Observational Study

Medicine

OPEN

Peak oxygen uptake and respiratory muscle performance in patients with chronic obstructive pulmonary disease

Clinical findings and implications

Hee-Eun Choi, MD[a], Eun-Ho Min, MD[a,*], Hyun-Kuk Kim, MD[b], Hyo-Jung Kim, MD[b], Hang-Jea Jang, MD[b]

Abstract

The maximal oxygen uptake (VO_{2max}) is the gold standard measure of aerobic exercise capacity and is an important outcome measure in patients with chronic obstructive pulmonary disease (COPD). And respiratory muscle performance is also an important functional parameter for COPD patients. In addition to the traditional respiratory muscle strength test, the Test of Incremental Respiratory Endurance has recently been introduced and validated in patients with COPD. However, the relationship between VO_2 and respiratory muscle performance in COPD is not well understood. Therefore, this study investigated the correlations among VO_2 and respiratory muscle performance and other functional markers in COPD. A total of 32 patients with COPD were enrolled. All study participants underwent the following assessments: cardiopulmonary exercise test, pulmonary function test, respiratory muscle strength test, peripheral muscle strength test, and bioelectrical impedance analysis. When comparing VO_{2peak} and respiratory muscle parameters, the sustained maximal inspiratory pressure (SMIP) was the only factor with a significant relationship with VO_{2peak}. Among other functional parameters, the forced expiratory volume in one second (FEV_1) showed the strongest correlation with VO_{2peak}. It was followed by phase angle values of lower limbs, leg extension peak torque, age, and total skeletal muscle mass. When comparing respiratory muscle performance with other functional parameters, the SMIP showed the strongest correlation with hand grip strength, followed by peak cough flow, forced vital capacity, maximal inspiratory pressure, and FEV_1. The results showed that the SMIP was more significantly correlated with VO_{2peak} than the static measurement of respiratory muscle strength. This suggests that TIRE may be a useful assessment tool for patients with COPD. Additionally, FEV_1 and other functional markers were significantly correlated with VO_{2peak}, suggesting that various parameters may be used to evaluate aerobic power indirectly.

Abbreviations: BMI = body mass index, COPD = chronic obstructive pulmonary disease, CPET = cardiopulmonary exercise test, FEV_1 = forced expiratory volume in one second, FFM = fat-free mass, FVC = forced vital capacity, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, mMRC = modified Medical Research Council, PCF = peak cough flow, SMIP = sustained maximal inspiratory pressure, SMM = skeletal muscle mass, TIRE = Test of Incremental Respiratory Endurance, VE/VCO_2 = minute ventilation/carbon dioxide production, VO_2 = oxygen uptake.

Keywords: aerobic power, chronic obstructive pulmonary disease, muscle strength, peak oxygen uptake, pulmonary function test

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an airway disease characterized by progressive and irreversible airway obstruction, usually caused by exposure to noxious particles or gases.[1] The global prevalence of COPD in people over 30 years of age increased from 10.7% in 1990 to 11.7% (men, 14.3%; women, 7.6%) in 2010.[2] Many COPD patients experience dyspnea, exercise intolerance, and muscle dysfunction. Many parameters have been developed and widely used to assess these pathologic conditions.

Aerobic power is an important outcome measure, as many COPD patients complain of exercise intolerance and exertional dyspnea.[3] The maximal oxygen uptake (VO_{2max}) is the gold standard measure of aerobic exercise capacity, and the American Heart Association now considers VO_2 a vital sign.[4]

This work was supported by the 2019 Inje University research grant. The funder had no role in the design of the study; collection, analysis, and interpretation of data; or writing of the manuscript.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

[a] Department of Physical Medicine and Rehabilitation, Inje University Haeundae Paik Hospital, Busan, Korea, [b] Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan, Korea.

*Correspondence: Eun-Ho Min, Department of Physical Medicine and Rehabilitation, Inje University Haeundae Paik Hospital, 875, Haeun-daero, Haeundae-gu, Busan, Korea (e-mail: minis58@naver.com).

How to cite this article: Choi H-E, Min E-H, Kim H-K, Kim H-J, Jang H-J. Peak oxygen uptake and respiratory muscle performance in patients with chronic obstructive pulmonary disease: Clinical findings and implications. Medicine 2022;101:42(e31244).

Received: 9 December 2021 / Received in final form: 15 September 2022 / Accepted: 19 September 2022

http://dx.doi.org/10.1097/MD.0000000000031244

VO_2 can be measured through a cardiopulmonary exercise test (CPET). However, it is difficult to perform a CPET in a patient with poor physical function, gait impairment, or musculoskeletal disease.[5] And special equipment, including a treadmill, gas analyzer, electrocardiogram device, and blood pressure monitor, are needed to perform a CPET. So there have been many studies trying to establish simpler tests for assessing a patient's aerobic power. For example, a six-minute walk test is widely used to assess a patient's exercise tolerance. However, the six-minute walk distance is not a direct indicator of aerobic power and is affected by skeletal, muscular function, balance, and leg pain. Kim et al[6] also reported many limitations in predicting VO_2 through six-minute walk test.

Pulmonary function is decreased in COPD patients, and the parameters such as forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio are reduced. Chronic inflammation and structural changes in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature are the main pathophysiologies of COPD. Matarese and Santulli[7] reported that angiogenesis is also a crucial component of lung pathophysiology, and it can control and orchestrate the progression of airway remodeling. Respiratory muscle dysfunction is also an important clinical feature in COPD patients. Respiratory muscle performance has been assessed by measuring maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). Recently, the Test of Incremental Respiratory Endurance (TIRE) has been introduced and validated in patients with COPD.[8] This test can measure MIP, sustained maximal inspiratory pressure (SMIP), and inspiratory duration by recording the entire inspiratory process.

