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Influence of Low Peak Respiratory Exchange Ratio on Cardiac Rehabilitation in Patients With Coronary Artery Disease

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Objective To compare and analyze the effects of cardiac rehabilitation (CR) in two groups based on the peak respiratory exchange ratio (RER_{peak}) 1.1 values using the exercise tolerance test (ETT) results, and to investigate the reasons for early termination of ETT.

Methods Patients with acute coronary syndrome who participated in CR exercise training were selected and all subjects underwent 6 weeks of CR exercise training. ETT was performed on a treadmill using a Modified Bruce Protocol before and after CR exercise training. According to the result of the first ETT, the subjects were divided into two groups: those with an $RER_{peak} \geq 1.1$ (n=33) and those with an $RER_{peak} < 1.1$ (n=22). We investigated the reasons for ETT termination and compared the effect of CR between the groups.

Results The reasons for the early termination of the first ETT in the $RER_{peak} < 1.1$ group were subjective dyspnea, abnormal cardiovascular responses, leg fatigue and other problems. After a 6-week CR, the peak oxygen consumption (VO_{2peak}) and ETT time increased, and the rate of perceived exertion (RPE) and RPP (rate pressure product) at stage 3 decreased in both the $RER_{peak} < 1.1$ and $RER_{peak} \geq 1.1$ groups.

Conclusion CR exercise training improved exercise capacity, not only in the $RER_{peak} \geq 1.1$ group, but also in the $RER_{peak} < 1.1$ group. This means that patients with a lower exercise tolerance could also benefit from the effects of CR. Thoughtful consideration to identify the direct and indirect causes for the early termination of ETT would be necessary to improve the efficiency of CR.

Keywords Coronary artery disease, Oxygen consumption, Rehabilitation, Exercise test

INTRODUCTION

Appropriate cardiac rehabilitation (CR) exercise training improves functional capacity and reduces mortality rates and the recurrence of acute coronary syndrome (ACS) [1]. The exercise tolerance test (ETT) is generally used as a preliminary test for diagnosing coronary artery disease; but, in the context of CR, it is conducted to assess patient function, determine the effects of recent treatments, including coronary intervention or cardiac surgery, evaluate prognosis, and obtain information regarding exercise prescription [2].

Of the various indicators obtained from ETT, peak oxygen consumption (VO_{2peak}) is an important prognostic factor that serves as an indicator of improved cardiopulmonary function after CR. However, the value of VO_{2peak} is inaccurate if the patient makes insufficient effort in the test or if the test is ended prematurely. This limitation requires the assessment of patient efforts in the ETT, and reaching an established requirement of 85% of the age-predicted maximal heart rate (HR). The method, however, has a lower accuracy due to a broad error range (±12 beats/min) and is difficult to apply, especially in patients using beta-blockers. Aside from HR, the respiratory exchange ratio (RER), defined as the ratio of carbon dioxide production (VCO_2) and oxygen consumption (VO_2) measured via respiratory gas analysis, is an objective indicator. It is considered the minimal sufficient condition when the peak RER (RER_{peak}; the RER value at the end of the test) is ≥1.10 [3].

Patients with a lower RER_{peak} might not reach the peak ETT value, and few research studies have investigated whether such patients show insufficient benefits from the CR program or have enhanced exercise tolerance because of the CR program. The aims of this study are to compare and analyze the effects of CR in two groups based on the RER_{peak} 1.1 values using the ETT results before and after CR training, investigate the reasons for ending the ETT in the two groups, and identify the effects of a lower peak RER on CR.

MATERIALS AND METHODS

Subjects

The medical records of subjects enrolled in the CR clinic between January 2012 and April 2014 were retrospectively analyzed. Subjects who participated in a CR program after undergoing successful percutaneous coronary intervention (PCI) with a drug-eluting stent, were recruited. Among them, patients who completed a 6-week CR program (a total of 18 sessions), and underwent ETT before and after CR, were chosen as study subjects. Patients with cerebrovascular disease, balance dysfunction, musculoskeletal disorders that limit gait, or changes in medications taken during the study period, were excluded from this study. Among the 81 participants who were chosen as subject candidates, 26 were excluded from the analysis due to incomplete medical records, including gas analyzing data and missing data of reasons for termination, etc. Therefore, a total of 55 subjects were ultimately selected as study subjects and divided into two groups according to the first ETT: those with an RER_{peak}<1.1 (n=33) and those with an RER_{peak}≥1.1 (n=22).

