscle mass index; 6MWD: 6-minute walking distance; SPPB: Short physical performance battery; IPAQ: International physical activity questionnaire; METs: Metabolic equivalents.

and physical activity (all items). Considering multicollinearity, physical activity related to gait was chosen as the factor to be included in the multiple regression analysis of the IPAQ items. The results of the multiple regression analysis demonstrated that only gait speed significantly correlated with exercise tolerance (β=0.75, P<0.01). This study found no significant correlations between exercise tolerance in HFpEF and cardiac function, BNP levels, muscle mass, or sarcopenia.

The factors that define exercise tolerance in patients with HFrEF are illustrated in Table 3. In the single regression analysis, the factors that significantly correlated with exercise tolerance were locomotor disease (β=-0.53, P<0.01), cerebrovascular disease (β=-0.45, P=0.01), BNP (β=-0.45, P=0.01), SPPB (β=0.78, P<0.01), gait speed (β=0.90, P<0.01), and grip strength (β=0.39, P=0.04). In the multiple regression analysis, the factors that significantly correlated with exercise tolerance were gait speed (β=0.65, P<0.01) and BNP (β=-0.21, P=0.03), which differed from the HFpEF, in that a significant difference was found between the BNP levels.

The correlations between the 6-minute walking distance, gait speed, and BNP in each group are illustrated in Figure 1.

Discussion

This study evaluated the factors indicating exercise tolerance in patients with HFpEF from various perspectives. The Japanese HFpEF is characterized by a lower BMI and prevalence of obesity compared to other regions (JASPER: 23.9±4.7 kg/m^2, GWTG-HF: 29 kg/m^2) [25, 26].

The 6-minute walking distance of patients with HFpEF in this study was similar to or lower than that reported in previous studies [27-29]. This may be due to the high proportion of patients with severe diseases, such as subjects who were noncompliant with the treatment due to the function of the university hospital in question. Gait speed significantly correlated with exercise tolerance in patients with HFpEF. In the past, gait speed showed a strong positive correlation (r=0.80, P<0.01) with 6-minute walking distance in older cardiac patients with heart

