**Original Article**

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# Comparison of functional capacity and symptoms of copd patients with and without pulmonary hypertension

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**Short title:** Functional capacity in COPD patients with Pulmonary hypertension

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# Comparison of functional capacity and symptoms of COPD patients with and without pulmonary hypertension

## Abstract

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

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

**Results:** Hospitalization history was higher in COPD-PH group than COPD-nonPH group (p=0.006). Six-minute walk test 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, maximum oxygen consumption ($VO_2$max) was lower, but the difference did not reach statistical significance (p=0.118). Although maximum load and minute ventilation were lower in the COPD-PH group, the end-tidal pressure of $CO_2$ ($PETCO_2$) was higher (p=0.033, p=0.036, and p=0.009, respectively). However, the CAT score and mMRC were similar between groups (p=0.405 and p=0.238, respectively).

**Conclusions:** Elevated PAP in COPD patients limits exercise capacity. Using CPET in the functional evaluation of COPD patients may be beneficial in the early detection of PH.

**Key Words:** 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 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 a decrease in the survival rate of COPD patients [4,5].

In COPD patients, the PH progression better correlates 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 varies between 20-90% [6,10,11]. As the incidence of PH is correlated with disease severity, it is more common in severe COPD patients.

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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 course in COPD [12]. They also affects the quality of life [13].

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

## Methods

### Study Design

This prospective cross-sectional study conducted at a single tertiary care hospital. The patients with COPD in our outpatient clinic were screened to enroll the study for 12 months in 2015. The study was approved by the Ethics Council of Faculty of Medicine, and written informed consent 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, no 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 COPD-PH (n:30) and COPD-nonPH(n:34) subgroups. The diagnosis of PH was based on echocardiography. Mean pulmonary artery pressure (mPAP) >30 mmHg on echocardiography considered as PH.

### Diagnostic Testing

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

*Pulmonary Function Test*

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

*Echocardiography*

All patients underwent conventional 2-D and Doppler echocardiographic examination in addition to tissue Doppler imaging (TDI) 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 end-inspiration and end-expiration on normal ventilation. M-mode, B-mode, color flow mapping, and pulse-wave Doppler records for each patient were obtained. Left ventricle diameter (LV), left atrium diameter (LA), right atrium diameter (RA), and right ventricle diameter (RV) were determined with a parasternal long-axis view. Left ventricular ejection fraction (LVEF) was calculated using a modified Simpson method [16]. Systolic pulmonary artery pressure (sPAP) was calculated by adding estimated right atrial pressure onto the regurgitation gradient through the tricuspid valve. For calculating the mean pulmonary artery pressure (mPAP), a pulmonary regurgitation (PR) signal is obtained in the parasternal short axis view using color doppler . CW doppler at a sweep speed at 100 mm/s is used to measure the peak PR velocity. Peak pressure difference(measured by the Bernoulli equation) is then added to the right atrial pressure. mPAPwas calculated by the formula mPAP = 4V (early peak pulmonary regurgitation velocity)2 + RA pressure [17,18].

*6MWT*

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-m corridor to cover as much ground possible in the given time. The test was observed by a supervisor, reminding the patient the remaining exercise time in every 2 minutes. The patients were permitted to halt and take a rest during the

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test but were instructed to re-start walking as quickly as possible. Dyspnea during the test was assessed with the modified Borg dyspnea score.

*CPET*

A cycle ergometer (Ergoselect Ergoline Viasprint 150P) was used for the test. The symptom-limited exercise was applied to all subjects while wearing a facemask (Rudolph Face Mask for Exercise Testing; Hans Rudolph Inc., Kansas City, MO, USA). Following 3-minute resting period records, 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. Peak oxygen uptake ($PVO_2$ mL/kg/min), peak $CO_2$ output, carbon dioxide production/oxygen uptake ($VCO_2/VO_2$), HRR (heart rate reserve), $VO_2$/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 were also noted.

## Statistical Analysis

For statistical analysis, SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA) was used. We used Mann Whitney-U 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 correlation analysis for continuous variables. Lineer regression analysis was performed for investigation of the association between CPET parameters and symptoms assesment tests.  A p-value of $<0.05$ was used for statistical significance.

**Results**

A total of 64 patients (34 COPD patients without PH, 30 COPD patients 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). Hospitalization rate was higher in COPD-PH patients than COPD-nonPH patients. The difference was statistically significant (p=0.006). However, CAT score and mMRC were similar between the groups (p=0.387 and p=0.275, respectively).

