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Original Research

Cardiopulmonary exercise test with bicycle stress echocardiography for predicting adverse cardiac events in patients with stage A or B heart failure

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ABSTRACT

Background: Given the high prevalence of stage A or B heart failure (HF), comprehensive screening for new-onset HF is cost-prohibitive. Therefore, further risk stratification is warranted to identify at-risk patients. This study aimed to evaluate the prognostic utility of cardiopulmonary exercise test (CPET) with bicycle stress echocardiography (BSE) in patients with stage A or B HF.

Methods: Among 687 consecutive patients who underwent CPET-BSE, 410 with stage A or B HF were analyzed. The association between the CPET-BSE parameters and adverse cardiac events (hospitalization for HF or cardiac-related death) was analyzed using the Cox proportional hazard model under univariate and multivariate analyses.

Results: After a median 9 years of follow-up, 47 (11.5 %) of the 410 patients had events. In the univariable analysis, age, diuretics, BUN, creatinine, peak oxygen uptake (VO2), ventilatory efficiency (VE/VCO_2), time to VT and peak exercise, left atrial volume index, rest and exercise E/e′, and tricuspid regurgitation velocity demonstrated significant parameters. In multivariate analysis, VE/VCO_2 (hazard ratio [HR] 1.205, 95 % CI 1.095–1.327) and VO_2 at peak exercise (HR 1.164, 95 % CI 1.022–1.325), time to VT (HR 0.993, 95 % CI 0.989–0.997), and exercise E/e′ (HR 1.582, 95 % CI 1.199–2.087) were only independent predictors for events.

Conclusions: In patients with stage A or B HF, four parameters of CPET-BSE were good predictors of future development of HF or cardiac death. If patients are unable to perform complete exercise, the time to VT may serve as a sufficiently predictive parameter for clinical events.

1. Introduction

Dyspnea, frequently reported in patients with risk factors, is a potent clinical indicator of heart failure (HF). However, various conditions besides HF can cause functional decline in at-risk patients. Therefore, clinical evaluation is frequently necessary for dyspnea. However, when baseline echocardiographic and pulmonary function tests yield normal results, clinicians tend to attribute this symptom to non-cardiac or non-pulmonary etiologies, potentially overlooking a critical diagnosis [1,2].

In most pre-HF or early HF cases, diastolic filling pressure is normal at rest but increases during exertion [3–5]. Furthermore, the functional reserve capacity of the integrated metabolic and physiological machinery required for exercise is impaired [6]. Therefore, comprehensively assessing these factors during exertion to determine whether the symptoms are cardiogenic is crucial. The combined approach of cardiopulmonary exercise testing and bicycle stress echocardiography (CPET-BSE) provides a multiparametric integrated interpretation [7]. This approach non-invasively estimates global oxygen consumption (VO_2), ventilatory response, and metabolic and cardiovascular physiology, as well as provides a thorough cardiac evaluation at rest and during exercise [2,8,9].

CPET-BSE is increasingly used, especially in patients with HF with

Abbreviations: CPET-BSE, cardiopulmonary exercise testing with bicycle stress echocardiography; HF, heart failure; LAVi, left atrium volume index; VT, ventilatory threshold; LVEF, left ventricular ejection fraction; VE, minute ventilation; VCO_2, carbon dioxide production; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.

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preserved ejection fraction and those at risk of HF, to clarify diagnosis and prognosis [7,10–12]. Various parameters have been proposed for diagnosing and predicting pre- or early-stage HF [13,14]; however, studies examining the real effect of these parameters on long-term clinical outcomes are limited.

We aimed to identify important parameters for risk stratification in patients with stage A or B HF who were at risk of developing a new-onset HF. This stratification is substantiated by its demonstrable effects on long-term clinical outcomes.

2. Materials and methods

2.1. Study population

We analyzed 687 consecutive patients aged >18 years who presented with dyspnea or chest discomfort and valvular disease and underwent simultaneous CPET and BSE at Seoul National University Bundang Hospital from September 2009 to December 2020. Among these patients, 410 classified as having stage A or B HF were included in the analysis. The median follow-up period was 96 (44.7, 135.7) months. The Institutional Review Board of Seoul National University Bundang Hospital approved this study (No. B-2203-744-102). This study adhered to the ethical guidelines of the Declaration of Helsinki and Good Clinical Practices. Given its retrospective nature, the institutional review board deemed informed consent requirements as non-applicable.

All participants in the study were classified according to the American College of Cardiology Foundation/American Heart Association criteria for HF, with individuals either in stage A (those with cardiovascular risk factors but no symptoms) or stage B (those with structural heart disease or evidence for increased filling pressures but without clinical signs or symptoms of heart failure) [15,16].

Patients with more than moderate primary valvular disease ($n = 22$), those unable to complete exercise (respiratory exchange ratio <1.0, during exercise) ($n = 42$), and those with poor echo quality ($n = 95$), congenital heart disease ($n = 3$), or acute myocardial ischemia ($n = 19$) were excluded. Among these, 95 patients met one or more of the criteria.

