Suzan Salama, Aliaë Abd-Rabou Mohamed-Hussein, Doaa M Magdy, Aliaa Salama

Department of Chest Diseases, Faculty of Medicine, Assuit University, Egypt

Cardiopulmonary exercise testing versus pulmonary function test in the assessment of respiratory impairment in chronic obstructive pulmonary disease patients

Abstract

Introduction: Cardiopulmonary exercise testing (CPET) is a non-invasive method for the determination of disability and comprehensive evaluation of exercise responses involving the cardiovascular, pulmonary and musculoskeletal systems.

Material and methods: To assess exercise performance measured by CPET in different chronic obstructive pulmonary disease (COPD) stages and to compare between pulmonary function test (PFT) and CPET in assessing the degree of respiratory impairment. Sixty patients diagnosed with COPD were enrolled in the study. Modified Medical Research Council scale (mMRC) and COPD assessment test (CAT) to evaluate dyspnea symptom. PFT and CPET were performed.

Results: There was a significant decrease in peak VO_2 and anaerobic threshold in patients with stages III, IV ($P < 0.001$), while COPD stage I, II had significantly higher minute ventilation, tidal volume and oxygen pulse ($P < 0.001$). 76.67% of patients were similarly classified by CPET and PFT, while 23.33% were found to be less impaired according to CPET when compared to PFT. A significant correlation between both VE/VO_2 ($r = 0.31$, 95% CI 0.19–0.92, $P < 0.001$) and VE/VCO_2 ($r = 0.69$, 95% CI 0.86–1.08, $P < 0.001$) with FEV_1. Whereas, an inverse correlation were found between both VE/VCO_2 ($r = -0.34$, 95% CI –0.77 –1.11, $P < 0.001$) and VE/VO_2 ($r = -0.55$, 95% CI –0.88 to –0.15, $P < 0.001$), with the degree of air trapping as estimated by RV/TLC ratio. No significant correlation between neither CAT nor MRC and exercise testing parameters.

Conclusions: CPET is an extremely valuable method for the determination of functional capacity and exercise intolerance in COPD rather than PFT. CPET is considered a gold-standard tool for better evaluation of respiratory impairment in COPD.

Key words: cardiopulmonary exercise testing, COPD, peak VO_2, pulmonary function test.

Adv Respir Med. 2022; 90: 202–210

Introduction

It is recognized that the burden of COPD is expected to increase and it is likely to become the third leading cause of death by 2030. Also, COPD has substantial progressive adverse effects on daily symptoms, functional ability, and health status [1]. COPD Assessment Test (CAT) and COPD Clinical Questionnaire (CCQ) are now being used extensively for assessing patients' symptoms and functional state in daily clinical practice. Besides this subjective measure, the functional capacity in COPD could be measured by objective tools such as CPET or 6-min walk distance (6MWD). The severity of COPD is graded by resting pulmonary function tests, however; they may not accurately predict exercise impairment. Exercise intolerance in COPD is usually complex and multifactorial; reflects not only cardiorespiratory status but the global disease severity and prognosis. Though, evaluating exercise capacity allows monitoring of disease and response to treatment [2].

Hypoxemia constitutes the signal limiting exercise performance in COPD documented by arterial blood gases (ABG) and/or pulse oximetry (SpO_2). Additionally, CPET may help to identify whether lung mechanics or another associated factor as skeletal muscle weakness is the main cause of exercise limitation [3].

CPET determines the cardiopulmonary oxygen transport system. It provides data on respiratory gas exchange, including oxygen uptake (VO_2)

Address for correspondence: Doaa M Magdy, Department of Chest Diseases, Faculty of Medicine, Assuit University, Egypt, e-mail: doaamagdy_2020@yahoo.com

DOI: 10.5603/ARM.a2022.0037 | Received: 04.02.2021 | Accepted: 14.12.2021 | Copyright © 2022 PTChP | ISSN 2451–4934 | e-ISSN 2543–6031

which estimate COPD severity. However, PFTs at rest don't reliably reflect exercise performance and exercise-induced hypoxemia [3].

CPET is a useful diagnostic test for evaluating exercise performance in COPD patients; using peak VO_2 as an assessment tool and other factors that may be contributing to exercise limitation [4]. Thus the current study aims to assess exercise performance measured by CPET in different COPD stages and to compare pulmonary function test (PFT) and CPET in the assessment of the degree of impairment.

Material and methods

This prospective cross-sectional analytic study has been conducted in Assiut University Hospital — Chest department, cardiopulmonary exercise testing unit & pulmonary function unit from May 2017 to January 2020. This study was approved by the Ethics of Committee, Faculty of Medicine. Written consent was taken.

