PTK
Physical Therapy Korea
https://doi.org/10.12674/ptk.2022.29.3.200
pISSN: 1225-8962 eISSN: 2287-982X
Phys Ther Korea. 2022;29(3):200-207

Original Article

Reliable Prognostic Cardiopulmonary Function Variables in 110 Patients With Acute Ischemic Heart Disease

Jeong Jae Lee[1,2,3], PT, MSc, Chan-hee Park[1,2], PT, MSc, Joshua (Sung) Hyun You[1,2], PT, PhD

[1]Sports Movement Artificial-Intelligence Robotics Technology (SMART) Institute, [2]Department of Physical Therapy, Yonsei University, Wonju, [3]Rehabilitation Team, Myongji Hospital, Goyang, Korea

Article Info
Received June 28, 2022
Revised August 5, 2022
Accepted August 6, 2022

Corresponding Author
Joshua (Sung) Hyun You
E-mail: neurorehab@yonsei.ac.kr
https://orcid.org/0000-0001-9931-2466

Key Words
Cardiac rehabilitation
Heart disease
Heart rate
Ventilation

Background: The oxygen uptake efficiency slope (OUES) is the most important index for accurately measuring cardiopulmonary function in patients with acute ischemic heart disease. However, the relationship between the OUES variables and important cardiopulmonary function parameters remain unelucidated for patients with acute ischemic heart disease, which accounts for the largest proportion of heart disease.

Objects: The present cross sectional clinical study aimed to determine the multiple relationships among the cardiopulmonary function variables mentioned above in adults with acute ischemic heart disease.

Methods: A convenience sample of 110 adult inpatients with ischemic heart disease (age: 57.4 ± 11.3 y; 95 males, 15 females) was enrolled at the hospital cardiac rehabilitation center. The correlation between the important cardiopulmonary function indicators including peak oxygen uptake (VO_2 peak), minute ventilation (VE)/carbon dioxide production (VCO_2) slope, heart rate recovery (HRR), and ejection fraction (EF) and OUES was confirmed.

Results: This study showed that OUES was highly correlated with VO_2 peak, VE/VCO_2 slope, and HRR parameters.

Conclusion: The OUES can be used as an accurate indicator for cardiopulmonary function. There are other factors that influence aerobic capacity besides EF, so there is no correlation with EF. Effective cardiopulmonary rehabilitation programs can be designed based on OUES during submaximal exercise in patients with acute ischemic heart disease.

INTRODUCTION

Oxygen uptake inefficiency is an important biomarker for accurately detecting or predicting cardiopulmonary function in patients with acute coronary artery disease, even during submaximal exercise [1]. Oxygen uptake inefficiency, which is associated with cardiopulmonary function, is determined by measuring peak oxygen uptake (VO_2 peak), minute ventilation (VE)/carbon dioxide production (VCO_2) slope, heart rate recovery (HRR), ejection fraction (EF), and oxygen uptake efficiency slope (OUES) parameters. Previous studies have reported a high prognostic value of OUES, VO_2 peak, VE/VCO_2 slope, HRR, and EF cardiopulmonary function testing parameters for cardiac-related events in patients with chronic heart failure [2-6]. Among the cardiopulmonary function testing parameters, OUES is an accurate indicator for estimating the level of exercise performance in patients with heart disease who cannot tolerate a maximum exercise stress test [7]. OUES was used as a quantitative measurement that estimates the VO_2 peak in a study involving submaximal evaluation of older patients with coronary artery disease [8]. Conventionally, VO_2 peak is the gold standard measure of cardiopulmonary function exercise capacity [9] and demonstrates the important relationship between the short-term survival rate and poor VO_2 peak (<10 ml/kg/min) [1,4]. It has also been used as an essential indicator of cardiac transplantation in patients with a VO_2 peak >14 ml/kg/min [1-7]. A delayed decrease in HRR reflects a decrease in vagal activity, which is a strong predictor of overall mortality regardless of exercise intensity or myocardial perfusion defects [10]. The VE/VCO_2 slope is a significant predictor of mortality, along with the OUES [11]. EF is a measure of the heart's movement efficiency; low EF is related to reduced left ventricular EF and exercise capacity and is a sign of heart failure [12].

