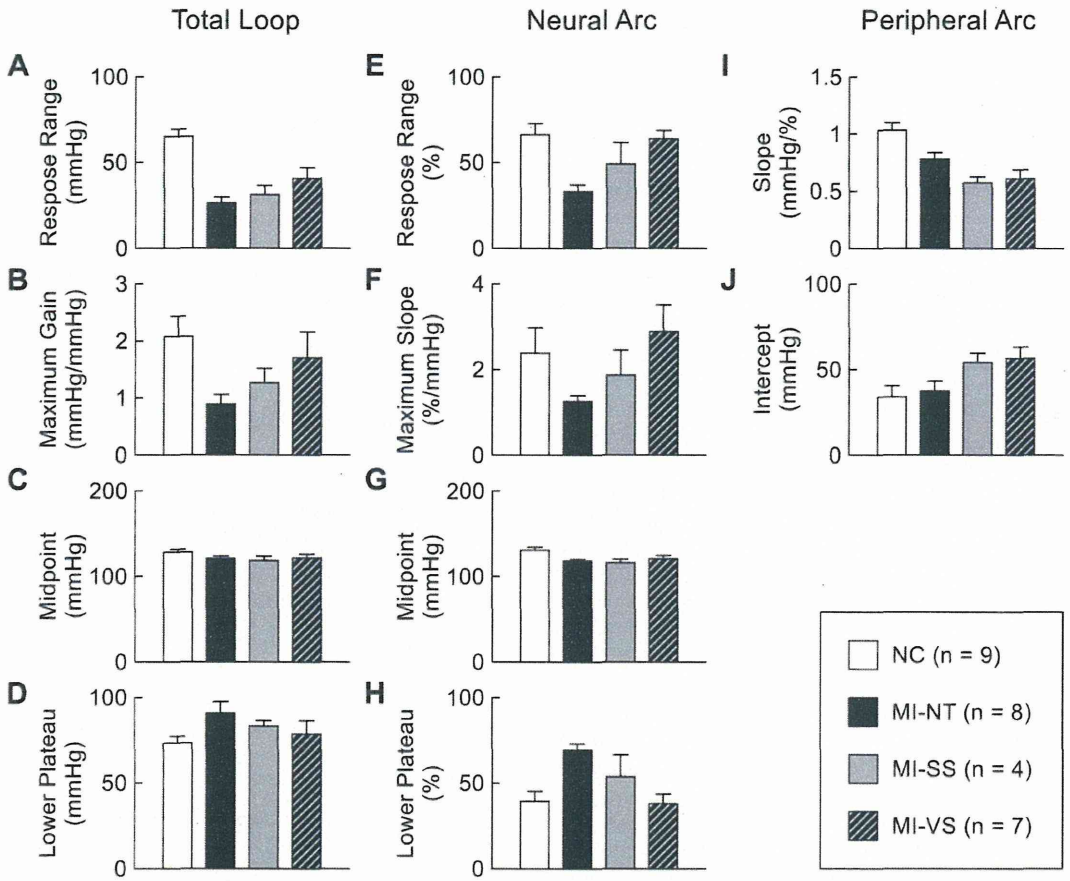

Fig. 6. Parameters of the baroreflex total loop (*A–D*), neural arc (*E–H*), and peripheral arc (*I* and *J*), including data from a group of myocardial infarction with second surgery (MI-SS, $n = 4$). Statistical analyses were not performed due to the small number of successful acute baroreflex studies in the MI-SS group. Judging from the mean parameter values of the total loop and the neural arc, the baroreflex function of the MI-SS group was not worse than that of the MI-NT group. See APPENDIX for details.

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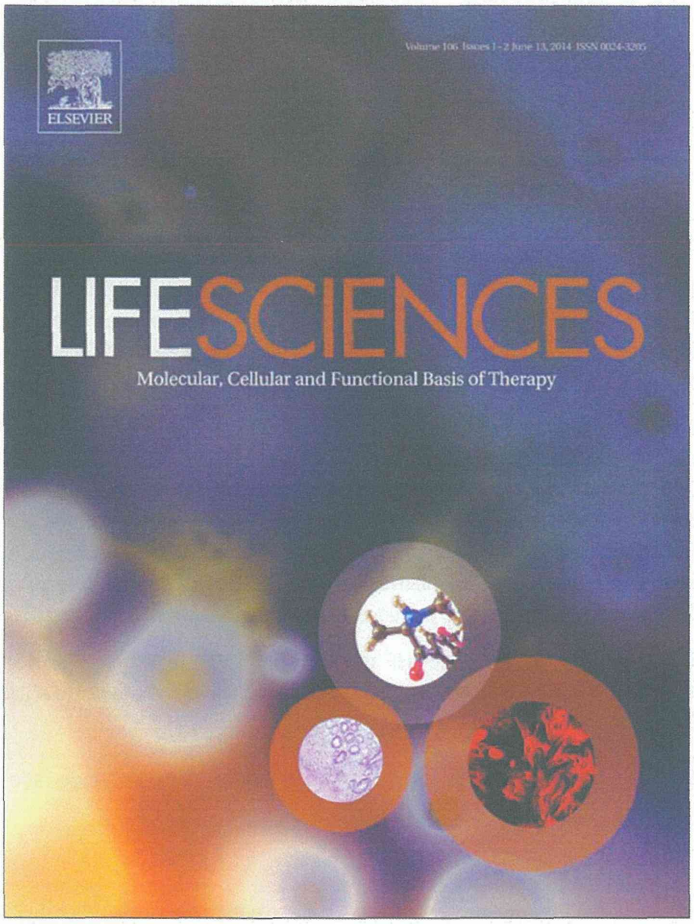

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Targeting of High Peak Respiratory Exchange Ratio Is Safe and Enhances the Prognostic Power of Peak Oxygen Uptake for Heart Failure Patients

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Background: Peak oxygen uptake ($\dot{V}O_2$) and ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$ slope) measured on cardiopulmonary exercise testing (CPX) are prognostic indicators in heart failure (HF) patients, but peak $\dot{V}O_2$ is influenced by patient effort. In CPX targeting a peak respiratory exchange ratio (pRER; an objective index of effort adequacy) higher than the commonly recommended level, we assessed the safety and prognostic value of CPX parameters compared with non-CPX parameters.

