

Comparison of Functional Capacity and Symptoms of COPD Patients with and without Pulmonary Hypertension

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ABSTRACT

Objective: Pulmonary hypertension (PH) is a common complication of chronic obstructive pulmonary disease (COPD) associated with a decrease in the survival rate of patients with COPD. Our aim was to investigate whether PH impairs the functional capacity and symptoms in patients with COPD. In addition, we aimed to evaluate the correlation between the functional capacity and symptoms score in patients with COPD.

Materials and Methods: This prospective cross-sectional study enrolled 64 patients with moderate to severe COPD, prospectively. All patients underwent the pulmonary function test, echocardiography, 6-minute walk test (6MWT), and cardiopulmonary exercise testing (CPET). We applied the modified Medical Research Council (mMRC) dyspnea scale and COPD Assessment Test (CAT) to all patients. The mean pulmonary arterial pressure (mPAP) >30 mmHg with echocardiography was considered as PH. The patients were grouped according to the presence of PH as COPD-PH (n=30) and COPD-nonPH (n=34).

Results: Hospitalization rate was higher in the COPD-PH group than in the COPD-nonPH group (p=0.006). The 6MWT results were lower in the COPD-PH group compared to the COPD-nonPH group (325±61 m vs. 354±46 m, respectively, p=0.025). In the COPD-PH group, the maximum oxygen consumption (VO_{2max}) was lower, but the difference did not reach statistical significance (p=0.118). Although the maximum load and minute ventilation were lower in the COPD-PH group, the end-tidal pressure of CO₂ (PETCO₂) was higher (p=0.033, p=0.036, and p=0.009, respectively). However, the CAT score and mMRC were similar between the groups (p=0.405 and p=0.238, respectively).

Conclusion: An elevated PAP in patients with COPD limits the exercise capacity. Using CPET in the functional evaluation of patients with COPD may be beneficial in the early detection of PH.

Keywords: Cardiopulmonary exercise test, COPD, pulmonary hypertension, 6MWT

Introduction

Chronic obstructive pulmonary disease (COPD) is a common public health problem worldwide that is characterized by respiratory symptoms and persistent airflow limitation due to airway or alveolar abnormalities resulting from the exposure to smoke, noxious gases, and particles [1]. It is the currently the fourth most common cause of death and is estimated to become the third cause by the year 2020 [2, 3]. Pulmonary hypertension (PH) is a common complication of COPD that is associated with a decrease in the survival rate of patients with COPD [4, 5].

In patients with COPD, the PH progression correlates better with the degree of airflow obstruction and pulmonary gas exchange impairment [6, 7]. Hypoxemia plays a major role in the development of PH [8]. Other factors that contribute to the development of PH are cigarette smoke, systemic inflammation, and oxidative stress [9]. The reported prevalence of PH in COPD patients is 20%-90% [6, 10, 11]. As the incidence of PH is correlated with disease severity, it is more common in patients with severe COPD.

Pulmonary hypertension is one of the causes of cor pulmonale, which is defined as a change in the structure and function of the right ventricle, secondary to underlying lung disease. The presence of PH and cor pulmonale is associated with increased mortality and a poorer clinical COPD course [12]. They also affect the quality of life [13].

In this study, we aimed to determine whether PH in COPD impairs the functional capacity and symptoms score and whether a correlation exists between the functional capacity and symptoms score.

Materials and Methods

Study Design

This prospective cross-sectional study was conducted at a single tertiary care hospital. The patients with COPD in our outpatient clinic were screened to enroll in the study for 12 months in 2015. The study was approved by the Ethics Council of Faculty of Medicine, and written informed consent was provided by all subjects.

Study Population

Seventy-nine patients with moderate to severe COPD were prospectively enrolled. Selection criteria were a clinical diagnosis of COPD according to the GOLD consensus [1] and having stable COPD, without exacerbation, during the examination for 4 weeks. The ones who could not perform exercise testing ($n=12$) or had systolic hypertension (>220 mmHg) during exercise testing ($n=3$) were excluded from the study. Also, patients with coronary artery disease and peripheral artery disease were excluded. A total of 64 patients with moderate to severe COPD were included in the study. The patients were divided into the COPD-PH ($n=30$) and COPD-nonPH ($n=34$) subgroups. The PH diagnosis was based on echocardiography. The mean pulmonary arterial pressure (mPAP) >30 mmHg on echocardiography was considered to indicate PH.

