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Effects of Respiratory Exchange Ratio on the Prognostic Value of Peak Oxygen Consumption and Ventilatory Efficiency in Patients With Systolic Heart Failure

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Abstract

Objectives—The purpose of this analysis was to evaluate the prognostic characteristics of peak oxygen consumption (Vo_2) and the minute ventilation/carbon dioxide (VE/VCO_2) slope of different peak respiratory exchange ratios (RERs) obtained from cardiopulmonary exercise testing in patients with heart failure (HF).

Background—For patients with HF, peak VO_2 and the VE/VCO_2 slope are used for assessing prognosis. Peak VO_2 is assessed in association with peak RER ≥1.10, indicating maximal effort and prognostic sensitivity. Conversely, the VE/Vco_2 slope provides effort-independent prognostic discrimination.

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Methods—Patients with HF scheduled to undergo cardiopulmonary exercise testing were enrolled. Patients were subclassified by peak RER (RER <1.00, RER 1.00 to 1.04, RER 1.05 to 1.09, RER ≥1.10) and followed for up to 3 years for major cardiac-related events (death, left ventricular assist device implantation, or cardiac transplantation).

Results—Included were 1,728 patients with HF (75% males; 40% ischemic etiology; age: 55 ± 14 years; left ventricular ejection fraction: 28 ± 10%). Two hundred seventy major events occurred, with no proportional differences across the RER subgroups. Multivariate Cox regression analysis indicated that the VE/VCO_2 slope and peak VO_2 remained prognostic within each subgroup; the VE/VCO2 slope remained the strongest predictor. Receiver-operating characteristic analysis demonstrated equitable prognostic cutoffs for the VE/VCO_2 slope (range: 34.9 to 35.7; area under the curve [AUC] range: 0.69 to 0.75) and peak Vo_2 (range: 13.8 to 14.0 $ml \cdot kg^{-1} \cdot min^{-1}$; AUC range: 0.68 to 0.75).

Conclusions—Peak VO_2 provided a sensitive assessment of prognosis in patients with HF in all RER subgroups. The VE/VCO_2 slope provided greater prognostic discrimination in all RER subgroups. Clinical consideration may be warranted for patients with low RER, low peak Vo_2, and an elevated VE/Vco_2 slope.

Keywords

cardiopulmonary exercise test; heart failure; respiratory exchange ratio

Peak oxygen consumption (VO_2) is a primary cardiopulmonary exercise testing (CPX) parameter for assessing prognosis in patients with heart failure (HF). Peak VO_2 cutoffs ranging from 10 to 14 $ml \cdot kg^{-1} \cdot min^{-1}$ have been reported as appropriate for cardiac transplant candidacy (1–4). Major criticisms of peak VO_2 are that it is effort dependent and highly influenced by patient motivation (5,6). While several criteria exist for assessing maximal exercise effort, the peak respiratory exchange ratio (RER) is used as an objective criterion of effort (7,8). Based on current guidelines, peak RER ≥1.10 is accepted to be indicative of maximal effort (9–11). Unfortunately, findings from the large cohort undergoing CPX in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcome of Exercise Training) study (12) suggest that as many as 50% of patients with HF are unable to achieve a peak RER ≥1.10. Considering these limitations, effort-independent parameters, such as the minute ventilation/carbon dioxide production (VE/Vco_2) slope, have emerged. The VE/Vco_2 slope is an independent predictive index of prognosis in patients with HF (13,14) and appears to provide a higher level of prognostic resolution compared with peak Vo_2 (13–15). The VE/Vco_2 slope has demonstrated high reproducibility, is less affected by irregular breathing, and is less dependent on patient motivation (16).

The influence of patients' effort on the clinical utility of CPX variables has been previously assessed (1,8,16), but analyses have lacked the sample size necessary to address the influence of a broad range of patient effort with appropriate statistical power. Thus, the purpose of this analysis was to evaluate the prognostic characteristics of peak VO_2 and the VE/Vco_2 slope of different peak RERs obtained from CPX in a large, multicenter HF cohort.