2.2. Protocols for CPET and supine bicycle exercise echocardiography

All patients underwent symptom-limited exercise tests in a semi-supine position after providing written informed consent. We determined the standard target heart rate using the formula: [(220-age) × 0.85] [17]. The protocol included a rest period, warm-up, 8–12 min of exercise, and a 5-min recovery phase, with intensity increasing by 25 W every 3 min. Test termination criteria included severe angina, diagnostic electrocardiogram positivity, and severe limiting side effects, such as hypertension (systolic blood pressure >220 mmHg, diastolic blood pressure >120 mmHg), exercise-induced hypotension (decrease in systolic blood pressure >20 mmHg), bradycardia, intolerable dyspnea, and complex arrhythmias.

We conducted standard M-mode, two-dimensional echocardiography, and Doppler blood flow measurements [18]. All echocardiographic measurements were performed using a standard ultrasound machine (Vivid E95, GE Vingmed Ultrasound) with a 2.5-MHz transducer. We measured changes in echocardiographic parameters from parasternal and apical views at baseline and during incremental workload using a variable-load bicycle ergometer (Lode B.V, Groningen). Furthermore, we assessed baseline values of s′, e′, systolic reserve ($=\Delta s' \times [1 - (1/\text{basal } s')]$, diastolic reserve ($=\Delta e' \times [1 - (1/\text{basal } e')]$, E/e′, LA strain, peak apical rotation, and peak apical untwist. We evaluated these parameters at various time points as the workload increased. For the diastolic stress test, exercise E/e′ was measured at a workload of 50 W, and in cases of E/A fusion, 25 W.

Cardiopulmonary variables such as minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide production (VCO_2) were acquired breath-by-breath, averaged over 30 s, and printed in rolling averages every 10 s using a CPET device (Quark, COSMED Srl) [19]. We evaluated aerobic capacity (VO_2 mL/min/kg) and maximal effort as metabolic response components, assessed ventilatory capacity (VE in L/min) and gas exchange efficiency (VE/CO_2) as indicators of ventilatory response, and examined cardiovascular response using the CPET. Ventilatory threshold (VT) was measured using the V-slope method [20]. Adequate maximal effort was determined by the presence of a respiratory exchange ratio >1.0, a clearly identifiable ventilatory threshold, or both.

2.3. Clinical outcomes

Adverse cardiac events were defined as HF hospitalization or cardiac death. HF hospitalization was defined as admission to the emergency or internal medicine department with dyspnea and edema symptoms, followed by intravenous administration of nitrates or diuretics. Causes of death were obtained upon request from the National Statistical Office or the Ministry of Public Administration and Security.

2.4. Statistical analysis

The clinical information of the patients, including baseline characteristics, CPET, and BSE, was summarized using appropriate statistical summaries. Categorical variables are presented as counts and percentages and were compared using the χ^2 test, whereas continuous variables are expressed as means and standard deviations and were compared using the Student *t*-test. The association between CPET and BSE parameters and adverse cardiac events was analyzed using the Cox proportional hazard model in univariate and multivariate analyses.

Variables with a *p*-value <0.05 in the univariate analysis were included in the subsequent multivariable analysis using stepwise selection for both stages. To ensure the validity of our model, the variance inflation factor was employed to assess multicollinearity among predictors. Consequently, age, diuretics, blood urea nitrogen, creatinine, VO_2 mL/min/kg at peak exercise, VE/VCO_2 slope at peak exercise, time to VT, time to peak exercise, tricuspid regurgitation, left atrium volume index, baseline and exercise E/e′, exercise s′, systolic reserve, and diastolic reserve were included in the multivariable analysis. The Cox proportional hazard model was used for subgroup analysis on VE/VCO_2 slope at peak exercise (<30, 30–36, >36), VO_2 mL/min/kg at peak exercise (<14, 14–20, >20), time to VT (<360, 360–480, >480 s), and exercise E/e′ (<15, ≥15). The risk of adverse cardiac events over the follow-up period was analyzed using Kaplan–Meier analysis and log-rank tests. All statistical analyses were conducted using R software (version 4.2.1; R Development Core Team), and all two-tailed p-values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 presents the baseline characteristics of the patients. The mean age of the 410 patients was 59.7 ± 12.5 years, with women constituting 41.2 % ($n = 169$), and the body mass index was 25.5 ± 3.3 kg/m^2. Most patients underwent CPET-BSE because of dyspnea (45.6 %) and chest discomfort (42.9 %). The underlying diseases included hypertension in 222 (54.1 %) and diabetes in 103 (25.1 %) patients. Consequently, over 90 % of the patients were taking at least one medication, with the highest prevalence of renin-angiotensin system blocker use ($n = 229$, 55.9 %). Laboratory findings, including the N-terminal prohormone of brain natriuretic peptide levels, were within normal ranges.

Tables 1 and 2 present the results of CPET-BSE for the patients. The average times to reach VT and peak exercise were 436.4 ± 174.5 s and 795.7 ± 204.4 s, respectively. The mean VO_2 values at these time points were 12.6 ± 3.7 mL/min/kg and 19.4 ± 4.7 mL/min/kg, respectively.

Table 1
Baseline characteristics of participants.