Peripheral muscle dysfunction also plays an important role in exercise intolerance in COPD patients. Several factors, including physical inactivity, malnutrition, and drug use, contribute to muscle dysfunction. Furthermore, Barreiro and Gea[9] reported that biological mechanisms, including systemic inflammation, muscle fiber changes, and reduced oxidative enzymes, also contribute to muscle dysfunction. Maltais et al[10] reported that reduced oxidative metabolism results in premature muscle acidosis and a higher accumulation of inorganic phosphate. Decreased capillary density is also considered to contribute to progressive muscle wasting. Basic et al[11] reported that tumor necrosis factor increases the expression of specific proteins and disturbs angiogenesis in skeletal muscle in COPD patients. Several parameters, including hand grip strength, quadriceps muscle strength, and muscle mass, have been widely used for evaluating peripheral muscle. Recent radiologic analysis of skeletal muscles is also used to measure muscle volume. Tashiro et al[12] compared the cross-sectional area of the pectoralis muscles and erector spinae muscles with VO_2 at peak exercise, and found a significant correlation between them.

Despite many previous studies, the relationship between VO_2 and respiratory muscle performance in COPD is not well understood. Therefore, this study aimed to investigate the relationship between VO_2 and respiratory muscle performance in patients with COPD. And we also analyzed correlations between VO_2 and other parameters to determine which parameters can be used to predict aerobic power in situations where a CPET cannot be performed.

2. Material and Methods

2.1. Experimental design

We performed the following assessments on COPD patients: CPET, pulmonary function test, respiratory muscle strength test, peripheral muscle strength test, and bioelectrical impedance analysis. And we analyzed the relationship between VO_{2peak} and respiratory muscle performance, the relationship between VO_{2peak} and other functional parameters, and the relationship between respiratory muscle parameters and other functional parameters. Additionally, we classified the patients into five groups according to the VO_{2peak} criteria and analyzed the differences in each outcome among the five groups.

2.2. Participants

A total of 32 patients with COPD (31 men and 1 woman) who visited the Department of Pulmonary Medicine of Inje University Haeundae Paik Hospital between April 2020 and April 2021 were enrolled in the study. The inclusion criteria were as follows: age > 40 years, diagnosis of COPD (the presence of a post-bronchodilator FEV_1/FVC < 0.70), and agreement to provide informed consent for the study. The exclusion criteria were as follows: inability to undergo the pulmonary function test and CPET, pregnancy or planning to conceive during the study period, respiratory disease other than COPD, neuromuscular disease, current immunosuppression treatment, and refusal to provide informed consent for the study.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Inje University Haeundae Hospital Institutional Review Board (approval no. 2020-03-007). All participants provided written informed consent after receiving a detailed explanation of the study protocol. In addition, this study was registered at the Clinical Research Information Service (approval no. KCT0005032).

2.3. CPET

To determine the individual's aerobic power, all participants underwent CPET using a modified Bruce protocol. CPET was performed using a real-time recording 12-channel electrocardiogram (CASE; GE Healthcare, Waukesha, WI), respiratory gas analyzer (Quark-CPET, COSMED, Rome, Italy), automatic blood pressure and pulse monitor (Tango M2; SunTech Medical, Morrisville, NC), and treadmill (T2100-ST2, GE Healthcare). The VO_{2peak} and minute ventilation/carbon dioxide production (VE/VCO_2) slope values were recorded.[5,13] VO_{2peak} was defined as the highest 20 seconds-interval average measured during the last one minute of the CPET. Termination of the CPET was determined according to the American College of Sports Medicine guidelines and included factors such as the achievement of a rate of perceived exertion of 17 (hard to very hard) and a respiratory exchange ratio of > 1.10. Additionally, the participants were classified into five groups (very poor, poor, fair, good, and very good) according to the VO_{2peak} criteria for healthy Korean adults[14] (see Table S1, http://links.lww.com/MD/H684, Supplemental Digital Content, which describes the VO_{2peak} criteria for healthy Korean adults).

2.4. Pulmonary function test

In accordance with the American Thoracic Society/European Respiratory Society guidelines, all participants underwent post-bronchodilator spirometry (VMAX 22 spirometer; Sensormedics, Yorba Linda, CA).[15] The participants inhaled 400 μg salbutamol 20 minutes before testing. We measured FVC, FEV_1, and FEV_1/FVC ratio.

The peak cough flow (PCF) was assessed using an Asthma Mentor Peak Flow Meter (Respironics, Murrysville, PA).[16] Participants performed a quick and explosive expiration after maximal inspiration in the sitting position. The average value from the three tests was calculated.

2.5. Respiratory muscle strength test

MIP and MEP were measured using Pony FX (COSMED).[17] The highest value among the three trials was adopted.

The TIRE was conducted using a PrO_2 device (PrO2 Health Incorporated, Smithfield, RI). The participants performed maximal sustained inspiration after maximal expiration in the sitting position.[8] SMIP, which represented the area under the inspiration curve, was measured.[18]

2.6. Peripheral muscle strength test

Hand grip strength was measured three times for each hand using a Jamar® Smart hand dynamometer (Patterson Medical Ltd., Nottinghamshire, UK). The highest value of the three measurements was recorded.[19] Isokinetic knee flexion and extension tests were performed at a velocity of 120°/s using a Biodex isokinetic dynamometer (Biodex Medical Systems, Shirley, NY).[20]

2.7. Bioelectrical impedance analysis

InBody S10 (InBody, Seoul, Korea) was used to measure skeletal muscle mass (SMM), fat-free mass (FFM), and phase angle.[21,22]

2.8. Statistical analysis

All continuous values are described as mean ± standard deviation, and categorical values are expressed as the absolute number. We calculated the Pearson correlation coefficients to assess the relationship between VO_{2peak} and other variables for which normality was assumed through Mardia's kurtosis test. For variables for which normality was not assumed, we calculated the Spearman correlation coefficient. Only total SMM was not assumed for normality and was therefore correlated by Spearman. To test for homogeneity of variance, we analyzed the spread of the scatterplot between variables. All variables showed a similar spread across their ranges, confirming the homogeneity of variance. Therefore, all variables except total SMM were correlated by Pearson. For comparisons among groups classified according to the VO_{2peak} criteria, we used the Kruskal–Wallis test because the sample size of group 2 was so small that normality was not assumed. We used R 4.0.2 (The R Foundation of Statistical Computing, Vienna, Austria) for Mardia's kurtosis test. SPSS 25 (SPSS Inc., Chicago, IL) was used for the rest of the statistical analyses. In all analyses, a P value < .05 was considered significant.