Methods and Results: We studied 283 consecutive HF patients with left ventricular ejection fraction (LVEF) ≤45% (mean, 26.3%) who underwent CPX targeting pRER >1.20. The attained pRER (mean, 1.26) was consistently high irrespective of LVEF, and there was no major exercise-related adverse event. The composite of all-cause death or HF hospitalization occurred in 111 patients (39%) during a median follow-up of 47 months. Among well-known prognostic markers, peak $\dot{V}O_2$ was the most powerful predictor of outcome as both a continuous and an optimal dichotomous variable, followed by $\dot{V}E/\dot{V}CO_2$ slope. On multivariate analysis, peak $\dot{V}O_2$ was a significant independent predictor, whereas $\dot{V}E/\dot{V}CO_2$ slope, B-type natriuretic peptide, and LVEF were not.

Conclusions: In CPX targeting pRER >1.20 for HF patients, peak $\dot{V}O_2$ is the most powerful among well-known predictors, without an increased risk of exercise-related events. These findings advocate a high target pRER in CPX even in advanced HF.

Key Words: Exercise; Heart failure; Oxygen uptake; Prognosis; Respiratory exchange ratio

Despite recent advances in medical therapy, the prognosis in patients with heart failure (HF) remains poor,[1,2] and risk stratification is an important issue. Cardiopulmonary exercise testing (CPX) provides important information on integrative exercise responses involving the pulmonary, cardiovascular and skeletal muscle systems.[3–6] Both exercise intolerance and ventilatory inefficiency, reflected by low peak oxygen uptake ($\dot{V}O_2$) and high minute ventilation–carbon dioxide production relationship ($\dot{V}E/\dot{V}CO_2$ slope), respectively, are associated with poor prognosis, independently of other clinical and hemodynamic parameters.[7–9]

Measurement of peak $\dot{V}O_2$ requires maximum effort and is, therefore, influenced by subjective factors such as patient motivation and exercise termination by the investigator. Peak respiratory exchange ratio (pRER: peak ratio of $\dot{V}CO_2$ to $\dot{V}O_2$) has been used as an objective means of quantifying effort: a value above 1.10 generally indicates good effort, while that below 1.00 indicates poor effort.[10–12] Indeed, peak $\dot{V}O_2$ has been shown to have poor prognostic reliability in cases of low pRER,[13] which can be explained by the underestimation of peak $\dot{V}O_2$.

$\dot{V}E/\dot{V}CO_2$ slope can be derived from submaximal exercise and is independent of subjective factors. Over the last decade, peak $\dot{V}O_2$ has been shown to provide inferior prognostic value compared with $\dot{V}E/\dot{V}CO_2$ slope in HF patients, but the mean pRER was relatively low (1.05–1.10) in those studies.[14–18] Targeting higher pRER than the commonly recommended level (>1.10) would enhance the prognostic power of peak $\dot{V}O_2$, but may increase the exercise-related risk, particularly in advanced HF patients.

The purpose of the present study was to assess the predictive value of peak $\dot{V}O_2$ and the safety in CPX targeting pRER >1.20 for HF patients receiving current optimal medical therapy.

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Table 1. Baseline Subject Characteristics

Characteristics	All patients (n=283)
Age (years)	61.8±13.5
Male sex	81%
Hypertension	59%
Diabetes	43%
BMI (kg/m²)	21.9±3.7
Ischemic	45%
AF rhythm	17%
Serum creatinine (mg/dl)	1.10±0.39
Hemoglobin (g/dl)	13.2±1.7
Serum sodium (mEq/L)	139.1±3.2
Plasma BNP (pg/ml)	291.7±318.1
LVDd (mm)	63.6±9.2
LVDs (mm)	53.7±10.3
LVEF (%)	26.3±8.0
LAD (mm)	45.2±8.1
Medications	
β-blocker	92%
ACEI or ARB	83%
Diuretic	82%
CPX parameters	
pRER	1.26±0.13
Peak work rate (W)	90.7±31.7
Peak $\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	17.0±4.4
$\dot{V}E/\dot{V}CO_2$ slope	34.3±8.1

Data given as mean±SD or %.
ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation (and including atrial flutter); ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CPX, cardiopulmonary exercise testing; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; pRER, peak respiratory exchange ratio; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen uptake.