Baseline patient characteristics	Stage A or B ($N = 410$)
Age (years, mean ± SD)	59.7 ± 12.5
Female sex (*N* (%))	169 (41.2)
BMI (kg/m^2, mean ± SD)	25.5 ± 3.3
Reason for CPET with BSE, *n* (%)	
Dyspnea	187 (45.6)
Chest discomfort	176 (42.9)
Valvular heart disease	32 (7.8)
Others	15 (3.7)
HF stage, *n* (%)	
A	219 (53.4)
B	191 (46.6)
Underlying disease	
Diabetes, *n* (%)	103 (25.1)
Hypertension, *n* (%)	222 (54.1)
Atrial fibrillation, *n* (%)	23 (5.6)
Medication	
Beta-blocker, *n* (%)	189 (46.1)
RAS blocker, *n* (%)	229 (55.9)
Diuretics, *n* (%)	90 (22.0)
Lab	
LDL (mg/dl, mean ± SD)	98.1 ± 31.3
HbA1c (%, mean ± SD)	6.2 ± 1.1
BUN (mg/dl, mean ± SD)	15.5 ± 4.8
Creatinine (mg/dl, mean ± SD)	0.9 ± 0.3
Hemoglobin (g/dL, mean ± SD)	14.2 ± 1.7
ProBNP (pg/ml, mean ± SD)	94.8 ± 95.8
Supine bicycle stress echocardiography	
LVMi (g/m^2, mean ± SD)	90.2 ± 24.1
LVEDV (mL, mean ± SD)	85.8 ± 22.9
LVESV (mL, mean ± SD)	32.6 ± 13.4
LVEF (%, mean ± SD)	61.0 ± 7.2
LAVi (mL/m^2, mean ± SD)	33.8 ± 17.5
RVSP (mmHg, mean ± SD)	26.8 ± 8.2
Baseline s′ (cm/s, max)	14.4
Baseline e′ (cm/s, max)	14.4
Exercise s′ (cm/s, max)	16.8
Exercise e′ (cm/s, max)	19.0
Baseline E/e′ (mean ± SD)	11.9 ± 6.4
Exercise E/e′ (mean ± SD)	12.5 ± 5.2
E/e′ change %	15.9 ± 34.7
Systolic reserve (mean ± SD)	1.7 ± 1.4
Diastolic reserve (mean ± SD)	2.5 ± 1.8

Values are given as the mean ± standard deviation (SD) or number with percentage (%).
BMI, body mass index; BUN, blood urea nitrogen; CPET-BSE, cardiopulmonary exercise test with bicycle stress echocardiography; HbA1c, glycated hemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; LDL, low-density lipoprotein; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; LVESV, left ventricular end systolic volume; LAVi, left ventricular volume index; ProBNP, pro b-type natriuretic peptide; RAS, renin-angiotensin system; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.
Diastolic reserve, longitudinal diastolic flow reserve, $\Delta e' \times [1-(1/\text{basal e}')]$, Systolic reserve, longitudinal systolic flow reserve $\Delta s' \times [1-(1/\text{basal s}')]$.

Furthermore, 56.4 % of the patients ($n = 229$) exhibited VO_2 values at peak exercise of ≤20 mL/kg/min. Furthermore, the mean VE/VCO_2 value at peak exercise was 30.9 ± 5.6, with 15.7 % of patients ($n = 62$) displaying a value above 36. In BSE measurements, baseline and exercise E/e′ values were 11.9 ± 6.4 and 12.5 ± 5.2, respectively. The E/e′ change (%) at each time point showed a value of 15.9 ± 34.7 %

3.2. Univariate and multivariate analyses

We conducted univariate and multivariate analyses to identify factors significantly affecting adverse cardiac events in patients with stage A or B HF (Table 3). In the univariate analysis, age, diuretics, blood urea nitrogen, and creatinine demonstrated significant effects. Significant

Table 2
Cardiopulmonary exercise testing characteristics at VT and peak exercise.

Cardiopulmonary exercise test	VT	Peak exercise
Time to each level (s, mean ± SD)	436.4 ± 174.5	795.7 ± 204.4
VO_2, mL/min/kg	12.6 ± 3.7	19.4 ± 4.7
VO_2, mL/min/kg category		
<14 mL/kg/min	289 (70.5 %)	46 (11.3 %)
14 ≤ mL/kg/min ≤20	108 (26.3 %)	183 (45.1 %)
mL/kg/min >20	13 (3.2 %)	177 (43.6 %)
VE/VCO_2	30.1 ± 4.8	30.9 ± 5.6
VE/VCO_2 category		
<30	229 (55.9 %)	174 (43.9 %)
30–36	166 (40.5 %)	160 (40.4 %)
>36	15 (3.7 %)	62 (15.7 %)

Values are given as the mean ± standard deviation (SD) or number with percentage (%).
VT, ventilatory threshold; VCO_2, volume of carbon dioxide production.
VE, minute ventilation, VO_2, volume of oxygen consumption.

variables related to CPET included VO_2 mL/min/kg at peak exercise, VE/VCO_2 slope at VT and peak exercise, and time to VT and peak exercise. Among echocardiographic variables, left atrium volume index, E/e′ at baseline and exercise, tricuspid regurgitation, e′ at baseline and exercise, exercise s′, systolic reserve, and diastolic reserve exhibited significant effects.

