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Relationship between the prognostic value of ventilatory efficiency and age in patients with heart failure

Yuko Kato[1], Shinya Suzuki[1], Tokuhisa Uejima[1], Hiroaki Semba[1], Osamu Nagayama[2], Etsuko Hayama[2], Takuto Arita[1], Naoharu Yagi[1], Hiroto Kano[1], Shunsuke Matsuno[1], Takayuki Otsuka[1], Yuji Oikawa[1], Takashi Kunihara[3], Junji Yajima[1] and Takeshi Yamashita[1]

Abstract

Background: Ventilatory efficiency decreases with age. This study aimed to investigate the prognostic significance and cut-off value of the minute ventilation/carbon dioxide production (VE/VCO_2) slope according to age in patients with heart failure.

Methods and results: We analysed 1501 patients with heart failure from our observational cohort who performed maximal symptom-limited cardiopulmonary exercise testing and separated them into three age groups ($\leq$55 years, 56–70 years and $\geq$71 years) in total and according to the three ejection fraction categories defined by European Society of Cardiology guidelines. The endpoint was set as heart failure events, hospitalisation for heart failure or death from heart failure. The VE/VCO_2 slope increased with age. During the median follow-up period of 4 years, 141 heart failure (9%) events occurred. In total, univariate Cox analyses showed that the VE/VCO_2 slope (cont.) was significantly related to heart failure events, while on multivariate analysis, the prognostic significance of the VE/VCO_2 slope (cont.) was poor, accompanied by a significant interaction with age ($P < 0.0001$). The cut-off value of the VE/VCO_2 slope increased with the increase in age in not only the total but also the sub-ejection fraction categories. Multivariate analyses with a stepwise method adjusted for estimated glomerular filtration rate, peak oxygen consumption, atrial fibrillation and brain natriuretic peptide, showed that the predictive value of the binary VE/VCO_2 slope separated by the cut-off value varied according to age. There was a tendency for the prognostic significance to increase with age irrespective of ejection fraction.

Conclusion: The prognostic significance and cut-off value of the VE/VCO_2 slope may increase with advancing age.

Keywords
Age, heart failure, ventilator efficiency, VE/VCO_2 slope

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Introduction

An increasing ageing population and burden of heart failure (HF) has become a global concern. Risk stratification for HF with more consideration of elderly patients is necessary.

Ventilatory efficiency is known to be a powerful prognostic indicator for HF-related mortality, cardiovascular events and the severity of HF as well as peak oxygen consumption (VO_2).[1–4] The slope of minute

[1]Department of Cardiovascular Medicine, The Cardiovascular Institute, Japan
[2]Department of Clinical Laboratory, The Cardiovascular Institute, Japan
[3]Department of Cardiovascular Surgery, The Cardiovascular Institute, Japan

Corresponding author:
Yuko Kato, The Cardiovascular Institute, Nishiazabu 3-2-19, Minato-ku, Tokyo 106-0031, Japan.
Email: kimuchi@nms.ac.jp

ventilation (VE) versus carbon dioxide (CO_2) (VE/VCO_2 slope), which is the most popular indicator of ventilatory efficiency obtained by cardiopulmonary exercise testing (CPET), was found to be positively associated with age in studies on subjects without HF.[5–7] However, its prognostic cut-off value for HF has been set as 32–35,[2–4,8,9] mostly in patients with reduced ejection fraction in whom the influence of age on the predictive significance of the VE/VCO_2 slope has not been considered. In an ageing society, a better understanding of the influence of age on ventilatory efficiency is essential.

The aim of this study was to investigate the prognostic significance and cut-off level of the VE/VCO_2 slope for HF, according to age.

