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The effect of endobronchial coil treatment (EBCT) on hemorheological parameters and oxidative stress: a pilot study

Endobronşiyal koil tedavisinin (EBCT) hemoreolojik parametreler ve oksidatif stres üzerine etkisi: pilot çalışma

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Abstract

Purpose: Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, curable disease characterized by persistent airflow limitation, respiratory symptoms due to airway and/or alveolar abnormalities caused by severe exposure to harmful particles, gases. During the endobronchial coil treatment (EBCT) process, the volume of the lung parenchyma is reduced by shrinking the elastic recoil. Although there are studies showing worsening of hemorheological parameters in COPD exacerbations, no study investigated whether hemorheological parameters are improved after coil. The aim of this study was to assess the effects of coil therapy on erythrocyte deformability, whole blood viscosity (WBV) measured at autologous, standard (40%) hematocrit and plasma viscosity (PV) in COPD patients.

Material and methods: Venous blood samples were taken once from the healthy control group (n=17) and before and 1 month after the treatment from the COPD patients who had been indicated for coil according to GOLD guidelines (n=20). To assess erythrocyte deformability, shear-dependent erythrocyte elongation was measured at 0.3-3.0 Pa by an ektacytometer (LORCA), while WBV, PV were measured using a rotational viscometer.

Results: Erythrocyte deformability measured at shear stresses between 0.3-5.33 Pa were found to be higher following treatment compared to pre-coil values. EBCT did not have a statistically significant effect on WBV measured at autologous, 40% hematocrit, PV and oxidative stress indices.

Conclusion: Increased erythrocyte deformability determined following EBCT at the shear stresses observed at the pulmonary level is a favourable finding, showing that the procedure may positively affect the hemodynamics of COPD patients as well as causing clinical improvement.

Keywords: Chronic obstructive pulmonary disease, endobronchial coil therapy, erythrocyte deformability, hemorheology, oxidative stress.

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Öz

Amaç: Kronik Obstrüktif Akciğer Hastalığı (KOAH), zararlı partiküllere, gazlara şiddetli maruziyetin neden olduğu hava yolu ve/veya alveolar anormalliklere bağlı kalıcı hava akımı kısıtlılığı, solunum semptomları ile karakterize yaygın, önlenebilir, tedavi edilebilir bir hastalıktır. Endobronşiyal koil tedavisi (EBCT) işlemi sırasında elastik geri tepme küçültülerek akciğer parankiminin hacmi azaltılır. KOAH alevlenmelerinde hemoreolojik parametrelerin kötüleştiğini gösteren çalışmalar olmasına rağmen, koil sonrası hemoreolojik parametrelerin iyileşip iyileşmediğini araştıran bir çalışma yoktur. Bu çalışmanın amacı, KOAH hastalarında koil tedavisinin eritrosit deformabilitesi, otolog, standart (%40) hematokritte ölçülen tam kan viskozitesi (WBV) ve plazma viskozitesi (PV) üzerindeki etkilerini değerlendirmektir.

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Gereç ve yöntem: Sağlıklı kontrol grubundan (n=17) ve GOLD yönergelerine göre coil için endikasyon konulmuş olan KOAH hastalarından (n=20) tedaviden önce ve 1 ay sonra venöz kan örnekleri alındı. Eritrosit deformabilitesini değerlendirmek için, kaymaya bağlı eritrosit uzaması 0,3-3,0 Pa'da bir ektasitometre (LORCA) ile ölçülürken, WBV, PV rotasyonel bir viskozimetre kullanılarak ölçüldü.
Bulgular: Eritrosit deformabilitesi 0,3-5,33 Pa arasındaki kayma streslerinde ölçülmüş ve tedavi sonrasında coil öncesi değerlere kıyasla daha yüksek bulunmuştur. EBCT'nin otolog, %40 hematokrit, PV ve oksidatif stres indekslerinde ölçülen WBV üzerinde istatistiksel olarak anlamlı bir etkisi olmamıştır.
Sonuç: EBCT sonrasında pulmoner düzeyde gözlenen kayma gerilimlerinde belirlenen artmış eritrosit deformabilitesi, işlemin KOAH hastalarının hemodinamiğini olumlu yönde etkileyebileceğini ve klinik iyileşmeye neden olabileceğini gösteren olumlu bir bulgudur.