In the multivariate analysis, the only significant CPET-related variables were the VE/VCO_2 slope at peak exercise, VO_2 mL/min/kg at peak exercise, and time to VT. Among the echocardiographic-related variables, only exercise E/e′ was identified as a factor influencing adverse cardiac events. Among the four significant indicators, VE/VCO_2 at peak exercise exhibited the most powerful effect on adverse clinical events (coefficient 0.107, concordance index, 0.74).

3.3. Clinical events

Forty-seven adverse cardiac events occurred during a median follow-up period of 96 months. The stages A and B groups experienced 3 and 4 cardiac-related deaths and 12 and 28 hospitalization cases, respectively (Supplementary Table 1). We conducted a survival analysis after a long-term follow-up on the four variables that significantly influenced the adverse cardiac events (Fig. 1). Three variables had significant effects in the CPET. We divided the patients into three groups based on VE/VCO_2 slopes at peak exercise cut-offs of <30, 30–36, and >36. The group with values between 30 and 36 demonstrated a 2.73 times higher incidence rate of adverse cardiac events than the group with values <30 [(1.391–5.367), $p = 0.003$]. The group with values >36 had a 7.15 times higher incidence rate [(3.565–14.353), $p < 0.001$] (Fig. 1A). Additionally, we examined the relationship between VE/VCO_2 and adverse cardiac events using a hazard ratio based on the continuous VE/VCO_2 slope (Fig. 2A). The restricted cubic spline (RCS) curve indicated a rising hazard ratio associated with elevated levels of VE/VCO_2, using a reference point of 30.

Subsequently, we categorized the patients into three groups based on their VO_2 mL/min/kg at peak exercise values: <14, 14–20, and >20 mL/min/kg, and compared the occurrence of adverse cardiac events among these groups. The incidence rate of adverse cardiac events was 3.29 times higher in the <14 VO_2 group [(1.616–6.709), $p = 0.001$] when the >20 VO_2 group was used as a reference (Fig. 1B). Additionally, the RCS indicated that lower VO_2 mL/min/kg at peak exercise values corresponded to an increased incidence of these events (Fig. 2B).

Furthermore, we conducted an analysis based on the time to VT tertiles: <360 s, 360–480 s, and >480 s. The group with time to VT <360 s had a 2.62 times higher incidence of adverse cardiac events [(1.265–5.424), $p = 0.009$] when the group with time to VT exceeding 480 s was used as the reference. (Fig. 1C). Additionally, examining adverse cardiac events with time to VT as a continuous variable using the RCS revealed a relationship between hazard ratios for adverse

Table 3
Univariable and multivariable analyses for adverse cardiac events in stage A or B.

	Univariate analysis		Multivariate analysis		Coefficient	Concordance index
	HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value		
Age (years)	1.043 (1.014–1.073)	0.003	1.021 (0.951–1.095)	0.559		
Sex	0.786 (0.442–1.399)	0.414				
BMI (kg/m^2)	0.918 (0.837–1.006)	0.067				
DM	1.417 (0.825–2.434)	0.206				
Hypertension	0.999 (0.578–1.727)	0.999				
Atrial fibrillation	1.524 (0.686–3.384)	0.301				
Beta-blocker	1.515 (0.859–2.671)	0.151				
RAS blocker	1.503 (0.768–2.939)	0.234				
Diuretics	2.845 (1.677–4.855)	<0.001	2.798 (0.915–8.554)	0.07		
LDL (mg/dL)	1.003 (0.992–1.013)	0.616				
HbA1c (%)	1.146 (0.694–1.891)	0.593				
BUN (mg/dL)	1.080 (1.023–1.140)	0.005	1.079 (0.960–1.212)	0.197		
Creatinine (mg/dL)	2.689 (1.210–5.979)	0.015	5.442 (0.982–30.141)	0.052		
Hemoglobin (g/dL)	0.958 (0.818–1.121)	0.595				
ProBNP (pg/mL)	1.003 (0.999–1.008)	0.123				
VO_2, mL/min/kg at VT	0.931 (0.864–1.003)	0.060				
VO_2, mL/min/kg at peak exercise	0.915 (0.862–0.971)	0.003	1.164 (1.022–1.325)	0.021	−0.089	0.69
VE/VCO_2 at VT	1.134 (1.090–1.181)	<0.001				
VE/VCO_2 at peak exercise	1.113 (1.076–1.152)	<0.001	1.205 (1.095–1.327)	<0.001	0.107	0.74
Time to VT (s)	0.997 (0.995–0.999)	0.002	0.993 (0.989–0.997)	0.002	−0.002	0.73
Time to peak exercise (s)	0.996 (0.994–0.997)	<0.001	0.999 (0.994–1.003)	0.694		
$PetCO_2$ at peak exercise	0.910 (0.868–0.954)	<0.001				
LVMi (g/m^2)	1.006 (0.997–1.015)	0.165				
LVEF (%)	0.983 (0.952–1.016)	0.325				
LAVi (mL/m^2)	1.015 (1.005–1.024)	0.002	1.009 (0.974–1.046)	0.606		
Baseline E/e′	1.039 (1.002–1.078)	0.040	0.896 (0.684–1.172)	0.423		
Exercise E/e′	1.042 (1.014–1.071)	0.003	1.582 (1.199–2.087)	0.001	0.041	0.61
TR (cm/s)	4.243 (1.939–9.284)	<0.001	2.093 (0.455–9.629)	0.342		
Exercise TR (cm/s)	1.387 (0.892–2.155)	0.146				
Baseline s′ (cm/s)	0.869 (0.724–1.045)	0.136				
Baseline e′ (cm/s)	0.763 (0.647–0.901)	0.001				
Exercise s′ (cm/s)	0.802 (0.670–0.960)	0.016	0.831 (0.587–1.177)	0.298		
Exercise e′ (cm/s)	0.737 (0.630–0.863)	<0.001				
Systolic reserve	0.729 (0.568–0.936)	0.013	0.799 (0.473–1.349)	0.401		
Diastolic reserve	0.809 (0.669–0.978)	0.029	1.125 (0.826–1.531)	0.453		

BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; DM, diabetes mellitus; HbA1C, glycated hemoglobin; HR, hazard ratio; LAVi, left ventricular volume index; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; VT, ventilatory threshold; ProBNP, pro b-type natriuretic peptide; RAS, renin-angiotensin system; TR, tricuspid regurgitation; VCO_2, volume of carbon dioxide production; VE, minute ventilation; VO_2, volume of oxygen consumption; $PetCO_2$, end-tidal carbon dioxide pressure.
Diastolic reserve, longitudinal diastolic flow reserve, e′ × [1−(1/basal e′)], Systolic reserve, longitudinal systolic flow reserve s′ × [1−(1/basal s′)].

cardiac events and time to VT values (Fig. 2C).

Exercise E/e′ was the only significant variable for clinical events in the BSE. An increase in exercise E/e′ correlated with a higher frequency of adverse cardiac events (Fig. 2D). A noticeable difference in these events over time emerged when we established a cut-off value of 15 and compared the two groups (hazard ratio: 2.58 (1.401–4.755), $p = 0.002$) (Fig. 1D).

4. Discussion

This study demonstrated critical multimodality parameters for risk stratification in patients with stage A or B HF. Our findings suggest the possibility of stratifying patients into stage A or B based on their risk of progressing to HF, establishing a foundation for proactive measures aimed at preventing HF onset (Central illustration).

Peak VO_2 (mL/kg/min) and VE/VCO_2 slope are well-known prognostic markers in patients with left ventricular systolic dysfunction and are frequently used in pre-transplant evaluations [21,22]. However, emerging studies indicate that the VE/VCO_2 slope is a better prognostic factor than peak VO_2 in patients with pre- or early HF.

Ponikowski et al. [23] demonstrated that among patients with chronic HF who have preserved exercise capacity (defined as peak VO_2 ≥18 mL/kg/min), those with a high VE/VCO_2 slope exhibited disrupted cardiorespiratory reflex control and poorer outcomes than those with a normal VE/VCO_2 slope. Additionally, in another study by Maro Guazzi et al. [19], 409 patients underwent CPET to evaluate the ability of peak VO_2 and the VE/VCO_2 slope to predict total mortality and hospitalization. In multivariate analysis, the VE/VCO_2 slope and peak VO_2 demonstrated similar predictive capabilities in patients with systolic HF. However, in patients with diastolic HF, the VE/VCO_2 slope demonstrated greater predictive power than peak VO_2 (mL/kg/min), in line with the findings of our study. This indicates that the importance of impaired ventilation as a prognostic indicator outweighs peak VO_2 (mL/kg/min) significance in patients at stage A or B. VE/VCO_2 slope may be more significant because compensatory mechanisms, such as heightened ventilatory reflex control, including augmented peripheral and central chemosensitivity, may be more active in maintaining homeostasis in HF early stages than in the advanced stages [24].

In addition to ventilatory inefficiency, this study highlights time to VT as an important CPET-related parameter. The ventilatory threshold, where the carbon dioxide elimination rate increases more disproportionately than the oxygen uptake, is visually identified using the V-slope method [25]. This ventilatory threshold has been proposed as an objective means of evaluating aerobic capacity [26].

Gitt et al. [22] demonstrated that among the indicators (VO_2, VE/VCO_2, and VO_2 at LT), VO_2 at LT exhibited the best predictive accuracy as a single indicator when CPET was conducted in patients with chronic HF to determine 6-month mortality. Additionally, the group with low VO_2 (mL/kg/min) at LT and high VE/VCO_2 had the highest odds ratio. This suggests that in patients with early HF, aerobic capacity, specifically the early accumulation of lactate in the blood, may be a sensitive prognosis indicator [25].

