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タイトル	Association of arteriosclerosis with early chronic obstructive pulmonary disease without respiratory symptoms
別タイトル	呼吸器症状の無い早期慢性閉塞性肺疾患と動脈硬化の関係
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Association of Arteriosclerosis with Early Chronic Obstructive Pulmonary Disease without Respiratory Symptoms

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ABSTRACT

Background: We examined the association between chronic obstructive pulmonary disease (COPD) and arteriosclerosis.

Methods: A total of 126 consecutive patients without respiratory symptoms were enrolled. COPD was classified into 4 stages according to forced expiratory volume in 1 second (FEV1.0) and percent predicted FEV1.0 (%FEV1.0). Patients with at least 3 of 4 arteriosclerosis risk factors (smoking, hypertension, diabetes, and dyslipidemia) were considered to have multiple arteriosclerosis risk factors. To evaluate associations with COPD stage, we evaluated arteriosclerosis markers, including estimated glomerular filtration rate (eGFR), carotid artery plaque score (PS), cardio-ankle vascular index (CAVI), and high-sensitivity C-reactive protein (hs-CRP), an inflammatory marker also known as an arteriosclerosis-promoting factor. Multiple regression analysis was used to identify associations between arteriosclerosis markers and %FEV1.

Results: Of the 126 patients enrolled, 87 had normal pulmonary function and 32 had early COPD (stage I: 22 patients, stage II: 10 patients). No patient had stage III or IV COPD. Stage II COPD was associated with an increased number of arteriosclerosis risk factors. As compared with patients with normal pulmonary function, higher percentages of patients with stage II COPD had multiple arteriosclerosis factors and marked changes in eGFR, PS, CAVI, and hs-CRP. An inverse association was noted between hs-CRP and %FEV1, which is used for stage classification of COPD. Moreover, multiple regression analysis with %FEV1 as an objective variable and the arteriosclerosis markers as explanatory variables revealed that hs-CRP was the most powerful explanatory variable.

Conclusions: Early COPD was closely associated with markers and risk factors for arteriosclerosis. The strong association with hs-CRP suggests that early COPD is closely associated with inflammation-induced arteriosclerosis.

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KEYWORDS: chronic obstructive pulmonary disease (COPD), arteriosclerosis, cardio-ankle vascular index, arterial stiffness

Chronic obstructive lung disease (COPD) is no longer regarded simply as a disease of airflow limitation in the lungs. It has been associated with a wide variety of systemic consequences, most notably systemic inflammation. Systemic inflammation induced by smoking can cause chronic heart failure, metabolic syndrome, and other chronic diseases, all of which may contribute to the clinical manifestations and natural history of COPD.¹⁾ Moreover, it has been reported that cerebrovascular and cardiovascular diseases account for approximately 30% of COPD mortality,²⁻⁴⁾ suggesting that the close association between COPD and arteriosclerosis may eventually influence vital prognosis. In the present study, we investigated the clinical relationship between COPD and arteriosclerosis.

We included estimated glomerular filtration rate (eGFR) as an index of arteriosclerosis in this study because chronic kidney disease is a risk factor for development of cardiovascular disease and a predictor of cardiovascular mortality.^{5,6)} We also used cardio-ankle vascular index (CAVI) as an indicator of arterial stiffness. Unlike pulse wave velocity (PWV), CAVI is independent of blood pressure and has adequate reproducibility in clinical use.⁷⁻⁹⁾

Methods

Patients

This study included consecutive patients (age ≤ 80 years) who presented between April 2011 and November 2011 and received ambulatory care at the Cardiovascular Center of the Toho University Sakura Medical Center. The inclusion criteria included stable cardiovascular parameters, normal chest X-ray results, without symptoms suggestive of respiratory disease, and ability to undergo pulmonary function testing.

The purpose of this study was explained to the participants, and consent for participation in the study and release of the study data was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki guidelines.