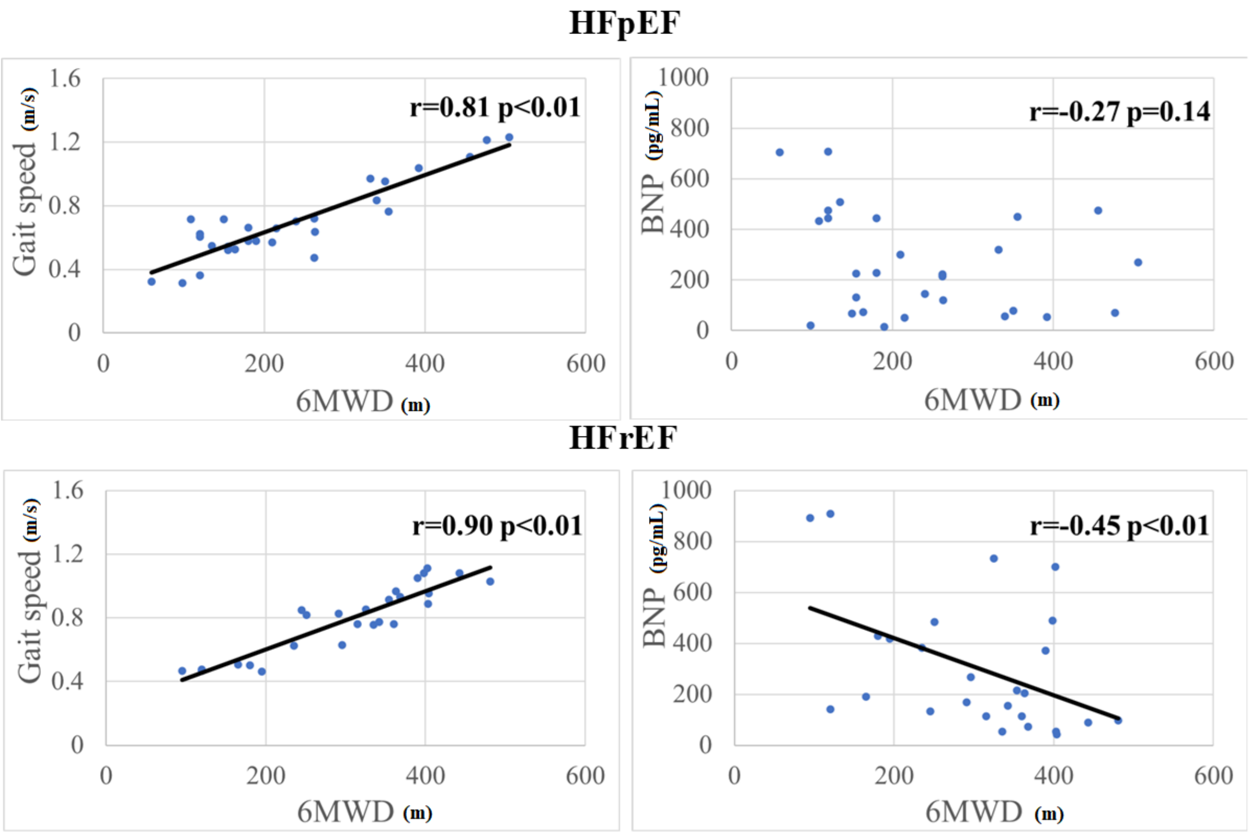

Figure 1. Correlation between 6-minute walking distance, gait speed, and brain natriuretic peptide in each group of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction

Table 2. Multiple regression analysis results in heart failure with preserved ejection fraction

Variables		Simple		Multiple	
		β	P	β	P
Sex		0.38	0.04	-0.09	0.55
Age (y)		-0.11	0.54	0.004	0.97
BMI (kg/m²)		0.003	0.98	-0.17	0.25
Comorbidities	Locomotor disorders	-0.65	<0.01	-0.20	0.11
	Cerebrovascular disease	-0.13	0.50		
	Respiratory disease	0.04	0.83		
	Kidney disease	-0.19	0.32		
	Diabetes mellitus	0.07	0.72		
	Hypertension	0.06	0.73		
	Atrial fibrillation	-0.09	0.62		
	Coronary artery disease	-0.10	0.60		
	Obesity	0.18	0.34		
Blood date	Sodium (mEq/L)	-0.06	0.73		
	White blood cells (10^3/µL)	0.36	0.05		
	Hemoglobin (g/dL)	0.38	0.04	0.06	0.58
	Total cholesterol (mg/dL)	-0.005	0.97		
	HDL cholesterol (mg/dL)	-0.13	0.49		
	LDL cholesterol (mg/dL)	0.06	0.75		
	Triglyceride (mg/dL)	0.21	0.26		
	Albumin (g/dL)	0.22	0.24		
	Creatinine (mg/dL)	-0.13	0.50		
	eGFR (mL/min/1.73 m²)	0.17	0.38		
	BNP (pg/mL)	-0.27	0.14		
	CRP (mg/dL)	-0.05	0.77		
Cardiac echography	IVSTd (mm)	0.06	0.75		
	PLVWd (mm)	0.11	0.56		
	LVEF (%)	-0.29	0.13		
	E/e’ ratio	0.03	0.87		
	E/A ratio	0.21	0.32		
	Septal e’ (cm/s)	0.07	0.69		

Variables		Simple		Multiple	
		β	P	β	P
Cardiac echography	Lateral e' (cm/s)	-0.03	0.84		
	Dct (ms)	-0.21	0.27		
	TRV (m/s)	0.02	0.89		
	LAVI (mL/m²)	-0.28	0.14		
Body composition	SMI (kg/cm²)	0.25	0.24		
	Total percentage fat (%)	-0.23	0.29		
	SPPB point	0.75	<0.01	-0.14	0.47
	Gait speed (m/s)	0.89	<0.01	0.75	<0.01
	One-leg standing time (s)	0.66	<0.01	0.07	0.65
	Grip strength (kg)	0.72	<0.01	0.12	0.55
	Isometric knee extension muscle strength (kgf/kg)	0.70	<0.01	0.006	0.97
	Arm circumference (cm)	0.16	0.40		
	Calf circumference (cm)	0.37	0.04	0.21	0.25
IPAQ (METs day/week)	Vigorous physical activity	0.43	0.02		
	Moderate physical activity	0.42	0.02		
	Walking physical activity	0.61	<0.01	-0.01	0.91
	Total physical activity	0.59	<0.01		
	Sarcopenia	-0.01	0.95		

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Abbreviations: BMI: Body mass index; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BNP: Brain natriuretic peptide; CRP: C-reactive protein; LVEF: Left ventricular ejection fraction; E: Early diastolic filling velocity; e': Early diastolic myocardial velocity; A: Atrial diastolic velocity; Dct: Deceleration time; TRV: Tricuspid regurgitation velocity; IVSTd: Interventricular septal thickness at end-diastole; PLVWd: Posterior left ventricular wall thickness in diastole; LAVI: Left atrial volume index; SMI: Skeletal muscle mass index; 6 MWD: 6-minute walking distance; SPPB: Short physical performance battery; IPAQ: International physical activity questionnaire; METs: Metabolic equivalents.

disease. It was useful as a reliable, sensitive, rapid, and simple risk stratification tool [30]. Therefore, it could also indicate exercise tolerance in patients with HFpEF. Furthermore, it has been reported to have a predictive value for all-cause mortality comparable to a 6-minute walking distance [30], suggesting that it could be a prognostic indicator for HFpEF.

