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ORIGINAL ARTICLE
Heart Failure

Heart Failure With Preserved Ejection Fraction vs. Reduced Ejection Fraction

— Mechanisms of Ventilatory Inefficiency During Exercise in Heart Failure —

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Background: Ventilatory inefficiency during exercise assessed using the lowest minute ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) ratio was recently proven to be a strong prognostic marker of heart failure (HF) regardless of left ventricular ejection fraction (LVEF). Its physiological background, however, has not been elucidated.

Methods and Results: Fifty-seven HF patients underwent cardiopulmonary exercise testing and exercise-stress echocardiography. The lowest $\dot{V}E/\dot{V}CO_2$ ratio was assessed on respiratory gas analysis. Echocardiography was obtained at rest and at peak exercise. LVEF was measured using the method of disks. Cardiac output (CO) and the ratio of transmitral early filling velocity (E) to early diastolic tissue velocity (e') were calculated using the Doppler method. HF patients were divided into preserved EF (HFpEF) and reduced EF (HFrEF) using the LVEF cut-off 40% at rest. Twenty-four patients were classified as HFpEF and 33 as HFrEF. In HFpEF, age (r=0.58), CO (r=–0.44), e' (r=–0.48) and E/e' (r=0.45) during exercise correlated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio ($P<0.05$ for all). In contrast, in HFrEF, age (r=0.47) and CO (r=–0.54) during exercise, but not e' and E/e', correlated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio.

Conclusions: Loss of CO augmentation was associated with ventilatory inefficiency in HF regardless of LVEF, although lung congestion determined ventilatory efficiency only in HFpEF.

Key Words: Cardiopulmonary exercise testing; Exercise-stress echocardiography; Heart failure; Lowest minute ventilation/carbon dioxide production ratio; Ventilatory efficiency

Despite development of treatment strategies for heart failure (HF), the clinical outcome is still poor, with an event-free survival of around 30% per 5 years both in HF patients with reduced left ventricular (LV) ejection fraction (EF; HFrEF) and in those with preserved EF (HFpEF).[1] To improve outcome, adequate management according to risk stratification is important, but accurate prediction of cardiovascular events is still challenging, and a reliable predictor is needed to facilitate development of a useful prediction model in HF. Cardiopulmonary exercise testing (CPX) has been widely used to estimate risk for adverse outcomes in patients with chronic HF, and peak oxygen consumption ($\dot{V}O_2$) has been established as a prognostic marker in chronic HF.[2,3] Meanwhile, in recent years, research has focused on ventilatory efficiency during exercise assessed on minute ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) using CPX. The $\dot{V}E/\dot{V}CO_2$ slope is calculated using the range from the point at which the minute ventilation during the ramp load begins to increase to the respiratory compensation (RC) point, and the lowest $\dot{V}E/\dot{V}CO_2$ ratio is calculated using the lowest value from anaerobic threshold (AT) to RC point.[4,5] $\dot{V}E$ and $\dot{V}CO_2$ correlate very well and represent a non-invasive index to estimate ventilatory inefficiency.[4,5] The higher $\dot{V}E/\dot{V}CO_2$ is, the more impaired the ventilation efficiency, and this ratio has been found to be as powerful a predictor of adverse outcomes in HF patients as peak $\dot{V}O_2$ is.[4–6] These associations between ventilatory efficiency and clinical outcome

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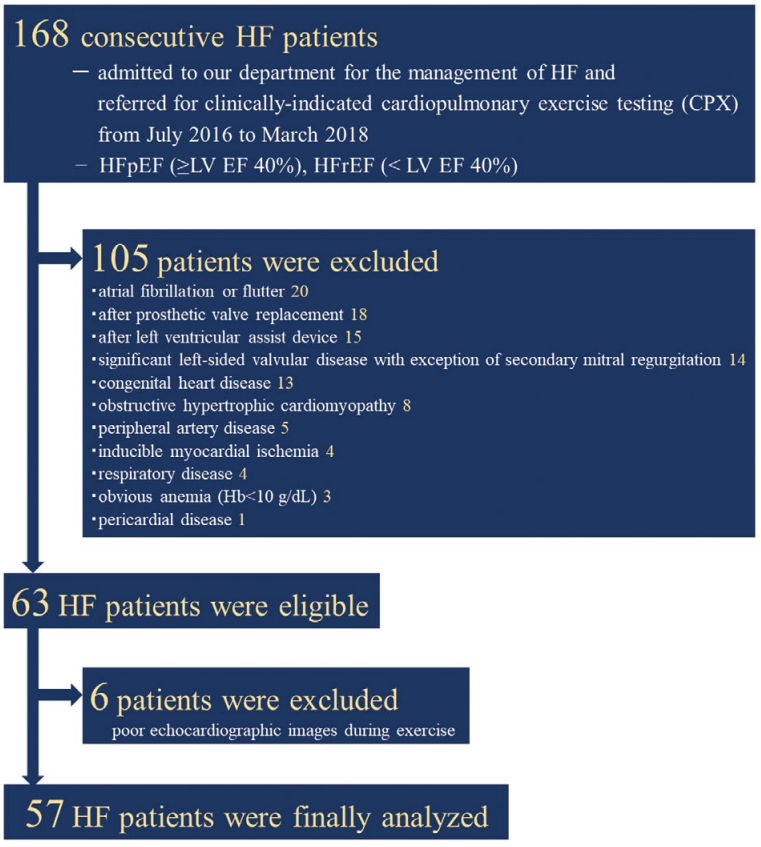

