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Cardiopulmonary exercise testing as prognostic indicators: Comparisons among heart failure patients with reduced, mid-range and preserved ejection fraction

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Abstract

Aims: We aimed to determine the differences of impact of cardiopulmonary exercise testing (CPX) parameters on prognosis of heart failure with reduced left ventricular ejection fraction (HFrEF), preserved ejection fraction (HFpEF) and mid-range ejection fraction (HFmrEF).

Methods: We compared clinical characteristics and CPX parameters among the three groups, and the value of each CPX parameter to predict adverse cardiac events (cardiac deaths and re-hospitalizations for heart failure), cardiac deaths and all-cause deaths.

Results: Of 1190 patients, 41.9% had HFrEF, 36.8% had HFpEF and 21.3% had HFmrEF. The patients in HFrEF group had higher rates of adverse cardiac events, cardiac death and all-cause death than those of HFpEF and HFmrEF groups. In HFrEF, the independent predictors of adverse cardiac events were peak oxygen consumption and oxygen uptake efficiency slope, predictors of cardiac death were peak oxygen consumption and oxygen uptake efficiency slope, and the predictor of all-cause death was peak oxygen consumption. In HFpEF, the predictor of adverse cardiac events was peak oxygen consumption, predictors of cardiac deaths and all-cause deaths were peak oxygen consumption and exertional oscillatory ventilation. In HFmrEF, predictors of adverse cardiac events were peak oxygen consumption and oxygen uptake efficiency slope, and the predictor of cardiac deaths and all-cause deaths was peak oxygen consumption.

Conclusion: Peak oxygen consumption is the strong predictor for adverse events in all groups. Oxygen uptake efficiency slope predicts adverse prognosis in HFrEF, but not in HFpEF. In contrast, exertional oscillatory ventilation is the predictor only in HFpEF. Thus, different CPX parameters may be able to differentially predict prognosis in HFrEF and HFpEF. Those for predicting prognosis in HFmrEF may be intermediate between HFrEF and HFpEF.

Keywords

Clinical outcomes, cardiopulmonary exercise testing, left ventricular ejection fraction

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Introduction

Parameters derived from cardiopulmonary exercise testing (CPX), such as peak oxygen consumption (PVO_2),[1] the minute ventilation carbon dioxide production slope (VE/VCO_2 slope),[2] the partial pressure of end-tidal carbon dioxide at the respiratory compensation point ($ETCO_2$ at RCP),[3] exertional oscillatory

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ventilation (EOV)[4] and oxygen uptake efficiency slope (OUES),[5] are important prognostic markers in patients with chronic heart failure (CHF). However, the impact of these parameters has primarily been examined in heart failure with reduced left ventricular ejection fraction (HFrEF),[6] whereas there are only a few reports in heart failure with preserved left ventricular ejection fraction (HFpEF).[7–9] In addition, heart failure with mid-range ejection fraction (HFmrEF) has been recently defined as left ventricular ejection fraction (LVEF) between 40% and 49% in the 2016 ESC (European Society of Cardiology) Guidelines for heart failure.[10] The clinical features and impact of CPX parameters on prognosis of HFmrEF have yet to be elucidated. Therefore, the aim of the present study was to compare the impact of CPX parameters on prognosis among patients with HFrEF, HFmrEF and HFpEF.

Methods

Study subjects and study protocol

We examined 1190 consecutive patients who were admitted to Fukushima Medical University Hospital for treatment of worsening CHF, and were discharged between July 2007 and January 2015. Our study complies with the Declaration of Helsinki, and the study protocol was approved by the ethical committee of Fukushima Medical University. Written informed consent was obtained from all study subjects. We comprehensively diagnosed CHF, based on several findings of symptoms, physical signs, chest X-ray, electrocardiogram, echocardiogram and natriuretic peptide, as presented in the ESC Guidelines for heart failure.[11] All patients received optimal medication and were in a stable condition before discharge including when undergoing echocardiography and cardiopulmonary exercise testing within three to five days prior to discharge. Blood samples were obtained immediately prior to CPX. The exclusion criteria of the present study were: decompensated heart failure; end stage renal disease (estimated glomerular filtration rates (eGFR) $< 15\,ml/min$ per $1.73\,m^2$); end stage liver disease; advanced malignant disease; acute coronary syndrome within six months prior to presentation; active inflammatory disease; and inability to perform CPX. The eGFR was defined according to the Modification of Diet in Renal Disease.[12] Patients were followed up after discharge to register several events. The endpoints were cardiac death (death due to worsening heart failure, acute coronary syndrome, arrhythmia or sudden cardiac death), adverse cardiac event (cardiac death or rehospitalization due to worsening heart failure) or all-cause death. The follow-up and events were adjudicated using medical records, death certificates and a questionnaire for the home doctors and the patients themselves. The median follow-up period was 1497 days (range 2–3203 days) and was completed for all patients, ending in March 2016. Echocardiography was performed blindly by experienced cardiac sonographers using standard techniques within three days of hospital discharge. An LVEF $>50\%$ was defined as HFpEF, an LVEF of 40% to 49% as HFmrEF and an LVEF of $<39\%$ as HFrEF.[10] We compared clinical characteristics, blood sampling data, systolic and diastolic function, the exercise parameters derived from CPX, cardiac event rate, the prognostic indicators derived from CPX among the HFrEF group, the HFmrEF and the HFpEF group.