Methods

The Shinken database is a single hospital cohort database comprising all new patients who visit the Cardiovascular Institute Hospital, Tokyo, Japan. From June 2004 to March 2015, 27,750 patients were registered. The details of the database have been reported previously;[10] all data on patient health status, the incidence of cardiovascular events and mortality are linked to electronic medical records. All events were ascertained by exchanging letters annually with each patient/patient's family, when the patients switched to a different hospital for their regular visits or moved to a different location. The subjects for the present study were selected from the database cohort and excluded patients with: (a) submaximal exercise evidenced by a peak respiratory exchange ratio (RER) ≤ 1.0; (b) acute coronary syndrome or recent myocardial ischaemic events within the past 3 months; (c) HF event at the initial visit; (d) a decrease in peripheral capillary oxygen saturation during exercise; (e) previously diagnosed/suspected lung disease by chest radiograph. We included 1501 patients with chronic HF who underwent symptom-limited maximal CPET. Chronic HF was defined as a history of HF exacerbation or left ventricular ejection fraction (LVEF) on echocardiogram less than 50% or a plasma brain natriuretic peptide (BNP) level of more than 100 pg/mL when LVEF was more than 50%.

The baseline patient characteristics, including age, sex, height, weight, cardiovascular diseases and medications were retrieved, along with cardiovascular risk factors. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese Society of Nephrology formulae for Japanese persons. The cardiovascular status of each patient in the present study was evaluated using electrocardiogram, chest radiography, blood examination, echocardiography and exercise testing at the initial visit. The presence of structural heart disease was also evaluated using magnetic resonance imaging or computed tomography, when available. Valvular disease was defined as valvular dysfunction of more than moderate grade, irrespective of a primary or secondary cause.

All patients underwent symptom-limited maximal CPET using a cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan) with a 10–20 Watts/min continuous ramp exercise protocol, after a 4-minute period of rest and a 4-minute period of 0–20 Watts/min warming-up. During CPET, we performed expired gas analysis (AE-310S; Minato Medical Science, Osaka, Japan), and monitored the electrocardiogram and blood pressure. Peak VO_2 was defined as the highest oxygen uptake value during the last minute of exercise. The VE/VCO_2 slope was calculated as the slope of a linear regression line between VE and VCO_2 from the start of the exercise to just before the respiratory compensation point. Because tidal volume (VT) is influenced by body constitution, we calculated VT at peak exercise corrected by body mass index (BMI). Exercise oscillatory ventilation was defined as three or more consecutive cyclic fluctuations in ventilation, with amplitude of oscillation greater than 5 L/min and an oscillatory cycle length of 40–140 s.[11]

The endpoint was set as HF-related events: hospitalisation for HF or HF-related death. The interval between the date of CPET to the occurrence of any HF event was defined as the duration of follow-up. Follow-up was closed in March 2016.

All data were analysed using SPSS version 19 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$. In terms of the interaction analysis, $P < 0.1$ was considered as statistical significance. First, the total cohort was divided into three age groups: 55 years or younger ($N = 431$); 56–70 years ($N = 703$); 71 years or older ($N = 367$). Second, the cohort was divided into three age groups according to the three EF categories based on European Society of Cardiology guidelines; reduced EF (rEF), mid-range EF (mrEF) and preserved EF (pEF). Continuous, normally distributed variables were summarised as mean ± standard deviation, and variables with non-normal distributions were summarised as median (interquartile range; IQR). Categorical data were reported as percentages. Group baseline characteristics were compared using an analysis of variance or Kruskal–Wallis analysis for non-normal distribution of continuous variables and the chi-square test for categorical variables. To examine the predictors of HF events, univariate and multivariate Cox regression analyses were performed including the VE/VCO_2 slope as a continuous variable. The interaction between age and the VE/VCO_2 slope was also tested. To determine

Table 1. Baseline characteristics of the three age groups according to the three ejection fraction categories.