Sixty patients (30 male and 30 female) diagnosed as COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [5], who are clinically stable with optimized pharmacological treatment, without a history of lower respiratory tract infection and/or COPD exacerbation within 6 weeks before evaluation were eligible for the study.

COPD patients classified regarding severity as follow: GOLD [(I & II) (n = 34) (mild and moderate) [FEV_1% predicted 80–50%], GOLD [(III & IV) (n = 26) (severe and very severe) $FEV_1 \leq 50\%$]. Furthermore, patients evaluated regarding severity of exercise impairment [peak VO_2] [60–80% = mild, 40–60% = moderate, and < 40% = severe].

Inclusion criteria: Stable COPD patients (at least 3 months without exacerbations) were included. Patients were selected randomly in cross-over 1:1.

Exclusion criteria: Patients with primary cardiac diseases, orthopaedic or neurological conditions, patients with previous lung resection or malignancies, acute pulmonary embolism and severe arterial hypertension.

The following descriptive variables were assessed:

I. Medical history including:

1. Socio-demographic data including age, sex, smoking status and presence of comorbidities.
2. Assessment of dyspnea symptoms using the modified Medical Research Council (mMRC) dyspnea scale [6]. Lower scores represent more breathlessness. The overall health status was assessed by using the COPD Assessment Test (CAT), an 8 items questionnaire. CAT score ranges from 0 to 40, with the higher scores, reflecting a greater burden of disease [7].

II. Resting pulmonary function:

pulmonary function tests were performed by trained technicians using (Cosmed SrL, Quark PFTs ergo, P/N Co9035-12-99, Italy) according to the recommended guidelines.

Measurements fulfilled the American Thoracic Society (ATS) [8] criteria for reproducibility (an agreement within 5%) was recorded in the analysis. Standard parameters were measured: forced expiratory volume in 1 s (FEV_1) and the forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio (FEV_1/FVC). Results were expressed in a litre, litre/second and as a percentage of normal value for gender, age, and height (% predicted) [9].

Whole-body plethysmography was performed, from which the residual volume (RV), total lung capacity (TLC) and RV/TLC ratios could be calculated to estimate gas trapping.

III. Cardiopulmonary exercise test:

All patients were evaluated with an incremental CPET, using treadmill exercise protocol in which the work rate increased at one-minute intervals. (Cosmed SrL, Quark PFTs ergo, P/N Co9035-12-99, Italy). All patients stopped the test due to dyspnea. No cardiovascular complication or primary cardiac reason for termination was observed [10, 11].

The following parameters were observed all over the test:

1. **Metabolic response:** Oxygen consumption VO_2 (mL/ min), VO_2 (mL/kg/min) and Anaerobic Threshold (AT);
2. **Ventilatory response:** Minute ventilation (VE), Breathing reserve (BR), Tidal volume (V_T) and Respiratory frequency (RF);
3. **Cardiovascular response:** Heart rate (HR), Oxygen pulse (VO_2/HR), HR reserve(HRR), Systolic and diastolic blood pressure (BP);
4. **Gas exchange response:** Oxygen saturation (SpO_2), ventilatory equivalent for VO_2 (VE/ /VO_2) and ventilatory equivalent for VCO_2 (VE/VCO_2).

Statistical analysis

Data were collected and analyzed using SPSS (Statistical Package for the Social Science, version

Table 1. Demographic and clinical data of COPD patients included in the study in different stages

	All patients (n = 60)	Stage (I, II) (n = 34)	Stage (III, IV) (n = 26)	P-value
Age (years)	55.70 ± 12.23	58.26 ± 10.73	52.34 ± 13.45	0.06
Gender				
Male	30 (50%)	18 (52.9%)	12 (46.2%)	0.79
Female	30 (50%)	16 (47.1%)	14 (53.8%)	
BMI (kg/m^2)	25.62 ± 3.94	26.02 ± 3.90	25.08 ± 4.01	0.36
Smoking status				
Smoker	9 (15%)	8 (23.5%)	1 (3.8%)	
Non-smoker	31 (51.7%)	16 (47.1%)	15 (57.7%)	0.11
Ex-smoker	20 (33.3%)	10 (29.4%)	10 (38.5%)	
Smoking index, pack\year	37.17 ± 18.03	41.05 ± 20.65	30.73 ± 10.57	0.13
mMRC dyspnea scale	2.65 ± 0.48	2.50 ± 0.51	2.84 ± 0.36	< 0.001
CAT assessment	21.20 ± 4.28	19.55 ± 4.38	23.34 ± 3.09	< 0.001
Number of exacerbations in the last year	6.06 ± 3.14	5.97 ± 3.45	6.19 ± 3.41	0.81
Number of hospital admission in the last year	1.75 ± 1.25	1.71 ± 1.44	1.80 ± 0.98	0.75

