European Review for Medical and Pharmacological Sciences 2016; 20: 4508-4515

Epicardial fat thickness is associated with severity of disease in patients with chronic obstructive pulmonary disease

K. KIRAZ[1], T. GÖKDENIZ[2], E. KALAYCIOGLU[3], A. BÖREKÇI[2], S. AKYOL[4], A.O. BAYKAN[4], A. ACELE[4], S. KARAKOYUN[2], T. SEKER[4], M. GÜR[2]

[1]Department of Chest Disease, Antalya Atatürk State Hospital, Antalya, Turkey.
[2]Department of Cardiology, Kafkas University, School of Medicine, Kars, Turkey.
[3]Department of Cardiology, Ahi Evren Chest and Cardiovascular Surgery Education and Research Hospital, Trabzon, Turkey.
[4]Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey.

Abstract. – OBJECTIVE: Cardiovascular diseases (CVD) are common in patients with chronic obstructive pulmonary disease (COPD) and the BODE index is an important tool for the prognostic assessment of COPD patients. It is well known that epicardial fat thickness (EFT) is related to CVD. However, there are very few data about the relationship between EFT and BODE index. The aim of this study is to investigate the relationship between EFT and BODE index in patients with COPD.

PATIENTS AND METHODS: We prospectively included 157 patients with COPD and 45 controls in the present study. All patients underwent pulmonary function tests and six-minute walking test. EFT and other echocardiographic parameters were measured using transthoracic echocardiography on admission. Patients were divided into four quartiles according to the BODE index scores (Quartile-1 (Q1): 0-2 points; Quartile-2 (Q2): 3-4 points; Quartile-3 (Q3): 5-6 points; Quartile-4 (Q4): 7-10 points). High sensitive C-reactive protein (Hs-CRP) and other biochemical parameters were measured in all participants.

RESULTS: COPD patients had higher EFT values compared with control group ($p<0.05$). When COPD patients were classified according to BODE index quartiles, the highest EFT values were observed in Q1 compared with other quartiles ($p<0.05$, for all). EFT values showed a decreasing trend from Q1 to Q4. Furthermore, EFT was independently associated with BODE index (β=0.405, $p<0.001$), Hs-CRP (β=0.300, $p<0.001$) and diabetes (β=0.338, $p<0.001$) in multivariate linear regression analysis.

CONCLUSIONS: Our findings suggested that EFT is independently and negatively associated with the severity of disease as indicated by BODE index in patients with COPD.

Key Words:
Pericardium, Chronic obstructive pulmonary disease, C-Reactive protein, Echocardiography.

Introduction

Chronic obstructive pulmonary disease (COPD) is a type of lung disease characterized by progressive development of obstructed airflow and an increased chronic inflammatory response in the airways[1]. COPD is a major cause of morbidity and mortality worldwide[2]. The BODE index, is an important prognostic predictor of COPD, and is a multidimensional scoring system, combining information about various clinical factors; including Body-mass index (BMI), airflow Obstruction (forced expiratory volume in 1 s [FEV_1]), Dyspnea (Medical Research Council [MRC] dyspnea scale), and Exercise capacity (6-min walk distance) in a score ranging from 0 to 10[1,3]. This prognostic index predicts mortality significantly better than lung function the traditional prognostic COPD indicator-alone. The BODE index has made a contribution to the recognition, which prognostic evaluation of COPD patients should be extended beyond the lung function measurements[2-4].

Cardiovascular diseases are commonly encountered in patients with COPD. The link between cardiovascular disease (CVD) and COPD are particularly remarkable and clinically relevant, because, CVD is the most common comorbidity and a major cause of hospitalization in patients having mild to moderate COPD[2,5]. Many epidemiological studies have demonstrated that COPD doubles the risk of CVD hospitalization and mor-

Corresponding Author: Kemal Kiraz, MD; e-mail: drkemalkiraz@gmail.com

tality due to independently smoking and aging process[2,5]. Epicardial fat thickness (EFT), which is a metabolically active organ producing several proatherogenic and proinflammatory cytokines have been recognized as a new predictor of cardiovascular risk[6-8]. Epicardial adipose tissue (EAT) is strongly associated with atherosclerosis, myocardial dysfunction, left ventricular hypertrophy and cardiomyopathy. Therefore, we suggested, that the EAT would be associated with the severity of COPD as indicated by BODE index in COPD patients. Although, Zagaceta et al[9] have demonstrated the relationship between COPD and epicardial adipose tissue, the relationship between EFT and BODE index, as an indicator of the severity of COPD, is yet to be fully clarified. Therefore, the objective of this study is to evaluate the potential relationship between EFT and BODE index in COPD patients.