Nevertheless, there is a dearth of information demonstrating the relationship between OUES data and other important cardiopulmonary function parameters, including VO_2 peak, VE/VCO_2 slope, HRR, and EF for patients with acute ischemic heart disease over the age of 55 years. The American Heart Association found that the incidence of cardiopulmonary disorder in US men and women is to 40% from 40–59 years, to 75% from 60–79 years, and to 86% in those above the age of 80 years [13]. Therefore, the present clinical study aimed to determine the multiple relationships among the cardiopulmonary function variables mentioned above in adults with acute ischemic heart disease. In a clinical setting, this information may provide important insights into the best predictive parameters for estimating cardiopulmonary function in adults with acute ischemic heart disease. This could aid in making clinical decisions regarding stress tests, cardiac rehabilitation and exercise prescriptions, and surgical procedures for acute ischemic heart disease. We hypothesized that there would be meaningful relationships between VO_2 peak, VE/VCO_2 slope, HRR, EF, and OUES measurement variables.

Table 1. Demographic and clinical characteristics of the patients (N = 110)

Parameter	Data
Sex (male/female)	95/15
Age (y)	57.4 ± 11.3
BMI (kg/m²)	25.1 ± 3.4
Past history	
Hypertension	54 (49)
Diabetes mellitus	27 (25)
Smoking	46 (42)
Alcohol	37 (34)
Acute coronary syndrome	
STEMI	53 (48)
NSTEMI	26 (24)
HF	12 (11)
Angina pectoris	37 (34)
Mitral valve prolapse	2 (2)
Major invasive management	
PTCA	93 (85)
CABG	2 (2)

Values are presented as number only, number (%), or mean ± standard deviation. BMI, body mass index; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; HF, heart failure; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

MATERIALS AND METHODS

1. Participants and Experimental Procedure

A convenience sample of 110 adult patients with ischemic heart disease (age: 57.4 ± 11.3 y; 95 males, 15 females) was enrolled as inpatient medical record chart at the hospital cardiac rehabilitation center (Table 1). As a cross sectional study, personal information is not collected and recorded, so it is Institutional Review Board (IRB) review exemption and is not subject to review (IRB exempt no. MJH2022-06-022). All patients underwent the necessary medical treatment, including the indicated procedures, such as percutaneous coronary intervention or coronary artery bypass graft (CABG), during the preliminary phases of their inpatient course in cardiac rehabilitation. The inclusion criteria were as follows: (1) diagnosis of ischemic heart disease, (2) participation in cardiopulmonary exercise testing (CPX) at the hospital cardiac rehabilitation center, and (3) evaluation of the cardiac rehabilitation CPX results from November 2018 to April 2020 for 18 months. The exclusion criteria were as follows: (1) severe heart failure, (2) unstable angina, (3) uncontrolled arrhythmia, (4) psychiatric illness (including dementia), (5) other significant non-cardiac-related comorbidities precluding the ability to exercise on the treadmill or lower extremity ergometer, and (6) readmission for subsequent acute myocardial infarction who had previously received the intervention [14].

The present investigation was a cross sectional study wherein we analyzed patients' medical records upon referral for cardiac rehabilitation from other departments of the medical center. Cardiac rehabilitation specialists (physical therapists and nurses) interviewed the potential enrollees to determine their suitability for CPX. Statistical power was set at 0.89, with a medium effect size of 0.3, an alpha error probability of 0.05, and a total sample size of 110, using G-power software (ver. 3.1.9.7; Franz Faul, Kiel University, Kiel, Germany) [15].