	Total	rEF ($N=314$)				mrEF ($N=142$)				pEF ($N=1043$)			
	($N=1501$)	≤55 years ($N=112$)	56–70 years ($N=146$)	≥71 years ($N=56$)	*P* value	≤55 years ($N=55$)	56–70 years ($N=61$)	≥71 years ($N=26$)	*P* value	≤55 years ($N=264$)	56–70 years ($N=494$)	≥71 years ($N=285$)	*P* value
Age	61 ± 13	45 ± 7	62 ± 4	76 ± 4	<0.0001	46 ± 9	63 ± 4	76 ± 4	<0.0001	45 ± 9	63 ± 4	76 ± 4	<0.0001
Male (%)	74	88	84	75	0.122	87	90	81	0.489	75	72	56	<0.0001
BMI	23.4 ± 4.7	25.2 ± 4.9	23.7 ± 10.2	22.3 ± 3.1	0.063	23.9 ± 4.7	24.3 ± 3.1	22.2 ± 2.8	0.048	23.6 ± 3.5	23.4 ± 3.4	22.4 ± 3.3	0.001
AF (%)	22	11	20	29	0.014	15	30	23	0.128	9	28	31	<0.0001
HT (%)	51	41	53	66	0.008	38	66	65	0.006	31	54	62	<0.0001
DLP (%)	40	37	45	38	0.390	25	49	50	0.017	27	43	44	<0.0001
DM (%)	28	23	49	38	<0.0001	16	36	23	0.050	14	28	32	<0.0001
HU (%)	34	55	53	59	0.725	29	34	31	0.825	23	29	29	0.112
NYHA ≥II (%)	56	84	88	86	0.396	40	60	62	0.037	34	46	57	<0.0001
IHD (%)	31	16	32	39	0.002	20	38	50	0.016	23	32	39	<0.0001
CM (%)	28	81	67	48	<0.0001	67	54	31	0.008	19	11	9	<0.0001
Valvular disease (%)	44	31	38	46	0.154	27	30	50	0.103	45	46	51	0.280
LVEF (%)	56 ± 18	26 ± 8	27 ± 8	28 ± 7	0.092	46 ± 16	45 ± 3	45 ± 3	0.055	65 ± 8	66 ± 8	68 ± 8	<0.0001
eGFR ($ml/min/m^2$)	54 ± 17	52 ± 15	45 ± 16	42 ± 16	<0.0001	61 ± 16	49 ± 17	43 ± 9	<0.0001	64 ± 18	55 ± 16	51 ± 16	<0.0001
Hb (g/dl)	13.7 ± 1.7	14.5 ± 1.8	13.7 ± 1.9	12.9 ± 1.5	<0.0001	14.5 ± 1.4	13.7 ± 2.1	13.7 ± 1.5	0.064	14.1 ± 1.6	13.8 ± 1.5	12.9 ± 1.7	<0.0001
BNP (pg/ml)	148 (53, 357)	336 (103, 780)	431 (173, 1085)	406 (212, 882)	0.097	46 (13, 155)	194 (73, 586)	235 (109, 461)	<0.0001	47 (16, 135)	126 (51, 216)	153 (80, 298)	<0.0001
B-Blocker (%)	41	70	67	70	0.369	42	49	54	0.382	26	34	35	0.147

rEF: reduced ejection fraction; mrEF: mid-range ejection fraction; pEF: preserved ejection fraction; BMI: body mass index; AF: atrial fibrillation; HT: hypertension; DLP: dyslipidaemia; DM: diabetes mellitus; HU: hyperuricaemia; NYHA: New York Heart Association classification; IHD: ischaemic heart disease; CM: cardiomyopathy; LVEF: left ventricular ejection fraction; HF pEF: heart failure with preserved ejection fraction; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; BNP: brain natriuretic peptide.

Table 2. Exercise characteristics among the three age groups according to the three ejection fraction categories.