Data were expressed in form of frequency (percentage), mean ± (SD). CAT — COPD assessment test; mMRC — modified medical research council

20, IBM, and Armonk, New York). Data were expressed in mean ± SD or number (percentage %). Chi^2-test was used to compare the nominal data of different groups while student t-test was used to compare mean of different two groups and paired t-test was used to compare data of the same group before and after exercise. Spearman's test was used to determine correlation coefficient (r) between the measured parameters. Correlations were considered of statistical importance if p-value was < 0.05.

Results

The patients were categorized into 34 (56.7%) group (1) stage I&II and 26 (43.3%) group (2) stage III and IV.

Table 1 showed that the mMRC dyspnea score and CAT assessment were significantly higher in COPD patients stage (III, IV) compared to stage (I, II) and no differences were observed regarding age, BMI, number of exacerbation and hospitalization.

A significant decrease in peak VO_2 and anaerobic threshold was observed in patients with stages III, IV. Thus, exercise performance measured by CPET results declines significantly with advanced COPD stages. COPD patients in stage I, II had significantly higher minute ventilation and tidal volume. Also, they had significantly lower VE/VO_2 and VE/VCO_2 in comparison to the stage (III, IV) ($P < 0.001$) (Table 2). The pulmonary function parameters of the studied group are presented in Table 3.

The degree of impairment of exercise capacity using the pulmonary function and CPET is shown in Table 4. Based on pulmonary function test; 34 (56.7%), and 26 (43.3%) COPD patients had moderate and severe impairment respectively, while based on a cardiopulmonary exercise test (CPET); 4 (6.7%), 42 (70%), and 14 (23.3%) patients had mild, moderate and severe impairment of exercise capacity.

It was noticed that 32 (94.1%) patients from those with moderate impairment of exercise capacity based on PFT had the same degree of impairment based on CPET while 2 (5.9%) patients from such patients had a degree of impairment with CPFT milder than PFT. In the case of patients with severe impairment with PFT; 14 (53.8%) patients had the same degree with CPET and 12 (46.2%) of them had a milder degree of impairment with CPET (Table 5).

On comparing CPET vs. PFT it was found that 76.6% of patients were similarly classified by both methods while 23.33% were found to be less impaired according to the CPET when compared to PFT. These showed that the PFT has some sort of overestimation of respiratory impairment while CPET is more accurate and more specific.

It was noticed that FEV_1 had a positive significant correlation with VO_2 (% predicted) (Figure 1). There was a statistically significant correlation between both VE/VO_2 (r = 0.31, 95% CI 0.19 to

Table 2. CPET parameters in different stages of COPD in the studied groups

Metabolic response	Stage (I, II) (n = 34)	Stage (III, IV) (n = 26)	P-value
VO_2 (mL/minute)	934.15 ± 126.38	636.15 ± 69.77	< 0.001
VO_2 (mL/minute/kg)	12.81 ± 0.89	10.81 ± 0.76	< 0.001
VO_2 (% predicted)	51.33 ± 5.08	41.76 ± 9.38	< 0.001
RER at (LT)	1.37 ± 0.35	1.41 ± 0.25	0.66
Lactate threshold (LT)(%)	55.47 ± 5.93	49.80 ± 6.14	< 0.001
Ventilatory response			
VE (L/minute)	45.57 ± 6.85	40.15 ± 4.69	< 0.001
BR (%)	27.20 ± 4.69	28.50 ± 4.43	0.26
Tidal volume (L)	1.76 ± 0.21	0.86 ± 0.16	< 0.001
RF (breath/minute)	32.67 ± 3.93	32.19 ± 3.64	0.62
Gas exchange parameters			
V_E/VO_2 at LT	42.88 ± 4.45	55.84 ± 5.99	< 0.001
V_E/VCO_2 at LT	33.17 ± 3.98	38.56 ± 4.79	< 0.001
Pre-SO_2 (%)	93.73 ± 1.76	91.92 ± 1.69	< 0.001
Post-SO_2 (%)	89.23 ± 2.01	87.19 ± 2.44	< 0.001
Cardiovascular response			
Resting HR (beat/min)	79.73 ± 9.25	80.11 ± 7.87	0.86
HR_{max} (beat/min)	130.02 ± 8.56	137.23 ± 13.51	< 0.001
HR reserve (beat/min)	18.61 ± 1.39	21.31 ± 2.53	< 0.001
Oxygen pulse	12.11 ± 1.27	8.51 ± 0.88	< 0.001
Pre-SBP (mmHg)	134.01 ± 6.28	131.56 ± 6.16	0.14
Post-SBP (mmHg)	163.67 ± 13.84	161.46 ± 9.78	0.49
Pre-DBP (mmHg)	74.41 ± 4.47	71.15 ± 5.71	< 0.001
Post-DBP (mmHg)	80.32 ± 3.39	80.19 ± 5.26	0.90