Anahtar kelimeler: Kronik obstrüktif akciğer hastalığı, endobronşiyal koil tedavisi, eritrosit deformabilitesi, hemoreoloji, oksidatif stress.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of morbidity and mortality worldwide [1]. COPD has two primary types as chronic bronchitis and emphysema [2]. Emphysema is a destructive process of the pulmonary parenchyma characterized by the permanent expansion of distal airways [3]. This results in dynamic hyperinflation, loss of elastic recoil, air trapping and decreased exercise capacity, shortness of breath and increased mortality [4].

Smoking cessation, pharmacological treatments, rehabilition, education & self management, oxygen support, vaccination programs are among the primary treatment options for COPD [3, 5, 6]. However, their effects in patients with emphysema are limited. Since the main pathology in emphysema is hyperinflation due to permanent elastic tissue damage, the search for novel treatment has come to the fore. Endoscopic volume reduction treatments can be considered as important alternatives in certain emphysema patients that are dyspneic despite optimal medical treatment [6]. There are many studies which report that endobronchial coil treatment (EBCT) which is one of the endoscopic volume reduction treatments, reduces hyperinflation while improving the quality of life of patients [7, 8].

Hemorheology is the scientific field interested in blood flow properties and deformability of its cellular components [9]. Its compnents may be summarized as red Blood Cell (RBC) deformability, viscosity of blood and hematocrit (Hct) [10]. Many studies suggest that flow behaviors of blood are essential for maintaining proper tissue perfusion [10].

It is known that, oxidative stress is effective in various physiological conditions and in many diseases including COPD pathogenesis [11]. Although enhanced oxidative stress and / or decreased antioxidant status were suggested to be involved in in the pathogenesis of COPD, the precise mechanism was not yet revealed [12]. Oxidative stress is the result of increased formation of reactive oxygen species and/or decreased antioxidant capacity [13, 14].

Oxidative stress is closely associated with hemorheological alterations [15]. Increment in oxidative stress was demonstrated to be responsible for certain hemorheological changes [16]. Oxidative stress was determined in order to explain the possible alterations in hemorheological parameters in the current study.

A limited number of studies have been carried out until now on the hemorheological parameters and oxidative stress in chronic pulmonary diseases [6, 15, 17, 18]. The aim of this study was to examine whether EBCT has an effect on hemorheological and oxidative parameters in patients with emphysema. As far as we have researched and found, no study has been found examining the effects of interventional treatment method on hemorheological and oxidative stress parameters.

Materials and method

Study population

All patients who underwent coil treatment between July 2019 and February 2020 and agreed to participate were included in the study. A total of 24 patients who were followed up at the Pulmonary Diseases clinic and diagnosed with stage 3 or stage 4 COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnosis criteria were involved [5]. These patients were also emphysematous and suitable for EBCT. The inclusion and exclusion criteria of the patients are given in Table 1 [19]. Cardiopulmonary rehabilitation programs of all patients were completed prior to the procedure.

Age and sex matched healthy voulnteers consisting the same number of individuals without chronic disease or smoking history were involved as the control group.

Table 1. Patient inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Patients undergoing optimal medical treatment (quitting smoking, maximum pharmacological treatment, pulmonary rehabilitation)	Severe PHT (PAP >50 mmHg in ECO)
GOLD Stage 3 or 4	Clinically severe bronchiectasis
CAT score ≥10, mMRC ≥2	Suspected pulmonary module
FEV_1 20-45%	Diagnosed lung cancer or suspicion
$RV_{expected}$ ≥175% or RV/TLC ≥58%	Interstitial fibrosis
6-minute walk test 100-500 m	Severe tracheobronchomalacia

GOLD: Global Initiative for Chronic Obstructive Lung Disease, CAT: COPD Assessment Test
mMRC Modified Medical Research Council Dyspnea Scale, FEV_1: forced expiratory volume in first second
RV: residual volume, TLC: total lung capacity, PHT: pulmonary hypertension, sPAP: systolic pulmonary arterial pressure

Procedure

Application of EBCT (PneumRx, Inc., MountainView, Calif., USA)