Pulmonary function test

Pulmonary function tests were performed using the CHESTAC-9800 (Chest MI Inc., Tokyo, Japan). Wearing a nose clip, patients inhaled from the rest inspiratory level to the maximum inspiratory level, and exhaled with best effort to the maximum expiratory level. The measurements were performed twice, and the maximum values were used for analysis. As pulmonary function parameters, actual/predicted value of vital capacity (%VC) and forced

expiratory volume in 1 second (FEV1.0)/forced vital capacity (FVC) were used to classify pulmonary function as follows: normal pulmonary function, obstructive pulmonary disease, restrictive pulmonary disease, and mixed (obstructive and restrictive) pulmonary disease. Furthermore, obstructive pulmonary disease was subdivided into the following 4 disease stages according to percent predicted FEV1.0 (%FEV1.0):¹⁰⁾ Stage I COPD (mild COPD)—mild airflow limitation (FEV1.0/FVC < 0.7 , %FEV1 $\geq 80\%$ predicted); Stage II COPD (moderate COPD)—worsening airway limitation (FEV1.0/FVC < 0.7 , $50\% \leq$ %FEV1 $< 80\%$ predicted); COPD stage III (severe COPD)—further worsening of airway limitation (FEV1.0/FVC < 0.7 , $30\% \leq$ %FEV1 $< 50\%$ predicted); COPD stage IV (very severe COPD)—severe airway limitation (FEV1.0/FVC < 0.7 , %FEV1 $< 30\%$ predicted or %FEV1 $< 50\%$ predicted, plus presence of chronic respiratory failure).

In the present study, bronchodilator inhalation was not included in the assessment of pulmonary function.

Examination of arteriosclerotic risk factors and indexes

The relationship between COPD and arteriosclerosis was evaluated in relation to arteriosclerotic risk factors [smoking, hypertension, diabetes mellitus (DM), dyslipidemia], high-sensitivity C-reactive protein (hs-CRP), and indexes of arteriosclerosis [eGFR, plaque score (PS), and CAVI]. For arteriosclerotic risk factors, percentages of patients with COPD and controls who had concomitant arteriosclerotic risk factors were compared. Moreover, patients were defined as having multiple risk factors if they had at least 3 of the 4 arteriosclerotic risk factors specified above, and the associations of these risk factors with COPD were analyzed. Values for hs-CRP and indexes of arteriosclerosis were compared between patients with COPD and controls. Regression analyses were used to assess associations of %FEV1.0, used in the diagnosis of COPD, with each index of arteriosclerosis.

Smoking status was recorded as positive for individuals with a current or past history of cigarette smoking (former smoking), and past smoking history was evaluated using the Brinkman index (number of cigarettes per day \times years of smoking). Hypertension was defined as a systolic pressure of 140 mmHg or higher or a diastolic pressure of 90 mmHg or higher. Blood samples were collected in the morning after an overnight fast of at least 12 hours. Serum was separated within 1 hour of sample collection, and samples were used for the measurement of the following

chemical parameters. Glycosylated hemoglobin (HbA1c) was measured by high-pressure liquid chromatography with the Hi-Auto A1c kit (Arkray, Inc., Kyoto, Japan). Triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and serum creatinine were measured with an automatic analyzer (Hitachi 7150, Hitachi High-Technologies Corp., Tokyo, Japan). High-density lipoprotein cholesterol (HDL) was measured by the selective inhibition method (Sekisui Chemical Co., Ltd., Tokyo, Japan). Dyslipidemia was defined as presence of high TG (≥ 150 mg/dl), high LDL-C (≥ 140 mg/dl), and/or low HDL-C (≤ 40 mg/dl). Hs-CRP level was determined using a latex turbidimetric immunoassay kit (Mitsubishi Chemical Medience Corp., Tokyo, Japan). Serum creatinine and eGFR were assessed as parameters of kidney function. Serum creatinine was assayed by an enzymatic method. GFR was estimated using the equation proposed by the Working Group of Japan Chronic Kidney Disease Initiative¹¹⁾ :

$$\text{eGFR (ml/min per } 1.73 \text{ m}^2) = 0.741 \times 175 \times \text{age}^{-2.203} \times \text{serum creatinine}^{-1.154} (\times 0.742, \text{ if female})$$

