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Can FVC/DLCO predict pulmonary hypertension in patients with chronic obstructive pulmonary disease?

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Abstract. – OBJECTIVE: The aim of the study was to investigate pulmonary function parameters in patients who did and did not have pulmonary hypertension, and the roles of forced vital capacity (FVC)/diffusing capacity of the lungs for carbon monoxide (DLCO) and FVC/DLCO/alveolar volume (VA) values in patients with COPD accompanied by pulmonary hypertension.

PATIENTS AND METHODS: This study included patients with stable and advanced COPD (groups C and D), who presented to the Chest Diseases outpatient clinic at our hospital. Parameters of age and sex, use of long-term oxygen therapy at home, and pulmonary function parameters were evaluated. In addition, systolic pulmonary artery pressure (sPAP) was evaluated on a transthoracic echocardiogram (TTE). Patients were grouped according to TTE sPAP values > 36, and those with normal sPAP values. The pulmonary function parameters of the two groups were compared.

RESULTS: PAP was found to be high in 19 patients (33.33%) and normal in 38 patients (66.67%). The BMI of the group with high PAP (23.54 ± 4.18) was also lower, compared to the group with normal PAP (26.91 ± 4.58) (p=0.010). The FVC/DLCO ratio of the group with high PAP (1.88 ± 0.69) was found to be higher compared to the group with normal PAP (0.90 ± 0.19) (p<0.001). The mean FVC/DLCO/VA ratio was higher in the group with high PAP (1.30 ± 0.68) compared to the group with normal PAP (p=0.001). When determining the height of PAP, cut-off values were examined for FVC/DLCO and FVC/DLCO/VA ratios. When the cut-off value for the FVC/DLCO ratio was taken as 1.31, the sensitivity was 96.8%, the specificity was 97.37%, the PPV was 95.00%, and the NPV was 92.86%. When the cut-off value for the FVC/DLCO/VA ratio was taken as 1.09, the sensitivity was 68.42%, the specificity was 97.37%, the PPV was 100.0%, and the NPV was 86.05%.

CONCLUSIONS: The FVC/DLCO and FVC/DLCO/VA ratios can be important to predict increased PAP in patients with COPD. Pulmonary function tests, which are performed as a routine, have gained importance in clinical practice for the detection of pulmonary hypertension in patients with COPD.

Key Words:
Pulmonary hypertension, Pulmonary function tests, FVC/DLCO, Chronic obstructive pulmonary disease.

Introduction

Pulmonary hypertension (PH) has been determined as an independent prognostic factor for chronic obstructive pulmonary disease (COPD)[1,2]. The key event causing increased pulmonary artery pressure in COPD is vascular remodeling[3,4]. Early diagnosis of PH is important in terms of prognosis, especially to prevent, slow down, and partially regress severe clinical outcomes[5]. PH is mostly characterized by oligemia in the peripheral lung area and enlargement in the diameter of the vascular hilum[3]. PH is harder to identify in COPD, particularly in the mildest form. It is also not easy to distinguish between the symptoms of PH and the clinical picture of COPD. The first suspicious finding is usually the presence of peripheral edema. In patients with COPD, it is difficult to hear the typical signs of PH (pulmonary ejection click, pansystolic murmur, or tricuspid regurgitation, and increased intensity in the pulmonary component of the second heart sound)[1]. Hypoxemia in arterial blood gas has been identified as the reason for pulmonary arterial hypertension in patients with COPD. It has been reported that decreased PaO_2 and SaO_2 have a negative correlation with PH[3].