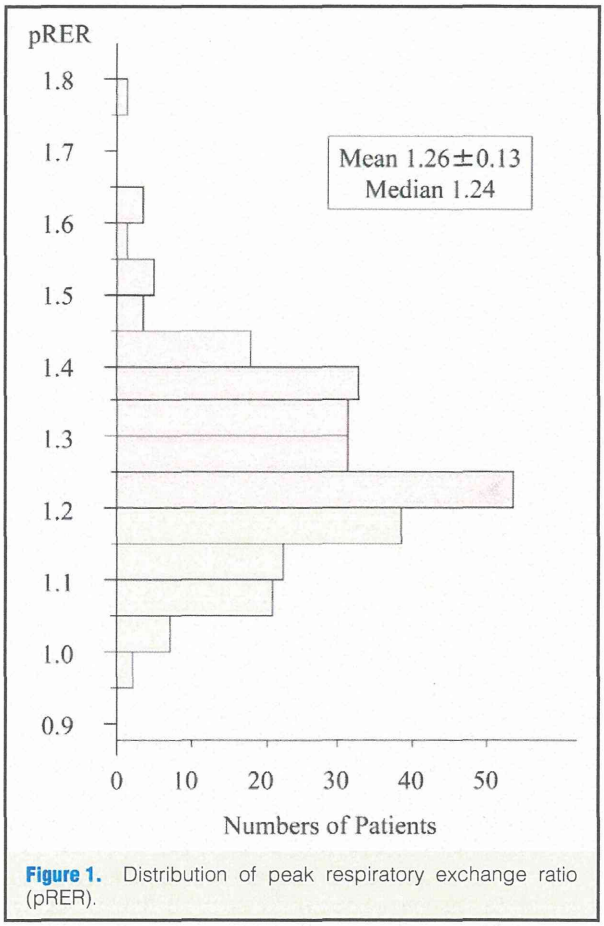

Figure 1. Distribution of peak respiratory exchange ratio (pRER).

Methods

Subjects

Consecutive HF patients who were admitted with HF and who underwent CPX between March 2002 and September 2012 at National Cerebral and Cardiovascular Center, Japan were screened retrospectively. Patients were excluded from the study if they had left ventricular ejection fraction (LVEF) >45%, serum creatinine >2.5 mg/dl, history of myocardial infarction within the preceding 3 months, or significant pulmonary disease. The presence of ischemic heart disease was confirmed on coronary angiography or documentation of myocardial infarction. Treatment for HF was tailored to all patients on the basis of current guidelines and was kept constant throughout the study. The study complies with the Declaration of Helsinki and was approved by the institutional ethics committee, and all patients gave written, informed consent.

CPX

Patients underwent symptom-limited CPX using a cycle ergometer with respiratory gas exchange analysis at a clinically stable stage after treatment with appropriate medications. The testing consisted of an initial 2 min of rest, 1 min of warm-up (0-W load), and full exercise by an individualized ramp protocol with increments of 10–15 W/min. Expired gas analysis was performed throughout testing on a breath-by-breath basis and VE, $\dot{V}O_2$, and $\dot{V}CO_2$ data were stored in a computer hard disk every 6 s for off-line analysis (AE-300S, Minato Medical Science, Osaka, Japan).

In 2001, we examined CPX data of 300 consecutive patients with cardiovascular disease at National Cerebral and Cardiovascular Center, and found that 266 of them achieved the respiratory compensation (RC) point, while 34 did not. All of the patients who did not achieve the RC point had pRER <1.20 (median, 1.06; range, 0.87–1.16). Among patients who achieved the RC point, the median pRER was 1.27 (range, 1.05–1.75), and the RER of the RC point was <1.15 in 77% and <1.20 in 94% (median, 1.10; range, 1.00–1.27). Based on these findings, we have identified the target pRER level as >1.20, and since the beginning of 2002, all subjects in CPX have been strongly encouraged to exercise toward the target pRER at National Cerebral and Cardiovascular Center.

Peak $\dot{V}O_2$ was determined as the higher value normalized to body weight ($ml \cdot kg^{-1} \cdot min^{-1}$) of either the greatest $\dot{V}O_2$ during exercise (smoothed after a 5-point moving average) or the average $\dot{V}O_2$ of the last 3 datapoints (18 s) before termination of exercise. $\dot{V}E$ was plotted against $\dot{V}CO_2$ to represent the $\dot{V}E/\dot{V}CO_2$ slope, excluding the part after the RC point where its slope started to increase.

Non-CPX Parameters

All patients underwent an echocardiographic evaluation at a clinically stable stage after treatment, and LV end-diastolic di-

Table 2. Cox Regression Analysis for Combined Event

Variables	Univariate analysis			Multivariate analysis	
	X^2	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (per 10-year increase)	0.56	1.06 (0.92–1.23)	0.45		
Male sex	0.34	1.16 (0.71–2.02)	0.56		
Hypertension	0.0016	1.01 (0.69–1.48)	0.97		
Diabetes	5.6	1.57 (1.08–2.29)	0.018	1.18 (0.79–1.77)	0.43
BMI (per 1.0-kg/m^2 increase)	0.40	0.98 (0.93–1.04)	0.53		
Ischemic	1.9	1.30 (0.89–1.89)	0.17		
AF rhythm	0.14	0.91 (0.53–1.47)	0.71		
Creatinine (per 1.0-mg/dl increase)	26.8	3.27 (2.13–4.93)	<0.0001	1.74 (1.02–2.93)	0.042
Hemoglobin (per 1.0-g/dl increase)	20.2	0.78 (0.69–0.87)	<0.0001	0.90 (0.78–1.04)	0.14
Sodium (per 1.0-mEq/L increase)	15.2	0.89 (0.85–0.94)	<0.0001	0.96 (0.90–1.02)	0.15
BNP (per 10-pg/ml increase)	21.2	1.012 (1.007–1.016)	<0.0001	1.003 (0.997–1.008)	0.29
LVDd (per 1.0-mm increase)	17.2	1.04 (1.02–1.06)	<0.0001	0.97 (0.89–1.04)	0.41
LVDs (per 1.0-mm increase)	19.5	1.04 (1.02–1.06)	<0.0001	1.07 (0.99–1.17)	0.079
LVEF (per 1.0% increase)	11.7	0.96 (0.93–0.98)	0.0006	1.01 (0.97–1.06)	0.61
LAD (per 1.0-mm increase)	20.8	1.06 (1.03–1.08)	<0.0001	1.03 (1.007–1.06)	0.012
Peak $\dot{V}O_2$ (per 1.0-ml·kg^{-1}·min^{-1} increase)	46.8	0.85 (0.80–0.89)	<0.0001	0.92 (0.86–0.99)	0.026
$\dot{V}E/\dot{V}CO_2$ slope (per 1.0 increase)	27.5	1.06 (1.04–1.08)	<0.0001	1.02 (0.99–1.05)	0.12

