Can the Function-Morphology Association Be a Model for the Early Detection of COPD in Asymptomatic Smokers?

KOAH'ın Erken Saptanması İçin, Semptomsuz Sigara İçenlerdeki Fonksiyon-Yapı İlişkisi bir Model Olabilir mi?

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Abstract

Objective: In the present study, we aimed to evaluate the morphological and functional characteristics in symptomatic and asymptomatic smokers in comparison to nonsmokers in order to gain better understanding of the pathogenesis and early diagnosis of Chronic Obstructive Pulmonary Disease (COPD).

Materials and Methods: A Randomized, double-blind, placebo -controlled, parallel-group trial vas performed. Patients and interventions: A total of 50 male patients (40 smokers and 10 non-smokers) who completed a questionnaire, between the ages of 18-60 (mean age 32), were included the study. Of the smokers, 23 were symptomatic, and 17 were asymptomatic. High-resolution computerized tomography (HRCT) and pulmonary function tests (PFTs) were performed in all cases.

Results: In the evaluation of all smokers, a comparison of the PFTs and morphological changes revealed a significant correlation between all morphological parameters and ΔN2/l. Although a relationship was found between the smoking score and the closing volume (CV), ΔN2/l and anatomic dead space (ADS) in all cases, the smoking score was significantly correlated with only the CV in symptomatic cases and with only the ADS in asymptomatic cases. There was a positive correlation between the emphysema parameters on HRCT and smoking, but no correlation was found between the parameters and the pulmonary function tests.

Conclusion: The relationship between morphology and function is better, although different, in the asymptomatic period of lung injury caused by smoking compared with the symptomatic period, and the relationship is increasingly weakened in the further stages of the disease.

Keywords: Chronic obstructive pulmonary disease, Smoking, Morphological changes

Özet

Amaç: *Bu çalışmada; kronik obstrüktif akciğer hastalığı'nın (KOAH) erken tanısı ve patogenezini anlamak için sigara içen semptomlu ve semptomsuz bireylere ait yapısal ve fonksiyonel değişimler, sigara içmeyen bireylerle karşılaştırılarak incelenmiştir.*

Gereç ve Yöntem: *Yaşları 18-60 arasında 50 kişi çalışmaya alındı. (40 sigara içen, 10 içmeyen) Sigara içen olguların 23'ü semptomlu, 17'si semptomsuz olarak değerlendirildi. Tüm olgulara yüksek rezolüsyonlu toraks tomografisi (YRBT) ve solunum fonksiyon testi (SFT) uygulandı.*

Bulgular: *Tüm sigara içenlerin değerlendirilmesinde morfolojik değişiklikler ve SFT'nin karşılaştırılmasında, tüm morfolojik parametrelerle yalnızca χN2/lt arasında anlamlı ilişki saptanmıştır.Tüm olgularda kapanma volümü (CV), χN2/lt ve anatomik ölü boşluk (ADS) ile içilen sigara miktarı arasında ilişki saptanırken, semptomlu olgularda yalnız kapanma volümü ile semptomsuz içicilerde ise anatomik ölü boşluk ile anlamlı ilişki bulunmuştur.YRBT'de saptanan amfizem göstergeleri ile sigara içimi arasında pozitif yönde ilişki saptanırken, fonksiyonel ölçütler ile YRBT ölçütleri arasında anlamlı korelasyon bulunmamıştır.*

Sonuç: *Sigaraya bağlı oluşan akciğer hastalığının semptomsuz döneminde yapı-fonksiyon ilişkisinin semptomlu döneme göre daha iyi ama farklı olduğu, hastalığın ilerleyen dönemlerinde bu ilşkinin daha da zayıfladığı düşünülmektedir.*

Anahtar Kelimeler: *Kronik obstrüktif akciğer hastalığı, Sigara, Morfolojik değişiklikler*

Introduction

The main risk factor for the development of chronic obstructive pulmonary disease (COPD) is smoking. In many studies, the lung destruction and functional loss caused by smoking have been used as a model for understanding the pathogenesis of COPD [1, 2]. However, the correlation between the morphological changes and smoking is still controversial and conflicting [3], and the respiratory symptoms are not well correlated with either the functional loss or the morphological changes [4]. Morphological changes have usually been observed in asymptomatic smokers without airway obstruction when these patients were evaluated for a model to detect the early stages of COPD [5-7]. In the surgical and post-mortem specimens of asymptomatic smokers, emphysematous changes of varying degrees have been observed. In addition, a correlation has been found in post-mortem specimens between the small airway pathology and the small airway tests, such as the closing volume (CV) and ΔN2/l [8].