Figure 1. Subject selection process. Hb, hemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

have been observed both in HFrEF and HFpEF, although the physiological response to exercise is different between these 2 entities.[7,8] Several investigators have investigated the pathophysiological mechanisms for impaired ventilatory efficiency in HFrEF,[9–11] but no studies have focused on the differences in determinants of ventilatory efficiency between HFrEF and HFpEF. If there were differences in these determinants between HFrEF and HFpEF, these would help to elucidate a therapeutic target in these entities. Therefore, the aim of this study was to identify the physiological determinants of ventilatory efficiency in HF patients according to LVEF status using exercise-stress echocardiography.

Methods

Subjects and Protocol

The screening process in this study is shown in **Figure 1**. The present study prospectively enrolled 168 consecutive and chronic HF patients admitted to Hokkaido University Hospital for the management of HF and referred for clinically indicated CPX from July 2016 to March 2018. From the 168 patients, we excluded those with atrial fibrillation (AF) or flutter, inducible myocardial ischemia, significant left-sided valve disease (with the exception of secondary mitral regurgitation; MR), moderate or severe aortic regurgitation, aortic stenosis, mitral stenosis, primary MR assessed on Doppler echocardiography according to the guidelines,[12] prosthetic valve replacement, obstructive hypertrophic cardiomyopathy, peripheral artery disease, obvious anemia (hemoglobin <10 g/dL), congenital heart disease, respiratory disease, pericardial disease, and LV assist device implantation. Accordingly, 63 HF patients were eligible for the present analysis. HFpEF was defined as HF symptoms or signs, elevated B-type natriuretic peptide (BNP; >35 pg/mL), plus evidence of echocardiographic abnormalities such as LV hypertrophy, left atrial (LA) enlargement, or evidence of diastolic function in the presence of LVEF ≥40%.[13] HFrEF was defined as HF symptoms or signs, and reduced LVEF (<40%) as per the guidelines.[13] After confirmation that HF was stable, CPX and exercise-stress echocardiography were performed without discontinuing β-blockers. The present study was performed in accordance with the Declaration of Helsinki and the ethics standards of the responsible committee on human experimentation (institutional and national). The study protocol was approved by the institutional review board of the Hokkaido University Hospital and written informed consent was obtained from all the patients.

CPX

Symptom-limited CPX was performed with the use of an upright electromechanical bicycle ergometer (Aerobike 75XLII; Combi Wellness, Tokyo, Japan) using a ramp protocol as previously described.[14] Peak oxygen consumption ($\dot{V}O_2$), defined as the highest value of maximum $\dot{V}O_2$ in the test, was measured using simultaneous respiratory gas analysis with a breathing apparatus (Aeromonitor AE-300S; Minato Medical Science, Osaka, Japan). The maximum work, peak respiratory exchange, and AT