Methods

This analysis was performed as a part of an HF consortium, a multicenter analysis that included patients with HF scheduled to undergo routine CPX (http://www.cardiology.org/projects_heart.html). The participating CPX laboratories include San Paolo Hospital, Milan, Italy; LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina; Stanford University, Palo Alto, California; VA Palo Alto Health Care System, Palo Alto, California; Brigham and Women's Hospital, Boston, Massachusetts; and Virginia Commonwealth University, Richmond, Virginia. Of 2,661 patients in the registry, 1,728 patients were included in this analysis. Inclusion criteria consisted of a diagnosis of HF (17) and evidence of left ventricular systolic dysfunction on 2-dimensional echocardiography obtained within 1 month of CPX (patients in the registry with a left ventricular ejection fraction ≥45% were excluded from analysis). Patients with a diagnosis of significant pulmonary disease (maintained on home oxygen therapy for lung disease and/or inhaled corticosteroids) are excluded from the registry. All patients completed a written informed consent form, and institutional review board approval was obtained at each institution.

Symptom-limited CPX was performed in all subjects utilizing progressive CPX protocols at all centers. Ventilatory expired gas analysis was performed using a metabolic cart (Medgraphics CPX-D and Ultima, Minneapolis, Minnesota; Vmax29, Sensormedics, Yorba Linda, California; or TrueOne 2400, Parvomedics, Sandy, Utah), as reported previously (18,19). Before each test, the equipment was calibrated in standard fashion. VE, Vo_2, and Vco_2 were acquired breath by breath and averaged over 10–s intervals. Peak Vo_2 and peak RER were expressed as the highest 10–s averaged sample obtained during the last 20 seconds of testing. VE and Vco_2 values, acquired from the initiation of exercise to peak (shown to be the optimal prognostic method [15]), were entered into spreadsheet software (Microsoft Excel, Microsoft Corporation, Bellevue, Washington) to calculate the VE/Vco_2 slope via least-squares linear regression ($y = mx + b$; m = slope).

Patients were followed up for major cardiac-related events (death, left ventricular assist device implantation, urgent heart transplantation) via medical chart review for up to 3 years or to first event. Follow-up was conducted by the HF program at each institution, which provided a high likelihood that all events were captured. All CPX and follow-up data were collected and reported by the individual centers.

Statistical analysis

Initially, patients were stratified into peak RER subgroups based on the ≥1.10 cutoff. Patients with a peak RER <1.10 were then subclassified based on the following peak RER cutoffs: 1.05 to 1.09, 1.00 to 1.04, and <1.00. These cutoffs were pre-determined on the basis of the existing literature. That is, several large-scale, multicenter studies involving patients with HF consider an acceptable "maximal" cutoff to be a RER ≥1.05 (20–22). The third subgroup was derived from recommendations suggesting that a peak RER ≥1.00 is likely acceptable (10,11). Lastly, all of the literature considered a peak RER <1.00 to be unacceptably submaximal, and this cutoff was used to define the fourth subgroup.

Log-rank testing was performed to determine the distribution of major cardiac-related events across the peak RER subgroups. Chi-square analysis was performed for all other categorical data. All data for continuous variables are presented as mean values ± SD, and categorical variables, as number (%). One-way analysis of variance (ANOVA) was performed for continuous data on key baseline and exercise variables across the peak RER subgroups. The Tukey honestly significant difference test was performed when findings on ANOVA were significant. Univariate and multivariate Cox regression analyses were performed on data from the entire cohort and from each peak RER subgroup. For the entire cohort and each subgroup, when peak Vo_2 or the VE/Vco_2 slope was found to be a univariate predictor on Cox regression analysis, receiver-operating characteristic (ROC) curve analysis was performed to determine an optimal prognostic cutoff. The ideal cutoff was determined on the basis of the value with the most even balance between sensitivity and specificity. A statistical software package (SPSS version 19.0, IBM SPSS Statistics, IBM Corporation, Armonk, New York) was used to perform all of the aforementioned analyses. A p value <0.05 was considered significant for all analyses.