Diagnostic Testing

Medical records were reviewed. After a physical examination, all patients underwent electrocardiography, pulmonary function test, echocardiography, 6-minute walk test (6MWT), and cardiopulmonary exercise testing (CPET). The modified Medical Research Council (mMRC) dyspnea scale and COPD Assessment Test (CAT) were performed in all patients.

Pulmonary Function Test

Each patient underwent a pulmonary function test that was performed using the American Thoracic Society/European Respiratory Society guidelines [14] and European predictive values [15].

Echocardiography

All patients underwent conventional two-dimensional and Doppler echocardiographic examination in addition to tissue Doppler imaging using a VIVID 7 (GE, NORWAY) echocardiography device with a 2.5 MHz transducer. In the left lateral decubitus position, echocardiograms were recorded on standard parasternal and apical images. The images were recorded at the end-inspiration and end-expiration on normal ventilation. The M-mode, B-mode, color-flow mapping, and pulse-wave Doppler records for each patient were obtained. The left ventricle diameter, left atrium diameter, right atrium diameter (RA), and right ventricle diameter were determined with a parasternal long-axis view. Left ventricular ejection fraction was calculated using a modified Simpson method [16]. Systolic pulmonary arterial pressure (sPAP) was calculated by adding estimated right atrial pressure onto the regurgitation gradient through the tricuspid valve. For calculating the mean pulmonary arterial pressure (mPAP), a pulmonary regurgitation (PR) signal was obtained in the parasternal short-axis view using a color Doppler. CW Doppler at a sweep speed of 100 mm/s was used to measure the peak PR velocity. The peak pressure difference (measured by the Bernoulli equation) is then added to the right atrial pressure. mPAP was calculated by the formula $mPAP=4V$ (early peak pulmonary regurgitation velocity) $2+RA$ pressure [17, 18].

6-Minute Walk Test

We performed the 6MWT in all patients according to the ATS guideline [19]. The patients were set to walk back and forth at their own pace in a 30-meters-long corridor to cover as much ground as possible in the given time. The test was observed by a supervisor, reminding the patient about the remaining exercise time every 2 minutes. The patients were permitted to halt and take a rest during the test but were instructed to re-start walking as quickly as possible. Dyspnea during the test was assessed with the modified Borg dyspnea score.

Cardiopulmonary Exercise Testing

A cycle ergometer (Ergoselect Ergoline Viasprint I50P) was used for the test. The symptom-limited exercise was applied to all subjects, who were wearing a facemask (Rudolph Face Mask for Exercise Testing; Hans Rudolph Inc., Kansas

City, MO, USA). Following a 3-minute resting period, a 3-minute warm-up period (60 rpm was the maintenance pedaling rate) was started, then incremental work (10-15 W elevation for each minute) was applied [20]. An automated exercise testing system (Desktop Diagnostics/CPX; Medical Graphics Corporation, St. Paul, MI, USA) was used to collect data. The maximum work rate for half a minute was saved. Continuous monitorization of 12-lead electrocardiography, blood pressure, and pulse oxygen saturation was performed during CPET. The peak oxygen uptake (PVO_2 mL/kg/min), peak CO_2 output, carbon dioxide production/oxygen uptake (VCO_2/VO_2), heart rate reserve (HRR), VO_2/HR , and minute ventilation/carbon dioxide production (VE/VCO_2) values were assessed. To determine the anaerobic threshold (AT L/min), the two-slope method was used. To determine age-predicted values, the equation of Wasserman et al. [20] was used. Symptoms occurred at the end of the test, including fatigue, dyspnea, and dizziness.

Statistical Analysis

For statistical analysis, the Statistical Package for the Social Sciences for Windows version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) was used. We used the Mann-Whitney U test for comparisons of continuous variables between the COPD-PH and COPD-nonPH groups and the chi-square test for comparisons of nominal variables. We performed Pearson's correlation analysis for continuous variables. A linear regression analysis was performed to investigate the association between CPET parameters and symptoms assessment tests. A p-value <0.05 was considered to be statistically significant.