Inflammatory changes are often observed in both symptomatic and asymptomatic smokers. In addition, these changes show a correlation with the FEV1 in both asymptomatic smokers and patients with COPD [9].

Due to the often asymptomatic nature of the early stages of COPD, the patients with COPD often do not present to a doctor until late in the illness. Thus, the COPD patients are usually diagnosed during the irreversible stage of the disease, and the burden of the disease is continuously increasing. A sensitive and useful tool is needed to diagnose COPD before the symptoms appear. Although morphological changes and functional impairment are observed in the asymptomatic smokers, they have no significant correlation, and thus, the search for a sensitive tool continues. On the other hand, the composition of COPD, which includes both parenchymal destruction and small airway disease, the chronic course of the pathology and the use of different functional parameters may produce confusion in the diagnosis. A tool for the early diagnosis of COPD should express the processes of inflammation and destruction, show the morphological changes and functional status in parallel and be sensitive and easily usable.

The sensitivity of the widely used FEV1/FVC and FEV1 tests is controversial. The lung damage due to COPD may be detected in symptomatic and asymptomatic smokers via different parameters. Moreover, the examination of asymptomatic smokers may be useful for determining a parameter that will contribute to the understanding of the COPD pathogenesis and to the early diagnosis of COPD. In the present study, the morphological and functional characteristics of symptomatic and asymptomatic smokers were investigated and compared with nonsmokers.

Table 1. Relationship between smoking, morphology and function in all cases

	r	p
	Smoking-function	
CV	0.341	0.036
ADS	0.371	0.018
DN_2/lit	0.418	0.010
	Smoking-Morphology	
EOA	0.553	0.000
DOA	0.503	0.001
EIO total	0.502	0.001
EIO apex	0.504	0.001
EIO carina	0.510	0.001
	Morphology-Function	
DN_2/lit with all morphological parameters	0.343-0.481	0.038-0.020

CV:Closing volume, ADS:Anatomic dead space, EOA: Extent of emphysema, DOA: Degree of emphysema, EIO: Expirium-inspirium obtain

Materials and Methods

The study protocol was approved by the Ethics Committee of the School of Medicine. The study population consisted of 50 volunteers (40 smokers and 10 nonsmokers), who were informed about the harmful effects of smoking in the conferences on smoking. None of the volunteers had been previously admitted to a health care facility due to respiratory symptoms. They were given the information about the study protocol, and their written consent was obtained. A questionnaire was used to collect their demographic characteristics and respiratory symptoms. High-resolution computerized tomography (HRCT) and pulmonary function tests (PFT) were also performed in all cases.

Questionnaire:

All of the patients included in the study answered a standard questionnaire from the European Committee of Respiratory Health Survey (ECRHS) to collect information on their respiratory symptoms and smoking history (1). The smoking history was classified as follows: 1 = less than or equal to 10 pack-years; 2 = 11-20 pack-years; 3 = 21-30 pack-years; 4 = 31-40 pack-years; 5 = 41-50 pack-years; and 6 = greater than or equal to 51 pack-years. In the evaluation of symptoms, the scores were obtained from the three symptoms, each with four options, as follows: cough, 0 = none; 1 = sometimes; 2 = in the morning; 3 = whole day; sputum, 0 = none; 1 = sometimes; 2 = in the morning; 3 = continuously; dyspnea, 0 = none; 1 = sometimes; 2 = with effort; 3 = every time. A case was considered symptomatic when the total score, obtained from the sum of each symptom, was greater than 1.