Results

Included were 1,728 patients with HF (75% males; 40% ischemic etiology;age: 55 ± 14 years; left ventricular ejection fraction: 28 ± 10%) scheduled to undergo CPX. Two hundred seventy major cardiac-related events occurred during the follow-up period (163 deaths, 39 left ventricular assist device implantations, and 68 transplantations). The overall group and subgroup baseline and CPX information are presented in Table 1. The mean peak RERs of the subgroups were significantly different from one another, suggesting an appropriate differentiation of groups. The peak RER <1.00 subgroup had a greater mean age than did the subgroups with the 2 highest peak RERs, and had a lower rate of prescribed beta-blocker and diuretic agents than did the peak RER ≥1.10 subgroup. Peak Vo_2 and peak heart rate achieved were significantly lower in the peak RER <1.00 subgroup compared with those in the highest 2 peak RER subgroups. However, the percentage of the age-predicted maximum heart rate was significantly different only between the lowest and highest peak RER subgroups. Table 1 demonstrates an even distribution of major cardiac-related events across the peak RER subgroups.

Table 2 demonstrates that both the VE/Vco_2 slope and peak Vo_2 remained strong univariate prognostic markers across all peak RER subgroups. Furthermore, across all peak RER subgroups, the VE/Vco_2 slope remained the strongest univariate marker. Table 3 demonstrates that both the VE/Vco_2 slope and peak Vo_2 were retained in the multivariate analysis for all peak RER subgroups. Except in the peak RER 1.05 to 1.09 subgroup, left ventricular ejection fraction was retained in the multivariate analysis.

Areas under the ROC curves (AUCs) of both peak Vo_2 and VE/Vco_2 slope were significant in all peak RER subgroups (peak Vo_2 range: 13.4 to 14.0 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} [AUC range: 0.68 to 0.75]; VE/Vco_2 range: 34.9 to 35.7 [AUC range: 0.69 to 0.75]) (Table 4). Between all subgroups, there did not appear to be significant variation in optimal prognostic threshold for either the VE/Vco_2 slope or peak Vo_2. Likewise, the sensitivity and specificity of these cutoff levels were consistent.

Discussion

CPX is considered the gold standard functional assessment due to its ability to accurately quantify patient effort. It has been a long-held notion, although not strongly supported by research, that a low peak RER invalidates the prognostic strength of key CPX variables. Similar to large-cohort studies such as HF-ACTION, which suggested that ~50% of patients with HF were unable to achieve a peak RER ≥1.10 (11,12), ~46% of patients in the current analysis were unable to achieve a peak RER ≥1.10. These results suggest that peak Vo_2 and VE/Vco_2 slope remain strong prognostic variables irrespective of peak RER. Specifically, peak Vo_2 and the VE/Vco_2 slope were significant univariate indicators of major cardiac-related events across all peak RER subgroups. When coupled with age and left ventricular ejection fraction in multivariate analysis, both peak Vo_2 and the VE/Vco_2 slope remained important prognostic variables.

These results conflict with those from previously published research. Mancini et al. (1) observed a lower survival rate in patients with a low peak Vo_2 who performed a “maximal” CPX, but peak RER was not reported. Mezzani et al. (8), who employed a peak Vo_2 cutoff of 10 ml · kg^{-1} · min^{-1}, demonstrated that patients with a peak Vo_2 ≤10 ml · kg^{-1} · min^{-1} and a peak RER ≥1.15 had significantly worse survival than did patients with peak Vo_2 ≤10 ml · kg^{-1} · min^{-1} and a peak RER <1.15. Furthermore, the latter group’s survival rate was similar to that of patients with a peak Vo_2 between 10 and 14 10 ml · kg^{-1} · min^{-1}, which led to the conclusion that patients should be encouraged to exercise until peak RER approaches 1.15 (8). However, in the peak Vo_2 ≤10 ml · kg^{-1} · min^{-1} group, there were 41 patients with a peak RER ≥1.15 and 39 patients with peak RER ≥1.15 (8). This small sample size may have limited these results. Moreover, 42% of the low peak RER subgroup were prescribed beta-blockers versus only 21% in the high peak RER subgroup. Because this study was done prior to the widespread use of beta-blockade in the management of HF, the survival benefit attributable to the use of beta-blockade may also have limited these results. Our cohort had a higher mean peak Vo_2 than did that from Mezzani et al., and this higher Vo_2 may have influenced our findings. However, when we isolated those with peak Vo_2 ≤10 ml · kg^{-1} · min^{-1} (n = 229), we found no differences in event rates across the peak RER groups (results not reported). Furthermore, in our analysis, 69% to 78% of patients were prescribed beta-blockade (Table 1), reflecting more widespread use of this pharmacologic class.