	Total	rEF ($N=314$)				mrEF ($N=142$)				pEF ($N=1043$)			
	Total ($N=1501$)	≤55 years ($N=112$)	56–70 years ($N=146$)	≥71 years ($N=56$)	*P* value	≤55 years ($N=55$)	56–70 years ($N=61$)	≥71 years ($N=26$)	*P* value	≤55 years ($N=264$)	56–70 years ($N=494$)	≥71 years ($N=285$)	*P* value
Peak VO_2 (ml/kg/min)	17.8 ± 6.2	18.0 ± 5.9	14.5 ± 4.5	12.2 ± 3.8	<0.0001	21.8 ± 6.7	16.5 ± 5.1	14.1 ± 3.2	<0.0001	23.1 ± 6.3	18.5 ± 5.4	14.4 ± 4.1	<0.0001
% Predicted peak VO_2	72 ± 23	66 ± 21	59 ± 18	54 ± 16	<0.0001	79 ± 23	68 ± 21	62 ± 14	0.001	86 ± 22	76 ± 22	62 ± 19	<0.0001
VE/VCO_2 slope	33.9 ± 8.4	32.1 ± 6.7	38.2 ± 9.7	41.6 ± 10.3	<0.0001	29.2 ± 8.8	34.1 ± 7.2	35.9 ± 7.4	<0.0001	29.3 ± 6.0	33.2 ± 7.1	37.6 ± 8.7	<0.0001
Rest HR (bpm)	78 ± 15	87 ± 14	81 ± 14	77 ± 15	<0.0001	83 ± 15	77 ± 15	74 ± 10	0.013	79 ± 14	76 ± 16	76 ± 14	0.015
Peak HR (bpm)	134 ± 32	144 ± 31	127 ± 27	113 ± 26	<0.0001	151 ± 33	132 ± 33	114 ± 22	<0.0001	152 ± 28	138 ± 34	121 ± 27	<0.0001
Rest SBP (mmHg)	120 ± 22	109 ± 22	110 ± 22	115 ± 23	0.287	121 ± 21	125 ± 25	124 ± 17	0.673	118 ± 21	123 ± 22	126 ± 22	<0.0001
Peak SBP (mmHg)	176 ± 38	162 ± 37	156 ± 40	148 ± 37	0.073	183 ± 41	178 ± 37	171 ± 33	0.454	186 ± 35	184 ± 37	173 ± 36	<0.0001
Peak RER	1.12 ± 0.09	1.13 ± 0.10	1.12 ± 0.10	1.06 ± 0.11	0.001	1.13 ± 0.08	1.11 ± 0.09	1.06 ± 0.02	0.015	1.15 ± 0.09	1.12 ± 0.08	1.08 ± 0.10	<0.0001
Peak RR (/min)	33.9 ± 7.6	33.7 ± 7.8	32.8 ± 7.7	31.8 ± 6.9	0.308	33.8 ± 8.2	32.4 ± 6.9	28.9 ± 6.4	0.023	35.7 ± 8.3	34.3 ± 7.4	33.4 ± 7.1	0.001
Peak VE (L/min)	48.8 ± 18.8	53.9 ± 18.6	44.4 ± 16.7	34.7 ± 11.1	<0.0001	58.4 ± 20.7	47.6 ± 15.7	36.0 ± 11.7	<0.0001	60.9 ± 19.8	49.9 ± 17.4	38.1 ± 13.9	<0.0001
Peak VT (ml)	1457 ± 466	1622 ± 450	1357 ± 394	1113 ± 279	<0.0001	1745 ± 434	1493 ± 395	1259 ± 329	<0.0001	1733 ± 440	1481 ± 446	1165 ± 389	<0.0001
Peak VT/BMI ($ml/m^2/kg$)		65.5 ± 18.3	58.9 ± 16.0	50.3 ± 12.1	<0.0001	73.9 ± 18.2	61.9 ± 17.5	56.8 ± 13.8	<0.0001	73.7 ± 17.3	63.7 ± 18.3	52.1 ± 15.9	<0.0001
EOV (%)		4	4	11	0.109	0	2	0	0.518	0	1	1	0.611

rEF: reduced ejection fraction; mrEF: mid-range ejection fraction; pEF: preserved ejection fraction; peak VO_2: peak oxygen consumption; VE/VCO_2 slope: the slope of minute ventilation to carbon dioxide output; HR: heart rate; SBP: systolic blood pressure; RER: respiratory exchange ratio; RR: respiratory rate; VE: minute ventilation; VT: tidal volume; BMI: body mass index; EOV: exertional oscillatory ventilation.

