

Acute exacerbation impairs endothelial function in patients with chronic obstructive pulmonary disease

Kronik obstrüktif akciğer hastalığında akut alevlenme atakları
endotel fonksiyonlarını olumsuz etkilemektedir

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Objectives: The effect of acute exacerbation of chronic obstructive pulmonary disease (COPD) on brachial artery flow-mediated dilation (FMD) has not been examined. The aim of this study was to assess the endothelial function of COPD patients during acute exacerbations.

Study design: The study included 30 consecutive patients (8 women, 22 men; mean age 64.2±10.9 years) who experienced acute exacerbation of COPD, defined according to the Anthonisen criteria (increased dyspnea, sputum, and sputum purulence). All patients received the same antibiotic and bronchodilator treatment. Endothelial function was assessed by brachial artery ultrasonography within the first 48 hours and after complete resolution of exacerbation symptoms. Flow-mediated dilation was defined as both the maximum absolute and maximum percentage changes in the vessel diameter during reactive hyperemia. The results were compared with those of 20 age- and sex-matched controls without COPD.

Results: The patient and control groups were similar in terms of age, gender, hypertension, diabetes, hyperlipidemia, coronary artery disease, heart rate, and blood pressure. Parameters of FMD during acute exacerbation were significantly lower than those obtained after recovery (absolute change: 0.23±0.12 mm vs. 0.38±0.17 mm, p<0.001; percentage change: 6.44±3.99% vs. 10.42±4.86%, p<0.001) and than those of the control group (absolute change: 0.36±0.13 mm, p=0.001; percentage change: 9.77±3.83%, p=0.003). Flow-mediated dilation increased significantly after recovery, yielding similar values to those of the controls. Improvements in FMD were significant in both sexes.

Conclusion: Acute COPD exacerbation is associated with worsening endothelial function, increasing the risk for cardiovascular morbidity.

Key words: Brachial artery/ultrasonography; endothelium, vascular; pulmonary disease, chronic obstructive.

Amaç: Kronik obstrüktif akciğer hastalığında (KOAH) akut alevlenme ataklarının brakiyal arter endotel bağımlı akıma bağlı dilatasyon (ABD) üzerine etkisi araştırılmamıştır. Bu çalışmada, KOAH hastalarında akut alevlenme sırasında endotel fonksiyonları değerlendirildi.

Çalışma planı: Çalışmaya, Anthonisen ölçütlerine göre (nefes darlığı, öksürük ve balgam miktarında artış) akut alevlenme tanısı konan ardışık 30 KOAH hastası (8 kadın, 22 erkek; ort. yaş 64.2±10.9) alındı. Tüm hastalara aynı antibiyotik ve bronkodilatör tedavisi uygulandı. Endotel fonksiyonları, akut alevlenme tanısından sonraki ilk 48 saat içinde ve akut alevlenmenin tamamen geçmesinden sonra, brakiyal arter ultrasonografisi ile değerlendirildi. Akıma bağlı dilatasyon, reaktif hiperemi sırasında damar çapında en yüksek mutlak ve yüzde değişiklikleri olarak tanımlandı. Sonuçlar yaş ve cinsiyet uyumlu ve KOAH olmayan 20 kişilik kontrol grubuyla karşılaştırıldı.

Bulgular: Hasta ve kontrol grupları, yaş, cinsiyet, hipertansiyon, diyabet, hiperlipidemi, koroner arter hastalığı, kalp hızı ve kan basıncı açısından benzerdi. Akut alevlenme döneminde ölçülen ABD değerleri, iyileşme sonrasındaki değerlerden (mutlak değişim: 0.23±0.12 mm ve 0.38±0.17 mm, p<0.001; yüzde değişim: %6.44±3.99 ve %10.42±4.86, p<0.001) ve kontrol grubu değerlerinden (mutlak değişim: 0.36±0.13 mm, p=0.001; yüzde değişim: 9.77±3.83%, p=0.003) anlamlı derecede düşük bulundu. İyileşmeden sonra ABD değerleri anlamlı artış gösterdi ve kontrol grubunun değerleriyle benzer hale geldi. Akıma bağlı dilatasyondaki düzelleme her iki cinsiyette de anlamlıydı.