3. Results

Table 1 shows the participants' baseline characteristics. The average age was 69.09 years, and the mean body mass index (BMI) was 22.58 kg/m². With respect to smoking status, ex-smokers were the most predominant (18 participants). Concerning the dyspnea score, participants with modified Medical Research Council (mMRC) grade 1 had the highest proportion (19 participants). The mean FEV_1/FVC was 57.31%, and the mean FEV_1 (% predicted) was 68.34%, corresponding to Global Initiative for Chronic Obstructive Lung Disease stage 2 (moderate disease).

3.1. Relationship between VO_{2peak} and respiratory muscle performance

Table 2 shows the relationship between VO_{2peak} and respiratory muscle performance. VO_{2peak} showed a significant positive correlation with SMIP (R = 0.450, P = .010). By contrast, it was not significantly correlated with MIP (R = 0.074, P = .689) and MEP (R = 0.032, P = .863).

Table 1

Participants' baseline characteristics.

Characteristics, N = 32	
Sex, male/female	31/1
Age (yr)	69.09 ± 5.47
Body weight (kg)	64.36 ± 8.21
Height (m)	1.69 ± 0.06
BMI (kg/m²)	22.58 ± 2.71
Hypertension	11 (34%)
Diabetes	7 (22%)
Dyslipidemia	4 (13%)
Smoking status	
Never smoker	6 (19%)
Ex-smoker	18 (56%)
Current smoker	8 (25%)
FEV_1 (% predicted)	68.34 ± 19.7
FEV_1/FVC (%)	57.31 ± 16.09
mMRC grade	
0	1 (3%)
1	19 (59%)
2	7 (22%)
3	5 (16%)
4	0 (0%)

BMI = body mass index, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, mMRC = modified Medical Research Council.

Table 2

Relationship between peak oxygen uptake (VO_{2peak}/kg) and respiratory muscle performance.

	Mean ± SD	Coefficient	P value
VO_{2peak}/kg (mL/min/kg)	21.75 ± 5.57	–	–
MIP (cm H_2O)	62.75 ± 20.25	0.074	.689
MEP (cm H_2O)	68.62 ± 21.39	0.032	.863
SMIP (PTU)	324.97 ± 147.08	0.450	.010*

MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, PTU = pressure time units, SD = standard deviation, SMIP = sustained maximal inspiratory pressure, VO_2 = oxygen uptake.

*A P value < .05 was considered significant.

3.2. Relationship between VO_{2peak} and other functional parameters

Table 3 shows the relationship between VO_{2peak} and the other functional parameters. Among the pulmonary function parameters, the FEV_1 (L) showed the strongest correlation with VO_{2peak} (the scatterplot is shown in Fig. 1). It was followed by FEV_1 (% predicted), FVC (L), FVC (% predicted), and PCF; however, VO_{2peak} was not significantly correlated with the VE/VCO_2 slope. VO_{2peak} was negatively correlated with age and not significantly correlated with BMI. VO_{2peak} showed positive correlations with all peripheral muscle strength parameters (hand grip strength, leg extension peak torque, and leg flexion peak torque), as well as with all Bioelectrical impedance analysis (BIA) parameters (except for the phase angle of the left arm).

3.3. Relationship between respiratory muscle performance and other functional parameters

Table 4 shows the relationship between respiratory muscle performance and other functional parameters. MIP was positively correlated with SMIP, right-hand grip strength, SMM of upper extremities, and phase angles of the right upper and left lower extremities. No parameters showed significant correlations with MEP. SMIP showed positive correlations with $VO_{2peak,}$ FVC (L),

Table 3

Relationship between peak oxygen uptake (VO_{2peak}/kg) and other functional parameters.

	Mean ± SD	Coefficient	*P* value
Age (yr)	69.09 ± 5.47	−0.557	<.001*
BMI (kg/m²)	22.58 ± 2.71	0.023	.899
VE/VCO_2 slope	38.91 ± 9.13	−0.312	.083
FVC (L)	3.74 ± 0.95	0.509	.003*
FVC (% predicted)	86.91 ± 19.64	0.444	.011*
FEV_1 (L)	2.09 ± 0.65	0.697	<.001*
FEV_1 (% predicted)	68.34 ± 19.70	0.540	.001*
FEV_1/FVC (%)	57.31 ± 16.09	0.220	.227
PCF (L/min)	288.12 ± 86.26	0.473	.006*
Hand grip strength Rt (kg)	31.52 ± 8.91	0.468	.007*
Hand grip strength Lt (kg)	30.63 ± 8.17	0.453	.009*
Leg extension peak torque Rt (N·m)	67.70 ± 21.42	0.508	.003*
Leg extension peak torque Lt (N·m)	71.07 ± 21.23	0.542	.001*
Leg flexion peak torque Rt (N·m)	33.47 ± 15.92	0.427	.015*
Leg flexion peak torque Lt (N·m)	36.32 ± 15.65	0.517	.002*
SMM_Total (kg)	27.77 ± 5.00	0.525	.002*
SMM_Rt upper limb (kg)	2.62 ± 0.51	0.411	.020*
SMM_Lt upper limb (kg)	2.61 ± 0.48	0.398	.024*
SMM_Rt lower limb (kg)	7.85 ± 1.18	0.510	.003*
SMM_Lt lower limb (kg)	7.81 ± 1.22	0.523	.002*
FFM_Total (kg)	48.75 ± 5.72	0.494	.004*
PhA_Rt upper limb (°)	5.34 ± 0.67	0.423	.016*
PhA_Lt upper limb (°)	5.26 ± 0.66	0.331	.064
PhA_Rt lower limb (°)	5.05 ± 0.86	0.568	<.001*
PhA_Lt lower limb (°)	4.90 ± 0.83	0.666	<.001*