Each subject's age, sex, body mass index (BMI), left ventricular ejection fraction (LVEF), presence of cardiovascular (CV) risk factors (diabetes, hypertension, dyslipidemia, and/or heart failure [HF]), rate of myocardial infarction and unstable angina in ACS, and medications taken were collected.

Exercise testing

The first day that the patient visited the CR clinic after discharge, symptom-limited ETT was conducted using a Modified Bruce Protocol and VO_{2peak}, exercise time, resting HR, peak HR, resting blood pressure (BP), peak BP, rate pressure product (RPP), RER, and the rate of perceived exertion (RPE) were measured. A real-time recording 12-channel electrocardiograph (Q4500; Quinton Instrument Co., Boston, MA, USA), respiratory gas analyzer TrueOne 2400 metabolic measurement system (Parvo Medics Inc., East Sandy, UT, USA), an automatic blood pressure and pulse monitor Model 412 (Quinton Instrument Co.), and a treadmill MedTrack ST55 (Quinton Instrument Co.) were used for the ETT. All tests were terminated according to the American Heart Association (AHA) termination criteria and the patients were instructed about the termination of ETT before the test. When the test was close to the end, patients were encouraged to endure the test and to stop only when experiencing intolerable dyspnea, unless there was an event which met the ETT termination criteria from the AHA guidelines.

Exercise training

The patients participated in the CR program for 6 weeks. Exercise intensities of 40% and 85% HR reserve were calculated using the Karvonen formula—([maximal HR–resting HR×%intensity]+resting HR)—based on the results obtained during the first ETT. The CR program was composed of 10 minutes of warm-up (stretching), 40 minutes of main aerobic exercise, and 10 minutes of cool down, three times a week for 6 weeks, for a total of 18 sessions. Following the completion of the 6-week CR programs, ETT were performed again. VO_{2peak}, ETT time, resting HR, peak HR, resting BP, peak BP, RER, RPP, and RPE were measured again during the second ETT. The ETT results of the $RER_{peak}<1.1$ and $RER_{peak}≥1.1$ groups were then compared.

Statistical analyses

Statistical analyses were performed using the SAS ver. 4.2 statistical analysis program (SAS Institute Inc., Cary, NC, USA). The patients' sex, medication, rate of myocardial infarction and angina pectoris in coronary artery disease, presence of CV risk factors (diabetes, hypertension, dyslipidemia, and/or HF), and number of occluded coronary arteries were compared using the χ^2 test. The mean BMI, LVEF, age, ETT time, VO_{2peak}, resting HR, peak HR, peak RPP, RPP at stage 3 were compared by independent t-test. However, the peak RPE, and RPE at stage 3 were not normally distributed according to the Kolmogorov-Smirnov test or the Shapiro-Wilk test, and were analyzed using the Mann-Whitney U-test. Comparisons of the variables before and after CR were assessed by paired t-test. However, peak RPE were not normally distributed according to the Kolmogorov-Smirnov test or Shapiro-Wilk test, and were analyzed using the Wilcoxon signed-rank test. The reasons for ETT termination were recorded, and the frequency of each reason between groups was compared using the χ^2 test. The frequency of the reasons for terminating ETT before and after CR were compared using the McNemar test. To determine the presence of an interaction of time with the group in VO_{2peak}, a repeated-measure ANOVA model was performed. To determine the interaction in VO_{2peak} after adjusting different baseline demographic characteristics, a linear mixed model was performed. The p-values less than 0.05 were considered as statistically significant.

RESULTS

Subject demographic and clinical characteristics

The subjects' characteristics are presented in Table 1. The $RER_{peak}<1.1$ and $RER_{peak}≥1.1$ groups were similar for most variables, such as sex, medication taken, rate of myocardial infarction and unstable angina in ACS, presence of CV risk factors (diabetes, hypertension, dyslipidemia, and/or HF), and the number of occluded coronary arteries, with the exception of age and BMI. The average subject age in the $RER_{peak}<1.1$ group (66.6±8.0 years) was older than that of the subjects in the $RER_{peak}≥1.1$ group (61.4±7.2 years). The BMI of the $RER_{peak}<1.1$ group (25.4±3.7 kg/m^2) was higher than that of the $RER_{peak}≥1.1$ group (23.7±2.2 kg/m^2).

