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Assessment of arterial stiffness in chronic obstructive pulmonary disease by a novel method

Cardio-ankle vascular index

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD), and nearly 33.6% of patients with COPD have coronary artery disease (CAD) [1, 2]. COPD and CVD share common risk factors including smoking, low socioeconomic class, and a sedentary lifestyle. The measure of forced expiratory volume in one second (FEV_1) reflects the disease severity of COPD and is associated with cardiovascular events in these patients [3].

The pathophysiological mechanism responsible for increased CVD in patients with COPD is still controversial. Increased arterial stiffness is one of the proposed mechanisms for the relationship between COPD and increased CVD. Systemic inflammation induced by COPD causes compositional changes in the arterial wall and loss of elastic fibers, consequently increasing arterial stiffness. Impaired arterial elasticity increases the myocardial afterload and induces ventricular hypertrophy, disturbs coronary blood flow, and contributes to the atherosclerotic process. Alternatively, patients with abnormal vascular stiffness may be susceptible to developing COPD. Not all smokers develop COPD, but those with stiff vessels may be prone to developing COPD. Perhaps this reflects an abnormal, genetically determined response to cigarette smoking. The difference could also be explained by the differential expression of inflammation or a matrix metalloproteinase or by accelerated vascular senescence. Increased arterial stiffness is related to CVD and it predicts cardiovascular outcomes [4, 5]. There are several methods for measuring arterial stiffness, such as pulse wave velocity (PWV), augmentation index (Alx), and aortic distensibility. The major limitation to measuring arterial stiffness is the influence of blood pressure. Arterial stiffness can be assessed noninvasively by measuring the cardio-ankle vascular index (CAVI), which is not influenced by blood pressure at the time of measurement and reflects the atherosclerosis of great arteries and subclinical atherosclerosis [6].

The association of arterial stiffness, a marker of cardiovascular events, with the spirometric severity of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria was not adequately evaluated. Hence, we studied the CAVI, a valuable marker of arterial stiffness, in patients with COPD.

Patients and methods

Study design

This was a cross-sectional study conducted from January 2012 to February 2013. All patients gave informed consent before enrollment and the study protocol was approved by Kartal Kosuyolu Heart Training and Research Hospital Ethics Committee (2012/3–12).

We enrolled 123 patients (102 men) and 35 non-COPD control subjects (26 men) who were admitted to the chest medicine and cardiology outpatient clinics from January 2012 to March 2013 consecutively. The control group consisted of consecutive patients admitted to the cardiology and chest medicine outpatient clinics because of chest pain, dyspnea, exercise intolerance, or a routine check-up. All subjects were examined by CAVI and spirometry testing. Patients with previously known CAD, peripheral artery disease, chronic renal failure, acute coronary syndrome, moderate-to-severe valvular heart disease, cardiomyopathy, left-sided heart

Tab. 1 Patient characteristics of COPD and control group

	COPD (n=123)	Control group (n=35)	p value
Male, n (%)	102 (82.9%)	26 (74.3%)	0.250
Age (years)	67.50±9.73	68.57±10.67	0.573
BMI (kg/m^2)	26.17±5.26	27.95±5.54	0.084
Hypertension, n (%)	54 (43.9%)	15 (42.9%)	0.912
Diabetes, n (%)	15 (12.2%)	4 (11.4%)	0.902
Hyperlipidemia, n (%)	6 (4.9%)	3 (8.6%)	0.416
CS, n (%)	61 (49.6%)	15 (42.9%)	0.482
SmD (year)	40 (20)	34 (20)	0.057
ACEi/ARB, n (%)	41 (33.3%)	9 (25.7%)	0.392
Beta blockers, n (%)	17 (13.8%)	7 (20.0%)	0.369
CCB, n (%)	30 (24.4%)	9 (25.7%)	0.873
Statins, n (%)	6 (4.9%)	3 (8.6%)	0.416
OAD, n (%)	14 (11.4%)	5 (14.3%)	0.768
FEV_1% predicted	57.85±25.82	83.25±21.23	<0.001
FEV_1/FVC	61.91±7.49	88.80±5.88	<0.001
HR (bpm)	75.46±9.66	74.26±8.01	0.503
EF (%)	61.41±5.27	62.80±5.49	0.173
MAP (mmHg)	108.61±17.58	112.27±17.54	0.278
CAVI	10.37±2.26	6.74±1.42	<0.001