Table 1. Baseline Clinical Characteristics

Variable	Overall (n=57)	HFpEF (n=24)	HFrEF (n=33)	P-value†
Age (years)	58±15	57±16	59±15	0.67
Male	35 (61)	15 (63)	20 (61)	0.93
BSA (m^2)	1.67±0.21	1.67±0.20	1.66±0.20	0.38
SBP (mmHg)	107±18	117±13	100±18	<0.01
DBP (mmHg)	64±12	67±10	61±12	0.03
Heart rate (beats/min)	67±11	66±12	68±11	0.41
NYHA functional class				<0.01
I	11 (20)	9 (38)	2 (6)	
II	20 (36)	8 (33)	12 (36)	
III	26 (46)	7 (29)	19 (58)	
Cardiac disease				<0.01
Dilated cardiomyopathy	20 (35)	3 (13)	17 (52)	
Ischemic heart disease	8 (14)	4 (17)	4 (13)	
Hypertensive heart disease	6 (11)	2 (8)	4 (13)	
HCM	7 (12)	4 (17)	3 (9)	
Others	16 (28)	11 (46)	5 (16)	
Comorbidity				
Hypertension	22 (39)	13 (54)	9 (33)	0.08
Dyslipidemia	26 (46)	13 (54)	13 (39)	0.25
Diabetes mellitus	11 (19)	2 (8)	9 (27)	0.04
Medication				
ACEI or ARB	49 (86)	19 (79)	30 (91)	0.11
β-blockers	45 (79)	14 (58)	31 (94)	<0.01
Calcium antagonists	6 (11)	4 (17)	2 (6)	0.23
Loop diuretics	33 (58)	8 (33)	25 (76)	<0.01
MCRA	25 (44)	3 (13)	22 (67)	<0.01
Tolvaptan	12 (21)	0 (0)	12 (36)	<0.01
Statin	25 (44)	12 (50)	13 (39)	0.18
Aspirin	10 (18)	4 (17)	6 (18)	0.80
Laboratory data				
Hemoglobin (g/dL)	13.5±2.1	13.8±1.7	13.3±2.4	0.43
Total protein (g/dL)	7.0±0.6	7.0±0.5	6.9±0.6	0.58
Albumin (g/dL)	4.1±0.4	4.2±0.4	4.1±0.4	0.19
Total bilirubin (mg/dL)	0.8±0.4	0.8±0.4	0.8±0.3	0.83
Creatinine (mg/dL)	0.9±0.3	0.8±0.3	1.0±0.3	0.13
Triglyceride (mg/dL)	110 (81–145)	117 (91–189)	102 (78–129)	0.06
HDL-C (mg/dL)	54±17	57±18	52±17	0.38
LDL-C (mg/dL)	112±32	113±58	112±29	0.89
HbA_{1c} (%)	6.0±0.6	5.8±0.4	6.1±0.7	0.07
BNP (pg/mL)	145 (60–352)	74 (50–150)	248 (126–468)	<0.01
Echocardiography data				
LVMI (g/m^2)	118 (90–149)	95 (87–123)	128 (105–151)	0.02
LVEF (%)	39±14	53±9	28±6	<0.01
Stroke volume (mL)	58±17	64±12	54±18	0.03
CO (L/min)	3.8±1.0	4.2±0.9	3.5±1.0	<0.01
s' (cm/s)	5.4±1.5	6.3±1.4	4.7±1.2	<0.01
e' (cm/s)	5.4±2.1	6.1±2.1	4.8±1.9	0.02
E/A ratio	1.3±0.8	1.2±0.8	1.3±0.7	0.79
E/e' ratio	14.0±5.8	12.1±5.1	15.4±5.9	0.03
LAVI (mL/m^2)	46±20	38±17	51±21	0.01
TRPG (mmHg)	21±9	23±11	19±6	0.13
MR				0.03
None or trivial	27 (47)	17 (71)	10 (30)	
Mild	21 (37)	5 (21)	16 (48)	
Moderate	9 (16)	2 (8)	7 (16)	

(**Table 1** continued the next page.)

Variable	Overall (n=57)	HFpEF (n=24)	HFrEF (n=33)	P-value†
CPX data				
Peak heart rate (beats/min)	119±29	128±28	112±28	<0.01
Peak load (W)	93±40	108±41	76±32	<0.01
Peak RER	1.2±0.1	1.2±0.1	1.2±0.1	0.90
Peak $\dot{V}O_2$ (mL/kg/min)	17.8±5.2	20.0±5.8	16.0±4.1	<0.01
AT (mL/kg/min)	11.0±3.2	11.6±2.8	10.5±3.6	0.26
Lowest $\dot{V}E/\dot{V}CO_2$ ratio	34±7	33±8	36±6	0.15

Data given as mean±SD, n (%) or median (IQR). †HFpEF vs. HFrEF. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AT, anaerobic threshold; BNP, brain natriuretic peptide; BSA, body surface area; CO, cardiac output; CPX, cardiopulmonary exercise testing; DBP, diastolic blood pressure; e', average of the peak early diastolic myocardial velocity from septal and lateral sites of the mitral annulus; E, peak early diastolic filling velocity; HbA_{1c}, hemoglobin A_{1c}; HCM, hypertrophic cardiomyopathy; HDL-C, high-density lipoprotein cholesterol; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MCRA, mineral corticoid receptor antagonists; MR, mitral regurgitation; NYHA, New York Heart Association; RER, respiratory exchange ratio; s', average of the peak systolic myocardial velocity from septal and lateral sites of the mitral annulus; SBP, systolic blood pressure; TRPG, tricuspid regurgitation pressure gradient; $\dot{V}E/\dot{V}CO_2$, minute ventilation/carbon dioxide production; $\dot{V}O_2$, oxygen consumption.

determined by the V-slope method[15] were also measured. The lowest $\dot{V}E/\dot{V}CO_2$ ratio during exercise was measured as a parameter of ventilatory efficiency during exercise, which has been reported as a stable marker of ventilatory inefficiency across laboratory sites, exercise mode, gender and age.[5]

Exercise-Stress Echocardiography

Exercise-stress echocardiography using a supine bicycle ergometer (Angio V2; Lode BV, Groningen, Netherlands) and iE33 ultrasound system with S5-1 transducer (Philips Ultrasound, Bothell, WA, USA) was performed ≤7 days after CPX. The mean time from CPX to exercise-stress echocardiography was 3±2 days. To adjust the workload during stress echocardiography, we determined peak workload as 80% of the CPX peak workload. Echocardiography including 2-D Doppler imaging was acquired at rest and peak exercise. Echocardiography measurements were obtained in accordance with the current guidelines of the European Association of Cardiovascular Imaging/American Society of Echocardiography.[16] LVEF was measured using the method of disks. LV mass was calculated according to the Devereux formula. Doppler imaging of LV outflow was recorded in the apical long-axis view and the time-velocity integral was measured for the estimation of stroke volume. Cardiac output (CO) was calculated as stroke volume×heart rate. Transmitral Doppler flow was recorded and peak early (E) and late diastolic velocity (A) were measured. Septal and lateral peak systolic annular velocity (s') as well as early diastolic peak of mitral annular velocity (e') were measured from the apical 4-chamber view using pulsed-wave tissue Doppler imaging, and the average of the septal and lateral velocities was used for subsequent analysis. The ratio of E to e' (E/e') was calculated.