the cut-off value of the VE/VCO_2 slope and the sensitivity and specificity of the VE/VCO_2 slope for the endpoint in each age group, a receiver operating characteristic curve analysis was employed. Using the cut-off values of the VE/VCO_2 slope in each age group, the contribution of each binary VE/VCO_2 slope with the endpoint was evaluated using univariate and multivariate Cox regression models in each age group. The multivariate Cox regression model with a stepwise method in each of the three age groups was adjusted for eGFR, BNP, atrial fibrillation (AF) and peak VO_2. Kaplan–Meier curves for the endpoint were drawn according to the two groups divided based on each cut-off value of the VE/VCO_2 slope in each age group in the total cohort and the sub-EF categories. We did not assess the prognostic value of the VE/VCO_2 slope in mrEF because of a small number of the endpoints in mrEF.

Results

The clinical characteristics of the patients are summarised in Table 1. With an increase in age, more female patients, lower BMI, higher prevalence of AF, more atherosclerotic risks, higher prevalence of ischaemic heart disease, lower prevalence of cardiomyopathy, lower eGFR and higher BNP value were observed in the total and irrespective of EF.

Exercise characteristics are summarised in Table 2. Peak VO_2/% predicted peak VO_2 was reduced and the VE/VCO_2 slope increased with the increase in age. The average peak RER was 1.12, indicating sufficient exercise volume. Not only was peak VE but peak VT/peak VT corrected by BMI was also significantly lower in the highest age group in the total and irrespective of EF.

During 1512 (IQR 566–2749) days of median follow-up, 141 patients (9%) experienced HF events (≤55 years, 36 (8%); 56–70 years, 55 (8%); ≥71 years, 50 (14%), respectively, rEF, 77 (25%); mrEF, 11 (8%); pEF, 53 (5%), respectively).

Results of the univariate and multivariate Cox regression analyses for the total cohort are shown in Table 3, in which the continuous values of the VE/VCO_2 slope were included. The VE/VCO_2 slope, peak VO_2, eGFR, AF and BNP were significant predictors of HF events on univariate analysis. On multivariate analysis, peak VO_2 was the strongest predictor of risk in the total cohort. The interaction between age and the VE/VCO_2 slope (cont.) was statistically significant (P for interaction = 0.001 for the total, 0.07 for rEF (data not shown in the table), 0.07 for pEF (data not shown in the table)).

The area under the receiver operating characteristic curve for the VE/VCO_2 slope was significant for all three age groups in the total cohort (≤55 years, 0.624, 95% confidence interval (CI) 0.525–0.724, $P = 0.013$; 56–70 years, 0.697, 95% CI 0.622–0.771, $P < 0.0001$; ≥71 years, 0.705, 95% CI 0.629–0.781, $P < 0.0001$). The optimal prognostic threshold of the VE/VCO_2 slope was 32 in the age group 55 years or younger, 35 in the age group 56–70 years and 40 in the age group 71 years or older in the total. Similar positive relationships between age and the cut-off value were also found in rEF and pEF (Table 4).

Kaplan–Meier analysis dichotomised at the VE/VCO_2 slope prognostic thresholds in each age group in the total and the EF subcategories are displayed in Figure 1. Each threshold effectively discriminated between patients who were event free and those who had a HF event.

Multivariate Cox regression models containing the binary VE/VCO_2 slope were constructed for each age group in the total and the sub-EF categories (Table 4). There was a difference in the significance of predictability of the VE/VCO_2 slope. In the youngest age group, peak VO_2 was the most powerful predictor for HF

Table 3. Univariate and multivariate Cox regression analyses for heart failure events in the total cohort.