Results

A total of 64 patients (34 patients with COPD without PH, 30 patients with COPD with PH) were included in the study. Baseline characteristics of the cases are summarized in Table 1. The mean age was similar between groups (60 [55-65] vs. 61 [55-72] years in COPD-nonPH and COPD-PH, respectively). The hospitalization rate was higher in patients with COPD-PH than patients without COPD-nonPH. The difference was statistically significant ($p=0.006$). However, the CAT score and mMRC were similar between the groups ($p=0.387$ and $p=0.275$, respectively).

The functional evaluation of the patients is shown in Table 2. The 6MWT results of the COPD-PH group were lower than in the COPD-nonPH group (337 [284-383] vs. 355 [341-381], respectively, $p=0.025$). In CPET, the COPD-PH group had a lower VO_{2max} (maxi-

Main Points

- Pulmonary hypertension in patients with COPD negatively impacts their functional capacity.
- An elevated PAP in patients with COPD limits the exercise capacity.
- Using CPET in the functional evaluation of patients with COPD may be beneficial in the early detection of pulmonary hypertension.

Table 1. Baseline characteristics of study groups

Group	COPD-nonPH (n=34)	COPD-PH (n=30)	p-value
Age, years, mean	60 (55-65)	61 (55-72)	0.360
Sex, male %	100	97	0.280
Diabetes, %	3	10	0.244
Hypertension, %	21	37	0.153
Current smoker, n (%)	33 (97%)	29 (97%)	0.928
Mean of pack year	40 (25-50)	40 (27-51)	0.570
Mean COPD exacerbation in a year	1 (0-3)	2 (1-4)	0.076
History of hospitalization in a year, n(%)	11 (32)	21 (70)	0.006
Inhaler treatment, %			
Single	65	55	0.090
Combined	35	45	0.100
LVDD, mm, mean	45 (41-48)	47 (40-52)	0.190
LAD, mm, mean	32 (28-40)	33 (28-44)	0.780
RAD, mm, mean	39 (35-45)	40 (38-46)	0.430
RVD, mm, mean	39 (36-44)	41 (36-46)	0.055
EF, %, mean	64 (60-67)	62 (59-66)	0.110
TAPSE, mm, mean	17 (15-23)	14 (11-17)	0.044
mPAP, mmHg, mean	18 (15-20)	40 (36-48)	<0.001
FVC, %, mean	88(76-99)	81 (69-95)	0.294
FEV ₁ , %, mean	60 (42-73)	54 (41-62)	0.075
FEV ₁ /FVC, mean	55 (46-60)	53 (46-63)	0.450
CAT score, mean	13 (9-18.5)	14.5 (12-20)	0.387
mMRC stage, n(%)			0.275
1	9 (27)	4 (13)	
2	7 (21)	9 (30)	
3	12 (35)	8 (27)	
4	6 (18)	8 (27)	
5	0	1 (3)	
GOLD stage, n (%)			0.096
A	8 (24)	3 (10)	
B	13 (39)	7 (23)	
C	3 (9)	2 (7)	
D	10 (29)	18 (60)	

CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; LVDD: left ventricular diastolic diameter; LAD: left atrial diameter; RVD: right ventricular diameter; RAD: right atrial diameter; FVC: forced vital capacity; FEV₁: forced expiratory volume at 1 second; GOLD: global obstructive lung disease; TAPSE: tricuspid annular plane systolic excursion; mPAP: mean pulmonary arterial pressure; mMRC: modified medical research council; PH: pulmonary hypertension

CAT ($p=0.026$, $p=0.001$, $p=0.009$, $p=0.014$, $p=0.027$, respectively). Statistically significant negative correlations were found between mMRC and AT, maximum load, BR, VE, and MVV ($p=0.017$, $p=0.046$, $p=0.041$, $p=0.019$, $p=0.010$, respectively). There was statistically significant correlation between Tricuspid annular plane systolic excursion (TAPSE) and 6MWT ($p=0.040$, $r=0.550$). However there was a poor correlation between mPAP and symptoms assessment tests (CAT score [$r=0.130$, $p=0.280$] and MMRC [$r=0.200$, $p=0.100$]).