Data were expressed in form of the mean (SD). BR — breathing reserve; DBP — diastolic blood pressure; HR — heart rate; HR_{max} — heart rate at maximum exercise; LT — lactate threshold; Post-SO_2 — post-test arterial oxygen saturation; Pre-SO_2 — pre-test arterial oxygen saturation; RER — respiratory exchange ratio; RF — respiratory frequency; SBP — systolic blood pressure; V_E — minute ventilation; V_E/VCO_2 — ventilatory equivalent for carbon dioxide; V_E/VO_2 — ventilatory equivalent for oxygen; VO_2 — oxygen consumption

0.92, $P < 0.001$) and VE/VCO_2 (r = 0.69, 95% CI –0.86 to 1.08, $P < 0.001$) with FEV_1 (Figure 2, 3).

Moreover, we found a statistically significant inverse correlation between both VE/VCO_2 (r = –0.34, 95% CI –0.7750 to 1.11, $P < 0.001$) and VE/VO_2 (r = –0.55, 95% CI –0.88 to –0.15, $P < 0.001$),with the degree of air trapping as estimated by the RV/TLC ratio (Figure 4, 5). Notably, we found no significant correlation between neither CAT nor MRC and VO_2 (% predicted) or VE/VCO_2 or VE/VO_2.

Discussion

The present study aimed to address the exercise capacity at a different stage of COPD. It was observed that there was a statistical difference in exercise capacity between patients with stages (III and IV) and patients with a stage (I and II). Thus, VO_2 max levels pointed to low exercise performance in moderate to severe COPD patients.

In agreement with our findings, Pinto-Plata et al. studied 453 patients with COPD. Incremental CPET and pulmonary function tests were performed. The patients were categorized into a control group with normal lung function and GOLD stages 1 to 4. The authors noted that exercise capacity decreased with advanced stage COPD, except for patients with stage 1, who had similar performance as the control group [12].

The current study revealed that maximal respiratory gas exchange ratio (RER) had no

Table 3. Pulmonary function in COPD patients in different COPD stages

	Stage (I, II) (n = 34)	Stage (III, IV) (n = 26)	P-value
FEV_1 (L)	1.56 ± 0.47	1.13 ± 0.38	< 0.001
FEV_1 (% predicted)	58.21 ± 5.64	41.89 ± 4.71	< 0.001
FVC (L)	2.14 ± 0.51	1.70 ± 0.51	< 0.001
FVC (% predicted)	83.23 ± 8.01	74.19 ± 9.78	< 0.001
FEV_1/FVC PB	56.35 ± 6.64	55.34 ± 7.71	0.59
MEF_{75} (L)	3.43 ± 0.58	3.49 ± 0.56	0.70
MEF_{75} (% predicted)	75.29 ±15.75	80.84 ± 9.54	0.11
MEF_{50} (L)	2.29 ± 0.66	2.34 ± 0.60	0.87
MEF_{50} (% pred.)	74.76 ± 16.07	75.88 ± 13.83	0.77
$MEF_{25–75}$ (L)	1.37 ± 0.58	1.35 ± 0.61	0.93
$MEF_{25–75}$ (% pred.)	64.08 ± 18.67	65.11 ± 14.55	0.82
RV (L)	3.71 ± 1.12	3.82 ± 1.65	0.32
RV (% predicted)	166 ± 37	175±38	0.01
TLC (L)	6.74 ± 1.75	6.92 ± 1.93	0.43
TLC (% predicted)	118 ± 28	120 ± 24	0.23
RV/TLC (%)	129 ± 13	132 ± 16	0.04

Data was expressed in from of mean (SD). FEV_1 — forced expiratory volume in the 1st second; FVC — forced vital capacity; $MEF_{25–75}$ — mean expiratory flow at 25–75% of the forced vital capacity; MEF_{75} — mean expiratory flow at 75% of the forced vital capacity; MEF_{50} — mean expiratory flow at 50% of the forced vital capacity; PB — post-bronchodilator; RV — residual volume; TLC — total lung capacity