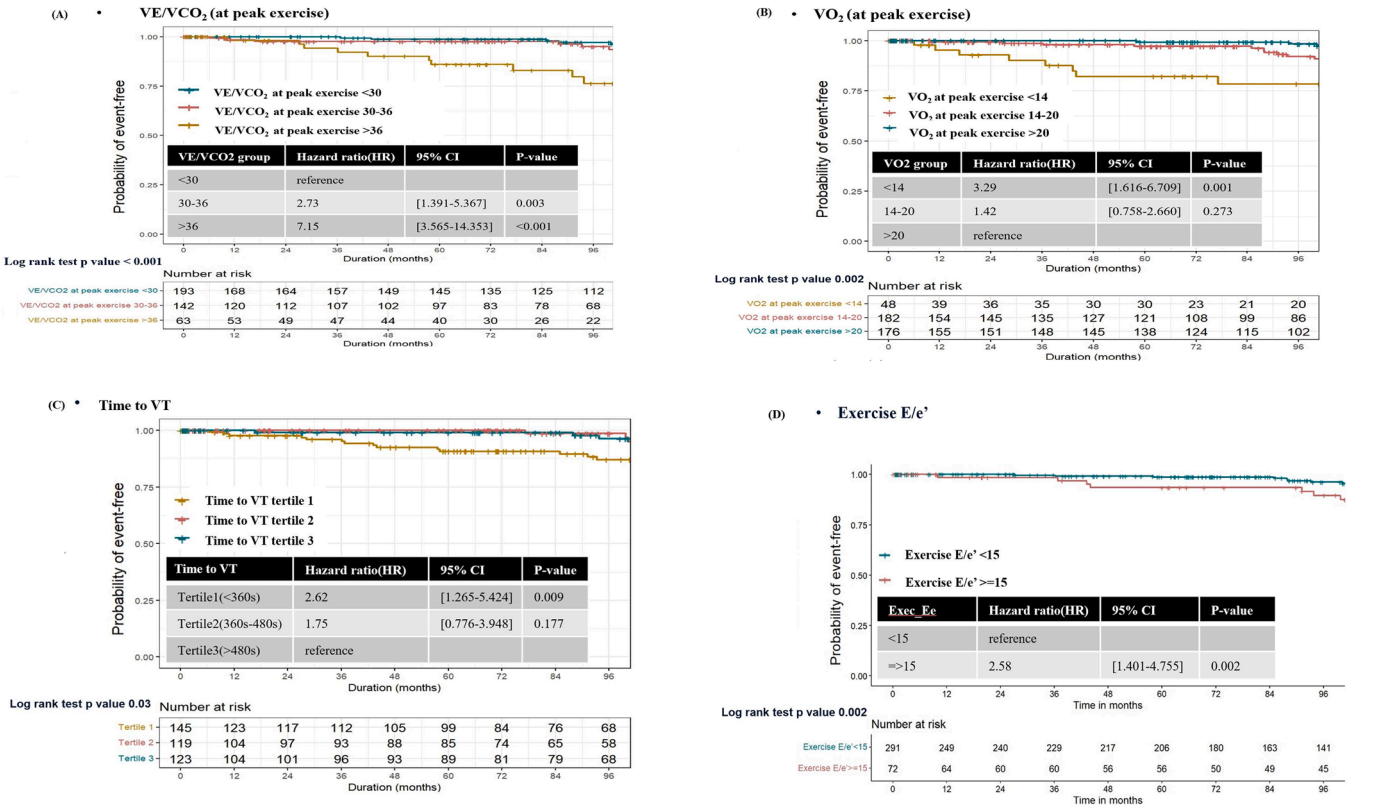


Fig. 1. Time to event curve for advanced cardiac events. Hazard ratios for adverse events based on parameters: (A) by VE/VCO_2 slope (<30, 30–36, >36), (B) across VO_2 mL/min/kg groups (<14, 14–20, >20), (C) in relation to time to VT (<360 s, 360–480 s, >480 s), and (D) by exercise E/e′ ratio with a cut-off at 15.
VT, ventilatory threshold; VCO_2, volume of carbon dioxide production; VE, minute ventilation; VE/VCO_2, ventilatory efficiency; VO_2, volume of oxygen consumption