Sonuç: Kronik obstrüktif akciğer hastalığında akut alevlenme endotel fonksiyonlarını kötüleştirmektedir; bu durum kardiyovasküler morbiditede artışa neden olabilir.

Anahtar sözcükler: Brakiyal arter/ultrasonografi; endotel, vasküler; akciğer hastalığı, kronik obstrüktif.

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Chronic obstructive pulmonary disease (COPD) is characterized by reduced maximum expiratory flow and slow forced emptying of the lungs. In the past, COPD was regarded solely as a lung disease. However, it is now accepted as a multicomponent disease characterized by an inflammatory response of the lungs to noxious particles with neutrophil, macrophage, and lymphocyte infiltration, and extrapulmonary effects that contribute to disease severity.^[1,2] Among the systemic effects associated with COPD are skeletal muscle dysfunction, nutritional abnormalities and weight loss, cardiovascular and nervous system abnormalities.^[3,4]

Exacerbations are major causes of morbidity and mortality in COPD. There is enhancement of both local airway and systemic inflammation during exacerbations.^[5,6]

Endothelial dysfunction plays a major role in the pathogenesis of various diseases including atherosclerosis, hypertension, and heart failure.^[7-9] All the well known risk factors of atherosclerosis including age, smoking, hypertension, hyperlipidemia, diabetes and hyperhomocysteinemia contribute to cardiovascular mortality and morbidity by impairing normal endothelial function.^[10-13] Brachial artery flow-mediated dilation (FMD) is a well-studied measure of endothelial function that has been used to noninvasively assess conduit artery and microvascular endothelial function.^[14-16]

Recent studies have shown that endothelial functions are impaired in COPD patients, correlating with the severity of the disease.^[17,18] Increased systemic inflammatory process with activated inflammatory cells, increased plasma levels of proinflammatory cytokines, hypoxia, and increased oxidative stress may be the leading causes of endothelial dysfunction in COPD patients. Although endothelial dysfunction has been shown in COPD patients, the effect of acute exacerbations of COPD on brachial artery FMD has not been studied. The aim of this study was to assess the endothelial function of COPD patients during acute exacerbations and to compare it with the FMD values obtained after recovery.

PATIENTS AND METHODS

Thirty patients with acute exacerbation of COPD were consecutively recruited to the study. The diagnosis of COPD was based on the guidelines of the American Thoracic Society/European Respiratory Society.^[19] Acute exacerbation of COPD was defined as the presence of worsening or increased dyspnea, increase in the amount of sputum production, and change in sputum purulence.^[20] All the patients had

Anthonisen type I exacerbation (all three symptoms present). None of the patients needed hospitalization. Exclusion criteria were severe COPD exacerbation requiring intubation, overt heart failure, atrial fibrillation, and severe neurological, endocrine, hepatic, or renal diseases.

The study was conducted in agreement with the principles of the Declaration of Helsinki. The study was approved by the local ethical committee and all participants gave written informed consent.

All patients were given the same antibiotic treatment (amoxicillin 1x2 g per day for 14-21 days) and bronchodilators (tiotropium bromide, long-acting beta-2 agonist plus inhaler steroid). The patients were followed-up at one-week intervals. Resolution of COPD exacerbation was defined as improvement of all three symptoms (dyspnea, increase in sputum, and sputum purulence). There was no change in the routine medications of the patients throughout the study. Endothelial function was assessed within the first 48 hours following the diagnosis of COPD exacerbation and after complete resolution of the exacerbation.

Twenty patients who did not have a history of COPD were included as the control group.

Assessment of endothelial function. Endothelial function was assessed noninvasively by brachial artery ultrasonography based on the protocols described previously,^[14] using the Vingmed System V echocardiography/ultrasonography system (GE Medical Systems, Horten, Norway) and a 10-MHz linear transducer. Examinations were made by a single blinded ultrasonographer in a temperature-controlled room (22 °C) in the morning after a fasting period of 8-12 hours. Ingestion of substances that might affect measurements, such as caffeine, high-fat foods, and vitamin C was not allowed for 12 hours before the study. Any vasoactive medication was discontinued at least five serum half-lives before the brachial studies.