2. Cardiopulmonary Exercise Test

The CPX is a commonly used measure of cardiopulmonary function and fitness. All patients were required to refrain from strenuous physical activity and consumption of stimulants (coffee, tobacco, and alcohol) that could influence the heart rate for 24 hours before CPX. The test was performed at least two hours after eating a meal. All patients underwent CPX on a programmable treadmill in a room with controlled environmental conditions (21–23°C and 40%–60% relative humidity) between 10 am and 3 pm with a standard 12-lead continuous electrocardiogram monitor. Blood pressure was monitored by auscultation. VE, oxygen uptake, carbon dioxide output, and other cardiopulmonary variables were recorded breath-by-breath using a computerized system (COSMED Omnia 1.6.7; COSMED, Rome, Italy). Resting oxygen consumption and heart rate were computed as the mean of the final 30 seconds of the resting period, whereas peak effort (oxygen consumption) and heart rate were the mean values of the final 30 seconds of effort before exhaustion. Respiratory exchange ratios were recorded as the average of samples obtained during each stage of the protocol (Modified Bruce protocol or bike incline protocol at 5, 10, 15, and 20 W). The submaximal exercise test was implemented at 2.25 km/h with a resting interval of 5–10 to prevent venous pooling during the recovery phase. The reliability and validity of the CPX have been previously established, and the specific standardized procedure has been well documented [16].

3. Oxygen Uptake Efficiency Slope

The OUES was determined by evaluating the cardiopulmonary functional reserve resulting from the single-segment logarithmic relationship between oxygen uptake and VE through incremental exercise, which was presented as a new linear measure of the ventilatory response to exercise. The relationship between oxygen uptake and ventilation volume was stated using the OUES. This index is best described by a single-segment logarithmic curve-appropriate model using the equation $VO_2 = a \times \log VE + b$, in which the constant "a" characterizes the rate of increase in VO_2 in response to an increase in logVE. This constant "a" is called OUES. A steeper slope or higher OUES (Figure 1A) indicates a more effective oxygen efficiency capacity from the cardiopulmonary system by the active skeletal muscles, whereas a shallower slope or lower OUES (Figure 1B) indicates the need for ventilation and less effective oxygen uptake efficiency compared to steeper slopes. The reliability and validity of the OUES test have been established previously, and the specific standardized procedure is well documented [17].

4. VO_2 Peak

VO_2 peak was determined by assessing maximal oxygen consumption, termed "VO_2 max," which is defined as the volume of oxygen consumed by a participant during incremental exercise, and is the gold standard for assessing cardiopulmonary function [18]. However, achieving VO_2 max as defined by standardized criteria, including a plateau in oxygen consumption with incrementally increased work [19] may increase the risk for older adults [20] and the risk of adverse events (e.g., myocardial infarction and cardiac arrhythmia) [21]. A common resolution is to adapt the VO_2 max criteria (plateau in oxygen consumption) and use oxygen consumption level at peak exercise (VO_2 peak) as a measure of cardiopulmonary function [22]. The VO_2 peak (ml/min) was calculated as the mean of the two highest serials achieved VO_2 values in 10 seconds during peak or submaximal exertion. The reliability and validity of the VO_2 peak measurement have been established previously, and the specific standardized procedure is well documented [23].

5. VE/VCO_2 Slope

The VE/VCO_2 slope was determined by measuring the minute ventilation/carbon dioxide production, representing venti-