1) Measurement of intimal thickness of carotid artery

Duplex carotid ultrasonography was performed with linear-array 7.5-MHz transducers (Hitachi EUB-525, Hitachi Medical Corp., Tokyo, Japan; Toshiba SSA-260A, Toshiba Medical Systems Corp., Otawara, Japan). Intima-media thickness (IMT) was measured as reported previously.¹²⁾

PS was calculated as reported previously.¹³⁾ Briefly, plaques (localized increases in $\text{IMT} \geq 1.1$ mm) were detected by cross-sectional and longitudinal scanning of bilateral common and internal carotid arteries. PS was computed by summing the maximum thickness (in mm) of all plaques located in bilateral carotid arteries.

2) Measurement of CAVI

CAVI was measured with a CAVI device "VaSera" (Fukuda Denshi Co. Ltd., Tokyo, Japan) using previously described methods.⁷⁾ Briefly, cuffs were applied to bilateral upper arms and ankles, with the subject lying supine and the head held in the midline position. The examinations were performed after a 10-minute rest. To detect brachial and ankle pulse waves with cuffs, a low cuff pressure (30-50 mmHg) was used to minimize the effects of cuff pressure on hemodynamics, after which blood pressure was measured. CAVI was calculated using the formula

$$\text{CAVI} = a \{ (2\rho/\Delta P) \times \ln (P_s/P_d) \text{PWV}^2 \} + b$$

where P_s is systolic blood pressure, P_d is diastolic blood pressure, PWV is pulse wave velocity, ΔP is $P_s - P_d$, ρ is blood density, and a and b are constants.

Statistical analysis

All values are expressed as mean \pm SD and populations as number (%). Data were subjected to 1-way analysis of variance (ANOVA) to compare differences among groups. The t test was performed to compare the means of continuous variables, and categorical variables were analyzed using the χ^2 test. The association between hs-CRP and %FEV1.0 was analyzed using correlation analysis. Arteriosclerotic index and %FEV1.0 were analyzed using multiple regression analysis. In all comparisons, a p value less than 0.05 was considered statistically significant.

Results

Of the 126 patients eligible for the study (age 40-80 years; mean age 66 ± 5 years; 79% men), 87 (69%) had normal pulmonary function and 39 (31%) had pulmonary dysfunction. Among the latter group, 32 (25%) had COPD, 5 (4%) had restrictive pulmonary disease, and 2 (2%) had mixed pulmonary disease. In the present analysis, the 32 patients with COPD were compared with 87 control patients who had normal pulmonary function. COPD stage was I in 22 patients (17%) and II in 10 patients (8%), *i.e.*, all participants had early COPD; no patient had stage III or IV COPD. There was no significant difference in age, sex, or body mass index (BMI) between patients with early COPD and controls. Ankle brachial index, which is closely associated with CAVI, was normal (≥ 0.9) in all patients. The primary clinical diagnoses were hypertension (43%), angina pectoris (22%), old myocardial infarction (22%), arrhythmia (8%), and others (6%) (Table 1).

Relationship between COPD and arteriosclerotic risk factors

The percentages of participants with concomitant arteriosclerotic risk factors (hypertension, dyslipidemia, and DM) were higher among patients with early COPD than among controls. In particular, patients with stage II COPD had a significantly higher prevalence of diabetes and higher HbA1C values as compared with controls ($p < 0.05$). Moreover, use of antidiabetic agents increased from stage I COPD to stage II COPD, and significant differences were observed between control patients and those with stage I and stage II COPD in the prevalence of antidiabetic drug use. There was no difference in the use of other drugs (Table 2).