BMI body mass index, *CS* current smoking, *SmD* smoking duration, *ACEi/ARB* angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, *CCB* calcium channel blockers, *OAD* oral antidiabetics, *FEV_1% predicted* the predicted percent of forced expiratory volume in 1 s, *FVC* forced vital capacity, *HR* heart rate, *EF* left ventricle ejection fraction, *MAP* mean arterial pressure, *CAVI* cardio-ankle vascular index

failure, atrial fibrillation, pleural effusion, cerebrovascular disease, interstitial lung disease, acute COPD exacerbation within 6 weeks, lung cancer, bronchiectasis and tuberculosis were excluded from the study. Patients with a history of coronary artery bypass graft surgery, percutaneous coronary intervention, segmental wall motion abnormality on transthoracic echocardiography, and pathological Q waves on electrocardiography were accepted to have CAD. Patients with an ankle–brachial index of <1.0, intermittent claudication, a history of peripheral vascular surgery and peripheral vascular intervention were accepted to have peripheral arterial disease. Patients were considered to have chronic renal failure if they had an estimated glomerular filtration rate of <60 ml/min, a creatinine level of >1.3 mg/dl, or required hemodialysis. Acute coronary syndrome was excluded by the absence of ischemic electrocardiographic changes, a new wall motion abnormality, angina pectoris, or by cardiac biomarker negativity. Valvular heart disease, heart failure (left ventricular ejection fraction ≤%40), and cardiomyopathy were excluded by echocardiography. Twelve-lead surface electrocardiography was used to evaluate cardiac rhythm. Pleural effusion, bronchiectasis, tuberculosis, interstitial and lung cancer were evaluated with anteroposterior chest x-rays, high-resolution computed tomography, and the patients' history for these diseases.

Methods

CAVI was measured by using a VaSera VS-1000 CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan) with the methods described previously [6]. CAVI was measured in the morning after 15 min of rest. Briefly, a cuff was applied to the bilateral upper arms and ankles, with the subject supine and the head held in the midline position. Electrocardiography, phonocardiography, and the pressures and waveforms of the brachial and ankle arteries were measured; subsequently, pulse wave velocity and CAVI were calculated automatically. CAVI measurements were performed by an experienced cardiologist who was blinded to the spirometric test.

CAVI was determined with the following equation:

$$CAVI : a[(2r/\Delta P)x\ \ln(Ps/Pd)PWV^2] + b$$

Where Ps and Pd are systolic blood pressure and diastolic blood pressure, respectively, PWV is pulse wave velocity from the origin of the aorta to the junction of the tibial artery with the femoral artery, ΔP is Ps−Pd (systolic blood pressure–diastolic blood pressure), r is blood density, and a and b are constants. The equation is derived from the Bramwell–Hill equation and the stiffness parameter β, and CAVI was adjusted for blood pressure based on the stiffness parameter β. Therefore, CAVI reflects the stiffness of the aorta, the femoral artery, and the tibial artery as a whole; theoretically, it is not affected by blood pressure. After automatic measurements, the data obtained were analyzed using VSS-10 software (Fukuda Densi), and the values of the right and left CAVI were calculated. The average of the right and left CAVIs was used for analysis.

Based on postbronchodilator testing, $FEV_{1\%}$ was predicted using GOLD guidelines (stage I, FEV_1>80%; stage II, FEV_1 50–80%; stage III, FEV_1 30–50%; and stage IV, FEV_1<30% or FEV_1<50%) along with signs of right ventricular failure [7].