Although the actual mechanisms behind the findings of the current study were not investigated, there are plausible explanations. During exercise, central cardiovascular function may acutely decline in patients with HF. That is, these patients are near the plateau of the Frank-Starling curve, which leaves them unable to completely utilize the Frank-Starling mechanism and fully augment stroke volume during exercise (23), and which may contribute to increased dyspnea beyond a patient’s tolerance and lead to test termination before the exercising muscles are sufficiently stressed, thus producing a low peak RER. Therefore, low peak Vo_2 values still imply compromised central cardiovascular function and provide prognostic insight. Another possibility may be related to the prevalence of depression in patients with HF. A meta-analysis of data from 36 studies demonstrated a prevalence of depression of ~21% in patients with HF, and the presence of depression was associated with 2-fold increase in the relative risk of mortality (24). The presence of

depression is associated with lower functional capacity (25,26) and increased dyspnea with exertion (26). Unfortunately, the study reporting CPX results did not include peak RER data (25). Though speculative, it is possible that patients with significant depressive symptoms may experience early dyspnea, providing prognostic value to peak Vo_2.

It is not surprising that the VE/Vco_2 slope remains prognostic regardless of the peak RER achieved. It has been shown that the VE/Vco_2 slope values obtained are more resistant to influences of patient effort than is peak Vo_2, and that VE/Vco_2 slope is a valid marker of risk even when the test result is submaximal (13,14,16,27). Furthermore, we have also previously shown that an elevated VE/Vco_2 slope is associated with test termination due to dyspnea, and that patients with an elevated VE/Vci_2 slope tend to exhibit lower peak RER values compared with those who stop due to fatigue (18). Thus, these results add to the robust body of evidence supporting the prognostic power of the VE/Vco_2 slope.

Study limitations

First, we did not have invasive hemodynamic or exercise echocardiography data to test the hypothesis that declining central function was the reason that peak Vo_2 remained prognostic. However, the fact that CPX variables remained prognostic, in a large HF cohort sufficiently powered to address this issue, is compelling. Future research should be directed toward the physiologic response pattern in patients with a low versus a high peak RER. Second, using only CPX data, we were unable to distinguish patients who gave truly a submaximal effort from those who gave a maximal effort within each of the subgroups. The differentiation between maximal and submaximal effort can be difficult, and it is not always clear when patients reach a physiologic maximum. However, a technician's impression of a patient's effort may help to identify truly submaximal test results. We do not have this subjective information from each test to evaluate this possibility further. Last, New York Heart Association classification was inconsistently recorded into the database (and thus not reported); these data would have provided insight into how the patients in each subgroup perceived their functional capabilities.

Conclusions

Peak Vo_2 and the VE/Vco_2 slope appear to retain significant prognostic value irrespective of peak RER. These findings potentially validate CPX assessments clinically performed for prognostic purposes, even if a patient does not achieve or surpass previously recommended peak RER thresholds. Therefore, greater clinical consideration may be warranted in patients with RER <1.10, low peak Vo_2, and an elevated VE/Vco_2 slope.

Abbreviations and Acronyms

CPX	cardiopulmonary exercise testing
HF	heart failure
RER	respiratory exchange ratio
ROC	receiver-operating characteristic