The procedure was carried out at the operating room under general anesthesia with the accompaniment of fluoroscopy. The airway in the selected segment was first determined bronchoscopically and measured using a guide wire. The coil wire of suitable length (generally 100 mm, 125 mm or 150 mm) was left at the targeted segment using a carrier catheter which then takes on the shape of a coil. Airway shrinks as the coil wire pulls on the lobe, thus the lung collapses and shrinks. The targeted lobe was systematically treated with 10-14 coil wires on average. Initially one lobe was treated with the other targeted lobe in the opposite lung treated 4-8 weeks later [8, 19]. Postero-anterior radiography of the patient with bilateral coil procedure is shown in Figure 1.

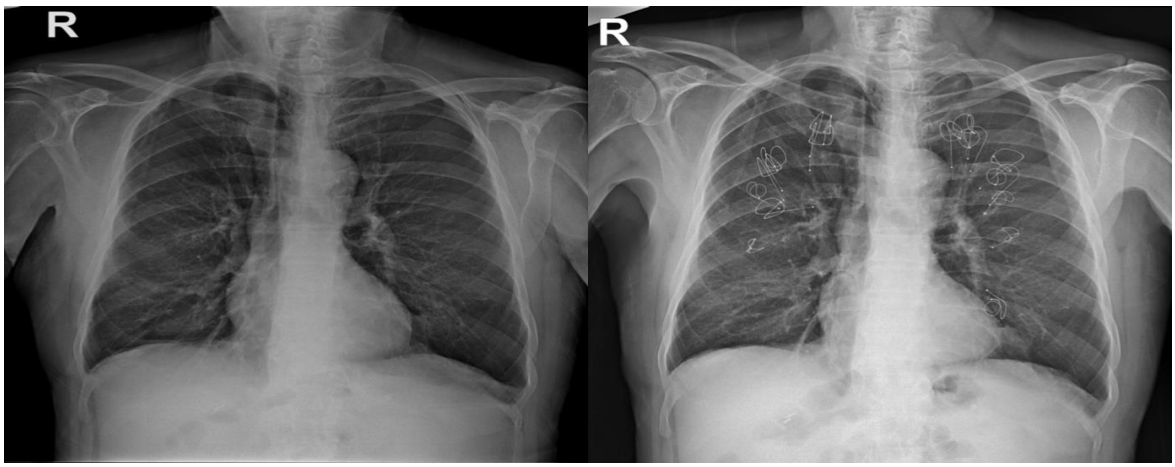

Figure 1. Postero-anterior radiography of the patient with bilateral coil

Samples and measurements

Blood samples were taken from the antecubital vein by venipuncture into standard tubes containing EDTA (1.5 mg/ml) for hemorheological measurements. Samples were taken after 12 hours of overnight fasting on the morning of the day before the coil treatment and in the first month after coil tratment. In the same way, blood was taken from healthy volunteers in the morning after fasting. After the samples were properly transferred to the Physiology Laboratory, hemorheological tests were performed within 3 hours according to the "new guidelines for hemorheological laboratory techniques" [20]. Hematological parameters were determined by an electronic hematology analyzer (Siemens ADVIA® 2120i System, Siemens Healthcare Diagnostics, Japan). For the determination of oxidative stress parameters, blood samples collected into yellow top blood collection tubes, were centrifuged at 5000 g for 6 min. The serum layer was separated and stored at -80°C until being used for the analysis.

Determination of erythrocyte deformability

RBC deformability was measured by laser diffraction analysis with an ektacytometer (Laser assisted optical rotational cell analyzer (LORCA), RR Mechatronics, Hoorn, The Netherlands) at various shear stresses between 0.3-30 Pa at 37°C as previously described [21]. RBC were suspended in isotonic 4% polyvinylpyrrolidone 360 solution (MW 360 kD; Sigma P 5288; St. Louis, MI). According to the LORCA instrument measuring principle, a laser beam was directed through the sample and the diffraction pattern produced by the shape-shifting erythrocytes was analyzed by a microcomputer. Results were given as elongation index (EI). EI=(L−W)/(L+W). L is the length and W is the width of the diffraction pattern.