Cardiopulmonary exercise testing

All subjects performed incremental symptom-limited exercise testing using an upright cycle ergometer with a ramp protocol (Strength Ergo 8, Fukudadenshi Co. Ltd, Tokyo, Japan). Breath-by-breath oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE) were measured during exercise using an Aeromonitor AE-300S (Minato Medical Science, Osaka, Japan). PVO_2 was measured as an average of the last 30 s of exercise. Ventilatory response to exercise (expressed as a VE/VCO_2 slope) was calculated as the regression slope relating VE to CO_2 using all CPX data.[13] EOV was defined as an oscillatory pattern at rest that persists for 60% of the exercise test at an amplitude of 15% of the average resting value.[13] The OUES was calculated from data collected during the first 75%, 90% and 100% of exercise duration. The OUES was derived from the following equation: $VO(2) = a \times \log V(E) + b$, where VO(2) is oxygen uptake (ml/kg per min), V(E) is minute ventilation (l/kg per min), and the constant 'a' represents OUES.[14]

Data and statistical analysis

Results are presented as mean ± SD for continuous variables and as numbers and percentages for categorical variables. The characteristics of the three groups were compared using analysis of variance followed by Tukey's post hoc test, and the Chi-square test was used for categorical variables. Significance was accepted as $p < 0.05$. The cardiac death, adverse cardiac event and all-cause death rates were compared using Kaplan–Meier analysis, and the log-rank test was used to compare the cumulative events among the HFrEF, HFmrEF and HFpEF groups. The Cox proportional hazard regression models determined which variables were associated with cardiac death, adverse cardiac

events and all-cause death. We entered age, gender (male), body mass index (BMI), anemia, chronic obstructive pulmonary disease (COPD), PVO_2 < median value, VE/VCO_2 < median value, $ETCO_2$ at RCP < median value, EOV and OUES < median value as variables for the three groups. In this model, we selected co-morbidities such as anemia and COPD, which are highly represented in HFpEF and would influence peak VO_2 and VE/VCO_2 slope.[15,16] Associated variables ($p < 0.10$) selected in the univariable analysis were entered into the multivariable analysis. All statistical analyses were performed using SPSS statistics version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of the study subjects

Comparisons of clinical characteristics, laboratory data and echocardiographic and CPX findings among the study subjects in the three groups are shown in Table 1. Of the 1190 CHF patients, 498 (41.9%) had HFrEF, 254 (21.3%) had HFmrEF and 438 (36.8%) had HFpEF. In summary, HFrEF patients had the lowest age and BMI, and the highest levels of B-type natriuretic peptide (BNP) and the lowest levels of sodium in the laboratory data, and the highest VE/VCO_2 slope, higher prevalence of EOV, and the lowest PVO_2 and OUES in the CPX parameters. In contrast, HFpEF patients had the highest eGFR and the lowest BNP levels in the laboratory data, and had the highest levels of systolic blood pressure, PVO_2 and OUES and the lowest VE/VCO_2 slope, and the lowest prevalence of EOV in the CPX parameters. HFmrEF patients had almost intermediate characteristics of parameters between HFpEF and HFrEF groups.

Cardiac events in study subjects

A total of 173 cardiac deaths were registered, including 159 deaths due to heart failure and 14 sudden cardiac deaths during the follow-up period (median 1497 days). A total of 408 adverse cardiac events were registered, including 31 cardiac deaths and 377 rehospitalizations due to worsening heart failure. A total 248 all-cause deaths were registered, including 173 cardiac deaths, 40 deaths due to malignant diseases, eight deaths due to infectious disease, eight deaths due to stroke and 19 deaths due to other causes. Kaplan–Meier analyses revealed that the HFrEF group had higher rates of adverse cardiac events, cardiac death and all-cause death than both HFpEF and HFmrEF groups (Figure 1). These adverse event rates did not significantly differ between the HFpEF and HFmrEF groups (Figure 1).