Table 4. Degree of impairment of exercise capacity by PFT and CPET in COPD patients

Degree of impairment	PFT	CPET
Mild	0	4 (6.7%)
Moderate	34 (56.7%)	42 (70%)
Severe	26 (43.3%)	14 (23.3%)

Data were expressed in form of frequency (percentage)

Table 5. Degree of impairment of exercise capacity by CPET in relation to PFT

Impairment by PFT	Degree of impairment by CPET vs PFT	
	Equal to PFT	Milder than PFT
Moderate (n = 34)	32 (94.1%)	2 (5.9%)
Severe (n = 26)	14 (53.8%)	12 (46.2%)
Total (n =60)	46 (76.67%)	14 (23.33%)

Data were expressed in form of frequency (percentage)

significant differences regarding disease severity. The maximal heart rate (HR) was increased with severe COPD (stage III and IV). The lower functional capacity displayed among the studied group of COPD patients may be related to decreased cardiac performance. oxygen pulse was continuously measured as an indirect estimate of cardiac stroke volume during exercise testing. As shown a significant decline were observed across disease severity, which are in agreement with previous studies for COPD patients [13, 14]. These data suggest a significant decline in cardiac stroke volume, which will significantly limit functional capacity. The mechanism for the observed reduction in stroke volume is unclear; however, it may be attributed to the acute and chronic deconditioning hypothesis. Thus, the relative contribution for such decrease in cardiac stroke volume may result from an accelerated deconditioning process and may be secondary to alterations in the myocardium, impairment in the control of capacitance vessels, or both [13, 14].

In this study, we observed that CPET is superior to the PFT for the detection of respiratory impairment. Trying, to assess the degree of agreement between the two measurements in patients with COPD, 34 (56.7%), and 26 (43.3%) patients had moderate and severe impairment as determined by pulmonary function test (PFT). On the

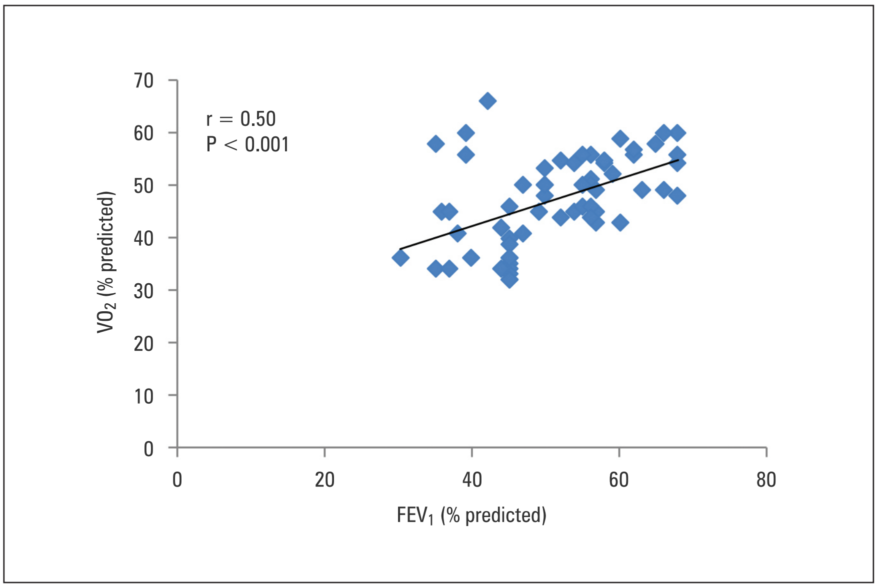

Figure 1. Correlation between FEV_1 (% predicted) and VO_2 (% predicted)