Comparison of the exercise parameters between groups

Table 2 shows the changes in exercise parameters between the groups before and after CR. In the first and second ETT, the mean resting HR, resting systolic and diastolic BP, peak systolic and diastolic BP, RPP at stage 3, and RPP peak were not different between the two groups. In the first ETT, the peak HR was 122±16 beats/min in the $RER_{peak}<1.1$ group and 140±20 beats/min in the $RER_{peak}≥1.1$ group. In the second ETT, the peak HR was 131±18 beats/min in the $RER_{peak}<1.1$ group and 146±17 beats/min in the $RER_{peak}≥1.1$ group. The intergroup difference of the peak HR was significant in the first and second ETT.

In the first ETT, the RPE at stage 3 was higher in the $RER_{peak}<1.1$ group (12.4±2.5) than $RER_{peak}≥1.1$ group (10.2±2.6). In the second ETT, the RPE at stage 3 in the $RER_{peak}<1.1$ group (10.2±2.6) was also higher than the $RER_{peak}≥1.1$ group (8.5±1.9). In the first ETT, VO_{2peak} was lower in the $RER_{peak}<1.1$ group (21.2±6.2 mL/kg/min) than $RER_{peak}≥1.1$ group (25.0±5.9 mL/kg/min). In the second ETT, the VO_{2peak} was also lower in the $RER_{peak}<1.1$ group (23.6±8.4 mL/kg/min) than the $RER_{peak}≥1.1$ group (29.6±5.9 mL/kg/min).

In the first ETT, RER_{peak} was lower in the $RER_{peak}<1.1$ group (1.00±0.06) than the $RER_{peak}≥1.1$ group (1.17±0.07). In the second ETT, the RER_{peak} was also lower in the $RER_{peak}<1.1$ group (1.08±0.09) than in the $RER_{peak}≥1.1$ group (1.15±0.12).

In the first ETT, the exercise time was shorter in the $RER_{peak}<1.1$ group (676±195 seconds) than the $RER_{peak}≥1.1$

Table 1. Subjects' baseline demographic characteristics

Characteristic	RER$_{peak}$<1.1 (n=33)	RER$_{peak}$≥1.1 (n=22)	p-value
Age (yr)	66.6±8.0	61.4±7.2	0.016*
Sex (male:female)	16:17	15:7	0.149
BMI (kg/m^2)	25.4±3.7	23.7±2.2	0.047*
LVEF (%)	57.53±13.43	56.46±14.27	0.778
Diagnosis			
UA	15 (45.5)	11 (50.0)	0.741
AMI	18 (54.5)	11 (50.0)	0.741
DM	11 (33.3)	7 (31.8)	0.907
Hypertension	22 (66.7)	12 (54.5)	0.365
HF	3 (9.1)	3 (13.6)	0.596
No. of diseased vessels			0.465
One	15 (45.5)	10 (45.5)	
Two	13 (39.4)	6 (27.3)	
Three	5 (15.2)	6 (27.3)	
Dyslipidemia	5 (15.2)	4 (18.2)	0.766
Medication			
Aspirin	33 (100)	22 (100)	1
Plavix	33 (100)	22 (100)	1
Statin	32 (97.0)	22 (100)	0.332
BB	25 (75.8)	14 (63.6)	0.332
CCB	7 (21.2)	9 (40.9)	0.115
ACEI	9 (27.3)	7 (31.8)	0.716
ARB	10 (30.3)	2 (9.1)	0.062
Nitrate	19 (57.6)	15 (68.2)	0.428
Diuretics	5 (15.2)	1 (4.5)	0.216

Values are presented as mean±standard deviation or number (%).