For each patient, vascular risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, smoking status, and smoking duration, were determined. Current smoking was defined as a history of smoking within the last 6 months. Patients with blood pressure of ≥140/90 mmHg on two occasions or on antihypertensive medication were accepted as being hypertensive. Diabetes mellitus was defined as a fasting blood glucose level of >126 mg/dl or patients on oral antidiabetic or insulin therapy. Hyperlipidemia was accepted as a fasting low-density lipoprotein (LDL) level of >160 mg/dl or patients on antihyperlipidemic therapy. The height and weight of patients were recorded and body mass index (BMI) was calculated. Left ventricular ejection fraction was measured according to the modified Simpson method.

Statistical analysis

SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Normally distributed contin-

uous variables were expressed as mean ± standard deviation (SD), non-normally distributed continuous variables were expressed as median (inter quartile range), and categorical variables were expressed as percentage. An analysis of normality of the continuous variables was performed with the Kolmogorov–Smirnov test. Comparisons of continuous variables were performed by using the unpaired Student t test and ANOVA and categorical variables were compared with the chi-square test. Tukey's honestly significant difference test was used for post hoc analysis. Pearson and Spearman correlation analysis was used for assessing correlations. Moreover, atherosclerotic risk factors including hypertension, smoking, diabetes mellitus, hyperlipidemia, gender, age and BMI, COPD duration, FEV_1% predicted, and left ventricular ejection fraction were entered into the multivariate regression analysis. Linear regression analysis was performed to find the independent associates of CAVI. The data were analyzed within the 95% confidence interval (CI 95%) and $p \leq 0.05$ was considered as statistically significant.

Results

We enrolled 123 patients (102 men) and 35 non-COPD control subjects (26 men), who were followed up in cardiology and chest medicine outpatient clinics. The clinical and spirometric parameters of the COPD and control groups are summarized in **Tab. 1**. The COPD and control group were similar in terms of age, sex, and demographical features. FEV_1% predicted, FEV_1/FVC, and CAVI measurements were significantly higher in the COPD group than in the control group. COPD patients were regrouped according to GOLD criteria. The patient characteristics of the subgroups are presented in **Tab. 2**. The disease duration of COPD in each group was 4.33±3.46 years in stage I, 6.73±3.78 years in stage II, 14.00±6.88 years in stage III, and 17.08±7.29 years in stage IV. The duration of COPD was significantly increased with increasing stages of COPD.

With advancing stages of COPD, CAVI was increased. Patients with stage-IV COPD had significantly higher CAVI values than stage-II patients (12.08±2.03

Abstract · Zusammenfassung

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Assessment of arterial stiffness in chronic obstructive pulmonary disease by a novel method. Cardio-ankle vascular index

Abstract

Background. Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of cardiovascular morbidity and mortality. Increased arterial stiffness is associated with the presence and severity of cardiovascular disease. The cardio-ankle vascular index (CAVI) is a new method for assessment of arterial stiffness that is not influenced by blood pressure at the time of measurement and is significantly correlated with the presence and severity of cardiovascular disease. The aim of the present study was to evaluate whether there is an association between the spirometric severity of COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, with arterial stiffness as assessed by CAVI.
Methods. We enrolled 123 patients with COPD (102 men) followed up by the chest medicine outpatient clinics and 35 healthy subjects (26 men). All patients were assessed with spirometry, CAVI, and clinical history.
Results. Patients with COPD had significantly increased CAVI values compared with control subjects (10.37±2.26 vs. 6.74±1.42, p<0.001). CAVI was correlated with FEV_1% predicted, FEV_1/FVC, and COPD stage (r: −0.54, p<0.001; r: −0.58, p<0.001 and r: 0.78, p<0.001, respectively). Multivariate regression analysis showed that CAVI was independently associated with GOLD stages (p<0.001).
Conclusion. In this study, we have shown that increased arterial stiffness assessed by CAVI is associated with the spirometric severity of COPD.