It has been previously reported that the cardiac function of HFpEF was not a determinant of exercise tolerance; that is, uptake oxygen content (VO_2) was poorly related to left ventricular filling pressure and stroke volume during exercise. Furthermore, calculated arterial-venous oxygenation difference was an independent predictor of peak VO_2, and peripheral factors other than the heart were important for decreasing exercise tolerance [16, 30]. Similarly, in the present study, HFpEF did not show a significant correlation between 6-minute walking distance and cardiac function.

There were no significant correlations between exercise tolerance and muscle mass or sarcopenia in HFpEF. Of the patients with HFpEF with preserved muscle mass, 75% (9 out of 12) had reduced exercise tolerance (6-minute walking distance <300 m), while 60% (6 out of 10) of the patients with HFpEF with reduced muscle

Table 3. Multiple regression analysis results in heart failure with reduced ejection fraction

Variables		Simple		Multiple	
		β	P	β	P
Sex		0.21	0.29	-0.10	0.35
Age (y)		-0.37	0.05	-0.16	0.37
BMI (kg/m²)		0.06	0.76	0.09	0.41
Comorbidities	Locomotor disorders	-0.53	<0.01	-0.01	0.92
	Cerebrovascular disease	-0.45	0.01	-0.15	0.15
	Respiratory disease	-0.18	0.36		
	Kidney disease	0.08	0.68		
	Diabetes mellitus	-0.01	0.64		
	Hypertension	-0.15	0.46		
	Atrial fibrillation	0.17	0.39		
	Coronary artery disease	-0.29	0.14		
	Obesity	-0.006	0.97		
Blood date	Sodium (mEq/L)	-0.13	0.52		
	White blood cells (10^3/μL)	6.00	0.73		
	Hemoglobin (g/dL)	0.28	0.16		
	Total cholesterol (mg/dL)	0.08	0.68		
	HDL cholesterol (mg/dL)	-0.19	0.33		
	LDL cholesterol (mg/dL)	0.08	0.67		
	Triglyceride (mg/dL)	0.22	0.27		
	Albumin (g/dL)	0.15	0.46		
	Creatinine (mg/dL)	0.03	0.87		
	eGFR (mL/min/1.73 m²)	0.33	0.09		
	BNP (pg/mL)	-0.45	0.01	-0.21	0.03
	CRP (mg/dL)	0.15	0.47		
Cardiac echography	IVSTd (mm)	-0.12	0.55		
	PLVWd (mm)	-0.19	0.33		
	LVEF (%)	-0.09	0.65		
	E/e’ ratio	-0.07	0.70		
	E/A ratio	-0.09	0.72		
	Septal e’ (cm/s)	0.38	0.05		
	Lateral e’ (cm/s)	0.18	0.36		

Variables		Simple		Multiple	
		β	P	β	P
Cardiac echography	Dct (ms)	0.05	0.78		
	TRV (m/s)	0.22	0.26		
	LAVI (mL/m²)	0.14	0.49		
Body composition	SMI (kg/cm²)	0.04	0.85		
	Total percentage fat (%)	0.27	0.26		
	SPPB point	0.78	<0.01	0.17	0.34
	Gait speed (m/s)	0.90	<0.01	0.65	<0.01
	One-leg standing time (s)	0.29	0.14		
	Grip strength (kg)	0.39	0.04	-0.05	0.79
	Isometric knee extension muscle strength (kgf/kg)	0.33	0.09		
	Arm circumference (cm)	0.26	0.18		
	Calf circumference (cm)	0.35	0.07		
	IPAQ (METs*day/week)				
	Vigorous physical activity	0.19	0.35		
	Moderate physical activity	0.29	0.14		
	Walking physical activity	0.26	0.19		
	Total physical activity	0.26	0.18		
	Sarcopenia	-0.28	0.23		