BMI = body mass index, FEV_1 = forced expiratory volume in one second, FFM = fat-free mass, FVC = forced vital capacity, Lt = left, PCF = peak cough flow, PhA = phase angle, Rt = right, SD = standard deviation, SMM = skeletal muscle mass, VE/VCO_2 = minute ventilation/carbon dioxide production.
*A *P* value < .05 was considered significant.

FVC (% predicted), FEV_1 (L), FEV_1 (% predicted), PCF, and MIP. SMIP was also positively correlated with the grip strength of both hands, left leg extension peak torque, SMM of upper extremities, total FFM, and phase angle of all extremities. Among all functional parameters, the right-hand grip strength showed the strongest correlation with SMIP (the scatterplot is shown in Fig. 2).

3.4. Comparisons among groups classified according to VO_{2peak}

Table 5 shows the comparisons among groups classified according to VO_{2peak}. On the basis of the VO_{2peak} criteria,[14] 20 patients were classified into the very poor group (Group 1), four patients into the poor group (Group 2), and eight patients into the fair group (Group 3). None of the patients belonged to the good or very good groups. Age and BMI showed no significant differences among the three groups. Of the pulmonary function parameters, FVC (L) was significantly different among the three groups; however, other parameters did not show significant differences. The respiratory muscle strength parameters (MIP, MEP, and SMIP) showed no significant differences among the three groups. Regarding the peripheral muscle strength parameters, only the right leg extension peak torque showed significant differences among the three groups. Of the BIA parameters, both leg SMM and total FFM showed significant differences among the three groups.

4. Discussion

This study investigated the relationship between VO_{2peak} and respiratory muscle performance in patients with COPD. Respiratory muscle dysfunction, resulting in decreased MIP and MEP, is often observed in patients with COPD.[23–25] In this study, the mean MIP was 62.75, and the mean MEP was 68.62, which were lower than the average values reported in healthy adults,[26,27] consistent with the general findings of the previous studies.[28] However, MIP and MEP did not show a significant correlation with VO_{2peak}. By contrast, SMIP, a parameter reflecting endurance, showed a significant correlation with VO_{2peak}. In other words, time-dependent respiratory pressure

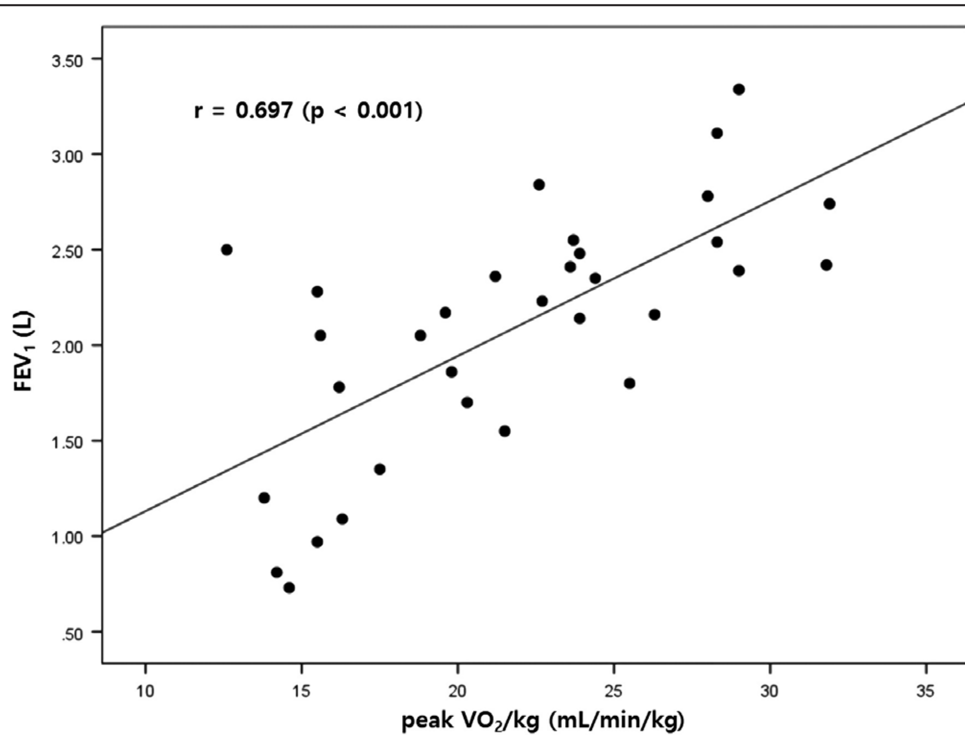

Figure 1. Scatterplot of the relationship between VO_{2peak}/kg and FEV_1 (L). FEV_1 = forced expiratory volume in one second, VO_2 = oxygen uptake.

Table 4

Relationship between respiratory muscle performance and other functional parameters.