Measurement of the whole blood and plasma viscosity

A cone-plate rotational viscometer (model DV-II+Pro, Brookfield engineering Labs, Middleboro, MA) was used to determine whole blood viscosity (WBV) and plasma viscosity (PV) at 37°C. WBV was measured at both native and standard (40%) Hct at shear rates of 38, 76 and 190 s^{-1}, whereas PV was measured at 190 s^{-1}.

2.6 Determination of total oxidant status (TOS) and total antioxidant status (TAS)

TOS and TAS were measured by commercial kits (Rel Assay Diagnostics, Turkey) according to the manufacturer's instructions [22, 23].

Calculation of oxidative stress index (OSI)

OSI was calculated using the following Formula;

OSI (arbitrary unit)=TOS (μmolH_2O_2 Equiv./L)/TAS (mmol Trolox Equiv./L)X100 [24].

Statistical analyses

All the statistical analyses of the obtained clinical and demographic data were carried out using Statistical Package for the Social Sciences (SPSS) v.25 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean (standard deviation (SD)), median (minimum and maximum values), while categorical variables as number and percentage. The suitability of the data for normal distribution was examined by the Shapiro-Wilk test. When parametric test conditions were satisfied Independent samples t test was used for comparisons among groups. If parametric test conditions were not satisfied, Mann Whitney U test was used for comparisons among groups. For pairwise comparisons; if parametric test conditions were satisfied Paired Samples t test; and if parametric test conditions were not satisfied Wilcoxon signed rank test was used. $P<0.05$ was considered statistically significant.

The present study was carried out in accordance with the Helsinki Declaration and was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee.

Results

Since 1 patient died during the follow-up after the procedure, 2 people did not come to

the follow-ups, and blood samples of 1 patient could not be analyzed due to technical issues, evaluations were carried out on 20 patients, although it was started with 24 patients. All patients were male and mean (SD) age was 66.75 (6.98). All of the 17 age- and sex-matched healthy control group were male and the mean (SD) age was 62.59 (6.66) (p>0.073). Table 2 presents the sociodemographic and clinical data of the patients.

Table 2. Sociodemographic characteristics and some clinical parameters

	Number (n)	**Percentage (100%)**
Procedure		
Unilaterale	11	55
Bilateral	9	45
Emphysema distribution		
Homogeneous	11	55
Heterogeneous	9	45
GOLD spirometric stage		
Stage 3	11	55
Stage 4	9	45
USOT use		
Yes	16	80
No	4	20
	Mean (SD)	**Median (min-max)**
Age	66.75 (6.98)	67.5 (49-76)
Used coil (qty.)	14.1 (5.12)	14.5 (6-22)
Respiratory Function Test		
FVC (%)	57.19 (15.76)	51.75 (34.6-94.3)
FEV_1 (%)	30.21 (8.01)	29.65 (20.2-44.6)
FEV_1/FVC (%)	41.43 (4.56)	40.90 (33.3-51.1)
RV (%)	378.05 (191.35)	312 (180-916)

Abbreviations: SD, Standard Deviation; min-max, minimum-maximum values; FVC, forced vital capacity; FEV_1, forced expiratory volume in first second; RV, residual volume

RDW (red blood cell distribution width) of COPD patients was higher compared to control group (p_1=0.012) whereas MCHC (mean corpuscular hemoglobin concentration) of COPD patients was lower than control group (p_1=0.001). Similarly, after the coil, RDW was higher and MCHC was lower in the COPD group compared to the control group (p_2). The RBC count, hemoglobin, Hct, RDW, MCV (mean corpuscular volume) and MCHC of each subject, before and after the procedure were similar (p_3) (Table 3).

Table 4 demonstrates erythrocyte deformability (given as EI) values of the subjects. RBC deformability of COPD patients was lower than control group (p_1). After EBCT, a statistically significant increase was observed in erythrocyte deformability at 0.30-5.33 Pa (p_3). Consistent with these findings, RBC deformability measured at shear stresses between 0.30 and 1.69 Pa in the COPD group after EBCT was not different from that of the control group (p_2).

It was observed that the effect size of the RBC deformability results obtained from 20 patients was at a strong level (dz=0.626) (for the pre-post treatment alteration obtained at 0.3 Pa). For this effect size, our study reached 85% power at 95% confidence level.