Patients and Methods

This was a single center case-control study. The cases were consecutive COPD patients, who were followed-up by the Department of Respiratory Medicine between August 2011 and January 2014. Our previous work[10] has shown existing 1.4 EFT difference between control and case groups. Based on this information 25 individuals in each group has been chosen and, assuming 1.4 EFT difference existed between control and case groups, which is lower than the case in this study, allows to detect the differences with 90% of a chance at the usual level of statistical significance (alpha=0.05). The diagnosis of COPD was based on a history of smoking at least 10 packs per year. Spirometric findings with a post-bronchodilator forced expiratory volume in one second/Forced vital capacity, (FEV_1/FVC) ratio <70% predicted and FEV_1 <80% predicted and, symptoms and radiographic findings suggesting COPD[1]. All patients were chosen from the people who were free of COPD exacerbations for at least six months at the time of enrolment. The control group was established to match age and sex (of case group) from healthy individuals. They were selected amongst people who were present in our hospital for various reasons (such as check-up).

The patients with a history of the following problems at the time of the study and poor echo-echocardiographic outlook were excluded from this study; coronary artery disease (CAD), echocardiographic evidence of regional or global wall motion abnormalities, angina pectoris, reduced left ventricle (LV) functions, right ventricle (RV) pacing, pulmonary artery stenosis or RV outflow obstruction, atrial fibrillation/flutter, positive nuclear perfusion stress or treadmill test, those having ischemic electrocardiographic findings, chronic renal failure, second or third-degree atrioventricular block, moderate to severe valvular heart disease, pulmonary embolism, idiopathic pulmonary hypertension, obstructive sleep apnea, structural tricuspid disease and patients with COPD exacerbation. The local Ethics Committee approved the study protocol and all patients have signed written informed consent.

Baseline demographics and clinical data were obtained from all cases and control groups. Medical histories of the patients were recorded and a detailed physical examination was performed. Blood analysis including fasting blood glucose, lipid parameters, hemoglobin values and creatinine was carried out following a fasting of 12 hours. Blood pressure measure was read using a sphygmomanometer with an appropriately sized cuff. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were calculated through an average of the second and third measurements. Hypertension was defined by previously received antihypertensive therapy or blood pressure, which exceeded 140/90 mmHg at least in three measurements. Smoking behavior was identified as being current and ex-smokers and pack smokers per year were recorded. Body mass index (BMI) was calculated by dividing the body weight (in kilograms) by the height (in meters) squared in meters ($BMI = weight/height^2$). Diabetes mellitus was defined as before receiving oral antidiabetics or insulin or having fasting glucose levels higher than 126 mg/dl. Estimated glomerular filtration rate (eGFR) was calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) study equation[11].

All COPD patients were evaluated through spirometry, echocardiography, arterial blood gas analysis, and six-minute walking test; respectively. All measurements were performed with patients at rest and breathing room air, while the control group underwent echocardiographic evaluation alone.

Pulmonary function tests were carried out as previously described[12]. FEV_1 and FVC were measured using a clinical spirometer (ZAN 100, Morgan Scientific, Inc., Haverhill, MA, USA).

The BODE index was calculated by the sum of the scores obtained from BMI, the modified Medical Research Council (mMRC) dyspnea scale[13], spirometric measurements and the six-minute walking

test. Six-minute walking test was performed twice with at least 30 min intervals and the longest walking distance was taken into account in the scoring[14]. The BMI, the mMRC values, the FEV_1 % and the six-minute walking test were incorporated into the BODE index. The BODE index ranged from 0 to 10 points for each patient, and then the patients were divided into four quartiles based on their BODE index score. Quartile-1 (Q1): 0-2 points; Quartile-2 (Q2): 3-4 points; Quartile-3 (Q3): 5-6 points; Quartile-4 (Q4): 7-10 points[3].