The sensitivity of electrocardiography (ECG) is very low in detecting PH. It has a diagnostic

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value in 25-40% of patients with right ventricular hypertrophy. Generally, the changes detected on ECG are not parallel with the severity of the underlying PH. Echocardiography has been identified as the most common method used in the routine examination of PH due to its harmless, repeatable, and non-invasive features, as well as good correlation with the results of the catheter[6]. Patients with suspected COPD accompanied by PH are usually recommended to undergo echocardiography for screening[7,8]. In addition, echocardiography requires a specific specialization. There is no specific pulmonary dysfunction linked to the elaboration of PH in the routine clinical picture. It is observed that the diffusing capacity of the lungs for carbon monoxide (DLCO) value decreases with PH according to the severity of the disease[9]. Pulmonary function tests may be useful in clinical practice to suspect pulmonary hypertension in pulmonary outpatient clinics. In studies[10,11] conducted on patients with systemic sclerosis, the forced vital capacity FVC/DLCO ratio was found to estimate the possibility of PH in the detection of individuals with suspected PH. A limited number of studies investigated the FVC/DLCO and other PH groups. In a study conducted on 83 patients with suspected PH, the FVC/DLCO value was found to be associated with the mean pulmonary arterial pressure (mPAP) gauged using right heart catheterization and systolic pulmonary artery pressure (sPAP) gauged using echocardiography, independent from etiology[12].

Therefore, it might be important to detect PH earlier, which has a substantial effect on patients with COPD in terms of the treatment strategy and clinical outcomes. There are insufficient studies on the evaluation of PH in patients with COPD using routine pulmonary function tests that do not require any other specialization.

In the present study, FVC/DLCO and FVC/DLCO/VA values were investigated in terms of their roles in predicting PH in patients with COPD.

Patients and Methods

In this study, we included 57 patients with stable advanced group C and D COPD, who presented to the Chest Diseases outpatient clinic at our hospital. Fifteen patients with cardiac failure, collagen vascular disease, rheumatic diseases, and interstitial lung disease were excluded. Parameters of age, sex, body mass index (BMI), long-term use of oxygen therapy at home, hospitalization within the last one year, the number of presentations to the emergency department, and the pulmonary function parameters were evaluated. In addition, systolic pulmonary artery pressure (sPAP) was evaluated on a transthoracic echocardiogram (TTE). Patients were examined in two groups, TTE sPAP $\geq$ 36 and those with sPAP < 36. Patients with sPAP $\geq$ 36 were evaluated as those with high sPAP, and patients with sPAP < 36 were considered as having normal sPAP. We recorded values of forced expiratory volume in 1 second (FEV_1 (L/sec), FEV_1(%), forced vital capacity (FVC%), FVC (I), FEV_1/FVC, DLCO, and DLCO/VA. The pulmonary function parameters of the two groups were compared. Informed consent forms were signed by the patients, and the approval of the ethics committee was obtained from our institution.

Echocardiography

The sum of the systolic pressure gradient between the right ventricle and the right atrium and the estimated pressure of the right atrium was used to calculate peak pulmonary artery pressures. This gradient was determined by calculating the peak velocity of the tricuspid regurgitation using the modified Bernoulli equation. Computation of the pressure of the right atrium was performed based on the dimension of the inferior vena cava and the alteration of dimension with respiratory activity[13].

Spirometry and Lung Diffusion Testing

Spirometry data were recorded as absolute measurements and percentages predicted for age, sex, and height indices measured in the study. The FVC (L), FEV_1 (L), and predicted percentage of FEV_1/FVC (ratio) were noted. To ensure that the repeatability and best measurements were accepted for the final analysis, a minimum of three measurements were performed for each variable of pulmonary function[14]. Patients were classified as mild ($FEV_1 \geq 80\%$), moderate ($50\% \leq FEV_1$ 80%), severe ($30\% \leq FEV_1$ 50%), and very severe ($FEV_1 \leq 30\%$), based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[15].