CPX parameters to determine adverse prognosis

In the HFrEF group, the ability of CPX parameters after adjusting for age, gender, BMI, presence of anemia and COPD, to predict adverse cardiac events, cardiac deaths and all-cause deaths in the HFrEF group was examined by univariate and multivariate Cox proportional hazard analyses (Table 2). In the multivariate Cox proportional hazard analysis, PVO_2, $ETCO_2$ at RCP and OUES were independent factors to predict adverse cardiac events. In addition, PVO_2 and OUES were independent factors to predict cardiac deaths, and only PVO_2 was the independent factor to predict all-cause deaths in the HFrEF group.

In the HFpEF group (Table 2), the multivariate Cox proportional hazard analysis shows that PVO_2 was the only independent predictor for adverse cardiac events. PVO_2 and EOV were independent predictors for cardiac death and all-cause death.

In the HFmrEF group (Table 2), PVO_2 and OUES were independent predictors for adverse cardiac events. PVO_2 was the only independent predictor for cardiac death and all-cause death.

Discussion

In the present study, adverse cardiac event rates, and cardiac and all-cause mortality were significantly higher in the HFrEF group than in the HFmrEF and HFpEF groups. To the best of our knowledge, we are first to present differences of impact of each CPX parameter on adverse prognosis among patients with HFrEF, HFmrEF and HFpEF. The current study suggests that PVO_2 is a very strong predictor for each adverse event in all HFrEF, HFmrEF and HFpEF groups. Additionally, OUES is a predictor for adverse prognosis in HFrEF, but not in HFpEF. On the other hand, EOV is a predictor for adverse prognosis in HFpEF, but not in HFrEF. Patients with HFmrEF have intermediate clinical features and predictors for adverse events between HFrEF and HFpEF groups.

Comparisons of clinical characteristics among patients with HFrEF, HFmrEF and HFpEF

The CPX results showed that PVO_2, as well as most other CPX parameters, was worst in the HFrEF group, followed by the HFmrEF group then the HFpEF group. Guazzi et al. reported that CPX parameters reflect similar pathophysiology and disease severity in HFrEF and HFpEF.[17] That study, however, included only 34 patients. Concordant with previous reports,[18,19] the present study demonstrated that the HFrEF group had more advanced heart failure patients than other groups, and the clinical characteristics

Table 1. Clinical characteristics of the study subjects.