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

ameter (LVDd), LV end-systolic diameter (LVDs), and left atrial diameter (LAD) were determined on 2-D echocardiography. LVEF was measured on echocardiography, radionuclide ventriculography, or LV angiography. Blood samples were drawn for standard measurements (serum creatinine, sodium, and hemoglobin) and B-type natriuretic peptide (BNP) within 3 days before or after CPX. Plasma BNP concentration was measured by radioimmunoassay (Shionoria BNP kit; Shionogi & Co Ltd, Osaka, Japan).

Endpoints

All patients survived to discharge. Follow-up data were determined from outpatient records, and at least 1 year of follow-up was available in all patients. Endpoints were composite outcome, defined as all-cause death or HF hospitalization and all-cause death, analyzed by time from the date of CPX to first event. HF hospitalization required that a patient had typical symptoms and signs, treatment with diuretics, and at least an overnight hospital stay. Event rate was assessed when patients were dichotomized at an optimal threshold value and were divided according to quartiles of each predictor.

Statistical Analysis

Continuous variables, presented as mean±SD, were compared using unpaired Student t-test, and categorical variables with the chi-squared test. Cox proportional hazard analysis was used to assess the association between variables and outcome. Variables with P<0.1 on univariate analysis were included in multivariate analysis. The optimal dichotomous values were identified on receiver operating characteristic (ROC) curve analysis. The association of specific variables with time to outcome was expressed as hazard ratio and 95% confidence interval (CI). Cumulative events were assessed using the Kaplan-Meier method, and differences in events were compared with log-rank test. P<0.05 was considered to be statistically significant.

Results

Baseline Characteristics

From March 2002 through September 2012, 283 consecutive patients met the inclusion criteria; baseline characteristics for the overall group are listed in **Table 1**. Overall, the mean age was 61.8 years, 81% were men, and 45% had ischemic heart disease. Most of the patients were treated with β-blockers (92%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (83%), and diuretics (82%).

The median time from HF hospitalization to CPX was 29 days. In CPX, the mean pRER was 1.26±0.13 (median, 1.24; range, 0.95–1.78), and pRER >1.10 and >1.20 was obtained in 89% and in 66%, respectively (**Figure 1**). When patients were divided into subgroups according to age or LVEF (**Table S1**), the mean pRER was >1.20 in all subgroups, except in the subgroup of patients aged ≥75 years (1.19±0.11). During CPX, asymptomatic ST-segment depression occurred in 32 patients (11%), asymptomatic non-sustained (3 or 4 beats) ventricular tachycardia in 7 patients (2.5%), and symptomatic post-exercise hypotension in 4 patients (1.4%), but all events resolved without any treatment during the recovery period. There was no exercise-related death or adverse event requiring hospitalization, including worsening HF, myocardial infarction, or sustained ventricular tachycardia.

Predictors of Composite Outcome

The median follow-up period was 47 months. The composite of all-cause death or HF hospitalization occurred in 111 patients (39.2%), and all-cause death in 48 patients (17.0%). The rate of the combined event was 15.9% at 1 year, 22.9% at 2 years, and 32.0% at 3 years. The all-cause mortality rate was 2.8% at 1 year, 6.5% at 2 years, and 10.3% at 3 years.

On univariate Cox regression analysis, serum creatinine, sodium, hemoglobin, BNP, LVDd, LVDs, LVEF, LAD, peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, and the presence of diabetes were all significantly related to composite outcome, while age, gender, body mass index, and presence of hypertension, ischemic heart disease, and atrial fibrillation were not (**Table 2**). Among them,