Definition of Ventilatory Insufficiency

Ventilatory insufficiency was determined using the cut-off of lowest $\dot{V}E/\dot{V}CO_2$ ratio ≥33 during CPX.[4]

Statistical Analysis

Quantitative variables are expressed as mean±SD if normally distributed, and as median (IQR) if non-normally distributed. Qualitative variables are reported using frequency and percentage. Parametric unpaired t-test or non-parametric Wilcoxon test was used to compare quantitative variables. To identify differences in hemodynamic and echocardiographic parameters between rest and peak exercise, the paired t-test was used for comparisons of continuous variables. The chi-squared test was used to compare qualitative variables. Pearson's correlation coefficient was used to examine the relationship between continuous variables. Linear regression analysis was used to identify cofactors associated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio. Moreover, we assessed associations between echocardiographic parameters and the lowest $\dot{V}E/\dot{V}CO_2$ ratio after adjustment for age, body surface area (BSA), and plasma BNP level, which were selected as significant clinical determinants of the lowest $\dot{V}E/\dot{V}CO_2$ ratio. For all tests, $P<0.05$ was considered statistically significant. Statistical analyses were performed using JMP Pro 13.1.0 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

Of the 63 eligible HF patients, 6 patients were excluded due to insufficient echocardiography image quality during exercise. Therefore, the final subjects consisted of 57 patients: 24 patients classified as having HFpEF and 33 with HFrEF. The baseline characteristics are listed in **Table 1**. Age, sex and BSA were similar in both groups. Systolic blood pressure was significantly higher in HFpEF than HFrEF, although heart rate was similar in both groups. HFrEF patients had more severe HF symptoms than HFpEF patients. There was a tendency for dilated cardiomyopathy to be more frequent and ischemic heart disease to be less frequent in the HFrEF group. The HFrEF group was more likely to have diabetes mellitus and to be treated with β-blockers, loop diuretics, mineral corticoid receptor antagonist and tolvaptan than the HFpEF group. BNP was lower in HFpEF than in HFrEF patients. With regard to the echocardiography parameters, LV mass index was larger and LVEF, stroke volume, and CO were lower in HFrEF than in HFpEF patients. E/e' was higher and LA volume index was larger in the HFrEF group. Secondary MR was more apparent in the HFrEF