Table 1 Patient characteristics (1)

	Controls	COPD stage I	COPD stage II
No.	87	22	10
Age (years)	66.9 ± 8.6	67.8 ± 5.9	68.7 ± 4.6
Male (%)	82	73	80
BMI (kg/m ²)	24.3 ± 3.0	24.7 ± 2.9	23.6 ± 1.4
Primary clinical diagnosis (%)			
Hypertension	43	36	50
Angina pectoris	22	32	10
OMI	22	18	20
Arrhythmia	8	9	—
Others	6	5	20

COPD: chronic obstructive pulmonary disease, BMI: body mass index, OMI: old myocardial infarction

Table 2 Patient characteristics (2)

	Controls	COPD stage I	COPD stage II
No.	87	22	10
Prevalence (%)			
Hypertension	93	96	100
Dyslipidemia	59	68	70
Diabetes mellitus	21	36	50 *
Fasting plasma glucose (mg/dl)	104.5 ± 30.4	111.2 ± 20.4	144.7 ± 58.0 *
HbA1C (%)	5.5 ± 0.7	5.7 ± 0.8	6.5 ± 0.9 *
Medication (%)			
Calcium antagonist	58	73	70
ACE-I/ARB	53	50	50
Hypolipidemic drug	45	55	60
β-blocker	32	41	50
Nitrate	21	18	20
Antidiabetic drug	9	27 *	50 **

*p<0.05 vs control, **p<0.01 vs control

COPD: chronic obstructive pulmonary disease, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker

As for the relation between smoking and COPD, 28% of the 78 smokers had COPD, and 69% of the 32 patients with COPD were smokers. The number of current smokers progressively increased from control to stage I COPD to stage II COPD. There were significantly more smokers among patients with stage II COPD than among the controls ($p<0.05$). In fact, all patients with stage II COPD were smokers (Fig. 1A). Brinkman index progressively increased from control to stage I COPD to COPD stage II. In particular, Brinkman index was significantly higher among patients with stage II COPD than among controls ($p<0.05$), which confirms the strong relationship between smoking and COPD (Fig. 1B).

Relationship between COPD and arteriosclerotic indexes (Fig. 2)

The proportion of patients with multiple risk factors progressively increased from control to stage I COPD to stage II COPD, and there was a significant difference between patients with stage II COPD and controls ($p<0.05$). eGFR values were lower among patients with stage II COPD than among those with stage I COPD, and values among patients with stage I and stage II COPD were lower than those of controls. PS progressively increased from controls to stage I COPD to stage II COPD, and was significantly higher among patients with stage II COPD than among controls. CAVI was lower among patients

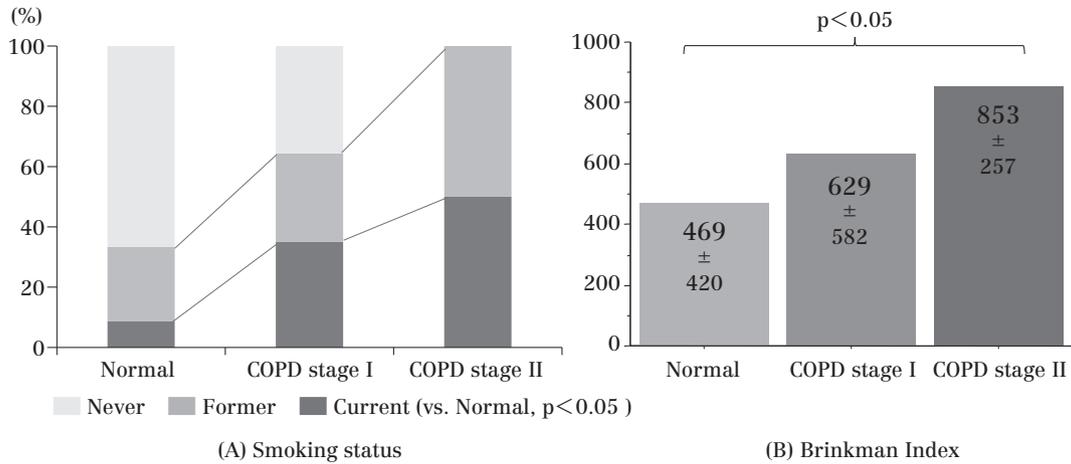


Fig. 1 Association of smoking status with COPD stage. (A) Smoking status and COPD stage, (B) Brinkman index and COPD stage. COPD: chronic obstructive pulmonary disease