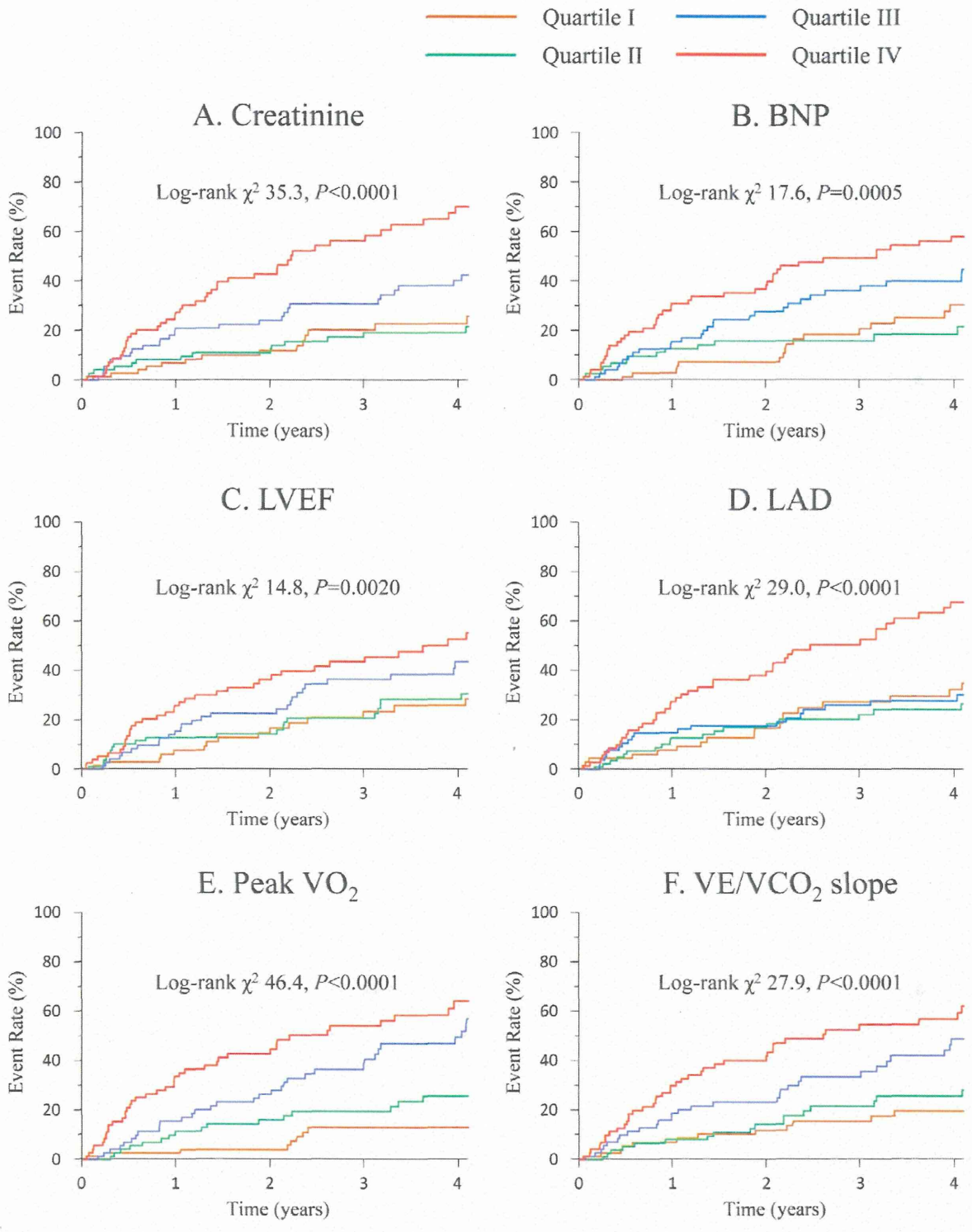

Figure 2. Kaplan-Meier cumulative curves for the combined event according to quartiles of major predictors. Patients were divided according to quartiles of each predictor as follows: (**A**) creatinine: quartile I, <0.83 (n=71); II, ≥0.83 to <1.03 (n=72); III, ≥1.03 to <1.26 (n=71); IV, ≥1.26 mg/dl (n=69); (**B**) BNP: quartile I, <96 (n=69); II, ≥96 to <200 (n=70); III, ≥200 to <370 (n=70); IV, ≥370 pg/ml (n=71); (**C**) LVEF: quartile I, >31 (n=72); II, >25 to ≤31 (n=67); III, >20 to ≤25 (n=77); IV, ≤20% (n=67); (**D**) LAD: quartile I, <40 (n=64); II, ≥40 to <45 (n=77); III, ≥45 to <51 (n=73); IV, ≥51 mm (n=68); (**E**) peak $\dot{V}O_2$: quartile I, >20.0 (n=72); II, >16.5 to ≤20.0 (n=70); III, >13.6 to ≤16.5 (n=70); IV, ≤13.6 ml·kg^{-1}·min^{-1} (n=71); and (**F**) $\dot{V}E/\dot{V}CO_2$ slope: quartile I, <29.0 (n=70); II, ≥29.0 to <32.3 (n=74); III, ≥32.3 to <38.0 (n=69); IV, ≥38.0 (n=70).

Table 3. Predictive Power of CPX Parameters According to pRER

Variables	Univariate analysis			Bivariate analysis	
	χ^2	HR (95% CI)	P-value	HR (95% CI)	P-value
Overall (n=283)					
Peak $\dot{V}O_2$ (per 1.0-ml·kg^{-1}·min^{-1} increase)	46.8	0.85 (0.80–0.89)	<0.0001	0.87 (0.82–0.92)	<0.0001
$\dot{V}E/\dot{V}CO_2$ slope (per 1.0 increase)	27.5	1.06 (1.04–1.08)	<0.0001	1.03 (1.004–1.05)	0.021
pRER ≥1.20 (n=188)					
Peak $\dot{V}O_2$ (per 1.0-ml·kg^{-1}·min^{-1} increase)	29.1	0.85 (0.80–0.90)	<0.0001	0.87 (0.81–0.94)	0.0001
$\dot{V}E/\dot{V}CO_2$ slope (per 1.0 increase)	15.9	1.05 (1.03–1.07)	<0.0001	1.02 (0.99–1.05)	0.22
pRER <1.20 (n=95)					
Peak $\dot{V}O_2$ (per 1.0-ml·kg^{-1}·min^{-1} increase)	17.6	0.83 (0.76–0.91)	<0.0001	0.84 (0.76–0.93)	0.0008
$\dot{V}E/\dot{V}CO_2$ slope (per 1.0 increase)	14.7	1.10 (1.05–1.15)	0.0001	1.08 (1.03–1.13)	0.0035

Abbreviations as in Tables 1,2.