We also generated a linear regression model for the prediction of the association with symptoms assessment tests and CPET parameters. We found that AT is an independent predictor of COPD assessment (CAT score), $p=0.005$.

Discussion

Our results show that pulmonary hypertension in patients with COPD negatively impacts their functional capacity, but there is no effect on symptoms assessment. To the best of our knowledge, ours is the first study to evaluate both the functional capacity and symptoms assessment in patients with COPD-PH.

Patients with COPD-PH exhibited a lower 6MWT distance, VO_{2max} , maximum load, and MVV, and a higher $PETCO_2$. An elevated PAP value led to both the reduced exercise capacity and abnormal gas exchange. There were no differences between patients with COPD with and without PH in terms of mMRC and CAT score.

The reduction of exercise capacity in COPD is multifactorial. An increased airway resistance and lung compliance lead to a dynamic hyperinflation, which together with respiratory muscle fatigue, reduces the ventilatory reserve [21-23]. The 6MWT and CPET are important in evaluating patients' exercise capacity. The gas exchange dysfunction can also be detected with CPET. Studies evaluating the exercise capacity in patients with COPD showed that patients with COPD-PH had a lower VO_{2max} , maximum load values, and 6MWT distance [24-27]. The COPD-PH group in the present study also had lower results with regard to these parameters when compared to patients with COPD without PH. These findings support the negative effect of PH development on exercise capacity in patients with COPD.

Evaluating gas exchange during CPET revealed that patients with COPD-PH have a higher $PETCO_2$. Although patients with isolated PH show lower $PETCO_2$ values secondary to increased ventilatory response, reduced maxi-

mum oxygen consumption), but the difference was not statistically significant ($p=0.210$). Although the maximum load and VE were lower in the COPD-PH group, end-tidal pressure of CO_2 ($PETCO_2$) was higher ($p=0.034$, $p=0.046$, and $p=0.045$, respectively). The correlations between VO_{2max} , $PETCO_2$, and mPAP are shown in Figure 1. The leg fatigue was the main cause for stopping the test in both groups (86% in the COPD-PH group, 58% in the COPD-nonPH group).

Correlations between CPET parameters and CAT, mMRC, and mPAP are shown in Table 3. While there were negative correlations between mPAP and VO_{2max} , VE, and maximum voluntary ventilation (MVV), a positive correlation was detected between mPAP and $PETCO_2$. These correlations were statistically significant ($p=0.028$, $p=0.008$, $p=0.008$, and $p=0.004$, respectively). Statistically significant negative correlations were detected between MVV, VO_{2max} , AT, maximum load, VE, and

Table 2. Functional evaluation of patients

Group	COPD-nonPH (n=34)	COPD-PH (n=30)	p-value
6-MWT, m	355 (341-381)	337 (284-383)	0.025
VO ₂ max, mL/kg/dk	1066 (912-1275)	1010 (826-1136)	0.210
VE/VCO ₂	35 (33-41)	36 (29-40)	0.840
Anaerobic threshold	778 (627-983)	772 (671-947)	0.810
Peak SpO ₂ value, %	92 (87-97)	88 (74-94)	0.028
Maximum load, watt	85 (71-105)	75 (57-90)	0.034
PETCO ₂ , kPa	4 (3.8-4.7)	4.4 (3.9-5.8)	0.045
VEmax, liter	46 (39-55)	42 (35-47)	0.046
MVV, L/minute	67 (51-89)	58 (43-74)	0.090

AE: anaerobic threshold; 6-MWT: 6-minute walking test; MVV: maximum voluntary ventilation; VO₂: oxygen consumption; VCO₂: carbon dioxide output; VE: minute ventilation; PETCO₂: end-tidal pressure of CO₂; Student's t-test was used.