Diffusion is an electrochemical event occurring between gas and liquid phases in the lungs, in the direction of the partial pressure gradient of gases. Diffusion capacity is the amount of any gas (mL) that passes through the alveolocapillary

Table I. Demographic characteristics and lung functions of patients.

	sPAP ≤ 36 n = 38	sPAP > 36 n = 19	p
Female/Male	8/30	7/12	0.202
Age	66 ± 10	67 ± 10	0.743
BMI (kg/m²)	26.91 ± 4.58	23.54 ± 4.18	0.010*
Hospitalization (during the previous year)	0.55 ± 0.89	0.69 ± 0.75	0.349
Emergency department admission (during the previous year)	1.77 ± 1.50	2.62 ± 1.33	0.068
Long-term oxygen therapy	11 (28.95%)	8 (42.11%)	0.321
The use of non-invasive mechanical ventilation	11 (28.95%)	4 (21.05%)	0.523
Comorbidity	5 (13.16%)	3 (15.79%)	0.787
FEV_1/FVC (%)	50.5 ± 12.76	50.3 ± 13.06	0.948
FEV_1 (%)	47.89 ± 25.41	42.24 ± 16.52	0.735
FEV_1 (L/sec)	1.19 ± 0.71	1.1 ± 0.44	0.879
FVC (%)	71.05 ± 25.95	62.13 ± 20.86	0.167
FVC (L)	2.31 ± 1.03	2.16 ± 0.93	0.578
DLCO (%)	70.61 ± 26.61	44.11 ± 18.17	< 0.001*
FVC/DLCO	0.9 ± 0.19	1.88 ± 0.69	< 0.001*
DLCO/VA (%)	80.5 ± 28.30	62.05 ± 23.68	0.015*

BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: carbon monoxide diffusing capacity. *$p < 0.05$.

membrane with a certain pressure difference (1 mm Hg) per unit time (minutes). It is expressed as mL/min/mm Hg. It is performed with hemoglobin correction, according to the European Respiratory Society/American Thoracic Society (ERS/ATS) criteria[16].

Statistical Analysis

The SPSS version 17.0 software was used for data analysis (SPSS Inc., Chicago, IL, USA). The variables were examined for normal distribution using histogram charts and the Kolmogorov-Smirnov test. Descriptive values were introduced as mean and standard deviation, and median. Comparisons were made in 2x2 tables using Pearson Chi-square and Fisher's exact tests. An independent *t*-test was operated for evaluating normally distributed (parametric) variables between the groups. The Mann-Whitney U test was used to compare groups without normally distributed variables (nonparametric). To identify the height of PAP, the cut-off value was evaluated for FVC/DLCO and FVC/DLCO/VA, using the receiver operating characteristic (ROC) analysis. The test results were considered statistically significant when there were *p*-values below 0.05.

Results

15 female (26.3%) and 42 male (73.7%) patients were included in the study. The sPAP was found to be high in 19 patients (33.3%) and normal in 38 patients (66.7%). The mean ages of the groups with high and normal PAP values were 67.32±10.12 years and 66.39±9.85 years, respectively (p=0.743). Demographic characteristics are presented in Table I.

The mean DLCO of the group with high sPAP (44.11±18.17) was determined to be lower compared with the group with normal sPAP (70.61±26.61) (p<0.001). The FVC/DLCO ratio of the group with high sPAP (1.88±0.69) was higher than the group with normal sPAP (0.90±0.19; p=0.001) (Figure 1). The mean FVC/DLCO/VA ratio was found to be higher in the group with high sPAP (1.30±0.68) compared with the group with normal sPAP (p=0.001) (Figure 2). The cut-

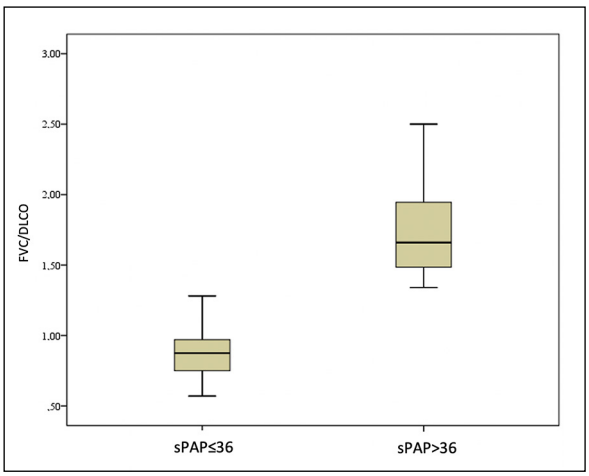

Figure 1. FVC/DLCO value according to pulmonary arterial pressure.