Echocardiographic examinations with two-dimensional and M-mode studies were performed through all standard echocardiographic windows using a commercially available echocardiography device (VIVID 7 General Electric Medical System Vingmed Ultrasound AS, Horten, Norway), which was equipped with the 3.6-MHz transducer. LV and RV measurements were carried out according to the guidelines published by the American Society of Echocardiography[15]. The electrocardiogram was recorded continuously during the echocardiographic examination. Left ventricle end diastolic and end systolic volumes and LV ejection fraction (LVEF) were measured from the apical four and two chamber views using the modified Simpson method[15]. Left ventricle dimensions (end-diastolic and end-systolic) and wall thickness (septum and posterior wall) were measured from the parasternal long axis with an M-mode cursor positioned just beyond the mitral leaflet tips and perpendicular to the long LV axis.

From 2-dimensional images, standard parasternal long-axis and short-axis views were used for the measurement of EFT on the right ventricle of patients with the left lateral decubitus position. These images were digitally stored and reviewed by the same echocardiologist who was blinded to the clinical data. Epicardial fat thickness obtained by echocardiography and was determined as relatively echo-lucent space between the outer wall of the myocardium and the visceral layer of the pericardium and was measured perpendicularly to the right ventricular free wall at the end-systole in 3 cardiac cycles. The average value of 3 cardiac cycles was determined from each echocardiographic view. Intra-observer and inter-observer variability of EFT measurements and other echocardiographic data were assessed in 25 randomly selected patients with COPD and calculated as the absolute difference divided by the average of two observations. Mean values of intra-observer and inter-observer variability were found as 4.6±3.3% and 3.9±3.1%, respectively.

Statistical Analysis

All statistical analyses were performed using SPSS 17.0 (SPSS for Windows 17.0, Chicago, IL, USA) software. Continuous variables are expressed as mean ± S.D. and categorical variables as percentages. $\chi 2$ test was used for comparison of categorical variables between the groups. Normality was analyzed with the Kolmogorov-Smirnov test. Independent samples t-test was used for comparisons of continuous variables between the two groups. Analysis of variance (ANOVA) was used in the analysis of continuous variables among the BODE quartiles. A stratified post hoc analysis was performed according to the BODE index. Independent relationships of EFT were determined using multiple linear regression analysis. All significant parameters in the univariate analysis were selected in the multivariate model. A p-value of less than 0.05 was considered significant for all statistical analyses.

Results

The study population consisted of 157 COPD patients and 45 control subjects. Comparison of baseline characteristics between the groups was given in Table I. According to the clinical characteristics, only two variables were found different between the two groups; incidence of current and ex-smoking was significantly higher in COPD group than the control group ($p<0.05$ for both). Hs-CRP and hemoglobin levels were significantly higher in the patients with COPD than in the control group ($p<0.05$ for both). Moreover, patients with COPD had higher EFT and systolic pulmonary artery pressure (sPAP) compared with control group ($p<0.05$ for all).

When patients were classified with respect to BODE index, 28.7% (n= 45) were in Q-1 group, 25.4% (n=40) in Q-2 group, 22.9% (n= 36) in Q-3 group and 22.9% (n=36) in Q-4 group. Comparison of EFT values amongst the BODE index groups is shown in Table II. Epicardial fat tissue values showed a decreasing trend from BODE Q-1 group to BODE Q-4 group. The lowest EFT values were observed in control group.

The bivariate and multivariate relationships of EFT were shown in Table III. EFT was associated with age (r=0.196, p=0.014), BMI (r=0.223, p=0.005), diabetes (0.254, p=0.001), Hs-CRP level (r=-0.229, p=0.001), FEV1 % predicted (r=-0.554, $p<0.001$), FEV1/FVC ratio (r=-0.439, $p<0.001$), sPAP (r=-0.341, $p<0.001$) and BODE index (r=-0.616, $p<0.001$). Multivariate linear

Table I. Comparison of baseline, laboratory, clinical and echocardiographic characteristics between the groups.