Table 3. Comparison of RBC, hemoglobin, Hct, RDW, MCV, MCHC control group and before and after EBCT

	Control group (n=17) Mean (SD)	Patient group (n=20)		P_1	P_2	P_3
		Before EBCT Mean (SD)	After EBCT Mean (SD)			
RBC (M/uL)	4.96 (0.51)	4.97 (0.59)	4.97 (0.5)	0.971 (t=-0.037) a	0.965 (t=-0.044) a	0.996 (t=-0.005) c
Hemoglobin (g/dL)	14.68 (1.22)	14.2 (1.73)	14.05 (1.83)	0.337 (t=0.973) a	0.23 (t=1.222) a	0.555 (t=0.601) c
Hct (%)	43.78 (3.5)	43.22 (5.96)	43.52 (5.25)	0.734 (t=0.342) a	0.859 (t=0.179) a	0.750 (t=-0.323) c
RDW (fL)	13.55 (1.38)	15.03 (2.02)	15.23 (1.64)	0.012* (z=-2.485) b	0.001* (z=-3.541) b	0.282 (t=-1.108) c
MCV (fL)	88.69 (6.25)	88.4 (6.55)	87.75 (6.93)	0.619 (z=-0.518) b	0.94 (z=-0.091) b	0.322 (t=1.017) c
MCHC (g(/dL)	33.56 (0.87)	32.37 (1.15)	32.27 (1.17)	0.001* (t=3.503) a	0.0001* (z=3.218) b	0.706 (t=0.383) c

Values are expressed as means±SD. Abbreviations: EBCT, endobronchial coil therapy;
SD, standard deviation; RBC, red blood cell; Hct, hemotocrit; RDW, red blood cell distribution width; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; P_1, difference between COPD patient group and control group before EBCT; P_2, difference between COPD patient group and control group after EBCT; P_3, difference before and after EBCT in COPD patients; a: Independent samples t test; b: Mann Whitney U test; c: Paired Samples t test

Table 4. Comparison of red blood cell deformability control group and before and after EBCT

Shear stress (Pa)	Control group (n=17) Mean (SD)	Patient group (n=20)		P_1	P_2	P_3
		Before EBCT Mean (SD)	After EBCT Mean (SD)			
0.3	0.05 (0.01)	0.03 (0.02)	0.04 (0.01)	0.005* (t=3.035) a	0.189 (t=1.341) a	0.029* (t=-2.37) c
0.53	0.1 (0.02)	0.08 (0.03)	0.09 (0.02)	0.004* (t=3.055) a	0.17 (t=1.401) a	0.030* (t=-2.348) c
0.95	0.19 (0.02)	0.17 (0.03)	0.18 (0.03)	0.005* (t=2.968) a	0.188 (t=1.342) a	0.034* (t=-2.28) c
1.69	0.3 (0.02)	0.27 (0.04)	0.29 (0.03)	0.003* (t=3.191) a	0.103 (t=1.676) a	0.045* (t=-2.146) c
3	0.41 (0.02)	0.37 (0.03)	0.39 (0.03)	0.0001* (t=4.210) a	0.012* (t=2.635) a	0.032* (t=-2.317) c
5.33	0.49 (0.01)	0.46 (0.03)	0.47 (0.02)	0.0001* (t=4.834) a	0.001* (t=3.729) a	0.05* (t=-2.059) c
9.49	0.55 (0.01)	0.52 (0.02)	0.53 (0.02)	0.0001* (t=4.444) a	0.0001* (t=4.133) a	0.17 (t=-1.426) c
16.87	0.59 (0.01)	0.57 (0.02)	0.58 (0.02)	0.0001* (z=-3.508) b	0.0001* (z=-3.646) b	0.603 (t=-0.529) c
30	0.62 (0.01)	0.61 (0.02)	0.61 (0.02)	0.0001* (z=-3.783) b	0.0001* (z=-3.663) b	0.982 (t=-0.023) c

Values are expressed as means±SD. Abbreviations: EBCT, endobronchial coil therapy;
SD, standard deviation; P_1, difference between COPD patient group and control group before EBCT; P_2, difference between COPD patient group and control group after EBCT; P_3, difference before and after EBCT in COPD patients; a: Independent samples t test; b: Mann Whitney U test; c: Paired Samples t test

Oxidative stress parameters (TAS, TOS, OSI) were also evaluated, and it was found that the oxidative stress index was higher in the COPD group than the control group (p_1=.0001). However, no statistically significant change in TAS, TOS, and OSI values following coil treatment in the COPD group were observed (Table 5).