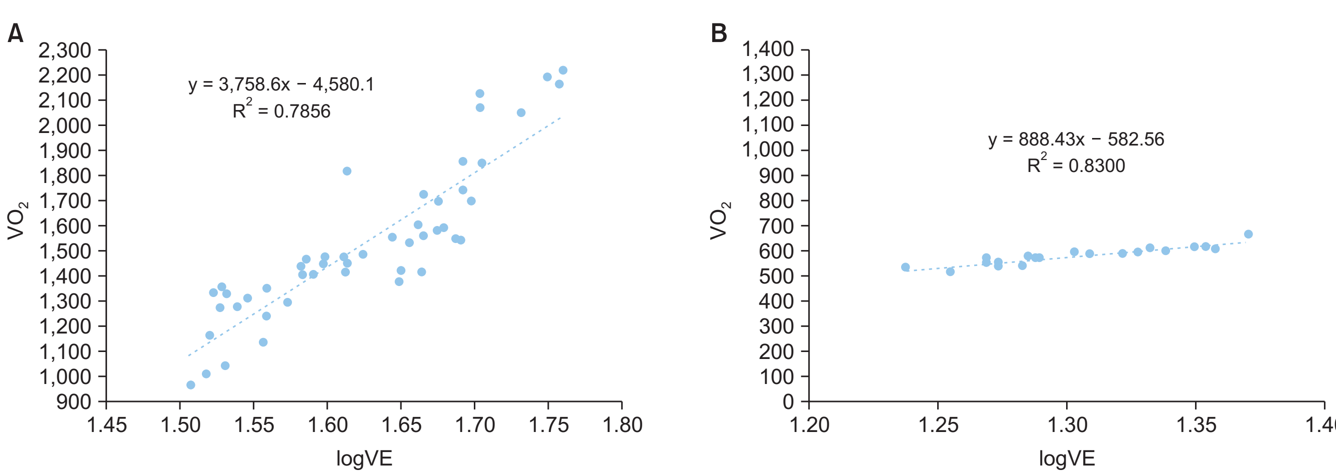

Figure 1. Higher and lower oxygen uptake efficiency slope. (A) Steeper slope, higher oxygen uptake efficiency slope; (B) shallower slope, lower oxygen uptake efficiency slope.

latory efficiency. Breath-by-breath gas exchange data were averaged using a 15-second sampling interval, and the VE/VCO_2 slope was determined using the metabolic cart's Omnia 1.6.7 software (Quark CPET; COSMED, Rome, Italy) by generating a graph of ventilation and VCO_2 and fitting a linear regression equation to the relationship. The reliability and validity of the VE/VCO_2 slope have been established previously, and the specific standardized procedure is well documented [24].

6. Heart Rate Recovery

HRR was defined as the decrease in heart rate from peak exercise exertion to one minute after exercise cessation. HRR was automatically recorded from the exercise phase to the 60-second post-recovery phase using the software.

7. Echocardiography

Heart thickness and blood flow were determined based on standardized EF measurements, which were consistently assessed by a licensed cardiologist. The patient was comfortably seated. Six different portable ultrasound machines were used; data were uploaded to the electronic medical record (EMR) system and made available for use in this study. All the data were measured by the same physician. Standard M-mode and 2-dimensional echocardiography, as well as Doppler blood flow measurements, were performed in accordance with the American Society of Echocardiography guidelines [24]. The left ventricular EF was calculated from 2-dimensional apical images using Simpson's method [25].

The reliability and validity of the EF have been established previously, and the specific standardized procedure is well documented [26].

8. Statistical Analysis

Statistical tests were expressed as means ± standard deviations. Pearson or Spearman correlation coefficients were used to determine the multidirectional relationships between the OUES and VO_2 peak, VE/VCO_2 slope, HRR, and EF variables measured during submaximal CPX. SPSS software (ver. 23.0; SPSS Inc., Chicago, IL, USA) was used to compute correlations at $p < 0.05$.

RESULTS

Table 2 presents the mean ± standard deviation, standard error and 95% confidence interval of OUES, VO_2 peak, VE/VCO_2 slope, HRR, and EF in the analysis, respectively.

Correlation between OUES and VO_2 peak, VE/VCO_2 slope, HRR, and EF showed a strong positive ($r = 0.832$, $p < 0.001$) (Figure 2), moderately negative ($r = -0.544$, $p < 0.001$) (Figure 3), moderately positive ($r = 0.344$, $p < 0.001$) (Figure 4), and no significant correlation ($r = 0.181$, $p = 0.065$) (Figure 5), respectively.

Table 2. OUES and other indicators

Parameter	Mean ± SD	SE	95% CI
OUES	1,877.2 ± 630.1	60.1	1,994.9–1,759.4
VO_2 peak	1,506.6 ± 457.2	43.6	1,592.0–1,421.1
VE/VCO_2 slope	33.7 ± 9.0	0.86	35.4–32.0
HRR	21.3 ± 10.8	1.0	23.3–19.3
EF	48.0 ± 11.5	1.1	50.2–45.9

SD, standard deviation; SE, standard error; CI, confidence interval; OUES, oxygen uptake efficiency slope; VO_2 peak, peak oxygen uptake; VE/VCO_2, minute ventilation/carbon dioxide production; HRR, heart rate recovery; EF, ejection fraction.