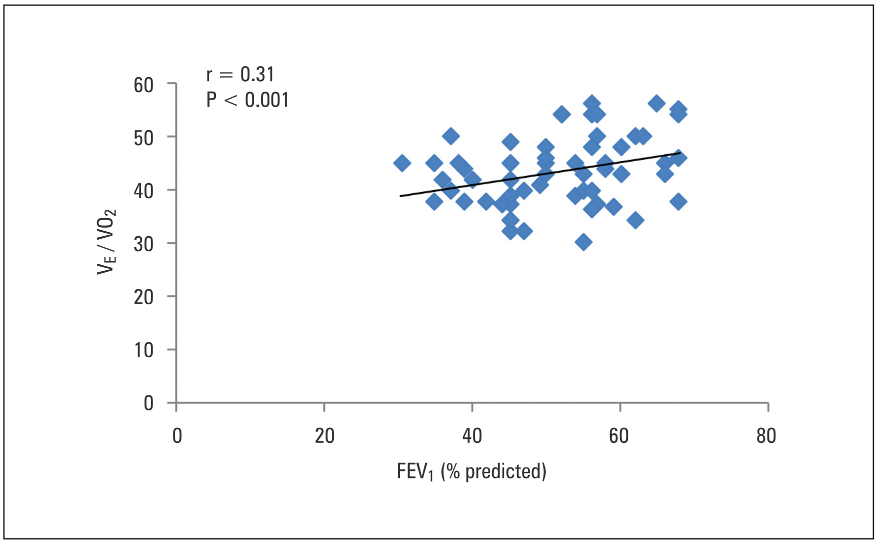

Figure 2. Correlation between FEV_1 (% predicted) and V_E/VO_2

other hand; 4 (6.7%), 42 (70%), and 14 (23.3%) patients had mild, moderate and severe impairment of exercise capacity based on a cardiopulmonary exercise test (CPET). Also, we found 23.3% had a milder impairment classification with the CPET than with the PFT. Though, the pulmonary function testing cannot accurately predict exercise performance in COPD patients and favours the use of the cardiopulmonary exercise test for the routine evaluation of respiratory impairment in COPD patients, particularly for patients with moderate or severe impairment.

Similarly, Fink et al. compared the results of the PFT and CPET in 216 COPD patients concerning the level of impairment. They found a very high rate of disagreement between the two tests. 30.1% were similarly classified by the two methods. On the other hand, 61.1% were found to be less impaired according to the cardiopulmonary exercise test as compared to PFT, and 8.8% were more impaired according to the PFT. Therefore, it may be difficult to predict exercise capacity from resting PFT, even in patients with similar FEV_1 [15].

Another study demonstrated that CPET is useful for determining exercise limitation and for assessing the maximal exercise capacity of patients with COPD [16].