Viscosity could not be studied in the control group due to technical problems. Statistically significant alterations were not observed in WBV measured at both autologous and standard (40%) Hct and PV values in the COPD group (Table 6).

Table 5. Comparison of oxidative stress parameters before and after EBCT

Oxidative stress parameters	Control group (n=17) Mean (SD)	Patient group (n=20) Before EBCT Mean (SD)	Patient group (n=20) After EBCT Mean (SD)	P_1	P_2	P_3
TOS ($\mu molH_2O_2$ Equiv. /L)	2.86 (1.48)	6.38 (4.28)	6.31 (2.32)	0.0001* (z=-4.426) b	0.0001* (z=-4.815) b	0.341 (z=-0.953) d
TAS (mmol Trolox Equiv./L)	2.67 (0.31)	1.07 (1.09)	1.08 (0.43)	0.0001* (z=-4.664) b	0.0001* (t=-12.689) a	0.126 (z=-1.531) d
OSI (arbitrary unit)	0.11 (0.05)	0.79 (0.48)	0.68 (0.37)	0.0001* (z=-4.345) b	0.0001* (z=-5.181) b	0.361 (t=0.936) c

Values are expressed as means±SD. Abbreviations: EBCT, endobronchial coil therapy; SD, standard deviation; TOS, total oxidant status; TAS, total antioxidant status; OSI, oxidative stress index; P_1, difference between COPD patient group and control group before EBCT; P_2, difference between COPD patient group and control group after EBCT; P_3, difference before and after EBCT in COPD patients; a: Independent samples t test; b: Mann Whitney U test; c: Paired Samples t test; d: Wilcoxon Signed Rank test

Table 6. Comparison of whole blood viscosity (WBV) at native, standard (40%) hematocrit and plasma viscosity (PV) before and after EBCT

	Before EBCT Mean (SD)	After EBCT Mean (SD)	*P* value
WBV at native Hct (38 s^{-1})	5.835 (0.832)	5.718 (1.73)	0.715 (z=-0.365) d
WBV at native Hct (76 s^{-1})	4.626 (0.866)	5.751 (1.144)	0.401 (z=-0.840) d
WBV at native Hct (190 s^{-1})	3.928 (0.687)	4.803 (1.167)	0.282 (t=-1.127) c
WBV at standard (40%) Hct (38 s^{-1})	5.363 (0.599)	5.028 (1.063)	0.465 (z=-0.730) d
WBV at standard (40%) Hct (76 s^{-1})	4.184 (0.972)	4.73 (0.591)	0.225 (z=-1.214) d
WBV at standard (40%) Hct (190 s^{-1})	3.93 (0.541)	4.231 (1.045)	0.760 (t=-0.312) c
PV (190 s^{-1})	1.943 (0.838)	1.953 (1.415)	0.333 (z=-0.968) d
Hct (%)	44 (4.46)	44.421 (4.776)	0.633 (t=-0.486) c

Values are expressed as means±SD. Abbreviations: EBCT, endobronchial coil therapy;
SD, standard deviation; WBV, whole blood viscosity; PV, plasma viscosity; Hct, hematocrit
c: Paired Samples t test; d: Wilcoxon Signed Rank test

Discussion

The results of the current study show significant changes in oxidative stress and hemorheological parameters, particularly erythrocyte deformability, whole blood viscosity (WBV), and plasma viscosity (PV), in patients with Stage 3 and 4 COPD following EBCT. To our knowledge, no other study in the literature has reported findings that overlap with these results. RBC deformability measured at share stresses of 0.3-5.33 Pa was increased following EBCT. The treatment applied did not affect WBV determined at either native, or standard (40%) Hct, PV and oxidative stress indices.