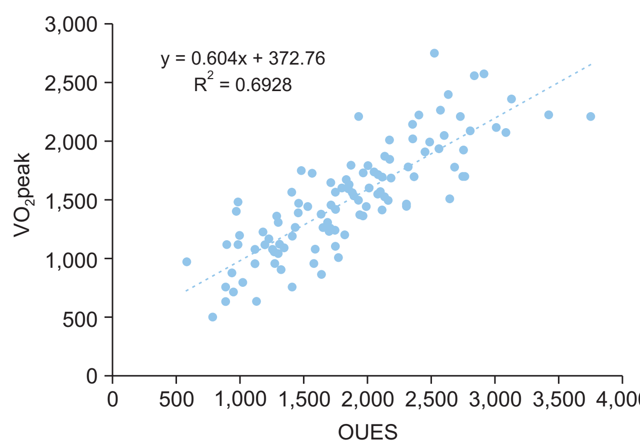

Figure 2. VO_2 peak and OUES correlation. VO_2 peak, peak oxygen uptake; OUES, oxygen uptake efficiency slope.

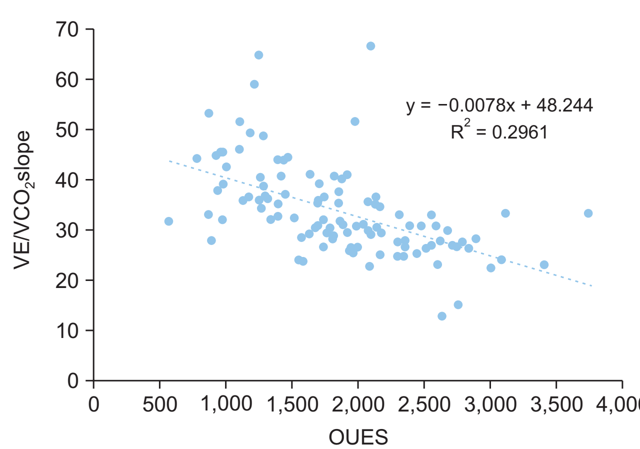

Figure 3. VE/VCO_2 slope and OUES correlation. VE/VCO_2, minute ventilation/carbon dioxide production; OUES, oxygen uptake efficiency slope.

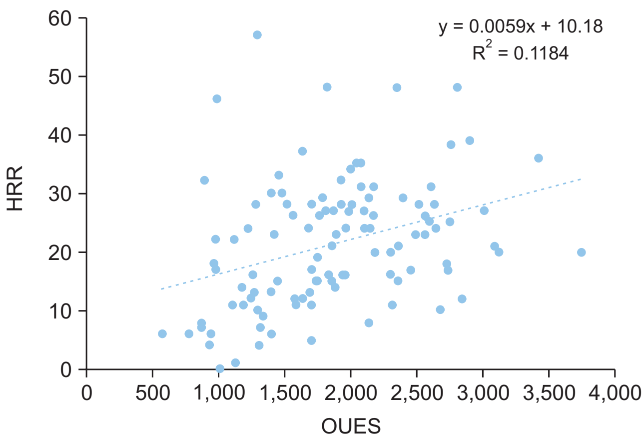

Figure 4. HRR and OUES correlation. HRR, heart rate recovery; OUES, oxygen uptake efficiency slope.

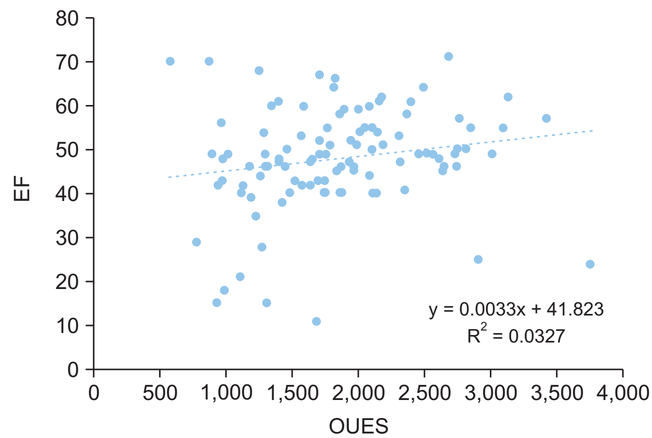

Figure 5. EF and OUES correlation. EF, ejection fraction; OUES, oxygen uptake efficiency slope.