RER$_{peak}$, peak respiratory exchange ratio; BMI, body mass index; LVEF, left ventricular ejection fraction; UA, unstable angina; AMI, acute myocardial infarction; DM, diabetes mellitus; HF, heart failure; BB, beta-blocker; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

*p<0.05 (RER$_{peak}$<1.1 vs. RER$_{peak}$≥1.1).

group (872±150 seconds). In the second ETT, the exercise time was shorter in the RER$_{peak}$<1.1 group (845±163 seconds) than the RER$_{peak}$≥1.1 group (978±116 seconds).

Comparison of the exercise parameters before and after CR

The mean resting HR, resting systolic and diastolic BP, peak systolic and diastolic BP, and RPE$_{peak}$ in each group were not different before, versus after CR.

The peak HR and RPP peak were increased in the RER$_{peak}$<1.1 group during CR, but it did not differ from that of the RER$_{peak}$≥1.1 group.

RPE at stage 3 was decreased during CR in the RER$_{peak}$<1.1 and RER$_{peak}$≥1.1 groups. The RPP at stage 3 decreased from 15,994±3,961 to 13,628±4,471 in the RER$_{peak}$<1.1 group and from 14,779±3,846 to 13,079±3,602 in the RER$_{peak}$≥1.1 group, during CR. There was a significant increase in exercise time in both groups following the 6-week CR exercise training.

After the 6-week CR exercise training, the VO$_{2peak}$ values were increased in both groups (p<0.01). No VO$_{2peak}$ interaction of time by group was identified by repeated-measures ANOVA, and the rate of change of VO$_{2peak}$ did not differ between the two groups. Also, after adjusting the age and BMI by the linear mixed model, the interaction of time and group of the VO$_{2peak}$ was not significant.

Table 2. Exercise parameters pre- vs. post-cardiac rehabilitation

Parameter		$RER_{peak}<1.1$	$RER_{peak}\geq1.1$
HR_{rest} (beats/min)	ETT_I	67.4±9.6	66.9±13.0
	ETT_{II}	66.9±12.0	66.9±10.3
HR_{peak} (beats/min)	ETT_I	121.6±15.8	139.9±20.1[b]
	ETT_{II}	130.6±17.9[a]	145.7±16.7[b]
SBP_{rest} (mmHg)	ETT_I	119.1±16.4	119.3±17.4
	ETT_{II}	119.4±14.3	119.6±20.6
DBP_{rest} (mmHg)	ETT_I	74.1±7.4	76.5±9.6
	ETT_{II}	75.6±6.9	75.6±9.1
SBP_{peak} (mmHg)	ETT_I	164.9±33.4	166.4±33.3
	ETT_{II}	170.6±36.4	170.4±33.4
DBP_{peak} (mmHg)	ETT_I	77.7±14.6	74.8±9.8
	ETT_{II}	80.5±13.1	74.1±13.4
ETT time (s)	ETT_I	675.8±195.1	872.0±149.6[b]
	ETT_{II}	845.2±163.2[a]	978.1±115.9[a,b]
VO_{2peak} (mL/kg/min)	ETT_I	21.2±6.2	25.0±5.9[b]
	ETT_{II}	23.6±8.4[a]	29.6±5.9[a,b]
ΔVO_{2peak} (%)	ETT_I	-	-
	ETT_{II}	11.32	15.54
RPP at stage 3	ETT_I	15,994±3,961	14,779±3,846
	ETT_{II}	13,628±4,471[a]	13,079±3,602[a]
RPE at stage 3	ETT_I	12.4±2.5	10.2±2.6[b]
	ETT_{II}	10.2±2.6[a]	8.5±1.9[a,b]
RPP_{peak}	ETT_I	20,264±5,565	25,802±15,408
	ETT_{II}	22,949±4,802[a]	24,938±6,105
RPE_{peak}	ETT_I	16.9±0.4	16.7±0.7
	ETT_{II}	16.8±0.6	16.9±0.4
RER_{peak}	ETT_I	1.00±0.06	1.17±0.07[b]
	ETT_{II}	1.08±0.09[a]	1.15±0.12[b]

Values are presented as mean±standard deviation.