Variables	Control group (n=45)	Patient group (n=157)	*p*-value
Baseline characteristics			
Age, (years)	67.5±4.1	69.6±10.5	0.203
Male, n (%)×	40 (88.9%)	146 (93.3%)	0.269
BMI (kg/m^2)	24.3±1.3	25.2±4.6	0.227
SBP (mmHg)	132.2±12.5	135.9±18.4	0.203
DBP (mmHg)	80.0±13.4	82.5±11.0	0.202
Heart rate (beat/min)	78.2±10.4	82.8±14.7	0.054
Hypertension, n (%)	17 (37.8%)	66 (42.0%)	0.369
Diabetes mellitus, n (%)	6 (13.3%)	22 (14.0%)	0.564
Hyperlipidemia, n (%)	6 (13.3%)	25 (15.9%)	0.436
Current smoking, n (%)	11 (24.4%)	70 (44.6%)	**0.011**
Ex-smoking, n (%)	6 (13.3%)	82 (52.2%)	**<0.001**
Laboratory findings			
Glucose (mg/dl)	99.7±19.3	103.4±18.2	0.234
Total cholesterol (mg/dl)	185.3±14.5	177.9±33.8	0.156
Triglycerides (mg/dl)	143.4±24.5	136.4±50.2	0.363
LDL-cholesterol (mg/dl)	122.9±14.3	118.7±26.6	0.302
HDL-cholesterol (mg/dl)	43.2±6.2	40.3±10.1	0.068
Creatinine (mg/dl)	0.94±0.2	0.96±0.2	0.575
eGFR ≥60 (mL/min/1.73 m^2), (n, %)	42 (93.3%)	136 (86.6%)	0.168
Hs-CRP (mg/dl)	0.44±0.18	0.79±0.48	<0.001
Hemoglobin (mg/dl)	12.8±0.7	13.2±1.5	**0.043**
WBC	8.3±1.6	8.9±2.3	0.123
Echocardiography			
LV end-diastolic volume (mL/m^2)	94.0±14.0	87.0±23.4	0.062
LV end-systolic volume (mL/m^2)	37.4±7.7	36.7±10.2	0.692
LV end-diastolic dimension (mm)	46.3±4.5	46.0±4.0	0.587
LV end-systolic dimension (mm)	27.7±3.9	28.7±3.0	0.070
LV ejection fraction (%)	60.4±4.7	59.0±5.3	0.080
Septal wall thickness (mm)	11.2±1.0	11.1±1.7	0.783
Posterior wall thickness (mm)	10.3±0.9	10.6±1.4	0.208
Leftatrium (mm)	33.7±3.8	33.1±3.0	0.287
Epicardial fat thickness (mm)	4.1±0.9	5.4±1.6	**<0.001**
sPAP	22.0±5.3	32.5±7.6	**<0.001**
Previous drug use			
Calcium-channel-blockers (%)	9 (20.0%)	24 (15.3%)	0.293
Beta-blockers (%)	4 (8.9%)	7 (4.5%)	0.210
ACE inhibitors or ARB (%)	12 (26.7%)	42 (26.8%)	0.577
Statins (%)	9 (20.0%)	30 (19.1%)	0.522
Oral anti-diabetics (%)	4 (8.9%)	17 (10.8%)	0.477
Insulin (%)	4 (8.9%)	6 (3.8%)	0.159

Abbreviations: BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL: Low density lipoprotein, HDL: High-density lipoprotein, eGFR: Estimated glomerular filtration rate Hs-CRP: High sensitivity C-reactive protein, WBC: White blood cell, LV: Left ventricle sPAP: Systolic pulmonary arterial pressure, ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker.

Table II. Comparison of EFT values among the BODE index groups.

Variables	Control	Q-1 group (Bode 0-2)	Q-2 group (Bode 3-4)	Q-3 group (Bode 5-6)	Q-4 group (Bode 7-10)	*p*-value
EFT, mm	4.1±0.9[a]	6.5±1.5[b]	5.6±1.1[c]	5.0±1.2[d]	3.9±1.3	<0.001

[a]$p<0.001$ *vs*. Q-1 and Q2 groups and $p=0.001$ *vs*. Q-3 group; [b]$p=0.001$ *vs*. Q-2 group, $p<0.001$ *vs*. Q3 and Q4 groups; [c]$p=0.035$ *vs*. Q-3 group and $p<0.001$ *vs*. Q4 group; [d]$p<0.001$ *vs*. Q4 group. Abbreviations: EFT: Epicardial fat thickness, Q: Quartile.

Table III. Bivariate and multivariate relationships of epicardial fat thickness in COPD.