HRCT Imaging:

The HRCT scans were taken in the supine position with a single-slice helical CT scanner (X-Vision Gx, Toshiba, Nasu, Japan) with 2 mm collimation, scanning time of 1.0 s, 120 kV electrical voltage and 250 mA electrical current. For each patient, three sections were taken with both inspiratory and expiratory air flow,

and the images were analyzed in the same window. The three sections obtained were at the apex level (2 cm above the superior margin of the aortic arch), at the carina level and at the pulmonary vein level (at the entrance level to the left atrium). A total of six different densities were measured covering each of the HRCT sections of the lung bilaterally.

For each level, the expiratory/inspiratory ratio (EIR) was calculated. The total EIR was also calculated from the sum of each level. The extent of emphysema (EOA) and the degree of emphysema (DOE) were evaluated. In the evaluation of the EOA, the emphysema was graded using the criteria of Jarden et al. (7); i.e., grade 1: < 25% of lung fields affected by emphysema; grade 2: 25-50% of lung fields affected by emphysema; grade 3: 50-75% of lung fields affected by emphysema; and grade 4: > 75% of lung fields affected by emphysema. To determine the DOE, each patient was grouped according to the presence of the LAAs as follows: 0, no emphysema; 1, LAAs in a 5 mm diameter; 2, presence of wider LAAs in addition to group 1; and 3, emphysema covering the whole section of the HRCT without any normal tissue.

Pulmonary Function Test (PFT):

All of the tests were performed by the same investigator via computerized spirometry (Sensor Medics Vmax 22) between 09:00 and 10:00 A.M. The patients were requested to abstain from smoking or taking any medication at least 24 hours before the tests. Both the PFTs and the DLCO test were done according to the ATS criteria.

The values of the FVC, FEV1, FEF25-75, PEF, FRC, TLC, RV, IC, CC, CV, DLCO and ΔN2/l were recorded as a percent of the predicted value, and the FEV1/FVC, RV/TLC, CC/TLC, DLCO/VA rates were calculated.

Statistical Analyses:

The collected data were evaluated in two steps: first, the association of smoking with function and morphology; and second, the association between the functional loss and morphological changes in symptomatic and asymptomatic smokers.

The data were analyzed using SPSS. A p-value of < 0.05 was considered significant. The Spearman test was used to compare the association of smoking with function and morphology. The Pearson's chi-square test was used for the other comparisons. For the comparison of changes in the parameters between and within groups, the repeated measures analysis of variance test was used.

Table 2. Relationship between smoking, morphology and function in symptomatic smokers

	R	P
	Smoking-Function	
CV	0.496	0.019
	Smoking-Morphology	
EOA	0.469	0.024
EIO	0.564	0.005
EIO apex	0.466	0.025
EIO carina	0.497	0.016
	Function-Morphology	
VC-EIO apex	-0.506	0.014
FEV_1-EIO carina	-0.481	0.020

CV: Closing volume, EOA: Extent of emphysema, VC: Vital capacity, EIO: Expirium-inspirium obtain

Table 3. Relationship between smoking, structure and function in asymptomatic smokers

	r	P
	Smoking-Function	
ADS	0.676	0.003
	Smoking-Morphology	
EOA	0.675	0.003
EIO	0.643	0.005
EIO apex	0.668	0.003
EIO carina	0.598	0.011
	Function-Morphology	
VC-EIO carina	-0.516	0.034
CV-EIO carina	0.559	0.024
ADS-EIO	0.544	0.024
ADS-EIO apex	0.724	0.001
ADS-EIO carina	0.597	0.011
ADS-EIO pulmonary vein	0.503	0.040
DLCO-EIO	0.510	0.036
DLCO-EIO apex	0.527	0.030
DLCO-EIO pulmonary vein	0.508	0.038

ADS: Anatomic dead space, EOA: Extent of emphysema, EIO: Expirium-inspirium obtain, CV: Closing volume,VC: Vital capacity, DLCO:Carbon monoocsit diffusion test

Results

A total of 50 male patients (40 smokers and 10 non-smokers), who responded to a questionnaire, between the ages 18-60 (mean age 32) were included the study. Of the smokers, 23 were symptomatic, and 17 were asymptomatic. Among the smokers, there was an average 27 pack-yr smoking history, and the smoking history was not significantly different between the symptomatic and asymptomatic patients.