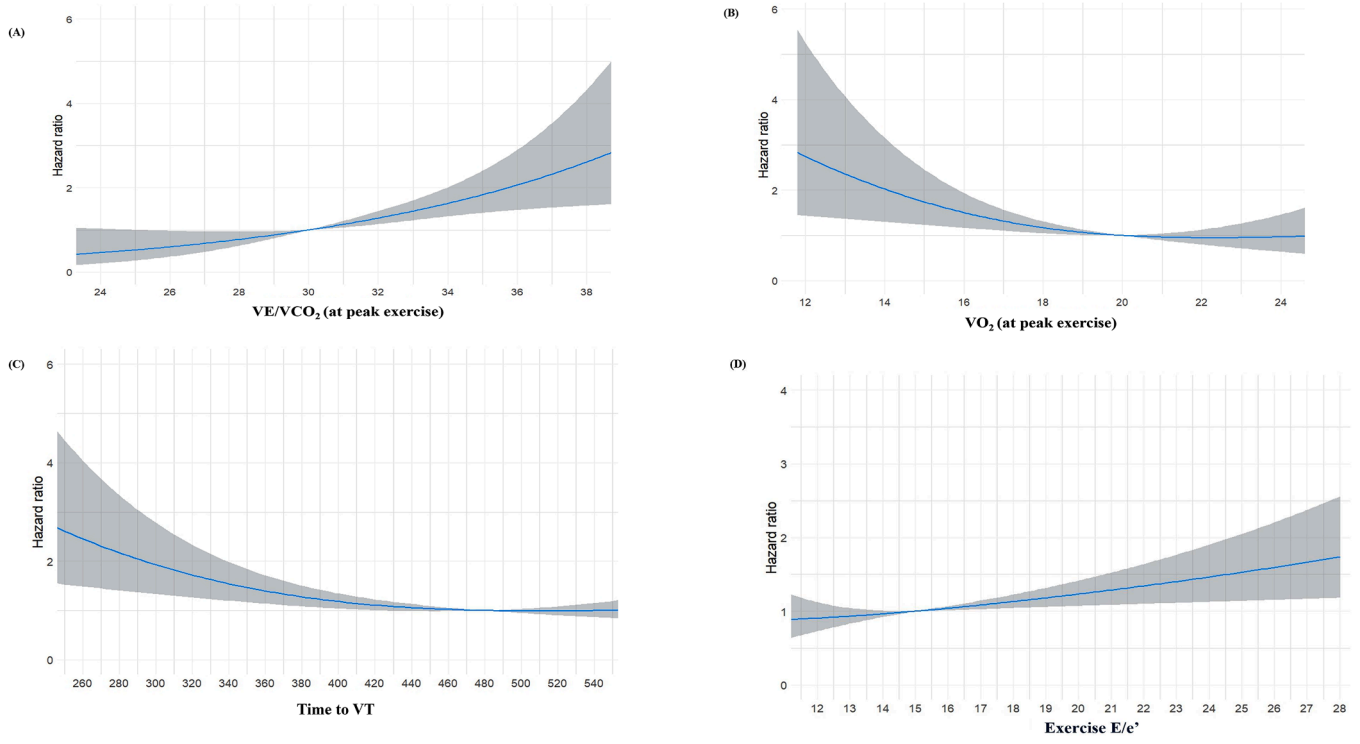
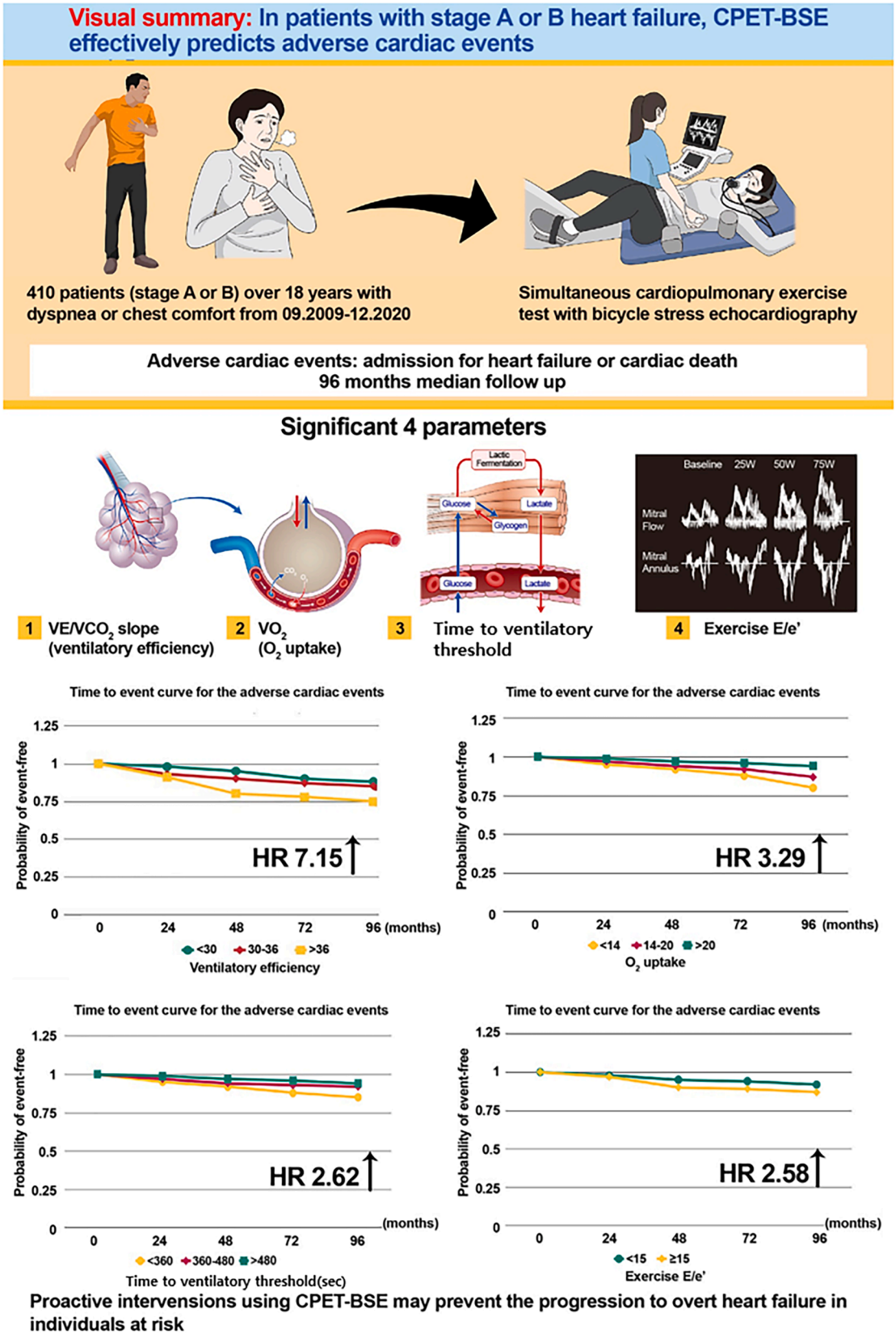


Fig. 2. RCS curves for adverse cardiac events using CPET and BSE variables. (A) VE/VCO_2 slope (reference at 30), (B) VO_2 mL/min/kg (reference at 20) (C) time to VT (reference at 480), and (D) exercise E/e′ ratio (reference at 15).
BSE, bicycle stress echocardiography; CPET, cardiopulmonary exercise test; VT, ventilatory threshold; RCS, restricted cubic spline; VE/VCO_2, ventilatory efficiency; VO_2, volume of oxygen consumption



Central illustration: CPET-BSE for prediction of cardiac events in patients with stage A or B heart failure.