	MIP (cm H_2O)		MEP (cm H_2O)		SMIP(PTU)	
Variable	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
VO_{2peak}/kg (mL/min/kg)	0.074	.689	0.032	.863	0.450	.010*
Age (yr)	–0.225	.216	–0.022	.906	–0.336	.060
BMI (kg/m²)	0.202	.267	0.156	.394	0.153	.404
VE/VCO_2 slope	0.242	.182	–0.073	.692	0.193	.291
FVC (L)	0.178	.330	0.061	.741	0.520	.002*
FVC (% predicted)	0.159	.386	–0.001	.997	0.560	<.001*
FEV_1 (L)	0.191	.295	0.064	.729	0.490	.004*
FEV_1 (% predicted)	0.127	.490	–0.001	.995	0.439	.012*
FEV_1/FVC (%)	0.053	.773	0.036	.844	–0.022	.904
Peak cough flow (L/min)	0.290	.107	0.196	.282	0.612	<.001*
MIP (cm H_2O)	–	–	0.344	.054	0.498	.004*
MEP (cm H_2O)	0.344	.054	–	–	0.042	.821
SMIP (PTU)	0.498	.004*	0.042	.821	–	–
Hand grip strength Rt (kg)	0.390	.027*	0.266	.141	0.673	<.001*
Hand grip strength Lt (kg)	0.210	.250	0.302	.093	0.626	<.001*
Leg extension peak torque Rt (N·m)	–0.111	.545	0.159	.384	0.285	.114
Leg extension peak torque Lt (N·m)	0.120	.515	0.069	.706	0.375	.035*
Leg flexion peak torque Rt (N·m)	0.123	.503	0.236	.194	0.296	.100
Leg flexion peak torque Lt (N·m)	0.122	.504	0.199	.275	0.330	.065
SMM_Total (kg)	0.223	.221	0.200	.271	0.280	.121
SMM_RtUEx (kg)	0.370	.037*	0.235	.195	0.421	.016*
SMM_LtUEx (kg)	0.369	.038*	0.272	.133	0.400	.023*
SMM_RtLEx (kg)	0.131	.476	0.109	.553	0.340	.057
SMM_LtLEx (kg)	0.123	.503	0.131	.477	0.308	.086
FFM_Total (kg)	0.319	.075	0.228	.210	0.351	.049*
PhA_RtUEx (°)	0.384	.030*	0.162	.376	0.460	.008*
PhA_LtUEx (°)	0.329	.066	0.153	.403	0.414	.018*
PhA_RtLEx (°)	0.328	.067	0.106	.562	0.472	.006*
PhA_LtLEx (°)	0.403	.022*	0.092	.617	0.504	.003*

BMI = body mass index, FEV_1 = forced expiratory volume in one second, FFM = fat-free mass, FVC = forced vital capacity, Lt = left, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, PCF = peak cough flow, PhA = phase angle, PTU = pressure time units, Rt = right, SMIP = sustained maximal inspiratory pressure, SMM = skeletal muscle mass, VE/VCO_2 = minute ventilation/carbon dioxide production, VO_2 = oxygen uptake.

*A *P* value < .05 was considered significant.

measurements could better reflect aerobic power than a static respiratory pressure measurement. It means that the TIRE, which measures SMIP, could be a useful tool for assessing aerobic power in patients with COPD. These findings are consistent with the study of Formiga et al,[29] which revealed that SMIP was significantly correlated with the six-minute walk distance. In other words, the TIRE better reflected the overall functional state of patients with COPD than traditional methods that measure MIP and MEP only.

Peripheral muscle dysfunction is also major comorbidity in patients with COPD. In this study, all peripheral muscle strength parameters showed significant positive correlations with VO_{2peak}, implying that patients with weak limb muscles have lower aerobic power. Furthermore, SMM, FFM, and phase angle showed a significant correlation with VO_{2peak}, confirming that muscle mass also plays an important role in an individual's aerobic power. Meanwhile, when comparing respiratory muscle and peripheral muscle parameters, SMIP and MIP showed more significant correlations with the upper limb muscle parameters than the lower limb muscle parameters. This implies that upper limb exercise is important to strengthen respiratory muscle, which is consistent with DePalo et al[30]

Among the pulmonary function parameters, FEV_1 (L) was most strongly correlated with the VO_{2peak}. FEV_1 (% predicted) also showed a strong positive correlation with VO_{2peak}, indicating that patients with more severe COPD had lower aerobic power. These results are consistent with those of other studies by Ganju et al[31] and Babb et al,[32] which reported significant correlations between FEV_1 and VO_{2peak}. FVC also showed a significant positive correlation with VO_{2peak}, consistent with previous studies.[33,34] Yuan et al[35] reported that the difference between forced and slow vital capacity, which indicates small airway collapse, significantly correlated with VO_{2peak}. FVC and FEV_1 were also strongly correlated with SMIP. These findings are consistent with the study of Formiga et al,[36] which reported that SMIP was correlated with pre- and post-bronchodilator FVC and FEV_1.

The average PCF value in our patients was 288 L/min, which was lower than the normal value of healthy adults. Cardoso et al[37] reported that the mean PCF values ranged from 316 to 499 L/min in healthy men. It is known that PCF can be used as an assessment tool to identify the risk of developing frequent exacerbation in patients with COPD.[16] In our study, PCF showed a significant correlation with SMIP. This suggests that SMIP can be used as a biomarker for predicting acute exacerbation in patients with COPD. We are conducting further research in this area.

The VE/VCO_2 slope is a well-established CPET measure of ventilatory efficiency, reflecting the matching of alveolar ventilation and pulmonary perfusion.[13,38] In our study, the VE/VCO_2 slope did not show a significant correlation with VO_{2peak}. However, its value in our participants was 38.9 ± 9.13, which corresponds to the worst 10 percentile of healthy men in their 60s and 70s.[39] Neder et al[40] also reported that patients with COPD have high VE/VCO_2 values and that VE/VCO_2 can be used to estimate the risk of all-cause and respiratory mortality in patients with COPD.