Keywords
Cardio-ankle vascular index · Arterial stiffness · Chronic obstructive pulmonary disease · GOLD criteria · Forced expiratory volume in one second

Beurteilung der arteriellen Steifigkeit bei chronisch obstruktiver Lungenerkrankung anhand einer neuen Methode. Herz-Knöchel-Gefäßindex

Zusammenfassung

Hintergrund. Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) weisen ein erhöhtes Risiko kardiovaskulärer Morbidität und Mortalität auf. Erhöhte arterielle Steifigkeit steht mit dem Vorliegen und dem Schweregrad kardiovaskulärer Erkrankungen in Zusammenhang. Der Herz-Knöchel-Gefäßindex („cardio-ankle vascular index", CAVI) ist eine neue Methode zur Beurteilung der arteriellen Steifigkeit, welche nicht durch den Blutdruck zum Zeitpunkt der Messung beeinflusst wird und die signifikant mit dem Bestehen und der Schwere von Herz-Kreislauf-Erkrankungen korreliert ist. Ziel der vorliegenden Studie war zu untersuchen, ob ein Zusammenhang zwischen dem spirometrischen Schweregrad der COPD gemäß den Kriterien der Global Initiative for Chronic Obstructive Lung Disease (GOLD) und der arteriellen Steifigkeit gemäß CAVI-Untersuchung besteht.
Methoden. In die Studie wurden 123 Patienten (102 Männer) mit COPD aufgenommen, welche ambulant durch die pulmologische Klinik versorgt wurden, und 35 gesunde Teilnehmer (26 Männer). Bei allen Patienten erfolgten Spirometrie, CAVI und klinische Anamneseerhebung.
Ergebnisse. Bei Patienten mit COPD sind die CAVI-Werte gegenüber den Kontrollen signifikant erhöht (10,37±2,26 vs. 6,74±1,42; p<0,001). Der CAVI war mit dem vorhergesagten FEV_1%, FEV_1/FVC und dem COPD-Stadium korreliert (r: −0,54; p<0,001; r: −0,58; p<0,001 bzw. r: 0,78; p<0,001). Die multivariate Regressionsanalyse zeigte, das der CAVI unabhängig mit den GOLD-Stadien assoziiert war (p<0,001).
Schlussfolgerung. In dieser Studie wurde gezeigt, dass eine erhöhte arterielle Steifigkeit in der CAVI-Untersuchung mit dem spirometrisch erhobenen Schweregrad der COPD assoziiert ist.

Schlüsselwörter
Vaskulärer Herz-Knöchel-Index · Arterielle Steifigkeit · Chronisch obstruktive Lungenerkrankung · GOLD-Kriterien · Forciertes expiratorisches Einsekundenvolumen

Tab. 2 Patient characteristics of COPD stages and control group

	Control group (n=35)	Stage I (n=30)	Stage II (n=37)	Stage III (n=30)	Stage IV (n=26)	p value
CAVI	6.74±1.42	8.53±1.40	9.80±1.41	11.43±2.41	12.08±2.03	<0.001
Male, n (%)	26 (74.3%)	22 (73.3%)	32 (86.5%)	24 (80.0%)	24 (92.3%)	0.279
Age (year)	68.57±10.67	64.80±12.73	67.49±7.60	68.90±8.89	69.00±9.24	0.447
BMI (kg/m^2)	27.95±5.54	26.18±5.42	28.12±5.74	26.29±4.29	23.27±4.23	0.003
HT, n (%)	15 (42.9%)	6 (20.0%)	19 (51.4%)	16 (53.3%)	13 (50.0%)	0.054
Diabetes, n (%)	4 (11.4%)	2 (6.7%)	7 (18.9%)	5 (16.7%)	1 (3.8%)	0.883
HL, n (%)	3 (8.6%)	0 (0%)	1 (2.7%)	4 (13.3%)	1 (3.8%)	0.800
CS, n (%)	15 (42.9%)	13 (43.3%)	20 (54.1%)	17 (56.7%)	11 (42.3%)	0.660
SmD (year)	34 (20)	40 (20)	37.5 (20)	40 (12.5)	40 (13.5)	0.173
ACEi/ARB, n (%)	9 (25.7%)	6 (20.0%)	14 (37.8%)	11 (36.7%)	10(38.5%)	0.404
BB, n (%)	7 (20.0%)	3 (10.0%)	5 (13.5%)	7 (23.3%)	2 (7.7%)	0.602
CCB, n (%)	9 (25.7%)	1 (3.3%)	12 (32.4%)	6 (20.0%)	11(42.3%)	0.074
Statins, n(%)	3 (8.6%)	0 (0%)	1 (2.7%)	4 (13.3%)	1 (3.8%)	0.800
OAD, n (%)	5 (14.3%)	2 (6.7%)	6 (16.2%)	5 (16.7%)	1 (3.8%)	0.617
HR (bpm)	74.26±8.01	72.43±9.33	75.14±9.18	76.30±10.23	78.42±9.51	0.161
EF (%)	62.80±5.49	61.07±5.62	62.05±5.27	61.10±5.62	61.23±4.63	0.622
MAP (mmHg)	112.27±17.54	106.99±13.34	111.51±19.64	107.25±21.33	107.92±14.15	0.620