	All $N = 1190$ (100.0%)	HFrEF $n = 498$ (41.9%)	HFmrEF $n = 254$ (21.3%)	HFpEF $n = 438$ (36.8%)	p value
Age, years	61.0 ± 14.5	59.1 ± 14.4	63.4 ± 13.5**	61.8 ± 14.3*	0.001
Body mass index, kg/m^2	23.4 ± 4.1	22.9 ± 4.1	23.7 ± 3.9*	23.8 ± 4.1**	0.002
Male, *n* (%)	969 (81.4)	419 (84.1)	211 (83.1)	339 (77.4)	0.024
Atrial fibrillation, *n* (%)	285 (23.9)	140 (28.1)	71 (28.0)	74 (16.9)	<0.001
COPD, *n* (%)	131 (11.0)	44 (8.8)	45 (17.7)	42 (9.6)	0.001
Anemia, *n* (%)	494 (41.5)	330 (42.6)	118 (46.5)	164 (37.4)	0.056
Diabetes mellitus, *n* (%)	346 (29.1)	142 (28.5)	87 (34.3)	117 (26.7)	0.102
Ischemic etiology, *n* (%)	391(32.9)	153 (30.7)	95 (37.4)	143 (32.6)	0.181
NYHA class, I/II/III	164/828/198	38/345/115	29/186/39	97/297/44	<0.001
Laboratory data					
Hemoglobin, g/dl	13.1 ± 1.9	13.1 ± 2.0	13.1 ± 2.0	13.1 ± 1.7	0.992
BUN, mg/dl	19.8 ± 9.0	21.2 ± 10.0	20.1 ± 9.3	18.0 ± 7.1**,****	<0.001
Creatinine, mg/dl	1.03 ± 0.40	1.10 ± 0.43	1.03 ± 0.39	0.95 ± 0.35**,***	<0.001
eGFR, ml/min per 1.73m^2	62.8 ± 21.5	60.0 ± 20.5	62.1 ± 21.8	66.7 ± 21.8**,***	<0.001
Sodium, mEq/dl	139.3 ± 2.9	138.6 ± 3.1	139.6 ± 2.8**	139.9 ± 2.5**	<0.001
Log BNP	4.72 ± 1.25	5.25 ± 1.00	4.67 ± 1.23**	4.16 ± 1.27**,****	<0.001
Echocardiographic parameters					
LVEF, %	44.1 ± 14.8	29.7 ± 6.9	44.5 ± 2.5**	60.2 ± 6.3**,****	<0.001
LVEDV, ml	128.7 ± 67.8	170.7 ± 75.1	113.6 ± 46.5**	89.8 ± 34.3**,****	<0.001
LVESV, ml	78.2 ± 58.7	121.9 ± 63.8	63.6 ± 26.3**	37.0 ± 18.2**,****	<0.001
LAVI, ml/m^2	46.3 ± 31.5	51.4 ± 28.9	44.4 ± 30.4**	41.6 ± 34.1**	<0.001
CPX parameters					
Resting heart rate, beats/min	73.6 ± 13.4	75.7 ± 13.2	73.8 ± 13.6	71.1 ± 13.4**,****	<0.001
Resting SBP, mmHg	111.9 ± 20.6	104.6 ± 17.9	114.3 ± 20.1**	118.8 ± 21.2**,***	<0.001
Peak heart rate, beats/min	118.6 ± 28.2	116.6 ± 27.8	117.7 ± 30.0	121.5 ± 27.5*	0.027
Peak SBP, mmHg	156.6 ± 33.8	143.4 ± 29.8	156.4 ± 31.3**	170.0 ± 33.7**,****	<0.001
Peak VO_2, ml/kg per min	16.4 ± 5.0	15.2 ± 4.3	16.3 ± 5.1*	17.8 ± 5.3**,****	<0.001
VE/VCO_2 slope	34.2 ± 7.4	36.0 ± 7.8	33.8 ± 7.2**	32.3 ± 6.5**,***	<0.001
Minimum VE/VCO_2	34.7 ± 13.2	35.6 ± 6.8	35.1 ± 18.1	33.4 ± 15.4*	0.041
$ETCO_2$ at RCP	37.0 ± 5.3	35.9 ± 5.6	37.3 ± 4.9**	38.2 ± 4.9**	<0.001
EOV, *n* (%)	94 (7.9)	67 (13.5)	16 (6.3)	11 (2.5)	<0.001
OUES	1414 (1046–1790)	1242 (916–1642)	1422** (1099–1792)	1571**,*** (1216–1948)	<0.001
Pharmacotherapy					
Digitalis, *n* (%)	132 (11.1)	85(17.4)	23 (9.1)	24 (5.5)	<0.001
ACEI or ARB, *n* (%)	1029 (86.5)	455 (91.4)	225 (88.6)	349 (79.7)	<0.001
Beta-blocker, *n* (%)	1060 (89.1)	485 (97.4)	227 (89.4)	348 (79.5)	<0.001
Statin, *n* (%)	524 (44.0)	220 (44.2)	117 (46.7)	187 (42.7)	0.688
CCB, *n* (%)	243 (20.4)	59 (11.8)	60 (23.6)	124 (28.3)	<0.001
MRA, *n* (%)	576 (48.4)	345 (69.3)	107 (42.1)	124 (28.3)	<0.001
Diuretic, *n* (%)	687 (57.7%)	376 (75.5)	148 (58.3)	163 (37.2)	<0.001

*$p < 0.05$ and **$p < 0.01$ versus HFrEF.

***$p < 0.05$ and ****$p < 0.01$ versus HFmrEF.

HFpEF: heart failure with preserved left ventricular ejection fraction; HFmrEF: heart failure with mid-range left ventricular ejection fraction; HFrEF: heart failure with reduced left ventricular ejection fraction; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LAVI: left atrial volume index; CPX: cardiopulmonary exercise testing; SBP: systolic blood pressure; VO_2: oxygen consumption; VE/VCO_2: the minute ventilation carbon dioxide production; $ETCO_2$ at RCP: end-tidal carbon dioxide at respiratory compensation; EOV: exertional oscillatory ventilation; OUES: oxygen uptake efficiency slope; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CCB: calcium channel blocker; MRA: mineral corticoid antagonist