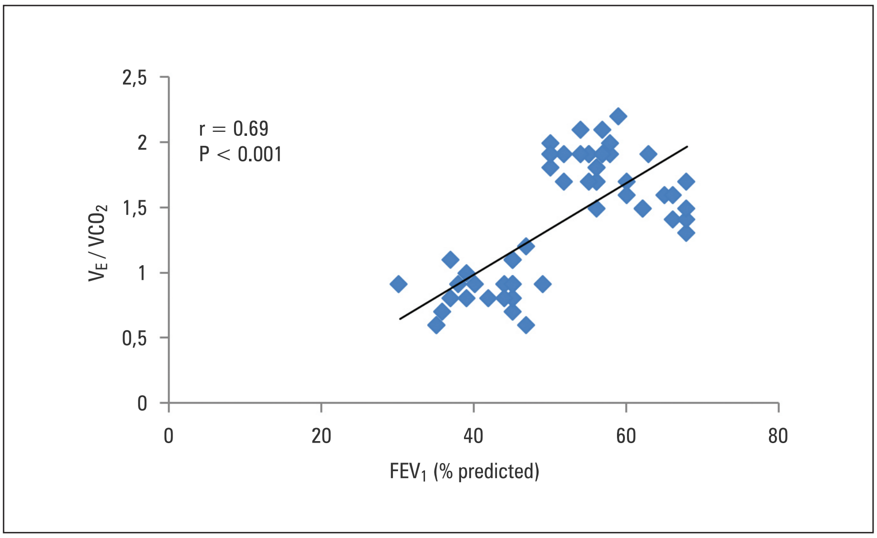

Figure 3. Correlation between FEV_1 (% predicted) and V_E/VCO_2

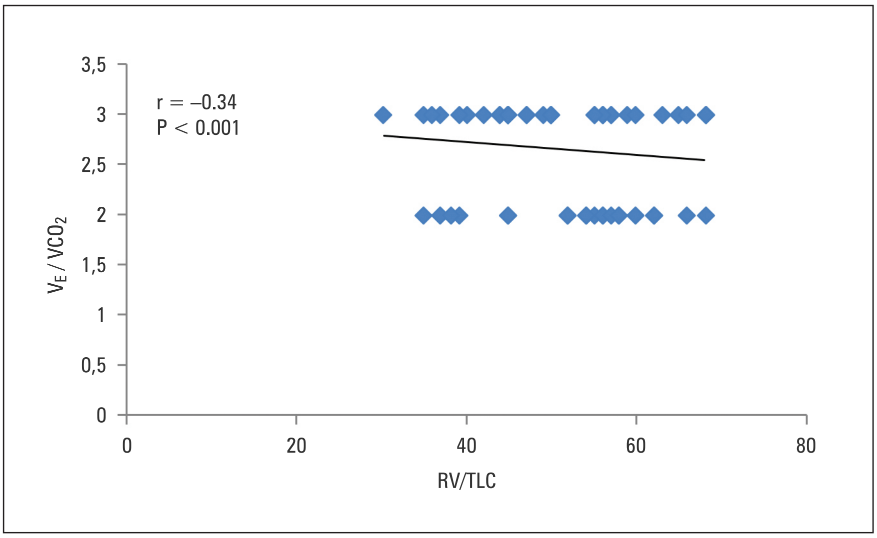

Figure 4. Correlation between RV/TLC and V_E/VCO_2

Also, Ortega et al. studied 78 patients with stable COPD, of whom 39 had severe impairment according to the resting respiratory function. In both, non-severe and severe groups, the respiratory function was not a reliable indicator of exercise performance; the authors recommended that the CPET deemed to be used for more accurate assessment [13]. Similarly, Cotes et al. noted that patients in whom exercise capacity was limited by pulmonary factors, this limitation could not be predicted accurately by FEV_1, FVC and diffusion capacity; thus rather, prediction of VO_2 was improved by considering age, free-fat mass, and submaximal exercise ventilation [17]. The resting PFT is widely used as the first method of assessment in respiratory impairment and work disability in patients with suspected lung disease. Furthermore, authors have suggested that the accuracy of the resting PFT in predicting exercise tolerance renders this test of limited value [17].

We examined the possible correlation between findings on exercise testing and other static parameters of pulmonary function. Notably, we found a significant correlation between both VE/VO_2 and VE/VCO_2 with FEV_1 (% predicted). These findings are similar to earlier studies, revealing a significant correlation between FEV_1% predicted and VO_2max % predicted in COPD patients. There was a wide range of peak VO_2 for a given degree of airflow obstruction (16,18).

There was a negative correlation between $\Delta V_E/VCO_2$ and VE/VO_2 with the degree of air

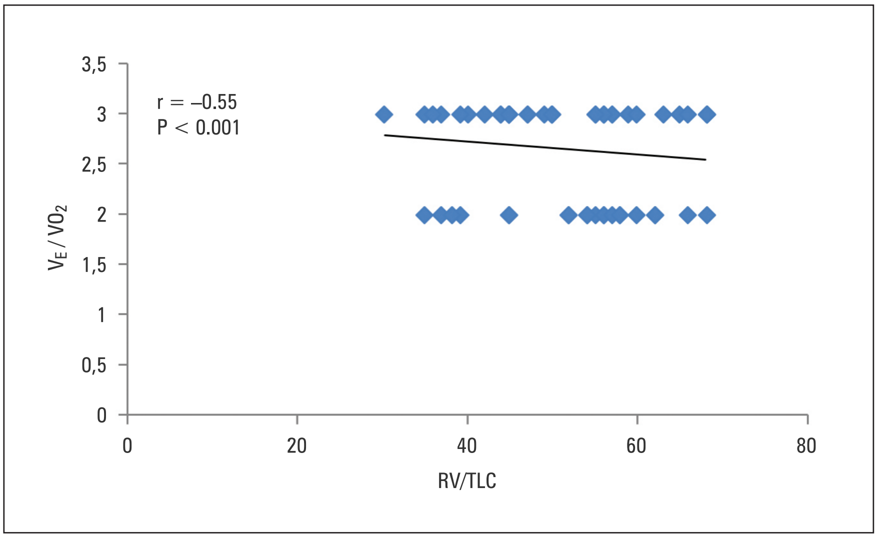

Figure 5. Correlation between RV/TLC and V_E/VO_2

trapping as estimated by the RV/TLC ratio. however, we did not find a correlation between CAT or MRC with exercise parameter resting. A recent study showed that increased RV/TLC which reflects air trapping and hyperinflation can be present, with airway narrowing. Therefore, it seems that the lack of increments in ventilatory equivalents is correlated with air trapping [19].

The cardiopulmonary exercise test measures gas exchange performance, offering an objective assessment of exercise capacity and limitation. the CPET is a useful clinical tool for the determination of the degree of respiratory impairment rather than the PFT [14].

The points of strength in this study include its randomized design. All patients were subjected to PFT before CPET. Also, we compared the degree of impairment of CPET by PFT. Moreover, there were some limitations; the small number of patients, and also we don't address the effect of smoking on CPET outcome.