In general, the VO_{2peak} value decreases with increasing age.[41] Therefore, we classified the participants into groups according to the VO_{2peak} criteria for Korean adults to adjust for the

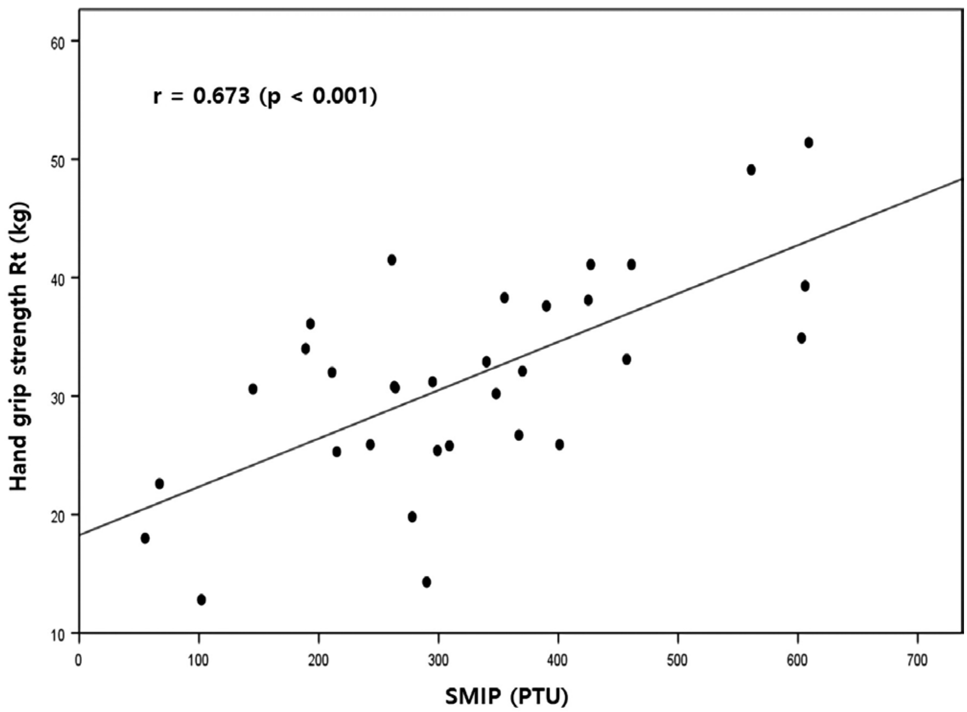

Figure 2. Scatterplot of the relationship between SMIP and right-hand grip strength. PTU = pressure time units, Rt = right, SMIP = sustained maximal inspiratory pressure.

Table 5

Comparisons among groups classified according to VO_{2peak}.

Variable	Group 1 (N = 20)	Group 2 (N = 4)	Group 3 (N = 8)	*P* value
VO_{2peak}/kg (mL/min/kg)	19.45 ± 5.44	25.82 ± 5.53	25.46 ± 1.90	.008*
Age (yr)	68.55 ± 5.92	67.50 ± 6.03	71.25 ± 3.81	.423
BMI (kg/m^2)	22.01 ± 2.52	24.53 ± 2.47	23.04 ± 3.04	.190
VE/VCO_2 slope	39.38 ± 10.35	40.00 ± 3.72	37.20 ± 8.25	.693
FVC (L)	3.41 ± 0.90	4.53 ± 0.76	4.17 ± 0.81	.037*
FVC (% predicted)	80.55 ± 18.50	103.50 ± 20.86	94.50 ± 15.96	.066
FEV_1 (L)	1.91 ± 0.71	2.46 ± 0.63	2.34 ± 0.30	.187
FEV_1 (% predicted)	63.00 ± 21.43	78.25 ± 18.89	76.75 ± 10.08	.337
FEV_1/FVC (%)	57.85 ± 19.09	55.00 ± 15.01	57.12 ± 7.53	.842
PCF (L/min)	269.50 ± 92.31	307.50 ± 51.23	325.00 ± 77.09	.225
MIP (cm H_2O)	63.10 ± 18.91	68.50 ± 26.64	59.00 ± 22.50	.950
MEP (cm H_2O)	65.25 ± 22.61	71.25 ± 21.95	75.75 ± 18.39	.418
SMIP (PTU)	318.60 ± 145.10	328.75 ± 77.21	339.00 ± 189.08	.987
Hand grip strength Rt (kg)	30.14 ± 9.47	33.95 ± 6.95	33.75 ± 8.57	.655
Hand grip strength Lt (kg)	29.28 ± 8.61	31.62 ± 9.17	33.51 ± 6.58	.539
Leg extension peak torque Rt (N·m)	59.97 ± 15.79	89.45 ± 33.23	76.16 ± 18.97	.043*
Leg extension peak torque Lt (N·m)	64.66 ± 17.05	83.85 ± 24.98	80.69 ± 24.97	.116
Leg flexion peak torque Rt (N·m)	29.44 ± 14.61	40.85 ± 19.73	39.84 ± 15.91	.158
Leg flexion peak torque Lt (N·m)	32.17 ± 16.45	40.55 ± 15.96	44.59 ± 10.16	.108
SMM_Total (kg)	27.18 ± 5.83	29.52 ± 0.78	28.35 ± 3.91	.074
SMM_Rt upper limb (kg)	2.47 ± 0.50	2.97 ± 0.16	2.84 ± 0.54	.055
SMM_Lt upper limb (kg)	2.46 ± 0.46	2.98 ± 0.12	2.82 ± 0.50	.058
SMM_Rt lower limb (kg)	7.47 ± 1.14	8.76 ± 0.21	8.36 ± 1.22	.012*
SMM_Lt lower limb (kg)	7.38 ± 1.15	8.76 ± 0.10	8.42 ± 1.22	.013*
FFM_total (kg)	46.72 ± 5.07	53.30 ± 0.80	51.54 ± 6.50	.009*
PhA_Rt upper limb (°)	5.22 ± 0.71	5.75 ± 0.42	5.44 ± 0.66	.346
PhA_Lt upper limb (°)	5.14 ± 0.66	5.65 ± 0.67	5.36 ± 0.66	.359
PhA_Rt lower limb (°)	4.85 ± 0.89	5.70 ± 1.04	5.24 ± 0.53	.132
PhA_Lt lower limb (°)	4.66 ± 0.87	5.52 ± 0.96	5.18 ± 0.35	.106