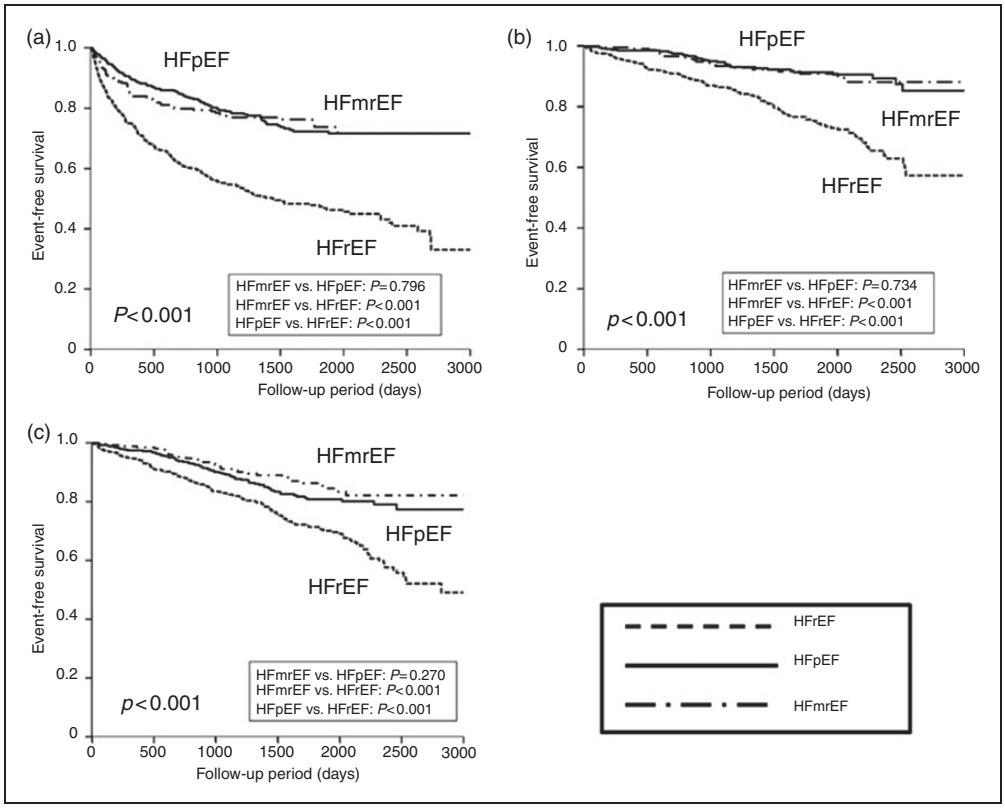

Figure 1. Cumulative event-free rates for (a) adverse cardiac event-free survival, (b) cardiac death-free survival and (c) survival with HFrEF, HFmrEF or HFpEF.
HFrEF: heart failure with reduced left ventricular ejection fraction; HFmrEF: heart failure with mid-range left ventricular ejection fraction; HFpEF: heart failure with preserved left ventricular ejection fraction

differed among the three groups. Notably, most CPX parameters in HFmrEF were intermediate between HFrEF and HFpEF groups in the present study. However, HFmrEF has not been well characterized, and further research is required.

Prognostic CPX parameters in patients with HFrEF

PVO_2, $ETCO_2$ at RCP and OUES were independent predictors for cardiac events in HFrEF patients in the current study. It was previously reported that the following parameters derived from CPX are important prognostic markers: PVO_2,[1,20] VE/VCO_2 slope,[2] EOV,[3] $ETCO_2$ at RCP[4,21] and OUES[5] in CHF. In addition, according to a recent report, PVO_2, OUES and VE/VCO_2 were independent predictors of the adverse outcome (worsening heart failure and cardiac death) and only PVO_2 was an independent predictor of mortality.[22] In the present study, PVO_2 and OUES were independent predictors for cardiac death in HFrEF patients. PVO_2 was routinely used in the determination of candidacy for cardiac transplantation in a study by Mancini et al.[1] However, many prognostic factors have been identified in CHF. We should evaluate the candidates of cardiac transplantation according to not only a single prognostic marker, such as PVO_2, but to several factors.[23] In addition, PVO_2 requires intense physical effort, while the VE/VCO_2 slope and OUES do not. Some CHF patients cannot perform the incremental symptom-limited exercise testing due to cardiac cachexia, sarcopenia, age, etc. We should consider whether patients with HFrEF are cardiac transplant candidates, and use several parameters derived from CPX.

Prognostic CPX parameters in patients with HFpEF

The only independent predictor of adverse cardiac events was PVO_2, and PVO_2 and EOV were independent predictors of cardiac and all-cause death in the HFpEF group. Although the prognostic value of CPX parameters in HFpEF patients has been reported in a few previous studies, these are not yet fully established.[7–9] One study reported that VE/VCO_2 slope and PVO_2 in patients with HFpEF were both significantly related to all-cause mortality and hospitalization.[7] Another study reported that VE/VCO_2 slope was the

Table 2. Independent factors to predict events in HFrEF, HFmrEF and HFpEF patients.