COPD is characterized by airflow obstruction and an abnormal inflammatory response of the lungs to noxious particles or toxic gases. Since considerable evidence supports the hypothesis that oxidative stress plays an important role in the development of COPD [25], we aimed to demonstrate oxidative response to EBCT in grade 3 and 4 COPD patients. Previous studies on COPD and oxidative stress indicate that especially TAS was reduced in patients with COPD, TOS was increased thus leading to increased OSI [15, 26, 27]. Similarly, in our study, oxidative stress parameters were found to be statistically significantly increased in the COPD group compared to the healthy control group. The alterations in oxidative stress markers in patients with COPD were shown to be correlated with the progression of the disease [28, 29]. Inflammatory cells also play a pivotal role in COPD as they are involved in the release of a variety of mediators, such as proteases, oxidants, and cytokines [30]. RDW is another parameter which may be associated with inflammation is. Although RDW is often used for the differential diagnosis of anemia, it was also demonstrated to increase in cardiovascular diseases, cancer, and diabetes. RDW has been reported to be related to inflammation. There are also studies demonstrating its correlation with severity of the disease and exacerbations in patients with COPD [6, 31, 32]. In our study, RDW was significantly increased in COPD patients compared to the healthy control group. Few studies showing the relationship between COPD and MCHC have reported that MCHC is associated with prognosis in COPD exacerbations. Although the precise mechanisms underlying the association cannot be clearly elucidated, it has been reported that the decrease in MCHC may be related to the intensity of inflammation [33, 34]. In the current study, MCHC was found to be lower in the COPD group compared to the control group.

Although it is possible to measure components of oxidative pathways separately from biological samples in humans, it could be time-consuming and expensive. Instead, determining TOS and TAS, reflecting synergistic and cumulative action of oxidant and antioxidants, is a more practical method to examine oxidant/antioxidant balance [22, 35]. For these reasons TOS and TAS were determined in the current study [22, 35]. Similarly, OSI was calculated to determine the overall oxidative stress in the organism. As far as we know, no report exists in literature demonstrating oxidative stress response to EBCT in COPD. Our results demonstrate that, TOS, TAS and OSI were not altered in COPD patients 1 month after EBCT. The limited patient number and post-procedure follow-up period may be among the causes of these results. Since the patients were severe, frequently experienced attacks and the mortality rate was high, we concluded the study in the 1st month following EBCT.

Blood rheology plays an important role in maintaining the microcirculation properly and impaired hemorrheological parameters are associated with many diseases [17, 36, 37]. Hemorrheology is interested in flow properties of blood and the blood - vessel relationship. Erythrocyte deformability, RBC aggregation, hematocrit, WBV and PV are among the main components of blood rheology [10, 38]. Erythrocyte deformability may be defined as the ability of the RBC to adopt blood flow properties by changing its shape under shear stress, and enhanced elongation index (EI) is associated with increased erythrocyte deformability [10]. The ability of RBC to change its shape is especially important for microcirculation, where erythrocytes have to pass through vessels smaller than their own diameter. Erythrocyte deformability is also an important parameter determining blood flow resistance and plays an important role in the pathogenesis of ischaemia [39, 40]. Rheological properties of blood are affected by a number of pathophysiological processes, including a variety of pulmonary diseases, leading to an increase in the clinical

importance of hemorrheological field [36, 41]. It may be suggested that, impaired RBC deformability and aggregation may be realted with COPD pathogenesis [6]. A decrement in RBC deformability may diminish lung oxygenation and also pulmonary functions. Hypoxia is one of the prognostic factors in COPD [42].