In the evaluation of the relationship between smoking and the PFTs, there was a significant correlation between the smoking score and the CV, ΔN2/l and ADS (Table I). A significant increase in the FRC and RV and a significant decrease in the DLCO were observed in the smokers compared with the non-smokers (p=0.049, p=0.037 and p=0.031, respectively).

In the evaluation of all smokers, there was a significant correlation between the smoking score and all of the morphological parameters. In the comparison of the PFTs and morphological changes, there was a significant correlation between all morphological parameters and ΔN2/l (Table I).

In the symptomatic smokers, there was a correlation between the smoking score and the CV. In the evaluation of the correlation between morphology and function, there was a negative correlation between the VC and EIO at the apex and between

the FEV1 and EIO at the carina (Table II).

In the asymptomatic smokers, there was only significant positive correlation between smoking and the ADS among the pulmonary function tests. A relationship was found between smoking and all parameters that are investigated as markers of emphysema in nonsmokers. However, the number of parameters in nonsmokers was higher compared with the smokers (Table III).

Discussion

In the present study, it was found that, in the earlier stages, smoking had an effect on the CV and ADS rather than the parameters that are used in the determination of airway obstruction, such as the FEV1/FVC and FEV1. Although a relationship was found between the smoking score and the CV, ΔN2/l and ADS in all cases, the smoking score was significantly correlated with only CV in the symptomatic cases and only ADS in the asymptomatic cases. The CV and ΔN2/l may show the early changes in function of the small airways, and a correlation with histopathological changes has been shown [10].

Smoking is known to cause inflammation and destruction of the lung parenchyma in the small airways. In our study, there was a positive correlation between the emphysema parameters on the HRCT and smoking, but no correlation was found between the parameters and the pulmonary function tests. It is known that chronic bronchitis develops in some smokers, and airway obstruction will be developed in some smokers. The definitions of emphysema as histopathological and chronic bronchitis as clinical can also increase confusion.

The presence of a correlation between morphology and only the VC and FEV1 in the symptomatic cases was an interesting finding, although there was a correlation between all emphysema parameters on the HRCT and smoking in all cases. In the asymptomatic cases, the VC, CV, AD and DLCO were shown to have a positive correlation with smoking (Table II and III).

It is known that pulmonary function tests and the presence of emphysema are not well correlated (3, 4), and it has been suggested that the obstruction parameters may be affected by the location of the pathologies caused by smoking [11]. For example, the correlation of the FEV1/FVC was better in the cases with centrilobular emphysema when an additional apparent small airway involvement was present compared to the cases with panlobular emphysema with slight small airway involvement. Although panlobular emphysema is known to be associated with age and alpha-1 antitrypsin deficiency, in that study, it was emphasized that the ages of both groups were similar [11].

The CV is a test capable of early detection of the disturbances in airway functions. An increase in the CV may result from the destruction (loss of elastic recoil) or pathologies of small airways. However, both the functional and morphological determinations of the causes may be difficult. It has been suggested that newer imaging techniques may be able to differentiate the decreased density on HRCT between a decreased attenuation due to the destruction and an air-trapping due to small airway disease. In order to establish a correlation between the pathological changes resulting from small airway inflammation and the determined changes on the HRCT, the pulmonary vascular shadows and bronchiolar structures should be examined in addition to the decreased attenuation.

In the early periods of small airway disease, decreased attenuation may not be observed. The progress in radiologic imaging and image processing may affect the results. It has also been suggested that different results may be obtained if the images are taken in different positions, such as the supine, prone or upright positions [12]. In a study investigating the relationship between the structure and function of COPD, it was found that the evaluation of either the inner or outer areas of the lung parenchyma may affect the functional correlation [13]. In our study, the presence, size and extent of low attenuation areas of the lung parenchyma were studied only in the slices taken in the supine position.

When the inflammatory changes in small airways were compared with the tests that provide early diagnosis, the ΔN2/l values were well correlated with pigment deposition in the respiratory bronchioles, goblet cell metaplasia in the respiratory bronchioles, and goblet cell metaplasia in both the respiratory and membranous bronchioles, especially when the FEV1 was greater than 80% of the predicted value [14]. In another study, it was reported that the values of the CV and ΔN2/l were well correlated with mural inflammation, increased airway muscle and the total inflammation score [8].