BMI = body mass index, FEV_1 = forced expiratory volume in one second, FFM = fat-free mass, FVC = forced vital capacity, Lt = left, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, PCF = peak cough flow, PhA = phase angle, PTU = pressure time units, Rt = right, SMIP = sustained maximal inspiratory pressure, SMM = skeletal muscle mass, VE/VCO_2 = minute ventilation/carbon dioxide production, VO_2 = oxygen uptake.

*A *P* value < .05 was considered significant.

age factor and further analyzed the differences in functional parameters among the groups. Only eight participants (25%) had average aerobic power according to the VO_{2peak} criteria, and none of them had good or very good exercise capacity. This means that even ambulatory COPD patients with mild dyspnea have low aerobic power compared with healthy adults of the same age, which was consistent with previous studies.[3,42,43] The FVC (L), right leg extension peak torque, SMM of both legs, and total FFM showed significant differences among the three groups. Interestingly, only the parameters of the lower extremities, not the upper extremities, showed significant differences among groups. This means that lower limb muscle function is more important in aerobic power. Since aerobic power was measured using a treadmill in this study, patients with greater lower limb muscle function could walk better on a treadmill and, as a result, could achieve higher VO_2.

To the best of our knowledge, this is the first study to examine the relationship between the TIRE measures and VO_{2peak} in subjects with COPD. Our findings confirmed that SMIP is significantly associated with the VO_{2peak} than the static measurement of respiratory muscle strength. However, this study also has limitations. First, when the participants were classified into groups according to VO_{2peak} criteria, the number of patients in each group was small. Future studies, including a large number of participants, are needed for higher reliability. Second, as our study participants showed a male predominance, it is difficult to apply the results of this study to female patients with COPD. Third, as this was a cross-sectional study, future studies will need to analyze the parameters that change prominently over time through follow-up investigations. Fourth, we could not control drugs such as diuretics and menstrual periods during the BIA test. This may have caused measurement bias of SMM, FFM, and phase angle.

5. Conclusion

We investigated the relationship between VO_2 and respiratory muscle performance in COPD patients. The results showed that the SMIP was more significantly correlated with VO_{2peak} than MIP and MEP, suggesting that respiratory endurance is an important factor for aerobic power in patients with COPD. And SMIP also showed significant correlations with many other functional parameters. Hence, TIRE could be a useful assessment tool for COPD patients. FEV_1, the severity marker of COPD, had the strongest correlation with $VO_{2peak.}$ And FVC, PCF, peripheral muscle strength, and muscle mass also showed significant correlations with VO_{2peak}. This suggests that various parameters may be used to indirectly evaluate the aerobic power of COPD patients in situations where a CPET cannot be performed.

Acknowledgments

We thank the Inje University Haeundae Paik Hospital for supporting the data analysis.

Author contributions

All authors have read and agreed to the published version of the manuscript.
Conceptualization: Hee-Eun Choi.
Formal analysis: Hee-Eun Choi, Eun-Ho Min.
Funding acquisition: Hee-Eun Choi.
Investigation: Hee-Eun Choi, Eun-Ho Min.
Methodology: Hee-Eun Choi, Eun-Ho Min, Hyo-Jung Kim.
Validation: Hee-Eun Choi, Hyun-Kuk Kim, Hang-Jea Jang.
Visualization: Eun-Ho Min.
Writing – original draft: Hee-Eun Choi, Eun-Ho Min.
Writing – review & editing: Hee-Eun Choi.