CAVI cardio-ankle vascular index, *BMI* body mass index, *HT* hypertension, *HL* hyperlipidemia, *CS* current smoking, *SmD* smoking duration, *ACEi/ARB* angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, *CCB* calcium channel blockers, *OAD* oral antidiabetics, *HR* heart rate, *EF* left ventricle ejection fraction, *MAP* mean arterial pressure

Tab. 3 Correlation between clinical parameters and CAVI

	p	r	Beta coefficient	95% CI
Sex	0.216	0.105	0.650	−0.384–1.684
Hypertension	0.279	0.063	0.450	−0.369–1.269
Diabetes mellitus	0.384	0.079	0.552	−0.698–1802
Hyperlipidemia	0.401	0.018	0.748	−1.007–2503
Current smoking	0.493	0.074	0.283	−0.531–1098
ACEi/ARB	0.143	0.082	0.648	−0.222–1519
Beta blockers	0.736	−0.034	−0.194	−1.329–941
CCB	0.107	0.096	0.769	−0.168–1.707
Statins	0.401	0.018	0.748	−1.007–2.503
OAD	0.545	0.047	0.385	−0.867–1.636
Age (years)	0.005	0.222	0.058	0.018–0.098
BMI (kg/m^2)	<0.001	−0.293	−0.142	−0.215–−0.069
Smoking duration, (year)	0.228	0.130	0.022	−0.014–0.057
COPD stage	<0.001	0.779	1.376	1.177–1.575
FEV_1% predicted	<0.001	−0.540	−0.052	−0.065–−0.039
FEV_1/FVC	<0.001	−0.579	−0.113	−0.138–−0.087
Heart rate (bpm)	0.045	0.160	0.044	0.001–0.088
LV ejection fraction (%)	0.077	−0.141	−0.068	−0.144–0.008
MAP (mmHg)	0.716	−0.029	−0.004	−0.028–0.019
COPD duration (year)	<0.001	0.360	0.110	0.058–0.161

ACEi/ARB angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, *CCB* calcium channel blockers, *OAD* oral antidiabetics, *BMI* body mass index, *FEV_1% predicted* the predicted percent of forced expiratory volume in 1 s, *FVC* forced vital capacity, *LV* left ventricle, *MAP* mean arterial pressure, *CAVI* cardio-ankle vascular index

vs. 9.80±1.41, p<0.001), stage-I patients (12.08±2.03 vs. 8.53±1.40, p<0.001), and control subjects (12.08±2.03 vs. 6.74±1.42, p<0.001). Although patients with stage-IV COPD had higher CAVI values than stage-III patients, it was not significant (12.08±2.03 vs. 11.43±2.41, p=0.626). Patients with stage-III COPD had significantly higher CAVI values than stage-II patients (11.43±2.41 vs. 9.80±1.41, p=0.002), stage-I patients (11.43±2.41 vs. 8.53±1.40, p<0.001), and control subjects (11.43±2.41 vs. 6.74±1.42, p<0.001). Patients with stage-II COPD had significantly higher CAVI values than stage-I patients (9.80±1.41 vs. 8.53±1.40, p=0.030) and control subjects (9.80±1.41 vs. 6.74±1.42, p<0.001). Patients with stage-I COPD had higher CAVI values than control subjects (p=0.001).