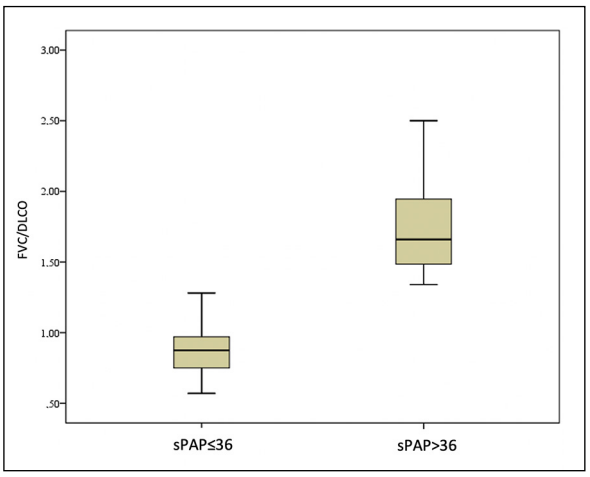

Figure 2. FVC/DLCO/VA value according to pulmonary arterial pressure.

off value for FVC/DLCO and FVC/DLCO/VA ratio was examined for determining the height of sPAP. When the cut-off value for the FVC/DLCO ratio was taken as 1.31, the sensitivity was 96.8%, the specificity was 97.37%, the positive predictive value (PPV) was 95.00%, and the negative predictive value (NPV) was 92.86%. When the cut-off value for the FVC/DLCO/VA ratio was taken as 1.09, the sensitivity was 68.42%, the specificity was 97.37%, the PPV was 100.0%, and the NPV was 86.05% (Table II). The BMI of the group with high sPAP (23.54±4.18) was found to be lower compared with the group with normal sPAP (26.91±4.58) (p=0.010). In terms of long-term oxygen therapy, the use of non-invasive mechanical ventilation, and comorbidity rates, the group with high sPAP did not differ significantly from the group with normal sPAP.

Discussion

In the present study, the pulmonary function parameters of FVC/DLCO and FVC/DLCO/VA were examined in terms of their role in predicting pulmonary hypertension in patients with COPD. In the high PAP group, the FVC/DLCO and FVC/DLCO/VA values were higher than in the group with normal PAP. DLCO was found to be lower in the high PAP group compared with the normal PAP group. In our study, the sensitivity and specificity levels of the FVC/DLCO were sufficiently high to predict PH in patients with COPD. Early recognition of PH is important for prognosis in COPD.

Table II. The best cut-off value for predicting pulmonary hypertension.

	FVC/DLCO	FVC/DLCO/VA
Area	0.996	0.773
Cut-off point	1.31	1.09
Sensitivity	96.80%	68.42%
Specificity	97.37%	97.37%
Positive predictive value	95%	100.0%
Negative predictive value	92.86%	86.05%

The number of studies that explored the predictive value of FVC/DLCO for PH in COPD is insufficient. In a study[17] conducted on patients with systemic sclerosis, the value of FVC/DLCO above 1.5 was determined to be useful in identifying PH. In a study[12] conducted on 83 subjects with suspected PH, which also included patients with COPD, the FVC/DLCO value was found to be associated with mPAP computed using right heart catheterization, and the sPAP, as evaluated using echocardiography, independent from etiology. We determined the FVC/DLCO value as a non-invasive method and a prognostic marker in identifying PH.