The right brachial artery was imaged above the antecubital fossa in the longitudinal plane. Upon acquisition of a clear image, the surface of the skin was marked and the arm and the ultrasound probe were kept in the same position during the entire study. Continuous electrocardiographic (ECG) monitoring was obtained. The diameter of the brachial artery was measured from longitudinal images in which the lumen-intima interface was visualized on the anterior and posterior walls at end-diastole (the onset of R wave on the ECG). The mean of three highest measurements from five consecutive cardiac cycles

Table 1. Demographic and clinical characteristics of the patients and controls

	COPD patients (n=30)			Controls (n=20)			<i>p</i>
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			64.2±10.9			61.9±7.4	0.351
Sex							0.895
Females	8	26.7		5	25.0		
Male	22	73.3		15	75.0		
Hypertension	26	86.7		18	90.0		1.00
Diabetes	13	43.3		9	45.0		0.907
Hyperlipidemia	17	56.7		14	70.0		0.341
Coronary artery disease	10	33.3		8	40.0		0.630
Body mass index (kg/m ²)			29.1±4.0			28.7±3.8	0.927

COPD: Chronic obstructive pulmonary disease.

was taken. After baseline measurements of the lumen diameter and blood flow at rest, a sphygmomanometer cuff was placed on the forearm and inflated to 250 mmHg for five minutes to induce arterial occlusion. Then, the cuff was deflated and the lumen diameter was estimated one minute after deflation to assess the endothelium-dependent FMD. Flow-mediated dilation was defined as both the maximum absolute and maximum percentage changes in the vessel diameter during reactive hyperemia. After 10 minutes of rest following reactive hyperemia, 5 mg nitroglycerin (NTG) was given sublingually to determine endothelium-independent vasodilation. The lumen diameter was measured 4-5 minutes after NTG administration. Endothelium-independent NTG-mediated vasodilation was also expressed as both the maximum absolute and maximum percentage changes in the vessel diameter.

To determine intraobserver variability, the observer measured the brachial artery diameters of 10 healthy controls and repeated the measurements on the following two days. Then, the three sets of measurements were compared with the Friedman test (repeated measures from a single sample). The *p* value of the test was not significant. The intraobserver variability for repeated measurements (the mean of the differences) was 0.00±0.11 mm in our laboratory.

Statistical analysis. All statistical tests were performed using the SPSS 11.0 statistical analysis program (for Windows). Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentages. Wilcoxon test and Mann-Whitney U-test were used to compare quantitative nonparametric data obtained during acute COPD exacerbation and recovery and from COPD patients and controls, respectively. Correlation analysis was performed by the Spearman's correlation test. *P* values <0.05 were considered statistically significant.

RESULTS

General characteristics of the patients and controls are shown in Table 1. There were no significant differences between COPD patients and controls in terms of age, gender, hypertension, diabetes, hyperlipidemia, and coronary artery disease. All COPD patients and controls were ex-smokers. Since pulmonary function test is not a necessity for the diagnosis of COPD exacerbation, pulmonary function test was not performed during exacerbations, but pulmonary function tests performed within the three months before the occurrence of exacerbations were recorded. The results of pre-exacerbation pulmonary function tests are presented in Table 2.

Heart rate, blood pressure, and brachial artery measurements of COPD patients during acute COPD exacerbation and after recovery and those of the controls are shown in Table 3. The mean interval between the baseline and final measurements of endothelial function was 30±7 days in COPD patients.

Blood pressures did not differ significantly from the baseline in COPD patients. Heart rate decreased with recovery compared to the baseline, but the difference was not statistically significant. Similarly, both baseline and recovery heart rate and blood pressure measurements of COPD patients did not differ significantly from those of the controls.

Table 2. Pre-exacerbation pulmonary function tests

	Mean±SD	Range
FEV ₁ /FVC (%)	57±9	46 - 69
FEV ₁ (%)	51±15	34 - 66
FVC (%)	75±20	52 - 107
FEF 25-75 (%)	20±10	11 - 37

COPD: Chronic obstructive pulmonary disease; FEV₁: Percent of predicted forced expiratory volume in one second; FVC: Percent of predicted forced vital capacity; FEV₁/FVC: FEV₁ as percentage of forced vital capacity; FEF 25-75: Forced mid-expiratory flow (average rate of flow between the 25% and 75% volume points of an FVC maneuver).