Table 3. Correlation between CPET parameters and CAT, mMRC, and mPAP

Parameters	CAT		mMRC		Mean PAP	
	r	p	r	p	r	p
VO ₂ max	-0.276	0.027	-0.182	0.149	-0.276	0.028
VE/VCO ₂	-0.078	0.540	-0.152	0.229	-0.061	0.630
Anaerobic threshold	-0.405	0.001	-0.301	0.017	-0.079	0.542
Peak SpO ₂ , %	-0.279	0.026	-0.339	0.006	-0.313	0.012
Max load	-0.325	0.009	-0.250	0.046	-0.268	0.032
VD/VT	0.022	0.866	-0.096	0.449	-0.038	0.765
BR	-0.139	0.273	-0.256	0.041	-0.122	0.338
PETCO ₂	0.154	0.223	0.175	0.166	0.351	0.004
RER	-0.030	0.816	-0.175	0.168	-0.074	0.563
VE max, liter	-0.305	0.014	-0.291	0.019	-0.329	0.008
MVV	-0.278	0.026	-0.321	0.010	-0.330	0.008

BR: breathing reserve; VO₂: oxygen consumption; VCO₂: carbon dioxide output; VE: minute ventilation; AT: anaerobic threshold; PETCO₂: end-tidal pressure of CO₂; MVV: maximum voluntary ventilation; Pearson's correlation was used.

The evaluation of patients' symptoms assessment using CAT and mMRC revealed no difference between the groups. Mirdamadi et al. reported a weak relationship between subjective symptoms and objective parameters in patients with COPD [28]. The negative correlations we observed between CPET parameters and CAT and mMRC scores support their findings, despite the fact that there was no difference based on PH.

In patients with COPD, the PH progression correlates better with the degree of airflow obstruction and pulmonary gas exchange impairment [6, 7]. Nevertheless, in our study, there was no difference in PFT parameters between groups. It may be due to fact that the majority of patients had moderate obstruction.

One of the limitations of our study is the small sample size. Another limitation is that PH was not confirmed with right heart catheterization. Instead, we calculated mPAP, which yields results comparable to catheterization. Patients were not evaluated according to systolic PAP.

An elevated PAP in patients with COPD limits the exercise capacity. There is a negative correlation between functional capacity and symptoms assessment. Using CPET in the functional evaluation of patients with COPD may be beneficial in the early detection of PH, further studies to confirm the diagnosis, and planning an appropriate treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of Ataturk University School of Medicine. (IR.B.34.4.ATA. 0.08.00/13)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

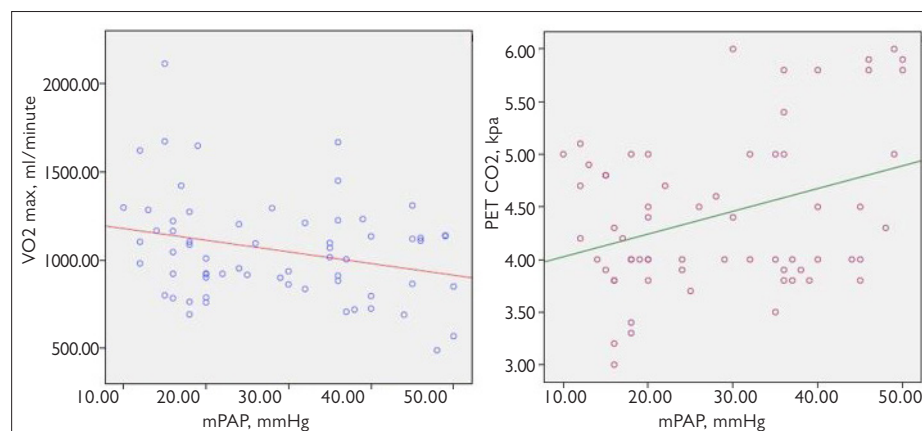
Author Contributions: Concept - F.K., E.Y.U.; Design - F.K., E.Y.U.; Supervision - O.A., K.K.; Resources - F.K., K.K.; Materials - F.K., E.Y.U.; Data Collection and/or Processing - F.K., E.Y.U.; Analysis and/or Interpretation - K.K., F.K.; Literature Search - F.K., K.K.; Writing Manuscript - F.K., K.K.; Critical Review - E.Y.U., O.A.

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**Figure 1.** Correlations Between VO₂max, PETCO₂, and mPAP

lum ventilation secondary to dynamic hyperinflation in COPD may explain the higher PETCO₂ values in patients with COPD-PH.

This finding may indicate that a high PETCO₂ in patients with COPD should raise suspicion of PH.

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