PH is an established complication of COPD. It usually occurs when airflow restriction is extreme and is linked to chronic hypoxemia, where chronic alveolar hypoxia is the key pathophysiologic trigger, even though new mechanisms have recently emerged. This complication has previously been linked to a higher risk of exacerbation and lower survival. Early detection of PH has gained importance for the prognosis of the disease. In a study, FVC/DLCO was identified as a biomarker in identifying subjects with a high risk of PH among patients with scleroderma[10]. In another study conducted on patients with systemic sclerosis, the use of FVC/DLCO values was recommended in the early detection of PH[11]. In the REVEAL study, it was demonstrated that symptoms started 2 years before the diagnosis of PH in 21% of the patients[18,19]. As with many diseases, detecting and treating PH earlier has gained importance. Low DLCO is considered a finding that reflects pathologic mechanisms such as muscularization of smaller and peripheral arteries of the lung, thickened media of muscle vessels, thickened intima, and a decreasing number of peripheral vessels in the case of PH[20]. Steen et al[21] demonstrated that patients with systemic sclerosis and a ratio of FVC/DLCO greater than 1.4 might lead to PH more frequently. Riad et al[22] found that the

optimal cut-off level of FVC/DLCO to suspect PH among patients was greater than 1.91, which exhibited 87.5% sensitivity and 100% specificity. In the study conducted by Nathan et al[23], the risk of PH in patients with idiopathic pulmonary fibrosis was found to have increased 2-fold in those with a value of FVC/DLCO greater than 1.5. In patients with idiopathic pulmonary fibrosis, PH was associated with FVC/DLCO values. In chronic obstructive pulmonary disease, the FEV_1 value indicates the severity of airflow restriction and decreases in advanced obstruction. Both FEV and FVC values decrease in restrictive lung disease, and the FVC value decreases in obstructive diseases, although the rate of decrease is less than FEV_1. The FVC/DLCO ratio suggests that it can be used for determining PH in patients with COPD because FVC is relatively preserved. Early detection has gained clinical importance because PH has a high incidence among patients with COPD[24,25]. The prognosis of patients with COPD accompanied by concurrent PH is poor. This is the first study to investigate the use of FVC/DLCO values to predict PH in patients with COPD in Turkey.

No definite relationship was found between FEV1 and pulmonary artery pressure in patients with COPD. Exertional dyspnoea is common in patients with COPD accompanied by severe PH. DLCO is significantly decreased, even though airway restriction is mild or moderate. Hypoxemia and hypercarbia are frequently seen in these patients[26].

The elaboration of PH is slow in patients with COPD. The values of the mean PAP and/or pulmonary vascular resistance have an inverse relationship with survival[27]. PH has been associated with a poor prognosis in the case of COPD. In previous research[26], age, DLCO, and SO_2 levels were determined to be independent predictors of survival in patients with COPD and PH.

According to the results of our study, when FVC/DLCO values were greater than 1.31, it resulted in high sensitivity and specificity in predicting PH. There was no specific pulmonary function parameter used for PH. A pulmonary function test may be guiding along with clinical findings because PH is a poor prognostic factor for COPD.

Limitations

The small number of participants and conducting the study in a single center were the limitations of our study.

Conclusions

It is substantial in the clinic to predict PH earlier using respiratory function tests performed as a routine. Accordingly, early diagnosis of PH using FVC/DLCO and FVC/DLCO/VA values, which can be established with ease, using non-invasive methods without special expertise, and referring patients with suspected PH for further examination is believed to be important for prognosis in clinical practice. More comprehensive studies would be useful for routine medical practice.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

Not applicable.

Informed Consent

Informed consent forms were signed by the patients.

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None.

Ethics Approval

The approval of the Ethics Committee for this study was obtained from Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey.

Authors' Contribution

SBS designed this study. SBS searched for articles. AF performed statistical analyses. SBS and AF performed data extraction. SBS wrote this article. SBS and AF made academic language and grammer editing.

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