RER_{peak}, peak respiratory exchange ratio; HR_{rest}, resting heart rate; HR_{peak}, peak heart rate; SBP_{rest}, resting systolic blood pressure; DBP_{rest}, resting diastolic blood pressure; SBP_{peak}, peak systolic blood pressure; DBP_{peak}, peak diastolic blood pressure; ETT, exercise tolerance test; ETT_I, first ETT; ETT_{II}, second ETT; VO_{2peak}, peak oxygen uptake; ΔVO_{2peak}, improvement rate of VO_{2peak}; RPP, rate pressure product; RPE, rate of perceived exertion.

[a]$p<0.05$ (ETT_I vs. ETT_{II}), [b]$p<0.05$ ($RER_{peak}<1.1$ vs. $RER_{peak}\geq1.1$).

After the 6-week CR exercise training, the RER_{peak} changed significantly from 1.00±0.06 to 1.08±0.09 in the $RER_{peak}<1.1$ group, however in the $RER_{peak}\geq1.1$ group the RER_{peak} did not differ during CR (1.17±0.07 to 1.15±0.12).

Analysis of ETT termination reasons

The reasons for ETT termination are shown in Table 3. In the first ETT, the subjects in the $RER_{peak}<1.1$ group ceased the ETT due to subjective dyspnea, without an ab-normal response (n=15; 45.5%), abnormal CV response, such as hypertensive response, ST elevation, and/or ST depression (n=6; 18.2%), other problems such as headache, dizziness, difficulty keeping a hard grasp, and back pain (n=5; 15.2%), leg fatigue (n=4; 12.1%), inability to keep treadmill pace (n=2; 6.1%), and cardiac origin chest discomfort (n=1; 3%). In the second ETT, the subjects in the $RER_{peak}<1.1$ group stopped the ETT due to subjective dyspnea without an abnormal response (n=23; 69.7%),

Table 3. Reasons for termination of exercise tolerance test (ETT)

Group	Reasons for termination	ETT$_I$	ETT$_{II}$
RER$_{peak}$<1.1 (n=33)	Dyspnea without abnormal response	15 (45.5)	23 (69.7)[a]
	Leg fatigue	4 (12.1)	6 (18.2)
	Unable to keep treadmill pace	2 (6.1)	2 (6.1)
	Abnormal cardiovascular response	6 (18.2)[b]	2 (6.1)
	Cardiac origin chest discomfort	1 (3)	-
	Other problems	5 (15.2)	-
RER$_{peak}$≥1.1 (n=22)	Dyspnea without abnormal response	14 (63.6)	16 (72.7)
	Leg fatigue	4 (18.2)	4 (18.2)
	Unable to keep treadmill pace	2 (9.1)	-
	Abnormal cardiovascular response	-	1 (4.5)
	Cardiac origin chest discomfort	1 (4.5)	1 (4.5)
	Other problems	1 (4.5)	-

Values are presented as number (%).
Abnormal cardiovascular response according to the termination criteria of exercise testing (American College of Cardiology/American Heart Association 2002 guideline for exercise testing), e.g., decreased systolic blood pressure, hypertensive response, ST elevation, ST depression; other problems included headache, dizziness, difficulty grasping, and back pain.
RER$_{peak}$, peak respiratory exchange ratio; ETT$_I$, first ETT; ETT$_{II}$, second ETT.
[a]p<0.05 (ETT$_I$ vs. ETT$_{II}$), [b]p<0.05 (RER$_{peak}$<1.1 vs. RER$_{peak}$≥1.1).

leg fatigue (n=6; 18.2%), inability to keep treadmill pace (n=2; 6.1%), and an abnormal CV response (n=2; 6.1%). In RER$_{peak}$<1.1 group, the number of patients who ceased due to subjective dyspnea without an abnormal response was increased during CR (p<0.05).

In the RER$_{peak}$≥1.1 group, the patients stopped the ETT due to subjective dyspnea without an abnormal response (n=14; 63.6%), leg fatigue (n=4; 18.2%), inability to keep treadmill pace (n=2; 9.1%), cardiac origin chest discomfort or pain (n=1; 4.5%), or other problems (n=1; 4.5%) in the first ETT. In the second ETT, patients in the RER$_{peak}$≥1.1 group stopped the ETT due to subjective dyspnea without abnormal response (n=16; 72.7%), leg fatigue (n=4; 18.2%), cardiac origin chest discomfort or pain (n=1; 4.5%), and abnormal CV response (n=1; 4%). In the first ETT, more patients stopped ETT due to an abnormal CV response in the RER$_{peak}$<1.1 group than in the RER$_{peak}$≥1.1 group, whereas there was no intergroup difference in the number of patients who stopped the first and second ETT due to other reasons.