Many studies investigating the relationship between smoking, airway inflammation and parenchymal destruction have reported a relationship between the inflammatory cell number, function and mediator-receptor activation [15-19]. The studies utilizing lung biopsy specimens, bronchoalveolar lavage and, more recently, the induced sputum in the screening of inflammation have shown a relationship between airway obstruction and the increased neutrophil numbers in the cases with COPD [20].

Inflammation may cause both a narrowing of the small airways and the early closing at low lung volumes by changing the surface tension of fluid on the bronchial surface without the occurrence of apparent parenchymal destruction or the loss of elastic recoil. A scenario that describes the functional impairment caused by smoking in three stages has been suggested by Milic-Emili [21]. Briefly, there is an increase of the CV above the FRC at the first stage, the development of tidal expiratory flow limitation at the second stage, and finally, dynamic hyperinflation, dyspnea and exercise limitation in the final stage. The interest in small airway tests was increased when Casio et al. showed a relationship between the CV, ΔN2/l and morphological changes and peripheral airway disease in 1978 [10]. However, the interest has since decreased due to epidemiologic studies showing conflicting results.

Although an increase in the CV has been shown at low volumes, the FEV1 is a parameter determined only at high volumes. In addition, the FEV1 is not a good marker for determining the dynamic hyperinflation or in the screening of dyspnea and exercise capacity. According to the conclusions suggested by Milic-Emili, the inflammatory processes in the small airways initiated by smoking cause an increase of the CV at low lung volumes and a decrease of the maximum expiratory volumes (Vmax). When

the increase in CV occurs at the level of the tidal volume, the airways are mechanically injured. The continuous decrease of Vmax causes an expiratory flow limitation. This limitation leads to dynamic compression, and thus, the harmful effect continues to increase. In the third stage proposed by Milic-Emili, the dynamic hyperinflation leads to dyspnea and exercise limitation, as well as to a functional decrease of the FEV1/FVC. This period of the disease corresponds to when the cases are usually observed by a physician. Continued smoking and, accordingly, continued inflammation lead to increased mechanical injury and functional and morphological impairments of the lungs. According to this scenario, the crucial pathophysiological changes occur in stages I and II, corresponding to the GOLD stage 0 (normal FEV1/FVC and FEV1 but the presence of symptoms). If this hypothesis is valid, a treatment approach with bronchodilator and/or anti-inflammatory drugs at the beginning of the increase of the CV at low volumes may overwhelm the injury and break the vicious circle. The findings and opinions supporting the hypothesis of Milic-Emili will prompt more studies on this subject [22-26]. It has also been shown that smoking causes an up-regulation of collagen gene expression and a collagen increase in the airway wall without inflammation in the tracheal cell cultures [22]. This finding may help to explain the increases in the CV due to smoking.

On the other hand, there is increasing evidence to suggest that the cyclic stretching due to the repeated opening and closing of the lung parenchyma and airways leads to release of a variety of cytokine mediators that potentially drive inflammation and fibrosis, as well as cellular apoptosis and necrosis [23-26]. This observation may explain the continuing vicious circle in Milic-Emili's hypothesis.A long-term follow-up study of the pulmonary functions of smokers is necessary to prove that the two-way relationship between the CV and inflammation is a starting point of the pathogenesis of COPD and to be able to utilize the CV as a predictive test.

In conclusion, the obtained data suggest that the relationship between morphology and function is better, but different, in the asymptomatic period of lung damage caused by smoking compared with the symptomatic period; moreover, this relationship is weakened in the later stages. It is assumed that the functional changes in the early stages may be explained with the inflammatory mechanisms rather than morphological changes. However, various pulmonary mechanisms may affect the respiratory functions after the morphological changes occur. The pathogenesis of COPD likely originates from the morphological changes due to inflammation and destruction, which occur in the small airways and parenchyma, and from the increased functional impairments, which occur in those compartments by affecting each other. Clarifying the pathogenesis of COPD in the early stages will prompt the early determination and appropriate treatment of COPD. Therefore, long-term studies are necessary to investigate the stages, localization and extent of inflammation and the correlation of the results with the functional impairments.

Conflict interest statement The authors declare that they have no conflict of interest to the publication of this article.

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