Variables	r	*p*-value	β	p-value
Age (years)	0.196	0.014	0.101	0.097
Diabetes	0.254	0.001	0.237	<0.001
BMI (kg/m^2)	0.223	0.005	0.079	0.230
Hs-CRP (mg/dl)	-0.229	0.001	0.190	0.010
FEV1/FVC	0.439	<0.001	0.015	0.866
FEV1 predicted	0.554	<0.001	0.106	0.126
sPAP (mmHg)	-0.346	<0.001	-0.034	0.640
BODE index	-0.616	<0.001	-0.706	<0.001

Abbreviations: BMI: Body mass index, Hs-CRP: High sensitivity C-reactive protein, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, sPAP: Systolic pulmonary arterial pressure.

regression analysis revealed that EFT was independently correlated with diabetes (β=0.237, p<0.001), BODE index (β=-0.706, p<0.001) and Hs-CRP level (β=0.190, p=0.010).

Discussion

This is the first study in the literature evaluating the relationship between EFT and severity of disease, as assessed by BODE index, in COPD patients. We demonstrated that EFT is independently and negatively associated with BODE index in COPD patients. Although BMI values were similar between the groups in the present study, EFT values were found to be higher in COPD patients than in control group. Also, when COPD patients were classified regarding with their BODE index, EFT was found to be negatively correlated with the BODE index score.

Epicardial fat is a visceral fat deposit, located between the heart and the pericardium and independently reflects the intra-abdominal visceral fat and the intra-myocardial fat content[6,16]. Echocardiographic EFT has been demonstrated to strongly and independently reflect the intra-abdominal visceral fat deposits as measured with MRI[6]. Although EFT is associated with general body adiposity, echocardiographic EFT evidently represents visceral adiposity rather than general obesity[6,17]. Echocardiographic EFT is strongly correlated with cardiometabolic risk factors, independently from general adiposity[18].

Epicardial fat tissue acts not only as a hormone secreting endocrine organ but also as an inflammatory tissue secreting cytokines and chemokines[19]. EFT is located between the outer wall of the myocardium and the visceral layer of the pericardium and directly affects the myocardium and coronary arteries[20]. The relationship between EFT and cardiovascular disease including CAD, cardiomyopathies, and atrial fibrillation is well known[21], although the correlation of EFT with respiratory diseases is yet to be fully clarified. Few studies[18,22] have reported the correlation between EFT and obstructive sleep apnea syndrome. To the best of our knowledge, there is only one study reported that the EFT decreases in patients with COPD and it is also associated with the degree of RVSD[23]. Nonetheless, there is only one study in the literature indicating the relationship between EFT and COPD[9]. In that study[9], it was found that EFT was higher in COPD patients, but the relationship between EFT and severity of COPD was not studied.

Chronic obstructive pulmonary disease (COPD) is associated with increased cardiovascular morbidity and mortality, yet the exact pathophysiological links remain unclear. However, we found a relationship between EFT and the severity of COPD as assessed by BODE index. Decreased EFT and BMI may be amongst the responsible mechanisms in COPD patients. The current study has shown by BODE index that EFT ranged amongst the BODE quartiles in COPD patients and negatively associated with the severity of disease. Also, EFT was found to be reduced proportionally with the severity of the disease. Compared to other quartiles, we observed that the lowest EFT values were obtained in Q4 and we attributed this to obesity paradox observed in COPD. Epidemiological studies have reported that overweight or mild-to-moderate obese patients with COPD have a survival advantage compared with underweight patients[24]. It is also noteworthy that, despite the increased in metabolic and ventilatory requirements, obesity has the advantage of potential significant beneficial effects on exercise tolerance in COPD. Furthermore, decreased BMI in COPD patients is associated with worse prognosis. In this regard, decreased EFT values in higher BODE quartiles may be parallel to the reduction in BMI values. Previous studies[25] have reported that a low-calorie diet-induced weight loss results in decreased epicardial fat volume in obese patients. However, amongst the BODE index parameters, we found a significant and independent correlation between EFT, mMRC dyspnea scale and six-minute walking distance. Therefore, in our study, we may speculate that EFT is associated with the severity of COPD regardless BMI. Regarding pathophysiology, epicardial fat tissue has cardio protective effects; however, the pathological

enlargement and slimming of epicardial fat mass are significantly correlated with increased risk of CVD[26].