	HFrEF[a]				HFmrEF[b]				HFpEF[c]			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Adverse cardiac events												
Peak VO_2 < Median	3.32 (2.53–4.35)	<0.001	1.92 (1.40–2.65)	<0.001	4.13 (2.28–7.48)	<0.001	2.65 (1.29–5.45)	0.008	5.89 (3.53–9.81)	<0.001	3.53 (1.96–6.36)	<0.001
$VEVCO_2$ slope > < Median	3.18 (2.42–4.18)	<0.001	1.33 (0.88–2.02)	0.180	3.19 (1.83–5.57)	<0.001	1.81 (0.85–3.82)	0.122	3.52 (2.23–5.54)	<0.001	1.45 (0.75–2.80)	0.272
$ETCO_2$ at RCP < Median	2.84 (2.17–3.71)	<0.001	1.53 (1.05–2.24)	0.027	2.87 (1.66–4.96)	<0.001	1.10 (0.53–2.27)	0.806	2.89 (1.86–4.47)	<0.001	1.22 (0.67–2.25)	0.515
EOV	1.69 (1.23–2.33)	0.002	1.13 (0.82–1.58)	0.458	2.45 (1.12–5.39)	0.026	1.26 (0.55–2.86)	0.582	4 (2.13–9.06)	<0.001	2.02 (0.96–4.25)	0.064
OUES < Median	3.38 (2.56–4.45)	<0.001	1.68 (1.19–2.36)	0.003	3.81 (2.13–6.82)	<0.001	2.10 (1.04–4.24)	0.039	3.04 (1.96–4.70)	<0.001	1.16 (0.69–1.95)	0.584
Cardiac death												
Peak VO_2 < Median	3.59 (2.37–5.43)	<0.001	2.06 (1.28–3.32)	0.003	9.74 (2.27–41.8)	0.002	4.88 (1.05–22.73)	0.044	5.78 (2.23–14.98)	<0.001	5.82 (1.96–12.33)	0.002
$VEVCO_2$ slope > Median	3.31 (2.21–4.98)	<0.001	1.63 (0.90–2.95)	0.110	6.46 (1.90–21.9)	<0.001	2.32 (0.53–10.09)	0.261	2.60 (1.20–5.62)	0.015	1.63 (0.45–5.97)	0.458
$ETCO_2$ at RCP < Median	2.69 (1.82–3.98)	<0.001	1.13 (0.66–1.93)	0.657	9.79 (2.28–42.06)	0.002	1.97 (0.35–10.98)	0.439	2.15 (1.02–4.55)	0.045	0.63 (0.19–2.03)	0.437
EOV	1.69 (1.10–2.59)	0.016	1.2 (0.77–1.84)	0.426	0.74 (0.10–5.56)	0.773	–		9.52 (3.91–23.20)	<0.001	2.42 (1.21–16.7)	< 0.001
OUES < Median	4.22 (2.72–6.57)	<0.001	2.29 (1.32–3.96)	0.010	6.34 (1.87–21.54)	0.003	1.57 (0.41–6.03)	0.508	1.96 (0.94–4.06)	0.072	0.76 (0.30–1.93)	0.567
All-cause death												
Peak VO_2 < Median	2.89 (2.02–4.13)	<0.001	1.84 (1.22–2.78)	0.004	4.64 (1.92–11.25)	0.001	2.70 (1.20–2.13)	0.046	2.45 (1.47–4.10)	0.001	2.06 (1.13–3.78)	0.019
$VEVCO_2$ slope > Median	2.99 (2.09–4.29)	<0.001	1.36 (0.79–2.35)	0.266	4.09 (1.78–9.43)	0.001	1.29 (0.44–3.78)	0.643	1.69 (1.04–2.76)	0.036	0.61 (0.29–1.29)	0.194
$ETCO_2$ at RCP < Median	2.72 (1.91–3.88)	<0.001	1.32 (0.81–2.18)	0.269	4.63 (1.91–11.22)	0.001	1.53 (0.50–4.69)	0.456	2.07 (1.25–3.44)	0.005	1.48 (0.70–3.12)	0.308
EOV	1.71 (1.17–2.51)	0.006	1.19 (0.80–1.75)	0.393	0.468 (0.06–3.43)	0.455	–		4.07 (1.76–9.41)	0.001	2.65 (1.12–6.34)	0.029
OUES < Median	2.91 (2.03–4.18)	<0.001	1.47 (0.94–2.31)	0.091	2.45 (1.17–5.16)	0.018	1.10 (0.46–2.60)	0.837	1.41 (0.87–22.28)	0.164	–	

HFpEF: heart failure with preserved left ventricular ejection fraction; HFmrEF: heart failure with mid-range left ventricular ejection fraction; HFrEF: heart failure with reduced left ventricular ejection fraction; HR: hazard ratio; CI: confidence interval; VO_2: oxygen consumption; VE/VCO_2: the minute ventilation carbon dioxide production; $ETCO_2$ at RCP: end-tidal carbon dioxide at respiratory compensation; EOV: exertional oscillatory ventilation; OUES: oxygen uptake efficiency slope

[a]Median peak VO_2 = 14.7 ml/kg per min, median VE/VCO_2 slope = 34.8, median $ETCO_2$ at RCP = 36.0 mmHg and median OUES = 1242.