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 lower $VO_2$max (maximum oxygen consumption), but the difference was not statistically significant (p=0.210). Although 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 $VO_2$max, $PETCO_2$, and mPAP are shown in Figure 1. 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 $VO_2$max, 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, $VO_2$max, AT, maximum load, VE, and 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 TAPSE (Tricuspid annular plane systolic excursion) 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)].

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



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## Discussion

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

The COPD-PH patients exhibited lower 6MWT distance, $VO_2max$, maximum load, and MVV, and higher $PETCO_2$. Elevated PAP led to both reduced exercise capacity and abnormal gas exchange. There were no differences between COPD patients with and without PH in terms of mMRC and CAT score.

Reduction of exercise capacity in COPD is multifactorial. 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. Gas exchange dysfunction can also be detected with CPET. In studies evaluating exercise capacity in COPD patients have been shown that COPD-PH patients have lower $VO_2max$, maximum load values, and 6MWT distance [24-27]. The COPD-PH group in the present study also had lower results in these parameters when compared to COPD patients without PH. These findings support the negative effect of PH development on exercise capacity in COPD patients.

Evaluating gas exchange during CPET revealed that COPD-PH patients have higher $PETCO_2$. Although patients with isolated PH show lower $PETCO_2$ values secondary to increased ventilatory response, reduced maximum ventilation secondary to dynamic hyperinflation in COPD may explain the higher $PETCO_2$ values in COPD-PH patients. This finding may indicate that high $PETCO_2$ in COPD patients should raise suspicion of PH.

Evaluation of the patients' symptoms asessment using CAT and mMRC revealed no difference between the groups. Mirdamadi et al. reported a weak relationship between subjective symptoms and objective parameters in COPD patients [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 COPD patients, the PH progression better correlates with the degree of airflow obstruction and pulmonary gas exchange impairment [6,7]. Neverthless, in our study there was no difference according to PFT parameters between groups. It may be due to our majority of patients have 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.

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

**Conflict of interest statement**

The authors received no financial support for the research and/or authorship of this article.
The authors declare that they have no conflict of interest to the publication of this article.

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Figure 1. The correlations between VO2max, PETCO2, and mPAP.



**Table 1.** Baseline charecteristics 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 |
| **Diabet, %** | 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** |

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| | | | | |
|---|---|---|---|---|
| **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) | |

**Abbreviations: 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, $FEV_1$; Forced expiratory volume one 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,**

**Table 2.** The functional evalution of patients

| Group | COPD-nonPH (n:34) | COPD-PH (n:30) | p değeri |
|---|---|---|---|

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| | | | |
|---|---|---|---|
| **6-MWT,m** | 355(341-381) | 337(284-383) | **0.025** |
| **VO2 max, ml/kg/dk** | 1066(912-1275) | 1010(826-1136) | 0.210 |
| **VE/ VCO2** | 35(33-41) | 36(29-40) | 0.840 |
| **Anaerobic threshold,** | 778(627-983) | 772(671-947) | 0.810 |
| **Peak SpO2 değeri, %** | 92(87-97) | 88(74-94) | **0.028** |
| **Maximum load, watt** | 85(71-105) | 75(57-90) | **0.034** |
| **PETCO2, kPa** | 4(3.8-4.7) | 4.4(3.9-5.8) | **0.045** |
| **VEmax, litre** | 46(39-55) | 42(35-47) | **0.046** |
| **MVV, L/dakika** | 67(51-89) | 58(43-74) | 0.090 |

Data were expressed as mean and minimum-maximum, **AE**: Anaerobic threshold**, 6-MWT:** Six minute walking test, **MVV** : Maximum voluntary ventilation; **VO2**: Oxygen consumption; **VCO2**: Carbon dioxide output; **VE**: Minute ventilation; **PETCO2**: End tidal pressure of CO2; Student' t test were used.



**Table 3.** The correlation between CPET parameters and CAT, mMRC, 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/ VCO2** | -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 SpO2, %** | -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 |
| **PETCO2** | 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 **,$VO_2$**: Oxygen consumption; **$VCO_2$** : Carbon dioxide output; **VE** : Minute ventilation; **AT** : Anaerobic threshold; **PETCO2** : End tidal pressure of CO2; **MVV** : Maximum voluntary ventilation; Pearson correlation were used.

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