Epicardial fat features peculiar biochemical characteristics and plays an active role in lipid and energy homeostasis. Epicardial adipose tissue differs from the other visceral fat deposits primarily in its greater capacity of releasing free fatty acids (FFAs) and in up taking and lowering the rate of glucose utilization[27]. So far, the mechanisms through which the balance between protective and damaging effects of epicardial adipose tissue is regulated have not been clarified. Epicardial fat may exert its cardioprotective properties by local secretion of anti-atherogenic and anti-inflammatory adipokines, including adrenomedullin and adiponectin. Of note, expression of epicardial is independently correlated with intracoronary levels of adrenomedullin and adiponectin proteins[6]. The increase in the epicardial fat is associated with several cardiometabolic disorders including obesity, type 2 diabetes, metabolic syndrome, CAD, nonalcoholic fatty liver disease, and chronic kidney disease, as well as CVD risk factors such as hypertension, lipids, obesity markers, and carotid intima–media thickness[26]. Weight loss induced by a low-calorie diet (for 12 weeks) decreased the epicardial fat in obese men having a mean BMI of 30.5 kg/m^2; while 26.8% reduction in initial calorie intake resulted in 17.2% less epicardial fat[25]. In another work[28] with 20 severely obese patients have shown that 19% decrease in BMI-induced by a very low-calorie diet program (6 months) was associated with a significant decrease by 32% in epicardial thickness.

Epidemiological investigations[29,30] have shown that overweight or mild-to-moderate obese COPD patients have a survival advantage compared to their underweight counterparts. It is also noteworthy that, despite the increased metabolic and ventilatory requirements, obesity has the advantage of potential significant beneficial effects on exercise tolerance in COPD[31]. Various studies have also shown that low BMI values were associated with adverse prognosis in patients with COPD[24]. Landbo et al[30] reported that BMI had a significant effect of on all-cause mortality in patients with severe COPD, while mortality was the lowest in obese patients and highest in those with the smallest BMI. However, this observation was not the case in patients with milder COPD, suggesting that obesity may exert varying effects depending on disease severity. Consistently with the other researches[29,32], this study demonstrated that obesity may be protective in patients with advanced COPD.

Dyspnea is the most common symptom limiting exercise capacity and the major reason for referral to respiratory rehabilitation programs in patients with COPD[33,34]. Clearly, restricted airflow is critical in evaluating COPD. For a long time, FEV1 is known to reflect underlying airflow restriction in COPD and is a good marker for disease progression[35]. However, FEV_1 measurement is not a good surrogate for grading the dyspnea, which is a stronger predictor of mortality than the FEV_1[36,37]. Dyspnea can be reliably and accurately evaluated using unidimensional or multidimensional scales[35].

In the setting of COPD and other respiratory disorders, the BODE index, a composite but pragmatic multidimensional scoring system which evaluates systemic, respiratory, and whole-body functional capacity, is consistently shown to be a strong independent predictor of mortality beyond the traditional factors[3,38,39]. The BODE index contributed to the recognition that prognostic assessment in patients with COPD should be extended beyond lung function[4,40].

Leptin, secreted by adipose tissue, is a metabolism-regulating molecule such as resistin and adiponectin. Serum concentrations of leptin, associated with the amount of adipose tissue, decreases with weight loss and increases with obesity[41,42]. Increased total adipose tissue leads to a rise in leptin secretion, which decreases appetite, but not completely stops eating, by binding to long form receptors in hypothalamus[43]. The BODE index is related to the circulating levels of leptin in patients with COPD, suggesting a possible role for leptin in the systemic component of COPD[44]. leptin levels have been reported to be increased in patients with stable and unstable COPD[45,46]. Likewise, it has been shown that leptin levels are increased in patients with CAD[47]. In our study, we observed a paradoxically negative correlation between EFT, predictor of cardiovascular disease, and the severity of COPD. This paradox may be explained by the above-mentioned increase of leptin in patients with CAD and COPD.

Conclusions

Our report demonstrated that EFT is higher in patients with COPD. However, EFT decreased, as the BODE index which is a prognostic indicator of COPD increased. Further studies are needed to explain the possible pathophysiological mechanisms of paradoxical diminution of EFT in patients with severe COPD.

Conflicts of interest

The authors declare no conflicts of interest.

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