Table 3. Blood pressure, heart rate, and brachial artery measurements

	COPD patients (Exacerbation)	COPD patients (Recovery)	Controls	<i>p</i> [†]	<i>p</i> [‡]	<i>p</i> [§]
	Mean±SD	Mean±SD	Mean±SD			
Systolic blood pressure (mmHg)	140.0±24.8	139.1±25.5	136.4±21.0	0.750	0.439	0.897
Diastolic blood pressure (mmHg)	81.8±14.0	80.7±14.2	78.9±10.1	0.773	0.201	0.511
Heart rate (beat/min)	84±12	81±10	79±11	0.115	0.377	0.468
Baseline velocity (cm/sec)	55.2±21.0	54.4±17.0	53.4±19.2	0.891	0.721	0.494
Baseline diameter (mm)	3.76±0.68	3.78±0.63	3.80±0.45	0.991	0.968	0.835
Post-ischemic flow velocity (cm/sec)	107.6±33.5	124.3±47.8	108.3±27.0	0.057	0.984	0.143
Flow-mediated dilation						
Absolute (mm)	0.23±0.12	0.38±0.17	0.36±0.13	<0.001	0.001	0.627
Percentage (%)	6.44±3.99	10.42±4.86	9.77±3.83	<0.001	0.003	0.692
Nitroglycerin-mediated vasodilation						
Absolute (mm)	0.74±0.38	0.98±0.18	1.09±0.26	0.180	0.126	0.448
Percentage (%)	20.6±13.7	29.1±8.5	31.2±11.8	0.225	0.176	0.569

COPD: Chronic obstructive pulmonary disease; Comparisons [†]between acute exacerbation and recovery; [‡]during acute exacerbation and controls; [§]after recovery and controls.

Baseline velocity and brachial artery diameters measured both during acute exacerbation and after recovery were similar to those of controls. However, FMD values obtained during acute exacerbation were significantly lower than those obtained after recovery (absolute change: 0.23±0.12 mm vs. 0.38±0.17 mm, *p*<0.001; percentage change: 6.44±3.99% vs. 10.42±4.86%, *p*<0.001) and than those of the control group (absolute change: 0.36±0.13 mm, *p*=0.001; percentage change: 9.77±3.83%, *p*=0.003). Flow-mediated dilation increased significantly with recovery from acute exacerbation, yielding similar values to those of the control group. In addition, improvements in FMD values were significant in both sexes (males: 0.23±0.12 mm vs. 0.39±0.18 mm, *p*<0.001; females: 0.24±0.14 mm vs. 0.36±0.14 mm, *p*=0.042). Nitroglycerin-mediated dilation measured after recovery was higher than the baseline, but this difference was not significant.

As COPD severity is correlated with FEV₁ (forced expiratory volume in one second), we sought correlations between pre-exacerbation FEV₁ and FMD parameters. No significant correlation was found between pre-exacerbation FEV₁ and FMD during exacerbation (*r*=0.14, *p*=0.72) or after recovery (*r*=0.29, *p*=0.43).

DISCUSSION

Chronic obstructive pulmonary disease is a multi-component disease and an important risk factor for atherosclerosis.^[21-23] Cardiovascular conditions are the leading cause of mortality in patients with impaired lung function.^[21,23,24] Even modest reductions in expiratory flow volumes elevate the risk for coronary

artery disease, stroke, and sudden cardiac death 2- to 3-fold, independent of other risk factors.^[24,25] It has been demonstrated that decreased FEV₁ is associated with decreased ankle-brachial index and increased carotid artery intima-media thickness.^[26]