Table 4. Cox Regression Analysis for Combined Event as Optimal Dichotomous Value

Variables	Area under ROC curve	Optimal cut-off	Univariate analysis			Multivariate analysis	
			χ^2	HR (95% CI)	P-value	HR (95% CI)	P-value
Creatinine	0.660	1.03 mg/dl	22.1	2.50 (1.70–3.75)	<0.0001	1.57 (1.03–2.42)	0.038
Hemoglobin	0.626	13.2 g/dl	13.4	2.03 (1.39–3.00)	0.0002	1.74 (1.14–2.69)	0.011
Sodium	0.624	139 mEq/L	6.3	1.62 (1.11–2.38)	0.012	1.09 (0.73–1.65)	0.66
BNP	0.662	208.0 pg/ml	18.7	2.30 (1.57–3.42)	<0.0001	1.36 (0.90–2.09)	0.15
LVDd	0.635	63 mm	10.1	1.87 (1.28–2.82)	0.0015	1.58 (0.95–2.67)	0.077
LVDs	0.640	52 mm	7.4	1.72 (1.16–2.60)	0.0064	0.94 (0.53–1.68)	0.82
LVEF	0.606	30%	8.8	1.97 (1.25–3.25)	0.0029	1.72 (0.99–3.04)	0.0503
LAD	0.642	47 mm	13.8	2.03 (1.40–2.98)	0.0002	1.89 (1.25–2.89)	0.0024
Peak $\dot{V}O_2$	0.708	15.5 ml·kg^{-1}·min^{-1}	40.4	3.42 (2.34–5.06)	<0.0001	1.82 (1.16–2.90)	0.0086
$\dot{V}E/\dot{V}CO_2$ slope	0.668	34.7	22.2	2.46 (1.70–3.60)	<0.0001	1.52 (1.01–2.31)	0.046

ROC, receiver operating characteristic. Other abbreviations as in Tables 1,2.

Table 5. Cox Regression Analysis for All-Cause Mortality

Variables	Univariate analysis			Multivariate analysis	
	χ^2	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (per 10-year increase)	2.3	0.85 (0.69–1.05)	0.13		
Male sex	1.7	1.78 (0.77–5.15)	0.19		
Hypertension	1.5	0.70 (0.40–1.25)	0.23		
Diabetes	0.47	1.22 (0.69–2.16)	0.50		
BMI (per 1.0-kg/m^2 increase)	0.10	0.99 (0.91–1.07)	0.75		
Ischemic	0.46	1.22 (0.69–2.15)	0.50		
AF rhythm	0.36	1.24 (0.59–2.40)	0.55		
Creatinine (per 1.0-mg/dl increase)	8.2	2.84 (1.41–5.44)	0.0042	1.37 (0.59–3.05)	0.45
Hemoglobin (per 1.0-g/dl increase)	4.4	0.84 (0.71–0.99)	0.036	1.02 (0.84–1.25)	0.80
Sodium (per 1.0-mEq/L increase)	11.9	0.86 (0.80–0.94)	0.0006	0.94 (0.86–1.02)	0.16
BNP (per 10-pg/ml increase)	8.5	1.011 (1.004–1.017)	0.0036	1.003 (0.993–1.01)	0.51
LVDd (per 1.0-mm increase)	8.8	1.05 (1.02–1.07)	0.0030	1.01 (0.90–1.13)	0.83
LVDs (per 1.0-mm increase)	9.1	1.04 (1.02–1.07)	0.0026	1.02 (0.92–1.15)	0.71
LVEF (per 1.0% increase)	5.2	0.96 (0.92–0.99)	0.023	1.003 (0.95–1.07)	0.92
LAD (per 1.0-mm increase)	13.8	1.07 (1.03–1.11)	0.0002	1.04 (1.002–1.08)	0.038
Peak $\dot{V}O_2$ (per 1.0-ml·kg^{-1}·min^{-1} increase)	27.7	0.81 (0.75–0.88)	<0.0001	0.85 (0.76–0.95)	0.0041
$\dot{V}E/\dot{V}CO_2$ slope (per 1.0 increase)	11.3	1.05 (1.02–1.08)	0.0008	1.003 (0.96–1.04)	0.89

Abbreviations as in Tables 1,2.

peak $\dot{V}O_2$ was the most powerful predictor of combined event (χ^2=46.8; P<0.0001), followed by $\dot{V}E/\dot{V}CO_2$ slope (χ^2=27.5; P<0.0001). On multivariate analysis, peak $\dot{V}O_2$, creatinine, and LAD were significant independent predictors of the combined endpoint, while $\dot{V}E/\dot{V}CO_2$ slope, BNP, and LVEF were not.