	Univariate		Multivariate		P for interaction VE/VCO_2 slope age
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	
VE/VCO_2 slope (cont.)	1.064 (1.048–1.080)	<0.0001	1.017 (0.994–1.042)	0.145	0.001
Peak VO_2	0.868 (0.838–0.900)	<0.0001	0.898 (0.855–0.943)	<0.0001	
eGFR	0.977 (0.967–0.987)	<0.0001	0.990 (0.979–1.001)	0.066	
BNP	1.000 (1.000–1.001)	<0.0001	1.000 (1.000–1.000)	0.249	
Age	1.020 (1.005–1.035)	0.008	0.984 (0.967–1.002)	0.076	
AF	1.573 (1.098–2.251)	0.013	1.271 (0.850–1.899)	0.242	

VO_2: peak oxygen consumption; VE/VCO_2 slope: the slope of minute ventilation to carbon dioxide output; CI: confidence interval; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; AF: atrial fibrillation.

Table 4. Univariate and multivariate Cox regression analyses for heart failure events in each age group according to the three ejection fraction categories.

Variables		Univariate				Multivariate			
	Total					Total			
Binary VE/VCO_2 slope	Hazard ratio (95% CI) *P* value	rEF	mrEF	pEF		Hazard ratio (95% CI) *P* value	rEF	mrEF	pEF
≤55 years	≥32 Total≥35 rEF≥33 pEF	2.52 (1.31–4.86) 0.006	2.41 (1.08–5.38) 0.032	NA	2.77 (0.66–11.60) 0.163	1.38 (0.61–3.08) 0.439	2.74 (1.19–6.27) 0.017	NA	4.39 (0.88–21.79) 0.070
56–70 years	≥35 Total≥37 rEF≥35 pEF	4.91 (2.71–8.88) <0.0001	2.70 (1.29–5.66) 0.008	NA	5.52 (1.94–15.66) 0.001	2.46 (1.26–4.80) 0.009	2.16 (1.25–5.49) 0.011	NA	2.75 (0.82–9.18) 0.100
≥71 years	≥40 Total ≥40 rEF ≥42 pEF	2.86 (1.63–5.04) <0.0001	6.06 (1.97–18.64) 0.002	NA	2.87 (1.35–6.08) 0.006	1.87 (0.93–3.75) 0.079 2.35* (1.22–4.53) <0.0001	5.86 (1.90–18.06) 0.002	NA	3.54 (1.62–7.74) 0.002

rEF: reduced ejection fraction; mrEF: mid-range ejection fraction; pEF: preserved ejection fraction; VO_2: peak oxygen consumption; VE/VCO_2 slope: the slope of minute ventilation to carbon dioxide output; CI: confidence interval; NA: not assessed.
*Adjusted for estimated glomerular filtration, brain natriuretic peptide, peak VO_2 and VE/VCO_2 slope (cat.).

event (hazard ratio (HR) 0.88, 95% CI 0.81–0.94), not the VE/VCO_2 slope (HR 1.38, 95% CI 0.61–11.60) in the total. In the 56–70 years group, the binary VE/VCO_2 slope was significantly predictive (HR 2.46, 95% CI 1.26–4.80), while slightly poor predictive power was found in the 71 years or older group (HR 1.87, 95% CI 0.93–3.75) under full adjustment, which was significant after adjustment excluding AF from covariates (HR 2.35, 95% CI 1.22–4.53) in the total cohort. In sub-EF categorical analysis, there was also varied significance of predictability. In the rEF category, the VE/VCO_2 slope was an independent predictor irrespective of age, but its HR was higher as age rises. On the other hand, in the pEF category, the prognostic significance of the VE/VCO_2 slope was shown in only the oldest age group.

Discussion

The main findings of this study were: (a) a positive relationship between age and the VE/VCO_2 slope, consistent with previous reports; (b) the VE/VCO_2 slope prognostic threshold differed according to age; (c) the predictive power of the VE/VCO_2 slope varied according to age, reinforced by the statistically significant interaction between age and the VE/VCO_2 slope for HF event. These results were consistent at least in rEF and pEF.

A positive relationship between age and the VE/VCO_2 slope has been reported in a healthy population, which included a few elderly individuals.[5–7] Although the exact reason for this remains unclear, it is well known that ageing can reduce the strength of respiratory muscles[12] and ventilation at maximal exercise.[7] The VE/VCO_2 slope is determined using the modified alveolar equation as follows: $863/(PaCO^2*(1 - VD/VT))$[13] (VD/VT; fraction of the tidal volume (VT) that goes to dead space (VD)). Based on this formula, the VE/VCO_2 slope increases in proportion to a decline in VT, which means failure of an increase in VT during exercise would be a cause of a high VE/VCO_2 slope. In fact, in this study, either peak VT or peak VT/BMI decreased with age in the total and regardless of EF (Table 2).