Comparison of RER$_{peak}$ before and after CR as classified by RER$_{peak}$=1.1

As for the changes in the RER$_{peak}$ between the pre- and

Table 4. Changes in RER$_{peak}$ before and after cardiac rehabilitation

Group	ETT$_I$	ETT$_{II}$
RER$_{peak}$<1.1 (ETT$_I$) (n=33)	1.00±0.06	1.08±0.09[a]
RER$_{peak}$≥1.1 (ETT$_I$) (n=22)	1.17±0.07[b]	1.15±0.12[b]
RER$_{peak}$<1.1 (ETT$_{II}$) (n=27)	1.04±0.1	1.02±0.05
RER$_{peak}$≥1.1 (ETT$_{II}$) (n=28)	1.10±0.12[b]	1.19±0.08[a,b]

Values are presented as mean±standard deviation.
RER$_{peak}$, peak respiratory exchange ratio; ETT, exercise tolerance test; ETT$_I$, first ETT; ETT$_{II}$, second ETT.
[a]p<0.05 (ETT$_I$ vs. ETT$_{II}$), [b]p<0.05 (RER$_{peak}$<1.1 vs. RER$_{peak}$≥1.1).

post-CR, the RER$_{peak}$<1.1 group showed an increased RER$_{peak}$ (1.00–1.08) after CR, but the RER$_{peak}$≥1.1 group did not show any difference (1.17–1.15) when the subjects were classified using the first ETT. We saw subjects whose RER$_{peak}$ was <1.1 in the second test after CR; in order to identify the patients' characteristics, they were classified using RER$_{peak}$=1.1 in the second test. When RER$_{peak}$=1.1 served as the criterion at the second test, the RER$_{peak}$ values of the RER$_{peak}$<1.1 group (n=27) did not differ be-

tween the pre- and post-CR (1.04–1.02), whereas that of the RER$_{peak}$≥1.1 group (n=28) was increased after the CR (1.10–1.20) (Table 4).

DISCUSSION

ETT is widely used to assess various patients with cardiac disease, estimate its severity, assess patient function and prognosis, determine the effects of various CR treatments, and obtain information about exercise prescriptions [2]. The resulting test values are affected, depending on the subjects' abilities to reach sufficient exercise intensity levels. The RER is used as an objective measure to determine whether a person sufficiently achieves their maximal functional capacity. The RER is defined as the ratio of VCO$_2$ and VO$_2$, with values of 0.7–0.8 at a lower exercise level, 1.0 at a moderate exercise level, and 1.1–1.3 at a high exercise level [4]. If the RER$_{peak}$ exceeds 1.0, additional energy is supplied anaerobically, during which induced metabolic acidosis occurs, to increase VCO$_2$ [5]. Previous studies have usually focused on the importance of the RER$_{peak}$ in ETT in the context of HF because patients with HF generally have difficulty reaching RER≥1.0 during ETT, in such cases, the test results are deemed insufficient for estimating prognosis. Rostagno et al. [6] reported that one-third of patients with HF were unable to reach the minimal sufficiency requirement (e.g., RER≥1.10).

Based on the existing guideline, RER$_{peak}$=1.10 is the minimum effort requirement for ETT [3]. In Chase et al. [7], in which 1,728 patients with HF served as subjects, while an RER$_{peak}$≥1.05 was the indicator of maximum effort of the patients. The authors determined that the RER$_{peak}$≥1.00 was likely to be acceptable and RER$_{peak}$<1.00 was unacceptably submaximal [7]. Previous reports [8–11] determined that RER$_{peak}$≥1.00 was the indicator of proper effort from HF patients. Meanwhile, the guideline of the AHA on ETT considered RER$_{peak}$≥1.10 the maximal functional capacity of patients [12], a guideline that we followed in this study since we used RER$_{peak}$=1.10 as the requirement.