Conclusions

CPET is a useful instrument to evaluate exercise intolerance in COPD at different stages. It is a superior method for determining the degree of respiratory impairment and functional capacity rather than resting PFT. Exercise performance declines significantly with advanced COPD stages. Both mMRC scale and CAT are subjective while peak VO_2 is an objective method for determination of impairment of exercise capacity. This study favours the use of the CPET for the routine evaluation of respiratory impairment in patients with COPD.

Conflict of interest

None to declared.

References

5. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006; 3(11): e442, doi: 10.1371/journal.pmed.0030442, indexed in Pubmed: 17132052.
6. Probst VS, Troosters T, Pitta F, et al. Cardiopulmonary stress during exercise training in patients with COPD. Eur Respir J. 2006; 27(6): 1110–1118, doi: 10.1183/09031936.06.00110605, indexed in Pubmed: 16540501.
7. Aliverti A, Macklem PT. The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles. J Appl Physiol (1985). 2008; 105(2): 749–751; discussion 755, doi: 10.1152/japplphysiol.90336.2008, indexed in Pubmed: 18678622.
8. Datta D, Normandin E, ZuWallack R. Cardiopulmonary exercise testing in the assessment of exertional dyspnea. Ann Thorac Med. 2015; 10(2): 77–86, doi: 10.4103/1817-1737.151438, indexed in Pubmed: 25829957.
9. Singh D, Agusti A, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. Eur Respir J. 2019; 53(5), doi: 10.1183/13993003.00164-2019, indexed in Pubmed: 30846476.
10. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988; 93(3): 580–586, doi: 10.1378/chest.93.3.580, indexed in Pubmed: 3342669.
11. Global initiative for chronic obstructive lung diseases: Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary diseases. 2017 Edition. http://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf (2018 April 11).
12. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003; 167(2): 211–277, doi: 10.1164/rccm.167.2.211, indexed in Pubmed: 12524257.
13. Quanjer PH, Stanojevic S, Cole TJ, et al. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function

2012 equations. Eur Respir J. 2012; 40(6): 1324–1343, doi: 10.1183/09031936.00080312, indexed in Pubmed: 22743675.
14. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003; 167(2): 211–277, doi: 10.1164/rccm.167.2.211, indexed in Pubmed: 12524257.
15. Palange P, Ward SA, Carlsen KH, et al. ERS Task Force. Recommendations on the use of exercise testing in clinical practice. Eur Respir J. 2007; 29(1): 185–209, doi: 10.1183/09031936.00046906, indexed in Pubmed: 17197484.
16. Pinto-Plata VM, Celli-Cruz RA, Vassaux C, et al. Differences in cardiopulmonary exercise test results by American Thoracic Society/European Respiratory Society-Global Initiative for Chronic Obstructive Lung Disease stage categories and gender. Chest. 2007; 132(4): 1204–1211, doi: 10.1378/chest.07-0593, indexed in Pubmed: 17934113.
17. Carter R, Nicotra B, Huber G. Differing effects of airway obstruction on physical work capacity and ventilation in men and women with COPD. Chest. 1994; 106(6): 1730–1739, doi: 10.1378/chest.106.6.1730, indexed in Pubmed: 7988192.
18. Ward SA, Davis JA, Whipp BJ. The physiologic basis of exercise testing. Cardiovascular and Pulmonary pysiology. 1982: 23–26.
19. Fink G, Moshe S, Goshen J, et al. Functional evaluation in patients with chronic obstructive pulmonary disease: pulmonary function test versus cardiopulmonary exercise test. J Occup Environ Med. 2002; 44(1): 54–58, doi: 10.1097/00043764-200201000-00009, indexed in Pubmed: 11802466.
20. Ong KC, Ong YY. Cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease. Ann Acad Med Singap. 2000; 29(5): 648–652, indexed in Pubmed: 11126703.
21. Ortega F, Montemayor T, Sánchez A, et al. Role of cardiopulmonary exercise testing and the criteria used to determine disability in patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1994; 150(3): 747–751, doi: 10.1164/ajrccm.150.3.8087347, indexed in Pubmed: 8087347.
22. Ganju AA, Fuladi AB, Tayade BO, et al. Cardiopulmonary exercise testing in evaluation of patients of chronic obstructive pulmonary disease. Indian J Chest Dis Allied Sci. 2011; 53(2): 87–91, indexed in Pubmed: 21545069.
23. Kuint R, Berkman N, Nusair S. Ventilatory compensation during the incremental exercise test is inversely correlated with air trapping in COPD. F1000Research. 2019; 8: 1661, doi: 10.12688/f1000research.20444.1.