Table 2. Patient Characteristics vs. Ventilatory Efficiency Status

Variable	Overall (n=57)			HFpEF (n=24)			HFrEF (n=33)		
	Lowest V̇E/V̇CO₂ ratio <33 (n=29)	Lowest V̇E/V̇CO₂ ratio ≥33 (n=28)	P-value	Lowest V̇E/V̇CO₂ ratio <33 (n=14)	Lowest V̇E/V̇CO₂ ratio ≥33 (n=10)	P-value	Lowest V̇E/V̇CO₂ ratio <33 (n=15)	Lowest V̇E/V̇CO₂ ratio ≥33 (n=18)	P-value
Age (years)	52±15	64±13	<0.01	52±16	65±11	0.03	53±13	64±15	0.03
Male	19 (66)	16 (57)	0.52	10 (71)	5 (50)	0.29	9 (60)	11 (61)	0.95
BSA (m²)	1.73±0.23	1.59±0.17	0.01	1.75±0.23	1.57±0.12	0.04	1.72±0.24	1.61±0.19	0.04
SBP (mmHg)									
At rest	116±19	106±15	0.02	123±18	117±14	0.39	110±17	99±12	0.05
During exercise	164±30	145±25	0.01	173±27	164±21	0.36	156±31	134±20	0.03
Heart rate (beats/min)									
At rest	65±9	68±12	0.33	68±10	65±13	0.64	62±8	69±11	0.06
During exercise	112±16	95±19	<0.01	121±10	97±20	<0.01	103±16	94±20	0.17
Ischemic etiology	2 (7)	7 (25)	0.04	1 (7)	3 (30)	0.03	1 (7)	4 (22)	0.04
NYHA class III	6 (21)	19 (68)	<0.01	2 (14)	5 (50)	0.03	4 (29)	14 (78)	<0.01
Hb (g/dL)	14.0±2.2	13.0±1.8	0.06	14.1±1.6	13.2±1.9	0.21	13.9±2.7	12.9±1.8	0.20
Creatinine (mg/dL)	0.9±0.2	1.0±0.4	0.09	0.8±0.2	0.9±0.4	0.69	0.9±0.3	1.1±0.4	0.11
BNP (pg/mL)	119 (50–243)	214 (81–462)	0.03	72 (52–148)	104 (63–203)	0.23	148 (61–364)	341 (157–579)	0.03
CPX data									
Peak workload (W)	117±36	69±28	<0.01	134±35	77±27	<0.01	100±28	64±29	<0.01
AT (mL/kg/min)	12.1±3.6	9.8±2.4	<0.01	12.6±2.8	10.1±2.2	0.03	11.5±4.2	9.6±2.6	0.12
Peak V̇O₂ (mL/kg/min)	20.6±4.7	14.8±3.9	<0.01	23.2±4.7	15.7±4.1	<0.01	18.2±3.4	14.3±3.9	<0.01
Echocardiography data									
LVMI (g/m²)	110 (90–135)	127 (95–162)	0.33	98 (88–117)	95 (75–154)	0.66	125 (100–144)	133 (111–178)	0.24
LVEF (%)									
At rest	40±16	37±15	0.46	53±13	55±10	0.66	29±5	27±7	0.55
During exercise	47±19	42±19	0.34	63±16	64±12	0.83	33±6	30±9	0.28
Stroke volume (mL)									
At rest	64±14	52±17	<0.01	68±8	59±15	0.07	61±18	48±17	0.04
During exercise	74±18	58±21	<0.01	82±16	69±19	0.04	67±18	50±20	0.02
CO (L/min)									
At rest	4.1±0.9	3.4±0.9	<0.01	4.5±0.7	3.7±0.9	0.02	3.8±1.0	3.3±0.9	0.12
During exercise	8.4±2.4	5.3±2.3	<0.01	10.1±1.7	6.5±2.5	<0.01	6.9±1.9	4.6±2.0	<0.01
Change rate in CO during exercise	2.1±0.5	1.5±0.4	<0.01	2.2±0.4	1.7±0.5	0.02	1.9±0.5	1.4±0.3	<0.01
s' (cm/s)									
At rest	5.7±1.6	5.1±1.3	0.10	6.8±1.5	5.6±0.9	0.04	4.7±0.9	4.7±1.4	0.87
During exercise	7.6±2.5	6.1±2.0	0.02	8.9±2.6	7.4±1.7	0.03	6.3±1.7	5.3±1.7	0.10
e' (cm/s)									
At rest	6.0±2.4	4.7±1.4	0.01	7.0±2.2	4.9±1.2	0.01	5.1±2.2	4.6±1.6	0.42
During exercise	8.8±3.8	6.2±2.6	<0.01	11.3±3.4	7.6±2.7	0.01	6.3±2.1	5.3±2.1	0.22
E/e'									
At rest	12.4±4.9	15.7±6.2	0.03	10.4±3.8	14.5±5.9	0.04	14.3±5.2	16.4±6.4	0.33
During exercise	14.4±7.2	20.1±11.6	0.04	11.3±3.7	15.1±4.3	0.04	18.3±8.4	24.5±12.3	0.17
Change in E/e' during exercise	2.2±3.9	4.5±7.3	0.13	0.8±1.7	0.6±3.1	0.69	3.8±4.9	8.1±7.3	0.14
LAVI (mL/m²)	42±18	50±22	0.18	38±15	38±22	0.97	46±20	56±21	0.18
TRPG (mmHg)									
At rest	19±6	22±10	0.43	22±7	24±15	0.70	17±4	20±7	0.25
During exercise	34±14	39±14	0.19	31±21	36±14	0.59	35±10	42±13	0.15
Increase in MR to more than moderate	5 (17)	12 (43)	0.01	1 (7)	1 (10)	0.93	4 (27)	11 (61)	0.02

Data given as mean±SD, n (%) or median (IQR). Hb, hemoglobin. Other abbreviations as in Table 1.

Table 3. Determinants of Lowest $\dot{V}E/\dot{V}CO_2$ Ratio

Variable	HFpEF		HFrEF	
	r	P-value	r	P-value
Age	0.58	<0.01	0.47	<0.01
BSA	–0.41	0.04	–0.45	0.01
SBP at rest	0.04	0.84	–0.31	0.08
SBP during exercise	0.15	0.47	–0.28	0.13
Heart rate at rest	0.07	0.75	0.27	0.12
Heart rate during exercise	–0.51	0.01	–0.23	0.20
Hemoglobin	–0.38	0.06	–0.21	0.24
Creatinine	0.39	0.06	0.13	0.46
Log BNP	0.15	0.48	0.40	0.03
Stroke volume at rest	–0.25	0.24	–0.30	0.09
Stroke volume during exercise	–0.14	0.50	–0.44	0.02
CO at rest	–0.20	0.33	–0.24	0.18
CO during exercise	–0.44	0.04	–0.54	<0.01
LVEF at rest	–0.16	0.45	–0.14	0.44
LVEF during exercise	–0.07	0.76	–0.26	0.15
s' at rest	–0.24	0.27	–0.18	0.30
s' during exercise	–0.05	0.81	–0.44	0.01
e' at rest	–0.41	0.04	–0.21	0.25
e' during exercise	–0.48	0.03	–0.26	0.18
E/e' at rest	0.39	0.04	0.24	0.19
E/e' during exercise	0.45	0.03	0.20	0.33
TRPG at rest	0.19	0.43	0.35	0.07
TRPG during exercise	0.22	0.44	0.33	0.11

Abbreviations as in Table 1.

group. With regard to CPX data, peak heart rate and peak load were higher in the HFpEF group, and respiratory exchange ratio (RER) was similar between the groups with an average of >1.15, suggesting that adequate stress could be achieved in both groups. Peak $\dot{V}O_2$ was higher in HFpEF than in HFrEF patients. AT and the lowest $\dot{V}E/\dot{V}CO_2$ ratio were almost identical in the 2 groups.