The demographic data of the two groups, the RER$_{peak}$<1.1 group showed a higher age and BMI than the RER$_{peak}$≥1.1 group, indicating that the two factors affected the RER$_{peak}$. Other demographic data and CR program processes were found to be identical between the two groups.

In a comparison of the two groups, the peak HR, RPE at stage 3, VO$_{2peak}$, RER$_{peak}$, and exercise time were different between the two groups, in both the first and second ETT. As the subjects in the RER$_{peak}$≥1.1 group showed more sufficient effort on the ETT, it was shown as a longer exercise time, higher peak HR, and a higher VO$_{2peak}$ than the RER$_{peak}$<1.1 group. As the RPE at stage 3 was lower in the RER$_{peak}$≥1.1 group than the RER$_{peak}$<1.1 group, the subjects in the RER$_{peak}$≥1.1 group were more tolerable to submaximal effort exercise than the RER$_{peak}$<1.1 group.

After the 6-week CR, both groups showed a higher VO$_{2peak}$ than that of the first ETT. The RPE at stage 3 in both groups decreased from pre- to post-CR exercise training, indicating improved subjective functional capacity in the submaximal effort. The RPP at stage 3 in both groups also decreased after CR, indicating that the RPP in the submaximal effort decreased and the resistance of cardiac function against exercise increased. No interactions in VO$_{2peak}$ between the two groups were identified by repeated-measure ANOVA, and, using the linear mixed model to adjust the age and BMI indicating that there was no difference in the change in the rate of VO$_{2peak}$. The effects of the CR were expected to be relatively lower in the RER$_{peak}$<1.1 group due to their lower exercise tolerance, but the change in rate in VO$_{2peak}$ did not differ between groups, indicating that the effects of CR were similar between groups.

While the RER$_{peak}$ is estimated in the ETT, the reasons for ETT ending are also recorded to identify abnormal reactions, such as dizziness, cyanosis, and chest pain to identify risk factors such as decreased BP or arrhythmia and identify whether there are factors, such as knee pain or claudication that inhibit achieving the maximal functional capacity. When such limiting factors are identified, a more accurate ETT can be conducted using pain control, changing exercise methods, and/or customizing the exercise prescription based on the patient's condition. When other abnormal reactions do not occur, the ETT is continued until the patient almost achieves the maximal cardiopulmonary functional capacity and is only stopped when subjective dyspnea occurs. For both groups in the first and the second ETT rounds, the most common reason for stopping the ETT was dyspnea without an abnormal response (Table 3). In the first ETT of the RER$_{peak}$<1.1 group, the second most common reason for stopping the test was abnormal CV response and

other problems, whereas in the second ETT, the second most common reason for stopping the test was leg fatigue in both groups. Such results may be due to inappropriate hemodynamic reactions or arrhythmias that were more common in the first test and various other reasons for stopping the exercise, such as headache and back pain that occurred because of a general deconditioning. Although the $RER_{peak} \geq 1.1$ group stopped the ETT when subjects reached the sufficient exercise effort requirement, 7 (36%) subjects stopped the ETT due to of reasons other than dyspnea, indicating that one third of the group could reach the RER_{peak} of 1.1, even for reasons other than dyspnea. Meanwhile, the $RER_{peak} < 1.1$ group stopped the exercise without reaching the exercise effort requirement, and only 15 (45.5%) subjects stopped the test due to dyspnea without an abnormal response in the first ETT. The number of subjects that stopped the second ETT because of dyspnea without an abnormal response increased from 15 to 23 (69.7%) in the $RER_{peak} < 1.1$ group ($p < 0.05$). We stopped the ETT when the absolute or relative termination criteria [13] of the AHA regarding patient safety were met. In the $RER_{peak} < 1.1$ group, an abnormal CV response was the second most common reason for stopping the test before CR; in contrast, it was the third most common reason for stopping the test (after dyspnea and leg fatigue) after CR.