On the contrary, past studies showed that the elevated VE/VCO_2 slope in patients with HF is mainly contributed to by ventilation/perfusion mismatch due to reduced cardiac output and an increase in pulmonary vascular tone,[1,13,14] while the volume of increase in VT during exercise contributed only 30% of the VE/VCO_2 slope.[13,15] Most previous studies investigated patients with reduced EF and of a relatively younger age.

The cut-off values of the VE/VCO_2 slope varied among the three age groups in this study.

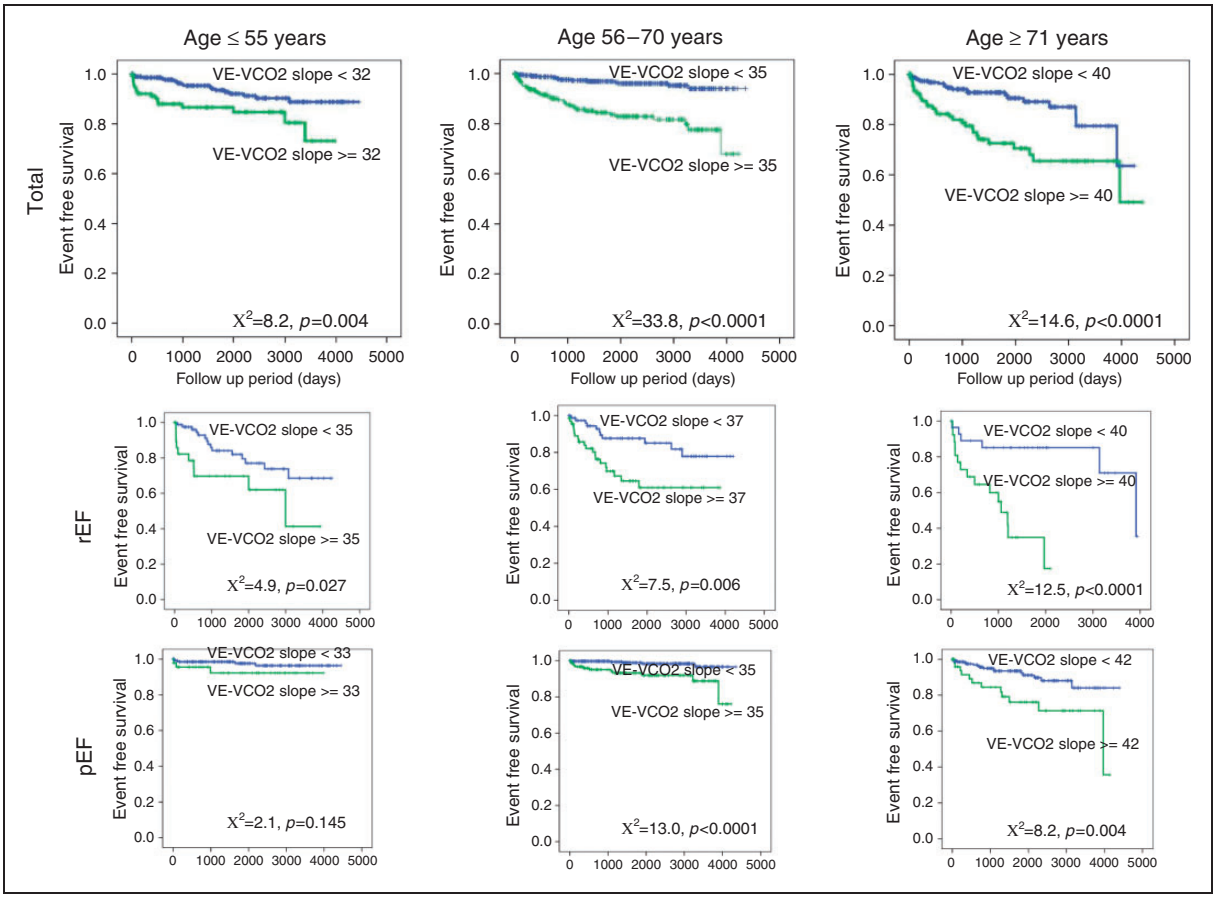

Figure 1. Kaplan–Meier analysis for heart failure event according to three age groups in the total, reduced ejection fraction and preserved ejection fraction.

The VE/VCO_2 slope is known to be a useful prognostic indicator[4,16,17] irrespective of EF. While the conventional cut-off value was set as 32–35, age has not been taken into account for it. Moreover, there are no reports of a comprehensive analysis consisting of a sufficient number of elderly patients, irrespective of EF, to understand the clinical impact of age on ventilatory efficiency in terms of the prognosis. In the present study including more elderly persons, the positive association of age with the cut-off value of the VE/VCO_2 slope was found in not only the total but also in rEF/pEF. A recent report on HF pEF with a mean age of 73 years demonstrated that the prognostic significance of the VE/VCO_2 slope is more evident in the group with the highest VE/VCO_2 slope of more than 38.4.[16] This indicates that the prognostic threshold of the VE/VCO_2 slope would be higher than the conventional cut-off, especially in elderly people, which supports our results.

In the present study, regardless of EF, there was a tendency towards a stronger impact of the VE/VCO_2 slope on the endpoints in older age. The significant interaction between age and the VE/VCO_2 slope for HF events was also found in not only the total but also the sub-EF categories. These results indicate that the prognostic significance of the VE/VCO_2 slope differs according to age across the HF patients in the present study. In terms of the prognostic predictability of CPET indices, many previous reports demonstrated the prognostic significance of the VE/VCO_2 slope, while some recent reports showed the less significant predictability of the VE/VCO_2 slope for mortality/heart transplantation[18–20] compared with exercise capacity. Sato et al.[20] recently demonstrated the prognostic power of the VE/VCO_2 slope was weaker than peak VO_2 irrespective of EF in a study with HF patients. The reason for this discrepancy in the predictive power of the VE/VCO_2 slope remains unclear. Further studies are necessary to analyse this apparently controversial topic considering an influence of age.