[b]Median peak VO_2 = 15.6 ml/kg per min, median VE/VCO2 slope = 32.5, median ETCO2 at RCP = 37.3 mmHg and median OUES = 1422.

[c]Median peak VO_2 = 17.1 ml/kg per min, median VE/VCO_2 slope = 31.1, median $ETCO_2$ at RCP = 38.7 mmHg and median OUES = 1571.

strongest predictor for cardiac events in HFpEF.[8] According to a recent study, percent predicted maximum oxygen uptake and PVO_2 were independent predictors for the composite outcome of all-cause mortality or cardiac transplant.[9] Our findings partly differed from these studies. The differences may have been caused by the following reasons. First, although patients with HFpEF are generally older than those with HFrEF,[24] the HFpEF patients included in the previous studies were 10 years younger than those included in the present study. Second, there were fewer patients with HFpEF in the previous studies than in the present study.[7–9] Third, clinical outcomes in the present study differ from previous studies.[7–9] EOV can occur in patients with HFpEF as well as HFrEF' in the section.[25] EOV is associated with reduced cardiac index and increased chemo-sensitivity to $PaCO_2$ and PaO_2.[26,27] Generally, cardiac index is preserved in patients with HFpEF. Concordant with these findings, there was higher prevalence of EOV in the HFrEF group than in the HFpEF or HFmrEF groups in the present study. Only a few (2.5%) patients with HFpEF exhibited EOV. Specific pathophysiology, such as increased chemo-sensitivity and reduced cardiac output, may have been involved in the adverse outcomes in these patients. Thus, EOV might have an adverse impact on prognosis in HFpEF patients. However, HFpEF with EOV has not been well characterized, and further research is required. On the other hand, PVO_2 was practically the only strong predictor of adverse cardiac events, cardiac death and all-cause death, whereas the other exercise variables did not offer any additional prognostic value as clinical predictors in HFpEF. HFpEF is a heterogeneous syndrome concomitant with various co-morbidities and has complex pathophysiology. Thus, PVO_2, which is affected by multiple factors, may be strongly associated with prognosis.

Prognostic CPX parameters in patients with HFmrEF

Since HFmrEF is a new concept; few have compared the prognostic factors for clinical outcomes among patients with HFrEF, HFmrEF and HFpEF,[19] and the impact of CPX parameters on prognosis in HFmrEF patients has never been studied. We first presented that the independent predictors of adverse cardiac events in the HFmrEF group were PVO_2 and OUES, and that of cardiac death and all-cause death was only PVO_2. CPX parameters in HFmrEF patients were intermediate between HFpEF and HFrEF, probably because the pathophysiology of HFmrEF overlaps with that of both HFpEF and HFrEF. Of note, the rates of adverse cardiac events, cardiac death and all-cause death did not significantly differ between the HFmrEF and HFpEF groups whereas the HFmrEF group had lower rates of these adverse cardiac events than the HFrEF group in the present study. This discrepancy may be due to the small size of the sample, and further studies with larger size are required.

Study limitations

There were some limitations to the current study. First, it was conducted in a single center, and may not reflect the general population of patients with CHF. Next, the present study excluded patients who could not undergo exercise testing, such as extremely elderly patients. Thus, the cardiac event rates reported in the present study might be lower than those in previous studies, and our data may not fully apply to patients with more advanced cardiac dysfunction. Furthermore, our conclusions may also not fully reflect patients with severely impaired renal function, as patients with end stage renal disease were excluded. As previously reported, the combined exercise stress test, echocardiography and CPX has recently been reported to identify patients with early and mild HFpEF.[28] These patients were not included in the present study. Had they been included, our findings may have changed.

Conclusions

To the best of our knowledge, this study is the first to analyze the impact of CPX parameters on adverse prognosis in patients with HFrEF, HFmrEF and HFpEF. PVO_2 is the strong predictor for adverse events in all groups. OUES predicts adverse prognosis in HFrEF, but not in HFpEF. In contrast, EOV is a predictor for adverse prognosis only in HFpEF. Thus, different CPX parameters may be able to differentially predict prognosis in HFrEF and HFpEF. Those for specifically predicting prognosis in HFmrEF may be intermediate between HFrEF and HFpEF, but remain to be further elucidated.