VE/Vco_2	minute ventilation/carbon dioxide production
Vo_2	oxygen consumption

REFERENCES

1. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778–86. [PubMed: 1999029]
2. Roul G, Moulichon ME, Bareiss P, et al. Exercise peak VO2 determination in chronic heart failure: is it still of value? Eur Heart J 1994; 15:495–502. [PubMed: 8070476]
3. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation 2005;111:2313–8. [PubMed: 15867168]
4. Arena R, Myers J, Abella J, et al. Defining the optimal prognostic window for cardiopulmonary exercise testing in patients with heart failure. Circ Heart Fail 2010;3:405–11. [PubMed: 20200329]
5. Myers J, Gullestad L, Vagelos R, et al. Cardiopulmonary exercise testing and prognosis in severe heart failure: 14 mL/kg/min revisited. Am Heart J 2000;139:78–84. [PubMed: 10618566]
6. Ramos-Barbon D, Fitchett D, Gibbons WJ, Latter DA, Levy RD. Maximal exercise testing for the selection of heart transplantation candidates: limitation of peak oxygen consumption. Chest 1999;115: 410–7. [PubMed: 10027440]
7. Howley ET, Bassett DR Jr., Welch HG. Criteria for maximal oxygen uptake: review and commentary. Med Sci Sports Exerc 1995;27: 1292–301. [PubMed: 8531628]
8. Mezzani A, Corra U, Bosimini E, Giordano A, Giannuzzi P. Contribution of peak respiratory exchange ratio to peak VO2 prognostic reliability in patients with chronic heart failure and severely reduced exercise capacity. Am Heart J 2003;145:1102–7. [PubMed: 12796770]
9. Thompson WR, Gordon NF, Pescatello LS, American College of Sports Medicine ACSM's Guidelines for Exercise Testing and Prescription. 8th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2010.
10. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010;122:191–225. [PubMed: 20585013]
11. Arena R, Myers J, Guazzi M. Cardiopulmonary exercise testing is a core assessment for patients with heart failure. Congest Heart Fail 2011;17:115–9. [PubMed: 21609384]
12. Bensimhon DR, Leifer ES, Ellis SJ, et al. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing). Am J Cardiol 2008; 102:712–7. [PubMed: 18773994]
13. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. Am Heart J 2004;147:354–60. [PubMed: 14760336]
14. Corra U, Mezzani A, Bosimini E, Scapellato F, Imparato A, Giannuzzi P. Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. Am Heart J 2002;143:418–26. [PubMed: 11868046]
15. Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. Heart Fail Rev 2008;13:245–69. [PubMed: 17987381]
16. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Influence of subject effort on the prognostic value of peak VO2 and the VE/VCO2 slope in patients with heart failure. J Cardiopulm Rehabil 2004; 24:317–20. [PubMed: 15602151]
17. Radford MJ, Arnold JM, Bennett SJ, et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Heart Failure Clinical Data Standards): developed in

collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. Circulation 2005;112:1888–916. [PubMed: 16162914]

18. Chase P, Arena R, Myers J, et al. Prognostic usefulness of dyspnea versus fatigue as reason for exercise test termination in patients with heart failure. Am J Cardiol 2008;102:879–82. [PubMed: 18805115]
19. Arena R, Guazzi M, Myers J, Ann Peberdy M. Prognostic characteristics of cardiopulmonary exercise testing in heart failure: comparing American and European models. Eur J Cardiovasc Prev Rehabil 2005; 12:562–7. [PubMed: 16319546]
20. Whellan DJ, O'Connor CM, Lee KL, et al. Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION): design and rationale. Am Heart J 2007;153:201–11. [PubMed: 17239677]
21. Abraham WT, Burkhoff D, Nademanee K, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with systolic heart failure: rationale, design, and baseline patient characteristics. Am Heart J 2008;156:641–8. [PubMed: 18926146]
22. Keteyian SJ, Brawner CA, Ehrman JK, et al. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise parameters: implications for clinical trials and clinical practice. Chest 2010;138:950–5. [PubMed: 20522572]
23. Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. J Am Coll Cardiol 1996;28: 1092–102. [PubMed: 8890800]
24. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 2006;48:1527–37. [PubMed: 17045884]
25. Blumenthal JA, Babyak MA, O'Connor C, et al. Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. JAMA 2012;308:465–74. [PubMed: 22851113]
26. Song EK, Moser DK, Lennie TA. Relationship of depressive symptoms to the impact of physical symptoms on functional status in women with heart failure. Am J Crit Care 2009;18:348–56. [PubMed: 19556413]
27. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. Chest 2003;124:720–7. [PubMed: 12907564]