Figure 2 shows Kaplan-Meier cumulative curves for the combined event according to quartiles of 6 major predictors. As compared with the highest quartile, the lowest quartile had

Table 6. Cox Regression Analysis for All-Cause Mortality as Optimal Dichotomous Value

Variables	Area under ROC curve	Optimal cut-off	Univariate analysis			Multivariate analysis	
			χ^2	HR (95% CI)	P-value	HR (95% CI)	P-value
Creatinine	0.610	1.34 mg/dl	17.9	3.85 (2.11–6.94)	<0.0001	1.54 (0.75–3.10)	0.23
Hemoglobin	0.578	13.6 g/dl	7.0	2.31 (1.23–4.64)	0.0082	1.83 (0.87–4.10)	0.12
Sodium	0.638	138 mEq/L	8.9	2.38 (1.35–4.29)	0.0028	1.46 (0.76–2.85)	0.26
BNP	0.662	256.0 pg/ml	10.9	2.63 (1.48–4.80)	0.0009	1.71 (0.91–3.27)	0.095
LVDd	0.628	66 mm	7.9	2.25 (1.28–4.03)	0.0051	1.87 (0.84–4.53)	0.13
LVDs	0.629	53 mm	9.2	2.53 (1.37–4.97)	0.0025	0.99 (0.36–2.61)	0.99
LVEF	0.570	29%	6.8	2.43 (1.23–5.36)	0.0092	1.47 (0.62–3.69)	0.39
LAD	0.676	49 mm	22.1	4.02 (2.24–7.46)	<0.0001	3.50 (1.81–7.01)	0.0002
Peak $\dot{V}O_2$	0.707	16.0 ml·kg^{-1}·min^{-1}	24.7	4.53 (2.45–8.92)	<0.0001	2.19 (1.05–4.73)	0.036
$\dot{V}E/\dot{V}CO_2$ slope	0.657	36.6	14.2	3.05 (1.72–5.42)	0.0002	1.46 (0.76–2.82)	0.26

Abbreviations as in Tables 1,2,4.

a hazard ratio of 6.08 (95% CI, 3.26–12.2) in peak $\dot{V}O_2$ and 2.28 (95% CI, 1.33–4.02) in LVEF. As compared with the lowest quartile, the highest quartile had a hazard ratio of 3.64 (95% CI, 2.11–6.58) in creatinine, 3.17 (95% CI, 1.86–5.59) in $\dot{V}E/\dot{V}CO_2$ slope, 2.63 (95% CI, 1.57–4.56) in LAD, and 2.50 (95% CI, 1.49–4.35) in BNP. The analysis confirmed the superior prognostic value of peak $\dot{V}O_2$ compared with the other predictors.

Predictive Power of CPX Parameters According to pRER

When patients were divided into subgroups according to pRER, peak $\dot{V}O_2$ was greater in predicting the combined endpoint than $\dot{V}E/\dot{V}CO_2$ slope among patients with pRER ≥1.20, whereas peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope had a similar predictive value among those with pRER <1.20. On bivariate analysis, peak $\dot{V}O_2$, but not $\dot{V}E/\dot{V}CO_2$ slope, was an independent predictor of the combined endpoint in the high pRER subgroup, while both peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope were independent predictors in the low pRER subgroup (**Table 3**).

Predictive Power as a Dichotomous Value

The area under the ROC curve was greater for peak $\dot{V}O_2$ (0.708) than for any predictors including $\dot{V}E/\dot{V}CO_2$ slope (**Table 4**). When patients were dichotomized at each optimal threshold value identified on ROC curve analysis, peak $\dot{V}O_2$ <15.5 ml·kg^{-1}·min^{-1} was the most powerful predictor of outcome, followed by $\dot{V}E/\dot{V}CO_2$ slope >34.7, creatinine >1.03 mg/dl, and BNP >208.0 pg/ml.

On multivariate analysis, peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, creatinine, hemoglobin, and LAD were significant independent predictors of the combined endpoint, while BNP and LVEF were not (**Table 4**).

Predictors of All-Cause Mortality

On univariate Cox regression analysis, peak $\dot{V}O_2$ was the most powerful predictor of all-cause mortality among well-known predictors as both a continuous and an optimal dichotomous variable (<16.0 ml·kg^{-1}·min^{-1}), and only peak $\dot{V}O_2$ and LAD were significant independent predictors on multivariate analysis (**Tables 5,6**).

Discussion

Peak $\dot{V}O_2$ is an established prognostic predictor in HF patients,[7] but is influenced by subjective factors such as patient effort. Although recent studies consistently reported that $\dot{V}E/\dot{V}CO_2$ slope was greater than peak $\dot{V}O_2$ in predicting outcome, the attained mean pRER, an objective index of effort adequacy, was relatively low (1.05–1.10) in those studies.[14–18] The main finding of the present study is that in HF patients with LV systolic dysfunction receiving current optimal medical therapy, peak $\dot{V}O_2$ has the most powerful predictive value for morbidity and mortality among well-known prognostic markers including $\dot{V}E/\dot{V}CO_2$ slope, when the patients are strongly encouraged to exercise toward a target pRER >1.20. Importantly, we also observed no major exercise-related adverse event despite maximum effort even in patients with advanced LV dysfunction.