Previous research of RER and cardiac disease has usually focused on the RER_{peak} values of HF patients [7,8] rather than the peak RER, however the submaximal RER is important for a proper understanding of the relevance of ETT and the significance of RER after exercise training. Submaximal RER is affected by functional capacity; subjects whose physical activities were vigorous who were undergoing exercise training showed a lower RER at submaximal exercise intensity compared with those who were not [14,15]. Additionally, endurance training improves the activities of oxidizing enzymes, delaying the time to reach fatigue during exercise, lowering the submaximal RER [16], indicating that a lower RER alone does not necessarily indicate a lower functional capacity, but that the subject does not reach his/her personal maximal exercise effort. A lower RER_{peak} in ETT is usually considered as a lower functional capacity, but if the test is stopped prematurely, the termination might not be attributable to the maximal RER reached, but instead to the patient's submaximal RER. This is why it is important to identify the reason for ETT termination. When ETT was conducted in our CR clinic, some factors indirectly affect termination. First, most patients complained of discomfort and stuffiness when wearing a face mask for gas analysis, saying, "I could do more exercise without this mask." Although all subjects wore face masks, the discomfort and adaptability varied subjectively among subjects. Second, patients who had recently overcome cardiac events usually stopped the test because of chest discomfort, dyspnea, or other symptoms that can be generally endured, due to "fear of another cardiac event." Third, some subjects terminated the test even when objective indicators, such as HR or RER_{peak}, were not high enough, because they were presumed to have subjectively lower thresholds for dyspnea.

The $RER_{peak} < 1.1$ group in the first ETT criterion generally increased the RER_{peak} post-CR (1.00–1.08). The mean value of the $RER_{peak} < 1.1$ group in the second ETT criterion, which did not differ even post-CR (1.04–1.02), indicating that some of the subjects in the $RER_{peak} < 1.1$ group consistently showed a maintained value, even following a 6-week CR exercise training. These phenomena may be due to various direct or indirect factors. It is our opinion that factors affecting RER_{peak} measurement include, not only situations in ETT as mentioned above, but also individual subject characteristics. As the RER is the ratio of VCO_2 and VO_2 it may be influenced by multi-organ systems, such as the cardiopulmonary system, vascular system, and the muscular system. Thus, subject characteristics, such as age, sex, BMI, drinking history, smoking history, exercise habits, pulmonary function, muscular, vascular, nervous system, psychological factors, and patient motivation, may influence the RER_{peak} under the same ETT protocol.

In this study, the $RER_{peak} < 1.1$ group had a higher mean age and BMI, but no intergroup difference was found in terms of sex and history of drug use. Patients with musculoskeletal and nervous diseases that inhibit gait were excluded from this study. In contrast, drinking history, smoking history, and exercise habit were not investigated, and an estimation of the various causes of lower exercise tolerance, such as mild osteoarthritis, diabetic neuropathy, dysfunction by old age, muscular strength declines, and pulmonary or vascular system dysfunction, was insufficient or difficult. Song et al. [17] reported that patients with accompanying depression showed a lower

functional capacity and more frequent dyspnea upon exercising; however, in this study, we did not estimate the psychological factors or motivation. By comparison, according to Chase et al. [7], the $RER_{peak}<1.0$ group had a higher mean age than the $RER_{peak}>1.0$ group, and according to Ingle et al. [18], the $RER_{peak}<1.0$ group included a higher proportion of women.

This study had several limitations: its number of subjects was relatively small, we did not identify patient characteristics and psychological status and could not correlate the difference in RER_{peak} or VO_{2peak} with psychological factors; and only short-term changes could be identified due to a limited CR duration of 6 weeks. As such, further studies are needed to understand the possible correlation between psychological status and lower RER_{peak} through a psychological evaluation of motivation or depressive symptoms and the assessment of individual subjects' characteristics on a more multilateral basis. Further investigations on the indirect factors affecting ETT termination may be helpful to improve the clinical usefulness of RER_{peak}.

In conclusion, we observed that the reasons for early termination of the first ETT in the $RER_{peak}<1.1$ group were subjective dyspnea without an abnormal response, an abnormal CV response, other problems, and leg fatigue (in decreasing order). A 6-week CR exercise training could increase the VO_{2peak} and ETT time and decrease the RPE and RPP at stage 3 in both $RER_{peak}<1.1$ and $RER_{peak}\geq1.1$ groups. Thoughtful consideration of how to best identify the direct and indirect causes for early termination of ETT would be required to improve the efficiency of CR exercise training, especially in patients with an $RER_{peak}<1.1$.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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