Exercise-Stress Echocardiography

During exercise, heart rate was increased in both groups (HFpEF, 66±12 to 111±12 beats/min, P<0.05; HFrEF, 68±12 to 99±12 beats/min, P<0.05) whereas stroke volume was increased in only HFpEF patients (HFpEF, 64±12 to 77±18 mL, P<0.05; HFrEF, 54±18 to 58±20 mL, P<0.05), resulting in greater achievement in CO in HFpEF than in HFrEF (8.6±2.7 vs. 5.8±2.2 L/min, P<0.01). Heart rate at peak exercise was significantly lower than that during CPX (112±16 vs. 119±29 beats/min, P=0.03) although there was a strong correlation between them (r=0.82). HFpEF patients had higher LVEF (63±14% vs. 31±8%, P<0.01), s' (8.2±2.3 vs. 5.8±1.8 m/s, P<0.01), and e' (9.7±3.6 vs. 5.7±2.1 m/s, P<0.01) at peak exercise than the HFrEF patients. In contrast, HFrEF patients had higher E/e' (16.4±6.7 vs. 21.7±11.0, P<0.01) than HFpEF patients. Tricuspid regurgitation pressure gradient at peak exercise was not different between the groups (HFpEF vs. HFrEF, 34±16 vs. 39±12 m/s, P=n.s.). Fifteen HFrEF patients (45%) had increased MR to more than moderate whereas only 2 HFpEF patients (8%) had an increase in MR.

Ventilatory Inefficiency: Patient Characteristics

Comparisons of clinical and stress test parameters are listed in **Table 2**. Patients with ventilatory inefficiency had higher age, lower BSA and CO during exercise as well as lower rate of change of CO during exercise than those without, consistent with previous reports.[4,5,10] Peak workload as well as peak $\dot{V}O_2$ was markedly reduced in patients with ventilatory insufficiency, suggesting reduced exercise capacity in these patients. Similar results were observed in both the HFrEF and HFpEF groups. Intriguingly, significantly lower heart rate, s', and e', and higher E/e' during exercise were observed in the ventilatory inefficiency group compared with the preserved ventilatory efficiency patients, only in the HFpEF group. Change in E/e' during exercise, however, was not significantly different according to ventilatory efficiency status in the overall patient group or in the HFpEF and HFrEF groups.

Determinants of Lowest $\dot{V}E/\dot{V}CO_2$ Ratio

On univariable analysis to determine the lowest $\dot{V}E/\dot{V}CO_2$ ratio in HFpEF and HFrEF (**Table 3**), age was significantly and positively correlated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio, whereas BSA was negatively correlated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio in each group. Plasma BNP was positively correlated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio in HFrEF but not in HFpEF. Other parameters were not associated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio. Of the echocardiographic parameters at rest, LVEF and CO were not associated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio in both groups, whereas e' and E/e' were associated the lowest $\dot{V}E/\dot{V}CO_2$ ratio only in HFpEF. In contrast, at exercise, CO was significantly and negatively correlated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio, whereas LVEF was not correlated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio in both groups. Interestingly, both e' and E/e'