Beta-blockers should be considered an important factor influencing the VE/VCO_2 slope, because some previous studies reported that β-blocker intake can significantly reduce the VE/VCO_2 slope[21–23] in patients with HF. In the present study, however, there

was no difference in β-blocker use among the three age groups.

AF should also be considered a factor increasing the VE/VCO_2 slope.[24] Although its prevalence increased with an increment in age, the interaction between AF and the VE/VCO_2 slope for the endpoint was not significant (data not shown) in the total and irrespective of EF.

Several limitations should be acknowledged in the present study. First, there could be some selection bias in the analysis because the decision to perform CPET at the initial visit was at the physicians' discretion and the patients' preferences. Second, the patients' medication during the observation period was unknown. Third, the reproducibility of CPET data in this study was not confirmed. Finally, the actual prevalence of chronic obstructive lung disease as a comorbidity was unknown, because a lung function test was performed only as needed.

Despite these limitations, this is the first report demonstrating the varied relationship between the prognostic value of the VE/VCO_2 slope and age, and presenting different prognostic thresholds of the VE/VCO_2 slope according to age. The results of the present study, which analysed HF patients with demographically diverse backgrounds and included many elderly persons, would provide an additional aid for a clinical interpretation of the VE/VCO_2 slope when risk stratifying HF patients based on CPET.

Author contribution

YK and TY contributed to the conception or design of the work. YK, TY, SS, HS, TU, TA, NY, HK, SM, TO, YO, JY, ON and EH contributed to the acquisition, analysis, or interpretation of data for the work. YK, TY and SS drafted the manuscript. YK, SS and TY critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Declaration of conflicting interests

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