Endothelial function is impaired in COPD patients, correlating with the severity of the disease. Moro et al.^[27] showed that endothelial-dependent and, to a lesser extent, endothelial-independent dilations were significantly impaired in COPD, and the impairment was proportional to the severity of bronchial obstruction. In our study, we did not find any significant association between FEV₁ and FMD parameters, which might be due to the small number of patients. Karoli et al.^[17] studied endothelial function by reactive hyperemia and nitroglycerin tests and blood levels of desquamated endothelial cells in 60 male patients with COPD. They found that COPD patients had a higher number of circulating endothelial cells and significantly decreased flow-dependent dilatation compared to controls. Signs of endothelial impairment and decrease in endothelium-dependent dilatation were most pronounced in patients with severe COPD. However, endothelial dysfunction of pulmonary arteries was shown even in patients with mild COPD.^[18] It was also shown that patients with bronchial asthma had decreased vasodilatory response to shear stress compared to controls.^[28]

The role of systemic inflammation has been well established in the pathogenesis of endothelial dysfunction and atherosclerosis. There is growing epidemiological evidence linking systemic inflammation to atherosclerosis, ischemic heart disease, stroke,

and coronary death.^[29,30] A persistent low-grade systemic inflammatory response is present in COPD and this may explain the poor endothelial function in these patients. Mendes et al.^[31] showed that endothelial dysfunction might be improved in the airway of lung-healthy current smokers with the use of an inhaled corticosteroid, suggesting the anti-inflammatory effect of corticosteroids. In our study, the use of an inhaled corticosteroid might also contribute to the improvement in endothelial function. There is also an increased oxidant burden in patients with COPD, which is detected in plasma as an increase in oxidative stress markers accompanied by a reduction in antioxidative capacity. Increased oxidative stress, hypoxia, metabolic dysfunction of the lung endothelium, elevated levels of biologically active substances including cytokines and leukotrienes may all cause endothelial dysfunction in COPD patients.^[17,32]

A novel finding of this study is the demonstration of a significant improvement in endothelial function after recovery from COPD exacerbation. To our knowledge, the effect of acute exacerbation of COPD on brachial artery FMD has not been examined. We found that FMD parameters significantly improved after recovery from acute exacerbation of COPD. Endothelial functions probably worsen during acute exacerbation and improve as the exacerbation resolves. Similarly, Karoli et al.^[33] investigated endothelial dysfunction in patients with bronchial asthma by assessment of circulating endotheliocytes and found significantly elevated levels during active exacerbation compared to post-exacerbation levels and healthy controls.

We believe that exacerbation-induced enhancement of systemic inflammation is one reason for further impairment of endothelial function during exacerbations. There is evidence that inflammation is amplified during exacerbations.^[34-36] Increased neutrophil counts have been found in the bronchial walls and in bronchoalveolar lavage fluid samples of COPD patients during exacerbations.^[37,38] Increases in various inflammatory markers including inflammatory cytokines, IL-6, endothelin-1, and neutrophil chemoattractants are observed during COPD exacerbation compared with the stable state.^[36,39,40] Increased oxidative stress might be another reason for poor endothelial function. Chronic obstructive pulmonary disease is associated with significantly increased systemic oxidative stress particularly during exacerbations.^[41-43] Rahman et al.^[41] found a marked redox imbalance during acute exacerbations of COPD. In

addition, sympathetic activation and parasympathetic withdrawal are commonly observed during acute exacerbations of COPD^[44] and may have an unfavorable effect on endothelial function.

Study limitations. The major limitation of the study was definitely the small sample size. Correlation analysis between pre-exacerbation pulmonary function tests and endothelial FMD parameters did not show significant associations probably due to the sample size. We did not study arterial blood gas, inflammatory markers, or oxidative stress markers during exacerbation and recovery periods, which would support their contributions to impaired endothelial function. Yet, to our knowledge, this is the first study evaluating the effect of acute exacerbation of COPD on endothelial function assessed by brachial artery FMD.

In conclusion, COPD is a multicomponent disease with pulmonary and extrapulmonary consequences. Individuals with COPD are at increased risk for cardiovascular diseases. There is a persistent low-grade systemic inflammation in COPD patients, which is upregulated during exacerbations. Endothelial functions are impaired in COPD patients and our study shows significant worsening of endothelial function during exacerbations. Endothelial dysfunction represents an increased risk for cardiovascular morbidity in COPD patients during acute exacerbations.

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