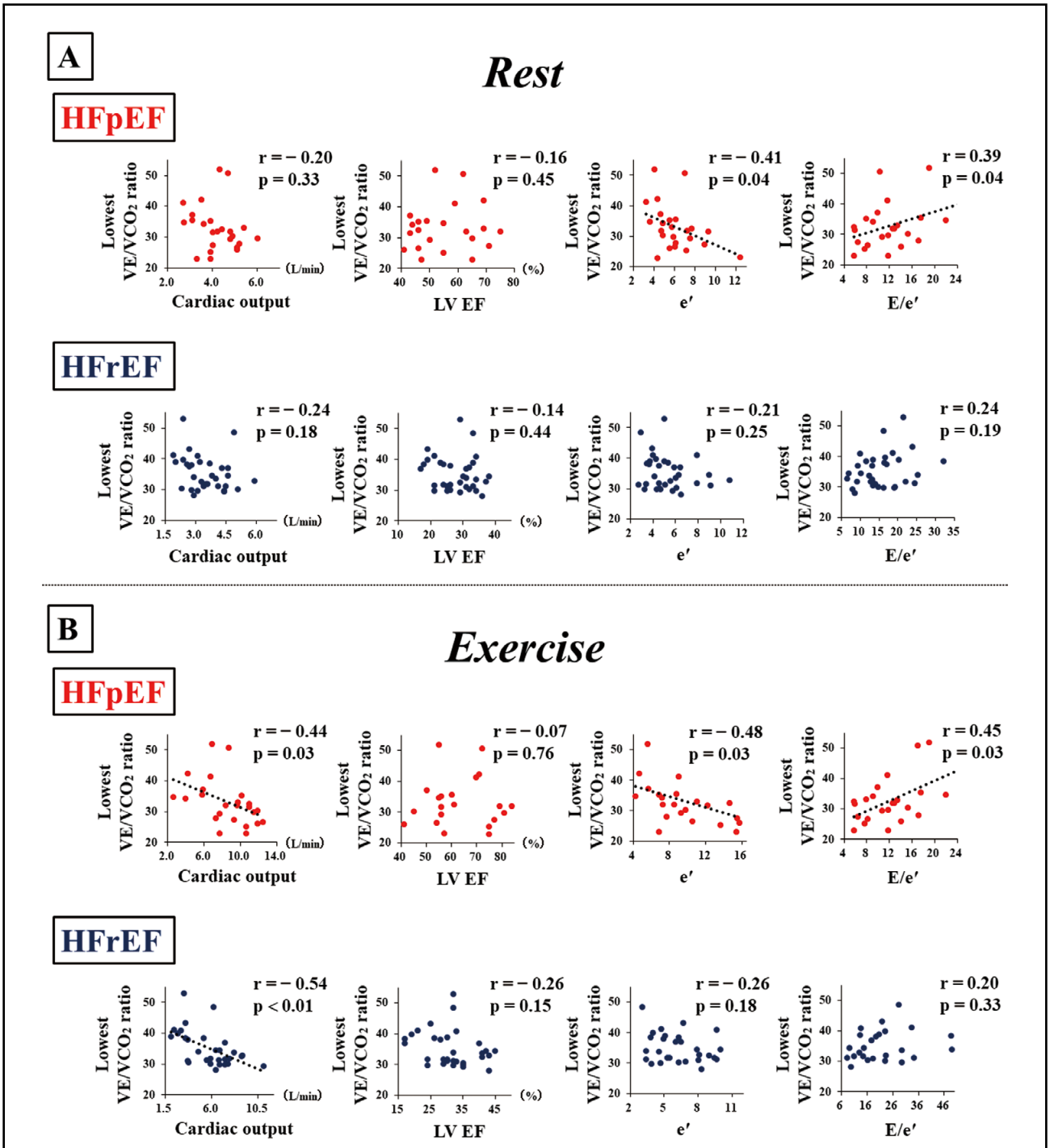

Figure 2. Correlations between the lowest minute ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) ratio and echocardiographic parameters (**A**) at rest and (**B**) at peak exercise in patients with heart failure with preserved ejection fraction (HFpEF,) and heart failure with reduced ejection faction (HFrEF). e', early diastolic mitral annular velocity; E, early diastolic transmitral flow velocity; LVEF, left ventricular ejection fraction.

during exercise were significantly correlated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio in HFpEF, but not in HFrEF (**Figure 2**).

These associations were significant after adjustment for age, BSA, and plasma BNP level (**Table 4**).

Discussion

In the present study, we investigated associations between the lowest $\dot{V}E/\dot{V}CO_2$ ratio and echocardiography parameters during exercise in chronic HF patients, and found an apparent difference in hemodynamic determinants of the

Table 4. Correlations Between Echocardiography Parameters and Lowest $\dot{V}E/\dot{V}CO_2$ Ratio†

Variable	HFpEF		HFrEF	
	β	P-value	β	P-value
CO at rest	–0.06	0.74	–0.05	0.76
CO during exercise	–0.41	0.03	–0.39	0.04
LVEF at rest	–0.16	0.41	–0.11	0.49
LVEF during exercise	–0.30	0.15	–0.13	0.47
e' at rest	–0.19	0.51	–0.11	0.55
e' during exercise	–0.36	0.04	–0.05	0.81
E/e' at rest	0.26	0.26	0.01	0.98
E/e' during exercise	0.44	0.04	0.07	0.70

†After adjustment for age, BSA and plasma BNP. β, standardized beta coefficient. Abbreviations as in Table 1.

lowest $\dot{V}E/\dot{V}CO_2$ ratio: CO as well as e' and E/e' during exercise in HFpEF; but only CO during exercise and not e' or E/e' in HFrEF. This suggests that blunted response in CO to exercise could determine ventilatory inefficiency both in HFpEF and HFrEF, whereas LV relaxation and subsequent lung congestion was associated with ventilatory inefficiency only in HFpEF. To the best of our knowledge, this is the first study to directly evaluated relationships between the lowest $\dot{V}E/\dot{V}CO_2$ ratio and exercise-stress echocardiographic parameters according to LVEF status.