Findings of our study demonstrate that, EBCT results in increment of RBC deformability measured 1 month after the procedure at shear stresses between 0.3-5.33 Pa. The shear stress level of normal pulmonary circulation was demonstrated to be around 2-3 Pa [43]. Thus, the finding that RBC deformability determined at 1.69 and 3 Pa increases after EBCT gains more impartance. Although tissue oxygenation primarily depends on alterations in perfusion-ventilation matching after the treatment, the rise in erythrocyte deformability may also be evaluated as a favorable alteration in terms of oxygenation. We observed that erythrocyte deformability was higher in the healthy control group of similar age and gender compared to COPD patients. Our results may demonstrate that EBCT may not only be beneficial by reducing hyperinflation through volume reduction, it may also contribute to the improvement of the patient's life quality by positively affecting perfusion through an enhancement in erythrocyte deformability. The increase in RBC deformability following EBCT in our study may indicate that the pulmonary functions and oxygenation may improve. The mechanism by which the EBCT causes increment of RBC deformability is unknown. One of the reasons for evaluating oxidative stress in this study was to contribute to the explanation of the mechanisms of the alterations in hemorheological parameters. The increase in oxidative stress in COPD patients reduces erythrocyte deformability and leads to hypoxia resulting in reduced life expectancy [15]. Since no statistically significant alteration in TOS, TAS and OSI following EBCT was observed and RDW, MCV and MCHC of each subject, before and after the procedure were similar, the rise in erythrocyte deformability cannot be explained by altered oxidative stress and hematological parameters mentioned above. 9.49-30 Pa shear stresses at which we did not find a statistically significant alteration in RBC deformability are quite high shear stresses that are not observed at the pulmonary level.

Other hemorheological parameters determined in the current study are the whole blood viscsity (WBV) and PV. Decreased RBC deformability was shown to lead increment of apparent blood viscosity and hence flow resistance in larger vessels [44]. Sınce plasma is the component of blood which is in contact with the vessle wall due to the axial migration, PV is an important parameter of the flow regulation [10].

Properties of plasma and the cellular components of blood as well as shear rate determine blood fluidity. Erythrocyte deformability, PV and Hct are important determinants of viscosity at physiological shear rates [45]. For these reasons, WBV was determined at both native and standard (40%) Hct and under shear rates of 38, 76 and 190 s^{-1} in our study. High Htc value may be considered as one of the factors enhancing blood viscosity in COPD [46]. However, our results demonstrate that, Hct value of Grade 3 and 4 COPD patients was unaltered 1 month after the treatment.

Cheng et al. [47] demonstrated that viscosity of blood has an important association with pulmonary blood flow and pulmonary vascular resistance in univentricular circulations where low-shear non-pulsatile blood flow is present in the pulmonary arterial tree. Almarshad and Hassan showed that smoking alters the rheological properties by increasing WBW and PV levels [48]. Moreover, Lowe and coworkers confirmed a significant reduced blood flow after smoking resulted from high blood viscosity and PV [49]. Our results demonstrate that PV and WBV determined at both native and standard Hct and under shear rates of 38, 76 and 190 s^{-1} were not affected following 1 month of EBCT in COPD patients. In our study, we did not observe significant changes in TOS, TAS, or OSI levels in COPD patients at the 1st month following EBCT. The lack of improvement in oxidative stress parameters suggests that the observed increase in erythrocyte deformability cannot be attributed solely to changes in oxidative stress, contrary to our expectations. Although there is strong evidence in the literature supporting the role of oxidative stress in the pathogenesis of COPD [25], we were unable to corroborate this improvement through oxidative stress parameters. This finding raises the possibility that the improvement in deformability could

be related to mechanisms other than oxidative stress, or that the blood samples taken at the 1st month might have been assessed at an early time point. Considering that the oxidative stress response may emerge over a longer period, improvements in TAS, TOS, and OSI could potentially be observed at later stages. However, due to the unstable nature of COPD patients, with frequent exacerbations and hospitalizations, we opted for a shorter follow-up period to minimize the risk of additional complications that could alter the parameters. To clarify these findings and better understand the relationship between oxidative stress and hemorheological parameters, further studies with larger patient cohorts and longer follow-up periods are needed.

The most important limitation of our study was the relatively smaller number of patients. The fact that we could not determine RBC aggregation, one of the hemorheological parameters due to technical problems can be considered as a second limitation. Additionally, this study does not reveal the effects of EBCT longer than 1 month. Even though interventional treatment options are included in the guidelines for COPD treatment, controversy over EBCT continues. The results of this pilot study suggest for the first time that EBCT may not only reduce hyperinflation but also potentially increase erythrocyte deformability, which could improve tissue perfusion in COPD patients under shear stresses observed at the pulmonary level. To our knowledge, there are no similar findings reported in the literature. Despite limitations, our results provide supportive evidence on the benefit of EBCT in the treatment of COPD.

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EU.: Conception, Design, Supervision, Materials, Literature Review, Writing.

E.K.T: Conception, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing

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