DISCUSSION

The present study established a relationship between OUES data and other important cardiopulmonary function testing parameters, including VO_2 peak, VE/VCO_2 slope, HRR, and EF, in older patients with acute ischemic heart disease. As anticipated, the OUES measurement data were correlated with VO_2 peak, VE/VCO_2 slope, and HRR, but not EF. Most importantly, this correlation information provides important clinical insights into the utility of a different yet accurate alternative cardiopulmonary testing procedure to assess cardiopulmonary function in older adults with acute ischemic heart disease who are unable to tolerate certain testing protocols owing to their medical condition.

Correlation analysis showed a strong relationship between the OUES and VO_2 peak ($r = 0.832$, $p < 0.001$). Previous correlation studies [1,27] in healthy young adults reported moderate correlations between submaximal OUES and age ($r = 0.557$–0.584) [26]. Another cardiopulmonary correlation study showed a moderate correlation ($r = -0.58$) between the OUES and peak VE/VO_2 in 398 patients with systolic heart failure. The strong correlation between submaximal OUES and VO_2 peak is also in line with the results of a study that reported a very strong correlation between submaximal OUES and VO_2 max ($r = 0.95$) [1]. This is consistent with our finding that the OUES is derived from the logarithmic relationship between oxygen uptake and VE during incremental exercise. VO_2 max is considered the gold standard for the stratification of patients with heart failure; however, its use is limited by the patient's condition, motivation, skeletal muscle structure, pulmonary function, and hemoglobin level. Thus, some patients do not achieve their anaerobic threshold during exercise, and the VO_2 peak or VO_2 max cannot be accurately assessed. To overcome these limitations, submaximal metabolic parameters have been proposed as surrogates for estimating the OUES.

Correlation analysis showed a moderately significant relationship between OUES and the VE/VCO_2 slope ($r = -0.544$, $p < 0.001$) and HRR and OUES ($r = 0.344$, $p < 0.001$). This finding was in line with that of a previous correlational study [28], which reported a strong correlation between VE/VCO_2 and OUES in 341 patients with heart failure ($r = -0.65$ to -0.61, $p < 0.001$) [28]. Another study demonstrated a moderate correlation between HRR and peak VO_2/kg in 58 patients with idiopathic pulmonary arterial hypertension ($r = 0.569$, $p < 0.001$) [29]. OUES is a novel index derived from the logarithmic relationship between oxygen uptake and VE during incremental exercise and best represents the development of metabolic acidosis, physiological dead space, and arterial CO_2 partial pressure [1]. Our correlational data corroborate that the OUES reflects a single physical index for cardiovascular and peripheral factors accounting for oxygen uptake and HRR, which influence the ventilatory response to exercise. Furthermore, the OUES had a strong prognostic value in identifying patients with acute ischemic heart disease who presented with a greater increase in ventilation per unit increase in VO_2 due to various metabolic, reflex, and gas exchange abnormalities [30-33]. Correlational data among the OUES, VO_2 peak, VE/VCO_2 slope, and HRR parameters may provide a specific pattern of ventilatory response to exercise having automatically "controlled" for abnormalities present during exercise because the OUES filters out or adjusts outliers to account for measurement errors that may occur during evaluation. It is important to determine exercise intensity using VO_2 peak value without controlling for outliers, as this may lead to an inappropriate exercise intensity. If the exercise is too intense, the patient may be unable to tolerate it.

In another correlation study [34] examining the relationship between VO_2 peak and EF before and after surgery, there was no correlation between EF and VO_2 peak before ($r = 0.123$, $p = 0.6$) and after ($r = 0.27$, $p = 0.2$) cardiac surgery in 6 months follow-up. A weak correlation was observed between the changes in VO_2 peak and EF from the preoperative period to the postoperative period ($r = 0.48$, $p = 0.048$). This is because the factors that affect the patient's aerobic capacity are not only the EF, but also the change of heart rate through the autonomic nervous system and the aerobic capacity of various muscles activated during exercise.