Recent reports have shown the usefulness of $\dot{V}E/\dot{V}CO_2$ slope during exercise as a prognostic marker in HF patients,[17–19] and increasing attention is being paid to the clinical significance of $\dot{V}E/\dot{V}CO_2$ in the field of HF. Despite the prognostic utility, knowledge of physiological determinants of $\dot{V}E/\dot{V}CO_2$ is still insufficient in HF. Because carbon dioxide production, the denominator of $\dot{V}E/\dot{V}CO_2$, reflects effective alveolar perfusion, $\dot{V}E/\dot{V}CO_2$ slope has been considered to reflect ventilation-perfusion mismatch during exercise.[20–23] In HF, it is reasonable that loss of CO response reduces $\dot{V}CO_2$, and lung congestion increases $\dot{V}E$ through the pulmonary vagus reflex, resulting in ventilation-perfusion mismatch during exercise. Therefore, CO and lung congestion are expected to be the main determinants of ventilatory efficiency at exercise in HF. In accordance with this theory, the associations of declining CO at rest or exercise, elevated mean pulmonary artery pressure or pulmonary artery wedge pressure during exercise with elevated $\dot{V}E/\dot{V}CO_2$ slope during exercise in HFrEF, in addition to elevated pulmonary vascular resistance, increased pulmonary dead space, and skeletal muscle dysfunction, have been noted as influencing factors.[5,24,25] In HFpEF, increased mean pulmonary artery pressure and pulmonary vascular resistance at rest were reported to be associated with elevated $\dot{V}E/\dot{V}CO_2$ slope.[26]

Consistent in part with the previous observations, we found that CO during exercise was associated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio independently of other clinical factors in HFrEF. However, E/e', a parameter of LV filling pressure, was not a significant indicator of this in the current HFrEF population, which is in contrast to the study by Ponikowski et al.[27] Because the present HFrEF patients had more advanced HF signs, manifesting as severely reduced LVEF of 28% on average and worse HF symptoms (NYHA class III in 58%), LV relaxation could have been highly impaired and elevated LV filling pressure could frequently be present even at rest and, as a result, the impact of LV relaxation reserve and of exercise-induced lung congestion might have been reduced in the present study. In addition, approximately half of the HFrEF patients had increased MR to more than moderate during exercise, in association with severely reduced LV systolic function, which could have resulted in reduced forward CO and subsequent accentuation of the influence of reduced CO on respiratory efficiency in HFrEF patients. In addition, it is well known that such patients in advanced HF have skeletal muscle dysfunction. Therefore, ergoreflex response, responsible for eliciting an exaggerated ventilatory drive during exercise, might have been disordered. As previously reported,[24] alteration of ergoreflex might also have affected the lowest $\dot{V}E/\dot{V}CO_2$ ratio in the present HFrEF patients.

In contrast, we showed that both CO and E/e' during exercise were associated with the lowest $\dot{V}E/\dot{V}CO_2$ ratio in HFpEF. Given the hemodynamics of HFpEF, which is characterized as blunted CO reserve and abnormal elevation of LV filling pressures during exercise,[8] the present observation is expected, although it had not been previously clarified. Further invasive study using exercise-stress right heart catheterization is needed to confirm these findings.

Study Limitations

First, as a single-center study, the sample size was small and the present results need to be confirmed in a larger population. In addition, we classified the patients using an LVEF cut-off of 40% because of the small sample size, and therefore the HFpEF group included HF with mid-range LVEF. The present observations thus can be interpreted as a differentiation of patients with apparent LV systolic dysfunction and those with relatively preserved LVEF. Second, due to the exclusion of 105 of 168 patients because of the diversity of HF in clinical practice, this narrows down the population to which the conclusions can be applied. In contrast, this strict selection could exclude potential confounding factors that would affect the assessment of LV diastolic function or of time-velocity integral of LV outflow. Third, to avoid the instability of echocardiographic parameters due to irregular heart beat, we excluded patients with AF, which frequently coexists in HF. Therefore the present results cannot be applied to patients with AF, and need to be tested in these patients by analyzing multiple heart beats. Fourth, because exercise-stress echocardiography was performed separately to CPX, the difference in posture and duration between the tests would have weakened the relationship between the lowest $\dot{V}E/\dot{V}CO_2$ ratio and the exercise-stress echocardiography parameters. Moreover, heart rates at peak exercise were slightly but significantly

higher in CPX than in exercise-stress echocardiography, which might have weakened the relationships between the parameters of these examinations. However, the strong correlations between these heart rates could justify the use of the parameters obtained from 2 separate examinations. Finally, we used lowest $\dot{V}E/\dot{V}CO_2$ ratio as a marker of respiratory inefficiency in the present study, which has been reported to be a stable parameter unaffected by physician judgement of AT point. In contrast, lowest $\dot{V}E/\dot{V}CO_2$ needs to be measured after the RC point and therefore depends on the sufficiency of the workload during CPX. Although the accuracy of $\dot{V}E/\dot{V}CO_2$ in the present study has been confirmed using peak RER, caution is needed to check this point when used in other laboratories not familiar with the use of this parameter.

Conclusions

In HFpEF, CO as well as lung congestion during exercise could determine ventilatory efficiency. In contrast, in HFrEF, CO, but not lung congestion, during exercise could determine ventilatory efficiency.

Disclosures

The authors declare no conflicts of interest.

IRB Information

The present study was approved by the institutional review board of the Hokkaido University Hospital (reference no.: 015-0440).

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