Our study divided patients into tertiles based on their time to VT and compared the incidence of adverse cardiac events. We observed a significant increase in this incidence in the first tertile (<360 s) than in the third tertile (>480 s). Determining the ventilatory threshold involves multifactorial factors; however, our findings highlight that the time to VT is an important potential prognostic predictor and suggests that even if patients cannot complete a full exercise test, the time to VT may be a sufficient predictive parameter for clinical events.

This study also identified exercise E/e′ as a parameter associated with BSE. Pre- or early HF is characterized by ventricular stiffening and impaired relaxation, leading to suboptimal filling and elevated left ventricular filling pressure. In healthy individuals, a concordant increase occurs in mitral E velocity and annular e′ velocity during exercise, without an overall change in the mitral E/e′ ratio. In contrast, patients with HF demonstrate increased mitral E velocity but minimal change in e′ during exercise, resulting in an increased E/e′ ratio [27]. The increase in left ventricular filling pressure due to diastolic dysfunction, reduced cardiac output, and circulatory delay during exercise, may enhance the ventilatory drive triggered by chemoreceptors. This could lead to a decreased partial pressure of carbon dioxide, potentially resulting in hypopnea [2,6]. However, the phenotype of early HF pathophysiology is diverse, and factors such as pulmonary vascular diseases and obesity can impair exercise capacity, leading to diastolic dysfunction [28].

A recent study measured the E/e′ ratio during low-level exercise (20 W) and evaluated its ability to predict normal pulmonary capillary wedge pressure (<25 mmHg) in patients undergoing right heart catheterization. This study suggests that it can assist in HF diagnosis with preserved ejection fraction [29]. In addition to CPET parameters like time to VT, future research could explore CPET and BSE variables in patients unable to achieve maximal exercise capacity, potentially guiding preventive strategies in this population. A prospective study involving 772 patients undergoing exercise echocardiography observed that the group that underwent exercise echocardiography detected events more sensitively than the group that did not undergo exercise echocardiography. Moreover, during the follow-up period, the group with an exercise E/e′ ratio >15 had a higher incidence of events [30]. In this study, multivariate analysis established exercise E/e′ as a significant predictive factor in patients with stage A or B HF and demonstrated that those with an exercise E/e′ >15 experienced significantly more adverse cardiac events during long-term follow-up, consistent with previous research.

Finally, based on the study findings, multifactorial factors, such as ventilatory inefficiency, O_2 uptake, time to VT, and exercise E/e′, significantly influenced adverse cardiac events in stage A or B patient groups. Additionally, ventilatory inefficiency is the most important predictive factor, and the time to VT proves effective in predicting adverse clinical events in patients unable to complete exercises.

This single-center, retrospective observational study had limitations in generalizing findings, owing to potential biases and residual confounders that could significantly influence the results beyond the collected data. Furthermore, technical limitations in measuring exercise echocardiography parameters, including the fusion of mitral inflow and tissue Doppler values and assessing valve regurgitation, may affect results. We excluded patients with higher than moderate primary valvular issues; however, the inability to assess valve conditions during and after exercise limited a comprehensive evaluation of exercise-induced valve conditions. Despite these limitations, we demonstrated that in patients with increased TR velocity during exercise, ventilatory efficiency-related variables were found to have greater correlation compared to the overall cohort, highlighting their importance in this specific population (Supplementary Table 2). Additionally, the potential effect of medication type, such as renin-angiotensin system blockers and beta-blockers, along with medication dosage and adherence, may have been underestimated. In the case of beta-blockers, which are known to influence CPET variables, we addressed this limitation by performing IPTW analysis (Supplementary Table 3). This analysis confirmed that beta-blocker use did not significantly impact the identification of key variables or the prediction of clinical outcomes in this study. Nevertheless, more studies are needed because of the limited understanding of precise pathophysiology and the particular significance of parameters in patients with stage A or B HF. Predicting HF onset may not solely rely on one parameter but also necessitates integrating multiple high-predictive parameters from CPET-BSE.

CRediT authorship contribution statement

Houng-Beom Ahn: Writing – original draft. **Jiesuck Park:** Formal analysis. **Hye Jung Choi:** Validation. **Hong-Mi Choi:** Writing – review & editing, Investigation. **In-Chang Hwang:** Writing – review & editing, Formal analysis. **Yeonyee E. Yoon:** Writing – review & editing, Conceptualization. **Goo-Yeong Cho:** Writing – review & editing, Validation, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100913.

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