The present study has some limitations that should be considered in future studies. This study was retrospective in nature, and we only evaluated exercise variables and did not include data obtained from echocardiography, which can provide prognostic information. In addition, there was a lack of follow-up evaluation, which can provide important correlations regarding therapeutic effects in patients with acute ischemic heart disease.

CONCLUSIONS

The present correlational study demonstrated that OUES was highly correlated with VO_2 peak, VE/VCO_2 slope, and HRR parameters but not with EF. These findings provide the important clinical insight that OUES can be used as an accurate alternative indicator to measure cardiopulmonary function in patients with acute ischemic heart disease during submaximal exercise to design cardiopulmonary rehabilitation programs more effectively.

FUNDING

None to declare.

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conceptualization: JJL, JHY. Data curation: JJL. Formal analysis: JJL, CP. Investigation: JJL. Methodology: CP. Project administration: JHY. Resources: JHY. Supervision: JHY. Validation: CP. Visualization: JJL, CP. Writing - original draft: JJL, CP, JHY. Writing - review & editing: CP, JHY.

ORCID

Jeong Jae Lee, https://orcid.org/0000-0003-2241-4178
Chan-hee Park, https://orcid.org/0000-0003-2262-8555

REFERENCES

1. **Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, et al.** Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. J Am Coll Cardiol 1996;28(6):1567-72.
2. **Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, et al.** The ventilatory classification system effectively predicts hospitalization in patients with heart failure. J Cardiopulm Rehabil Prev 2008;28(3):195-8.
3. **Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, et al.** Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO_2 slope and peak VO_2. Eur Heart J 2000;21(2):154-61.
4. **Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA.** Peak VO_2 and VE/VCO_2 slope in patients with heart failure: a prognostic comparison. Am Heart J 2004;147(2):354-60.
5. **Bard RL, Gillespie BW, Clarke NS, Egan TG, Nicklas JM.** Determining the best ventilatory efficiency measure to predict mortality in patients with heart failure. J Heart Lung Transplant 2006;25(5):589-95.
6. **Arena R, Guazzi M, Myers J, Chase P, Bensimhon D, Cahalin LP, et al.** The prognostic utility of cardiopulmonary exercise testing stands the test of time in patients with heart failure. J