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Abbreviations: BMI: Body mass index; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BNP: Brain natriuretic peptide; CRP: C-reactive protein; LVEF: Left ventricular ejection fraction; E: Early diastolic filling velocity; e′: Early diastolic myocardial velocity; A: Atrial diastolic velocity; Dct: Deceleration time; TRV: Tricuspid regurgitation velocity; IVSTd: Interventricular septal thickness at end-diastole; PLVWd: Posterior left ventricular wall thickness in diastole; LAVI: Left atrial volume index; SMI: Skeletal muscle mass index; 6 MWD: 6-minute walking distance; SPPB: Short physical performance battery; IPAQ: International physical activity questionnaire; METs: Metabolic equivalents.

mass had reduced exercise tolerance. Recently, dynapenia has been proposed as a disease concept that, unlike sarcopenia, refers to a condition in which the skeletal muscle mass is maintained; however, physical function is impaired [32]. In our study, the proportion of patients with dynapenia who had impaired exercise tolerance was 100% (8 out of 8). In comparison, the proportion of patients with sarcopenia who had impaired exercise tolerance was 66% (6 out of 9). In other words, HFpEF was likely to have more exercise tolerance and physical function in patients, even if skeletal muscle mass was maintained. The total fat percentage, an index of fat mass, did not significantly correlate with exercise tolerance. The accumulation of adipose tissue due to obesity has been reported to be associated with decreased muscle function and exercise tolerance [33]. However, the HFpEF in Japan is smaller than in other regions, suggesting no association between fat mass and exercise tolerance [26, 27].

HFpEF showed no differences in muscle mass and the severity of sarcopenia compared with HFrEF; however, it demonstrates a decrease in exercise tolerance and physical function. Since age and physical inactivity significantly differ between the groups and are risk factors for dynapenia [34], HFpEF patients may be more susceptible to decreased muscle performance regardless of muscle mass. Similarly, previous reports have shown that HFpEF has more skeletal muscle mass than HFrEF but poorer physical function (grip strength and gait speed) [35].

HFpEF did not significantly correlate with exercise tolerance and BNP, a biomarker for heart failure severity, compared to HFrEF. The reason for this could be that the onset of heart failure in HFrEF was at a younger age than that in HFpEF and was based on decreased left ventricular ejection fraction caused by myocardial damage. Meanwhile, in HFpEF, various factors, such as aging, physical inactivity, comorbidities [23, 36], and sex, had a long-term effect on exercise tolerance. Due to the long-term effects of various factors, such as physical inactivity, comorbidities, and sex, HFpEF could be influenced by factors other than heart failure. Alternatively, many patients with HFpEF could have impaired exercise tolerance at the onset of heart failure. Furthermore, from a therapeutic standpoint, HFrEF is mainly treated with medication, such as beta-blockers and cardiac resynchronization therapy, to improve circulatory dynamics. In contrast, although no standard treatment for HFpEF has been established, it has been reported that managing comorbidities other than heart disease was important for the prognosis [2, 37], suggesting that factors other than heart failure are essential.

The present study evaluated and clarified the factors that were indicators of exercise tolerance in patients with HFpEF from various perspectives. The results demonstrated that gait speed was a simple clinical indicator of exercise tolerance in HFpEF, similar to previous reports. As a clinical application, we believe that the gait speed of HFpEF patients can be assessed as a screening tool and shared with many professionals.

Additionally, HFpEF was not associated with BNP, which is considered a biomarker of heart failure severity and cardiac function due to the different pathological processes and characteristic factors from those of HFrEF. As prospects, the latest findings suggest that HFpEF can be classified into three subgroups according to the course of the disease [23]. Subsequently, it is necessary to examine the differences in the characteristics of the physical function in each subgroup.

Conclusion

Gait speed is a simple clinical indicator of exercise tolerance in HFpEF patients. Exercise tolerance in HFpEF poorly correlates with the results of BNP, an indicator of heart failure severity and hemodynamics, and echocardiography, used to measure cardiac function. In HFpEF, skeletal muscle mass was not necessarily associated with exercise tolerance. Furthermore, compared to HFrEF, muscle strength may be reduced even if skeletal muscle mass is maintained.

Study limitations

This study has several limitations. First, this study had few cases at a single institution. Therefore, the generalizability of our results is limited. Second, the results of echocardiography, commonly used in clinical practice, were used as an index of cardiac function. In the past, there was a report that the limiting factor of exercise tolerance in HFpEF was pulmonary artery pressure during exercise. Since echocardiography was only an index of resting circulation, it may not correlate with exercise tolerance.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Kumamoto University Hospital (No.: 1932). Sufficient written and oral explanations were provided to the subjects and informed written consent was obtained. This study followed the code of ethics set by the Declaration of Helsinki and all its future amendments or comparable standards.

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Authors' contributions

All authors contributed equally to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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