Author contribution

TS, YK, SS, AY, TY, KS, HK, KN, HS, SS, TI and YT contributed to the conception or design of the work. TS, YK, SS, AY, TY, KS, HK, KN, HS, SS, TI and YT contributed to the acquisition, analysis or interpretation of the data for the work. TS and YT drafted the manuscript. AY, TI and TY critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

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References

1. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; 83: 778–786.
2. Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation* 2001; 103: 967–972.
3. Matsumoto A, Itoh H, Eto Y, et al. End-tidal CO_2 pressure decreases during exercise in cardiac patients: Association with severity of heart failure and cardiac output reserve. *J Am Coll Cardiol* 2000; 36: 242–249.
4. Arena R, Myers J, Abella J, et al. Prognostic value of timing and duration characteristics of exercise oscillatory ventilation in patients with heart failure. *J Heart Lung Transplant* 2008; 27: 341–347.
5. Davies LC, Wensel R, Georgiadou P, et al. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: Oxygen uptake efficiency slope. *Eur Heart J* 2006; 27: 684–690.
6. Magrì D, Agostoni P, Corrà U, et al. Deceptive meaning of oxygen uptake measured at the anaerobic threshold in patients with systolic heart failure and atrial fibrillation. *Eur J Prev Cardiol* 2015; 22: 1046–1055.
7. Guazzi M, Myers J and Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol* 2005; 46: 1883–1890.
8. Klaassen SHC, Liu LCY, Hummel YM, et al. Clinical and hemodynamic correlates and prognostic value of VE/VCO2 slope in patients with heart failure with preserved ejection fraction and pulmonary hypertension. *J Card Fail*. Epub ahead of print 2017. DOI: 10.1016/j.cardfail.2017.07.397.
9. Shafiq A, Brawner CA, Aldred HA, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. The Henry Ford HospITal CardioPulmonary EXercise Testing (FIT-CPX) project. *Am Heart J* 2016; 174: 167–172.
10. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200.
11. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; 33: 1787–1847.
12. Matsuo S, Imai E, Horio M, et al. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982–992.
13. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation* 2012; 126: 2261–2274.
14. Baba R, Tsuyuki K, Kimura Y, et al. Oxygen uptake efficiency slope as a useful measure of cardiorespiratory functional reserve in adult cardiac patients. *Eur J Appl Physiol Occup Physiol* 1999; 80: 397–401.
15. Caughey MC, Avery CL, Ni H, et al. Outcomes of patients with anemia and acute decompensated heart failure with preserved versus reduced ejection fraction (from the ARIC study community surveillance). *Am J Cardiol* 2014; 114: 1850–1854.
16. Kwon BJ, Kim DB, Jang SW, et al. Prognosis of heart failure patients with reduced and preserved ejection fraction and coexistent chronic obstructive pulmonary disease. *Eur J Heart Fail* 2010; 12: 1339–1344.
17. Guazzi M, Labate V, Cahalin LP, et al. Cardiopulmonary exercise testing reflects similar pathophysiology and disease severity in heart failure patients with reduced and preserved ejection fraction. *Eur J Prev Cardiol* 2014; 21: 847–854.
18. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: An individual patient data meta-analysis. *Eur Heart J* 2012; 33: 1750–1757.
19. Tsuji K, Sakata Y, Nochioka K, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction – a report from the CHART-2 Study. *Eur J Heart Fail*. Epub ahead of print 2017. DOI: 10.1002/ejhf.807.
20. Opasich C, Pinna GD, Bobbio M, et al. Peak exercise oxygen consumption in chronic heart failure: Toward efficient use in the individual patient. *J Am Coll Cardiol* 1998; 31: 766–775.
21. Guazzi M, Cahalin LP and Arena R. Cardiopulmonary exercise testing as a diagnostic tool for the detection of left-sided pulmonary hypertension in heart failure. *J Card Fail* 2013; 19: 461–467.
22. Alba AC, Adamson MW, MacIsaac J, et al. The added value of exercise variables in heart failure prognosis. *J Card Fail* 2016; 22: 492–497.
23. Mehra MR, Canter CE, Hannan MM, et al., International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases Council; International Society for Heart Lung Transplantation (ISHLT) Pediatric Transplantation Council; International Society for Heart Lung Transplantation (ISHLT) Heart Failure and Transplantation Council. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J Heart Lung Transplant*. 2016; 35: 1-23.

24. Yancy CW, Lopatin M, Stevenson LW, et al; ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: A report from the Acute Decompensated Heart Failure National Registry (ADHERE) database. *J Am Coll Cardiol* 2006; 47: 76–84.
25. Guazzi M, Myers J, Peberdy MA, et al. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J* 2008; 29: 2751–2759.
26. Murphy RM, Shah RV, Malhotra R, et al. Exercise oscillatory ventilation in systolic heart failure. An indicator of impaired hemodynamic response to exercise. *Circulation* 2011; 124: 1442–1451.
27. Ponikowski P, Chua TP, Anker SD, et al. Peripheral chemoreceptor hypersensitivity: An ominous sign in patients with chronic heart failure. *Circulation* 2001; 104: 544–549.
28. Nedeljkovic I, Banovic M, Stepanovic J, et al. The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. *Eur J Prev Cardiol* 2016; 23: 71–76.