Patients with stage-IV COPD had significantly lower BMI than control subjects (23.27±4.23 vs. 27.95±5.54, p=0.005) and patients with stage-II COPD (23.27±4.23 vs. 28.12±5.74, p=0.003). There was no significant difference in terms of BMI between control subjects and stage-I and –II patients. There was no significant difference in terms of age, resting heart rate, mean arterial pressure, left ventricular

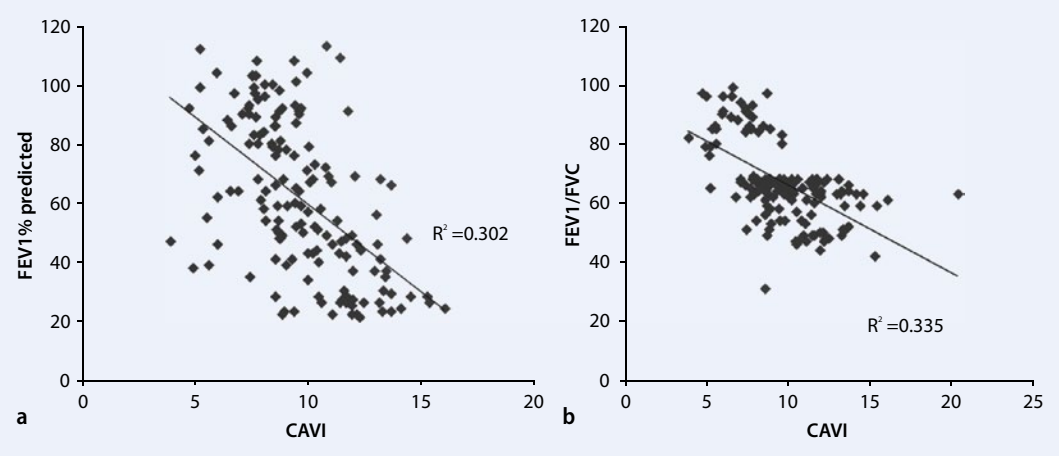

Fig. 1 ◀ **a** Scatter plot of the association between CAVI and FEV_1% predicted. **b**. Scatter plot of the association between CAVI and FEV_1/FVC

ejection fraction, gender and clinical features between the groups.

A positive correlation was found between CAVI and COPD stage (r=0.779 p<0.001). FEV_1% predicted (r: −0.540, p<0.001) and FEV_1/FVC (r: −0.579, p<0.001) were negatively correlated with CAVI (**Fig. 1**). Age (r: 0.222, p=0.005), BMI (r: −0.293, p<0.001), heart rate (r: 0.160, p=0.045), and COPD duration (r: 0.360, p<0.001) were weakly correlated with CAVI (**Tab. 3**).

COPD duration, FEV_1% predicted, age, hypertension, hyperlipidemia, diabetes, current smoking, sex, BMI, resting heart rate, and left ventricular EF were entered into stepwise linear regression analysis. FEV_1% predicted (p<0.001, B: −0.037, CI95%: −0.053–−0.021), age (p=0.002, B: 0.056, CI95%: 0.021–0.090), and BMI (p=0.004, B: −0.096, CI95%: −0.161–−0.031) were the independent variables of CAVI in the stepwise linear regression analysis.