Table 1

Overall and RER Subgroup Baseline Characteristics and CPX Tests Results

Variable	Overall (n = 1,728)	RER <1.00 (n = 319)	RER 1.00–1.04 (n = 218)	RER 1.05–1.09 (n = 256)	RER ≥1.10 (n = 935)
Age (yrs)	55 ± 14	57 ± 14	56 ± 14	54 ± 16 *	54 ± 13 *
Male	75%	72%	75%	75%	76%
BMI (kg/m^2)	28.5 ± 6.1	28.5 ± 6.2	29.1 ± 6.6	28.9 ± 6.5	28.2 ± 5.8
Ischemic etiology	40%	40%	44%	42%	38%
LVEF	28 ± 10%	29 ± 11%	28 ± 10%	29 ± 10%	28 ± 10%
Treatment history					
Beta-blocker	75%	69% †	72%	74%	78%
ACE-I	67%	68%	69%	65%	68%
Diuretic	60%	52% †	61%	58%	63%
Peak Vo_2 (ml·kg^{-1}·min^{-1})	16.2 ± 6.6	14.8 ± 5.9	15.6 ± 6.0	16.8 ± 7.5 *	16.7 ± 6.7 *
VE/Vco_2 slope	34.9 ± 9.7	35.4 ± 9.8	35.1 ± 9.9	34.5 ± 9.4	34.8 ± 9.7
Vital signs					
Peak HR (beats/min)	126 ± 25	120 ± 22	125 ± 23	126 ± 27 *	128 ± 26 *
Age-predicted peak HR (%)	72 ± 13%	68 ± 13%	73 ± 11%	70 ± 12%	74 ± 14% *
Resting SBP (mm Hg)	115 ± 21	119 ± 23	114 ± 20	115 ± 22	114 ± 21
Resting DBP (mm Hg)	72 ± 13	73 ± 14	73 ± 12	73 ± 12	72 ± 12
Peak exercise SBP (mm Hg)	144 ± 31	145 ± 31	144 ± 32	143 ± 29	145 ± 31
Peak exercise DBP (mm Hg)	76 ± 15	76 ± 17	78 ± 16	76 ± 13	76 ± 14
Peak RER †	1.11 ± 0.14	0.92 ± 0.06	1.02 ± 0.01	1.07 ± 0.01	1.21 ± 0.11
Major event ‡	270 (16%)	50 (16%)	37 (17%)	40 (16%)	143 (15%)

Values are mean ± SD %, or n (%).

* $p < 0.05$ versus RER <1.00 group.

† $p < 0.001$ between all RER subgroups.

‡ Death, left ventricular assist device implantation or heart transplantation (log-rank test of event-free survival, chi square: 0.5 on 3 degrees of freedom; $p = 0.911$).

ACE-I = angiotensin converting enzyme inhibitor; BMI = body mass index; CPX = cardiopulmonary exercise testing; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; Vo_2 = oxygen consumption; SBP = systolic blood pressure; RER = respiratory exchange ratio; VE/Vco_2 slope = minute ventilation/carbon dioxide production slope.

Table 2

Overall and RER Subgroup Univariate Cox Regression Analysis for Major Cardiac-Related Events*

Parameter/Statistic	Overall (n = 1,728)	RER <1.00 (n = 319)	RER 1.00–1.04 (n = 218)	RER 1.05–1.09 (n = 256)	RER ≥1.10 (n = 935)
VE/Vco_2 slope					
Chi square	244.3	31.3	21.6	25.3	162.3
p Value	<0.001	<0.001	<0.001	<0.001	<0.001
HR (95% CI)	1.065 (1.056–1.074)	1.060 (1.038–1.082)	1.049 (1.027–1.071)	1.054 (1.032–1.077)	1.076 (1.063–1.088)
Peak Vo_2					
Chi square	116.9	13.5	16.6	16.0	71.6
p Value	<0.001	<0.001	<0.001	<0.001	<0.001
HR (95% CI)	0.844 (0.820–0.868)	0.882 (0.826–0.941)	0.837 (0.771–0.908)	0.841 (0.779–0.912)	0.829 (0.796–0.863)
LVEF					
Chi square	98.7	28.3	16.6	2.0	54.1
p Value	<0.001	<0.001	<0.001	0.163	<0.001
HR (95% CI)	0.934 (0.921–0.947)	0.921 (0.892–0.951)	0.920 (0.882–0.959)	–	0.929 (0.911–0.948)
Age					
Chi square	0.38	0.13	0.57	1.48	0.32
p Value	0.539	0.716	0.449	0.223	0.571
HR (95% CI)	–	–	–	–	–