pRER >1.10 has been generally considered to be a good effort[10–12] and is used as a target level in clinical practice and trials, including the Heart Failure: A Controlled Trial Investigating Outcomes of exercise traiNing (HF-ACTION) study, the largest trial to test the effect of exercise training in HF patients with LV systolic dysfunction (median LVEF, 25%).[19] Peak $\dot{V}O_2$, however, was shown to be less prognostically reliable in HF patients with pRER <1.15 than in those with pRER ≥1.15.[13] Additionally, Arena et al evaluated the prognostic utility of CPX during 2 distinct time periods and showed that the predictive value of peak $\dot{V}O_2$ was greater during the recent period (mean pRER, 1.14) than during the previous period (mean pRER, 1.09).[20] In a study with a mean pRER of 1.19, Corrà et al reported that peak $\dot{V}O_2$, but not $\dot{V}E/\dot{V}CO_2$ slope, was an independent predictor of major cardiac events, but only a small proportion of their patients (31%) had received β-blocker therapy.[21] To the best of our knowledge, this is the first study evaluating the prognostic value of these parameters in CPX targeting pRER >1.20 (mean, 1.26) for HF patients receiving current optimal medical therapy (β-blockers, 92%). As both a continuous and an optimal dichotomous variable, peak $\dot{V}O_2$ was greater in predicting outcome than any prognostic markers. Furthermore, we found that peak $\dot{V}O_2$ was more powerful in predicting morbidity than $\dot{V}E/\dot{V}CO_2$ slope, the effort-independent predictor, among patients with pRER ≥1.20, while the 2 parameters had a similar predictive value among those with pRER <1.20. These findings suggest that targeting pRER >1.20 enhances the prognostic power of peak $\dot{V}O_2$.

Mezzani et al showed that among the subgroup of patients with reduced peak $\dot{V}O_2$, the composite event rate was significantly lower in patients with low pRER (<1.15) than in those with high pRER (≥1.15).[13] This can be explained by the underestimation of peak $\dot{V}O_2$ because of poor effort in their patients

with low pRER. In contrast to their results, we did not find that patients with pRER <1.20 had better outcome than those with pRER ≥1.20 among the subgroup of patients with reduced peak $\dot{V}O_2$ (<15.5 ml·kg^{-1}·min^{-1}). The most likely explanation is that the present patients with low pRER may have stopped their exercise tests for reasons other than poor effort, mainly exercise-limiting comorbidities associated with advanced disease severity.

In accordance with previous studies,[14–18] we observed the powerful prognostic value of $\dot{V}E/\dot{V}CO_2$ slope as both a continuous and an optimal dichotomous variable, and, particularly among the low pRER subgroup, $\dot{V}E/\dot{V}CO_2$ slope was similar to peak $\dot{V}O_2$ in predicting the combined endpoint. Because of the effort-independent characteristic, $\dot{V}E/\dot{V}CO_2$ slope is considered to be very useful for risk stratification in patients unable to exercise at maximum effort due to comorbidities such as joint disorder and aortic aneurysm.

The present study assessed the predictive value of well-known non-CPX parameters. Plasma BNP is a reliable and established prognostic biomarker in HF patients,[22,23] and previous studies showed that peak $\dot{V}O_2$ and BNP had an similar impact in predicting outcome among HF patients, although they did not report the attained pRER.[24–26] In the present study BNP was an inferior predictor compared with peak $\dot{V}O_2$ in CPX targeting pRER >1.20, and the predictive value was not significant in multivariate analysis including CPX parameters.

It has been demonstrated that LA size is a barometer of LV filling pressure and reflects the burden of diastolic dysfunction,[27] and that LA enlargement is associated with an increased risk of cardiovascular events and death.[28] But there are only limited data comparing CPX parameters with LA size as a prognostic marker, while many studies have compared CPX parameters with LV size or function. We found LAD to be a significant independent predictor of both morbidity and mortality on multivariate analysis. These findings suggest that LA size represents different aspects of HF physiology not reflected by exercise capacity, more greatly than LV parameters or BNP.

The safety of CPX has been evaluated in some studies. Among large series of subjects with and without known disease, serious complications have been reported to be rare.[29] In the HF-ACTION study, there were no deaths, and non-fatal major cardiovascular events occurred in <0.5 per 1000 tests among 2,037 HF subjects (median LVEF, 25%) who completed 4,411 CPX (median pRER, 1.09).[30] The incidence of adverse events, however, is likely to vary depending on the subjects or exercise effort. In this context, the fact that no major exercise-related adverse event occurred in the present patients with advanced LV dysfunction (median LVEF, 24%) and excellent effort (median pRER, 1.24) is an important point. Although further larger studies are needed to confirm the safety, it seems unlikely that CPX targeting a high pRER is associated with an increased exercise-related risk.

Study Limitations

This study has some limitations. First, we examined data obtained from routine CPX with a target pRER >1.20 at our institution, retrospectively. Prospective studies are required to determine the optimal target pRER for the most reliable risk stratification with peak $\dot{V}O_2$. Second, because we studied patients who underwent CPX among those admitted with HF, they were relatively young and the prognosis was less poor compared with general HF patients.[1,2] Similarly, given that the present cohort consisted of HF patients with impaired LV function and without severe renal dysfunction, it remains uncertain whether the present findings apply to HF patients with preserved EF or those with chronic renal failure. Finally, there are some major predictors for HF patients that were not available in this study, including echocardiographic indices of LV diastolic function, particularly tissue Doppler imaging, which has been shown to be a strong prognostic marker, independently of CPX parameters[31] or BNP.[32]

Conclusions

In CPX targeting pRER >1.20 for HF patients receiving current optimal medical therapy, peak $\dot{V}O_2$ had the most powerful predictive value of morbidity and mortality among well-known prognostic markers including $\dot{V}E/\dot{V}CO_2$ slope, BNP, and LVEF, without an increased risk of exercise-related events. The present results advocate a higher target pRER than the commonly used level (>1.10) in CPX even for advanced HF patients.

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Supplementary Files

Supplementary File 1

Table S1. Mean peak respiratory exchange ratio

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0047