Discussion

This study presents data regarding the relationships between arterial stiffness assessed by CAVI and pulmonary functions in patients with COPD. We have shown that arterial stiffness assessed by CAVI was significantly and independently increased in patients with COPD. Furthermore, the CAVI was associated with COPD severity and significantly correlated with FEV_1% predicted and FEV_1/FVC.

COPD is considered a systemic disease and characterized by a decreased FEV_1/FVC ratio [7, 8]. The presence and severity of COPD and reduced FEV_1 are related to increased cardiovascular events [3]. Reed et al. [9] showed that 60% of patients with advanced COPD had angiographically proven CAD. The mechanistic link between COPD and CVD may be mediated by arterial stiffness. Arterial stiffness is a marker of atherosclerosis and arteriolosclerosis [4, 5, 6]. Arterial stiffness is influenced by both structural and functional aspects of the conduit arteries and resistance beds. Contrary to other methods of arterial stiffness measurement, CAVI reflects the stiffness of the entire arterial tree including the aorta and the brachial and tibial arteries [6]. Additionally, CAVI is not influenced by blood pressure level at the time of measurement, unlike other methods [6]. Atherosclerotic risk factors including age, diabetes, abnormal glucose metabolism, hypertension, hyperlipidemia, and smoking habit are associated with increased CAVI values [10, 11, 12, 13]. Recently, it has been shown that CAVI was related to coronary artery disease complexity [14]. The presence of diabetes, hypertension, and hyperlipidemia was similar between patients with COPD and the control group in our study.

Systemic endothelial dysfunction and arterial stiffness result in vascular dysfunction. Maclay et al. [15] have shown the presence of vascular dysfunction in patients with COPD, and it was attributed to increased arterial stiffness rather than systemic endothelial dysfunction. We showed that arterial stiffness was significantly increased in COPD patients than in control subjects. In agreement with the literature, arterial stiffness was associated with aging in our study. With increasing stages of COPD, CAVI was increased and GOLD stage-IV patients had the highest CAVI values in our study. This finding indicated that increased arterial stiffness was more pronounced in severe and very severe COPD stages. Hypoxemia deteriorates vascular function [16], and the severity of hypoxemia is more evident with advanced stages of COPD. The chronic systemic inflammation induced by hypoxemia may be a major factor affecting arterial stiffness in patients with advanced COPD stages [17]. Janner et al. [18] demonstrated a significant relationship between FEV_1 and Alx in younger male patients (<60 years) recently. However, Alx is a suboptimal method for the evaluation of arterial stiffness in elderly patients and shows a plateau with age [19]. We evaluated the arterial stiffness with CAVI and showed a significant association of FEV_1% predicted and FEV_1/FVC with CAVI. Moreover, our study included older patients and a significant relationship was shown in older patients too. In our study, CAVI increased along with increasing severity of COPD.

Patients with abnormal vascular stiffness may be prone to COPD. Smoking is an important risk factor for the development of COPD but not all smokers develop the disease. Perhaps this reflects an abnormal, genetically determined response to cigarette smoke, which may also be related to stiffening of the vessels. This difference could be due to differential in-

flammation, a matrix metalloproteinase, accelerated vascular senescence, or a defect in the extracellular matrix of the vascular wall. However, the smoking habit was similar between the patients and control subjects in our study. Systemic susceptibility to elastin degradation and expression of matrix metalloproteinase increase in patients with COPD [20, 21]. Increased levels of MMP may cause increased arterial stiffness [22].

Study limitations

This study has several limitations. First, the sample size of all groups especially patients with stage-IV COPD was small. The GOLD criteria include spirometric parameters but functional capacity, arterial oxygenation, duration of disease, medication, and cough scale are also important determinants of COPD. Laboratory examinations including high-sensitivity C-reactive protein, von Willebrand factor, blood gas analysis, and assessment of endothelial dysfunction may provide additional information.

Conclusion

Increased arterial stiffness assessed by CAVI is associated with the severity of COPD and is an important indicator of increased CVD in patients with COPD. Therefore, patients with severe and very severe obstructive findings in spirometry testing may be followed up closely for CVD.

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Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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