*$p < 0.05$ considered significant. Major event = death, left ventricular assist device implantation, or heart transplantation.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

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Table 3

Overall and RER Subgroup Multivariate Cox Regression Analysis for Major Cardiac-Related Events *

Parameter/Statistic	Overall (n = 1,728)	RER <1.00 (n = 319)	RER 1.00–1.04 (n = 218)	RER 1.05–1.09 (n = 256)	RER ≥1.10 (n = 935)
VE/Vco_2 slope					
Chi square (residual chi square)	228.9	28.7	28.6	29.1	143.6
p Value	<0.001	<0.001	<0.001	<0.001	<0.001
Adjusted HR (adjusted 95% CI)	1.041 (1.029–1.052)	1.041 (1.014–1.069)	1.048 (1.016–1.081)	1.036 (1.010–1.063)	1.044 (1.027–1.061)
Peak Vo_2					
Chi square (residual chi square)	(108.0)	(12.7)	(14.7)	(15.3)	(67.8)
p Value	<0.001	<0.001	<0.001	<0.001	<0.001
Adjusted HR (adjusted 95% CI)	0.898 (0.868–0.928)	0.929 (0.868–0.994)	0.899 (0.820–0.985)	0.874 (0.801–0.954)	0.890 (0.847–0.936)
LVEF					
Chi square (residual chi square)	(94.1)	(27.9)	(15.5)	(2.2)	(52.2)
p Value	<0.001	<0.001	<0.001	0.140	<0.001
Adjusted HR (adjusted 95% CI)	0.954 (0.940–0.968)	0.927 (0.895–0.959)	0.936 (0.895–0.985)	–	0.955 (0.935–0.975)
Peak RER					
Chi square (residual chi square)	(1.9)	–	–	–	–
p Value	0.172	–	–	–	–
Adjusted HR (adjusted 95% CI)	–	–	–	–	–
Age					
Chi square (residual chi square)	(0.8)	(0.0)	0.3	(0.8)	(0.9)
p Value	0.358	0.995	0.566	0.357	0.333
Adjusted HR (adjusted 95% CI)	–	–	–	–	–

* Variables with $p \geq 0.10$ were not retained. Major event = death, left ventricular assist device implantation, or heart transplantation.

Abbreviations as in Tables 1 and 2.

Table 4

Overall and RER Subgroup ROC Curve Analysis

Parameter/Statistic	Overall (n = 1,728)	RER <1.00 (n = 319)	RER 1.00–1.04 (n = 218)	RER 1.05–1.09 (n = 256)	RER ≥1.10 (n = 935)
VE/Vco_2 slope					
Area under ROC curve (95% CI)	0.74 (0.71–0.77)	0.69 (0.61–0.77)	0.71 (0.63–0.80)	0.74 (0.66–0.82)	0.75 (0.71–0.80)
p Value	<0.001	<0.001	<0.001	<0.001	<0.001
Cutoff value (</≥)	35.4	35.6	35.7	34.9	35.7
Sensitivity/specificity (%)	67/67	64/62	67/67	68/67	69/69
Peak Vo_2					
Area under ROC curve ($ml \cdot kg^{-1} \cdot min^{-1}$) (95% CI)	0.73 (0.70–0.76)	0.68 (0.60–0.76)	0.71 (0.61–0.81)	0.73 (0.66–0.81)	0.75 (0.71–0.79)
p Value	<0.001	<0.001	<0.001	<0.001	<0.001
Cutoff value (≤/>)	13.8	13.4	13.8	13.7	14.0
Sensitivity/specificity (%)	67/66	62/62	62/63	68/67	69/68

ROC = receiver-operating characteristic; other abbreviations as in Tables 1 and 2.