References

[1] Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195:557–82.
[2] Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: systematic review and meta-analysis. J Glob Health. 2015;5:020415.
[3] Oga T, Nishimura K, Tsukino M, et al. Exercise capacity deterioration in patients with COPD: longitudinal evaluation over 5 years. Chest. 2005;128:62–9.
[4] Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. Circulation. 2016;134:e653–99.
[5] Guazzi M, Arena R, Halle M, et al. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Eur Heart J. 2018;39:1144–61.
[6] Kim C, Park YB, Mo EK, et al. Predicting oxygen uptake for men with moderate to severe chronic obstructive pulmonary disease. Tuberc Respir Dis. 2008;64:433–8.
[7] Matarese A, Santulli G. Angiogenesis in chronic obstructive pulmonary disease: a translational appraisal. Transl Med UniSa. 2012;3:49.
[8] Formiga MF, Roach KE, Vital I, et al. Reliability and validity of the test of incremental respiratory endurance measures of inspiratory muscle performance in COPD. Int J Chron Obstruct Pulmon Dis. 2018;13:1569–76.
[9] Barreiro E, Gea J. Respiratory and limb muscle dysfunction in COPD. COPD. 2015;12:413–26.
[10] Maltais F, LeBlanc P, Whittom F, et al. Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. Thorax. 2000;55:848–53.
[11] Basic VT, Jacobsen A, Sirsjö A, et al. TNF stimulation induces VHL overexpression and impairs angiogenic potential in skeletal muscle myocytes. Int J Mol Med. 2014;34:228–36.
[12] Tashiro H, Takahashi K, Tanaka M, et al. Skeletal muscle is associated with exercise tolerance evaluated by cardiopulmonary exercise testing in Japanese patients with chronic obstructive pulmonary disease. Sci Rep. 2021;11:1–8.
[13] Herdy AH, Ritt LE, Stein R, et al. Cardiopulmonary exercise test: background, applicability and interpretation. Arq Bras Cardiol. 2016;107:467–81.
[14] Gleim GW, Nicholas JA. Metabolic costs and heart rate responses to treadmill walking in water at different depths and temperatures. Am J Sports Med. 1989;17:248–52.
[15] Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med. 2019;200:e70–88.
[16] El Batrawy S, Elassal G. Is there a role for cough peak flow in assessment of patients with severe COPD? Egypt J Chest Dis Tuberc. 2014;63:837–41.
[17] Khalil M, Wagih K, Mahmoud O. Evaluation of maximum inspiratory and expiratory pressure in patients with chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc. 2014;63:329–35.
[18] Hoffman M, Montemezzo D, Lima S, et al. Sustained maximal inspiratory pressure as a measure to inspiratory muscle function. Eur Clin Respir J. 2015;46(suppl 59):PA4215.
[19] Lee SH, Kim SJ, Han Y, et al. Hand grip strength and chronic obstructive pulmonary disease in Korea: an analysis in KNHANES VI. Int J Chron Obstruct Pulmon Dis. 2017;12:2313–21.
[20] Zawadzki J, Bober T, Siemieński A. Validity analysis of the Biodex System 3 dynamometer under static and isokinetic conditions. Acta Bioeng Biomech. 2010;12:25–32.
[21] Barbosa-Silva MC, Barros AJ, Wang J, et al. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. Am J Clin Nutr. 2005;82:49–52.
[22] Bera TK. Bioelectrical impedance methods for noninvasive health monitoring: a review. J Med Eng. 2014;2014:381251.
[23] Barreiro E, De La Puente B, Minguella J, et al. Oxidative stress and respiratory muscle dysfunction in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171:1116–24.
[24] Marin-Corral J, Minguella J, Ramírez-Sarmiento AL, et al. Oxidised proteins and superoxide anion production in the diaphragm of severe COPD patients. Eur Respir J. 2009;33:1309–19.
[25] Ramirez-Sarmiento A, Orozco-Levi M, Barreiro E, et al. Expiratory muscle endurance in chronic obstructive pulmonary disease. Thorax. 2002;57:132–6.

[26] Neder JA, Andreoni S, Lerario MC, et al. Reference values for lung function tests: II. Maximal respiratory pressures and voluntary ventilation. Braz J Med Biol Res. 1999;32:719–27.
[27] Pessoa I, Sclauser M, Parreira VF, et al. Reference values for maximal inspiratory pressure: a systematic review. Can Respir J. 2014;21:43–50.
[28] Terzano C, Ceccarelli D, Conti V, et al. Maximal respiratory static pressures in patients with different stages of COPD severity. Respir Res. 2008;9:8.
[29] Formiga MF, Vital I, Urdaneta G, et al. The BODE index and inspiratory muscle performance in COPD: clinical findings and implications. SAGE Open Med. 2018;6:2050312118819015.
[30] DePalo VA, Parker AL, Al-Bilbeisi F, et al. Respiratory muscle strength training with nonrespiratory maneuvers. J Appl Physiol. 2004;96:731–4.
[31] Ganju A, Fuladi A, Tayade B, et al. Cardiopulmonary exercise testing in evaluation of patients of chronic obstructive pulmonary disease. Indian J Chest Dis Allied Sci. 2011;53:87.
[32] Babb T, Viggiano R, Hurley B, et al. Effect of mild-to-moderate airflow limitation on exercise capacity. J Appl Physiol. 1991;70:223–30.
[33] Zhou W, Li Y-Q, Chen W-H. Comparison of cardiopulmonary exercise test with resting pulmonary function test in evaluating pulmonary impairment in COPD patients. J Clin Res. 2008:05.
[34] Fatemi R, Ghanbarzadeh M. Relationship between airway resistance indices and maximal oxygen uptake in young adults. J Hum Kinet. 2009;22:29–34.
[35] Yuan W, He X, Xu Q-F, et al. Increased difference between slow and forced vital capacity is associated with reduced exercise tolerance in COPD patients. BMC Pulm Med. 2014;14:1–5.
[36] Formiga MF, Campos MA, Cahalin LP, et al. The test of incremental respiratory endurance is significantly related to pulmonary function in COPD. Eur Clin Respir J. 2017;50(suppl 61):PA2484.
[37] Cardoso FEF, de Abreu LC, Raimundo RD, et al. Evaluation of peak cough flow in Brazilian healthy adults. Int Arch Med. 2012;5:25.
[38] Holverda S, Bogaard HJ, Groepenhoff H, et al. Cardiopulmonary exercise test characteristics in patients with chronic obstructive pulmonary disease and associated pulmonary hypertension. Respiration. 2008;76:160–7.
[39] Arena R, Myers J, Harber M, et al. The VE/VCO2 Slope during Maximal treadmill cardiopulmonary exercise testing: reference standards from FRIEND (Fitness Registry and the Importance of Exercise: A National Database). J Cardiopulm Rehabil Prev. 2021;41:194–8.
[40] Neder JA, Alharbi A, Berton DC, et al. Exercise ventilatory inefficiency adds to lung function in predicting mortality in COPD. COPD. 2016;13:416–24.
[41] Wilson TM, Tanaka H. Meta-analysis of the age-associated decline in maximal aerobic capacity in men: relation to training status. Am J Physiol Heart Circ Physiol. 2000;278:H829–34.
[42] Couser JL, Jr., Guthmann R, Hamadeh MA, et al. Pulmonary rehabilitation improves exercise capacity in older elderly patients with COPD. Chest. 1995;107:730–4.
[43] Zwerink M, van der Palen J, van der Valk P, et al. Relationship between daily physical activity and exercise capacity in patients with COPD. Respir Med. 2013;107:242–8.