Cardiopulm Rehabil Prev 2012;32(4):198-202.
7. **Van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, Vanderheyden M.** Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. Am Heart J 2005;149(1):175-80.
8. **Van Laethem C, Van de Veire N, De Sutter J, Bartunek J, De Backer G, Goethals M, et al.** Prospective evaluation of the oxygen uptake efficiency slope as a submaximal predictor of peak oxygen uptake in aged patients with ischemic heart disease. Am Heart J 2006;152(2):297.e9-15.
9. **Hollenberg M, Tager IB.** Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol 2000;36(1):194-201.
10. **Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS.** Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341(18):1351-7.
11. **Arena R, Myers J, Hsu L, Peberdy MA, Pinkstaff S, Bensimhon D, et al.** The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. J Card Fail 2007;13(6):462-9.
12. **Hasselberg NE, Haugaa KH, Sarvari SI, Gullestad L, Andreassen AK, Smiseth OA, et al.** Left ventricular global longitudinal strain is associated with exercise capacity in failing hearts with preserved and reduced ejection fraction. Eur Heart J Cardiovasc Imaging 2015;16(2):217-24.
13. **Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al.** Cardiovascular risks associated with gender and aging. J Cardiovasc Dev Dis 2019;6(2):19.
14. **Dalal HM, Evans PH, Campbell JL, Taylor RS, Watt A, Read KL, et al.** Home-based versus hospital-based rehabilitation after myocardial infarction: a randomized trial with preference arms--Cornwall Heart Attack Rehabilitation Management Study (CHARMS). Int J Cardiol 2007;119(2):202-11.
15. **Faul F, Erdfelder E, Lang AG, Buchner A.** G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175-91.
16. **Choi JY, Jang KS, Choi SH, Hong MS.** Validity and reliability of a clinical performance examination using standardized patients. J Korean Acad Nurs 2008;38(1):83-91.
17. **Van Laethem C, De Sutter J, Peersman W, Calders P.** Intratest reliability and test-retest reproducibility of the oxygen uptake efficiency slope in healthy participants. Eur J Cardiovasc Prev Rehabil 2009;16(4):493-8.
18. **Poole DC, Jones AM.** Measurement of the maximum oxygen uptake $\dot{V}o_2$ max: $\dot{V}o_2$ peak is no longer acceptable. J Appl Physiol (1985) 2017;122(4):997-1002.
19. **Howley ET, Bassett DR Jr, Welch HG.** Criteria for maximal oxygen uptake: review and commentary. Med Sci Sports Exerc 1995;27(9):1292-301.
20. **Posner JD, Gorman KM, Klein HS, Woldow A.** Exercise capacity in the elderly. Am J Cardiol 1986;57(5):52C-58C.
21. **Gill TM, DiPietro L, Krumholz HM.** Role of exercise stress testing and safety monitoring for older persons starting an exercise program. JAMA 2000;284(3):342-9.
22. **Hollenberg M, Ngo LH, Turner D, Tager IB.** Treadmill exercise testing in an epidemiologic study of elderly subjects. J Gerontol A Biol Sci Med Sci 1998;53(4):B259-67.
23. **Amann M, Subudhi AW, Walker J, Eisenman P, Shultz B, Foster C.** An evaluation of the predictive validity and reliability of ventilatory threshold. Med Sci Sports Exerc 2004;36(10):1716-22.
24. **Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al.** ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (ACC/AHA/ASE Committee to update the 1997 guidelines for the clinical application of echocardiography). Circulation 2003;108(9):1146-62.
25. **Lebeau R, Di Lorenzo M, Amyot R, Veilleux M, Lemieux R, Sauvé C.** A new tool for estimating left ventricular ejection fraction derived from wall motion score index. Can J Cardiol 2003;19(4):397-404.
26. **Harnett JD, Murphy B, Collingwood P, Purchase L, Kent G, Parfrey PS.** The reliability and validity of echocardiographic measurement of left ventricular mass index in hemodialysis patients. Nephron 1993;65(2):212-4.
27. **Akkerman M, van Brussel M, Bongers BC, Hulzebos EH, Helders PJ, Takken T.** Oxygen uptake efficiency slope in healthy children. Pediatr Exerc Sci 2010;22(3):431-41.
28. **Arena R, Guazzi M, Myers J, Chase P, Bensimhon D, Cahalin LP, et al.** The relationship between minute ventilation and oxygen consumption in heart failure: comparing peak VE/VO_2 and the oxygen uptake efficiency slope. Int J Cardiol 2012;154(3):384-5.
29. **Wu C, Guo J, Liu H, Pudasaini B, Yang W, Zhao Q, et al.** The

correlation of decreased heart rate recovery and chronotropic incompetence with exercise capacity in idiopathic pulmonary arterial hypertension patients. Biomed Res Int 2017;2017:3415401.

30. **Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, et al.** Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation 2001;103(7):967-72.
31. **Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats AJ.** Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. Circulation 1996;93(5):940-52.
32. **Scott AC, Francis DP, Davies LC, Ponikowski P, Coats AJ, Piepoli MF.** Contribution of skeletal muscle 'ergoreceptors' in the human leg to respiratory control in chronic heart failure. J Physiol 2000;529(Pt 3):863-70.
33. **Sullivan MJ, Cobb FR.** The anaerobic threshold in chronic heart failure. Relation to blood lactate, ventilatory basis, reproducibility, and response to exercise training. Circulation 1990;81(1 Suppl):II47-58.
34. **Bocchi EA, Guimarães GV, Moreira LF, Bacal F, de Moraes AV, Barreto AC, et al.** Peak oxygen consumption and resting left ventricular ejection fraction changes after cardiomyoplasty at 6-month follow-up. Circulation 1995;92(9 Suppl):II216-22.