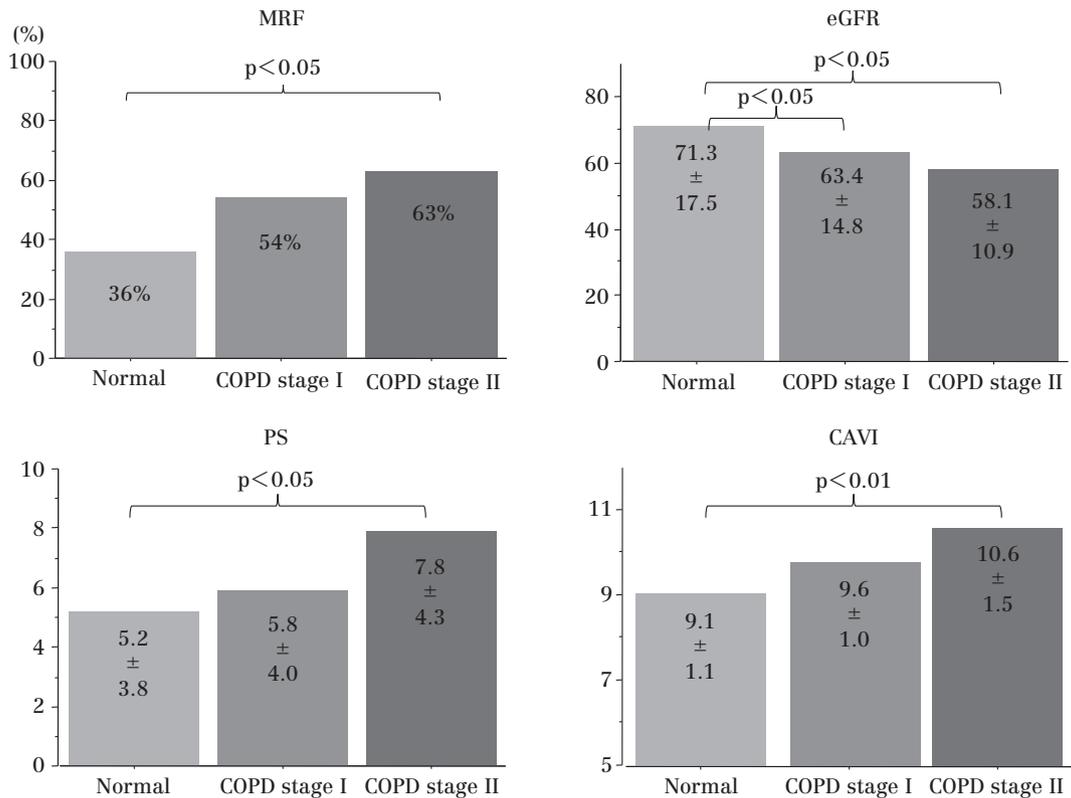


Fig. 2 Associations of MRF, eGFR, PS, and CAVI with COPD stage. MRF: multiple risk factors, eGFR: estimated glomerular filtration rate, PS: plaque score, CAVI: cardio-ankle vascular index, COPD: chronic obstructive pulmonary disease

with stage I COPD than among those with stage II COPD and was significantly higher among patients with stage II COPD as compared with controls.

Association between COPD and hs-CRP

High-sensitivity CRP progressively increased from con-

trols to stage I COPD to stage II COPD and was significantly higher among patients with stage II COPD as compared with controls (Fig. 3A). Correlation analysis showed a weak inverse correlation between %FEV1.0 and hs-CRP ($r = -0.272, p < 0.013$; Fig. 3B).

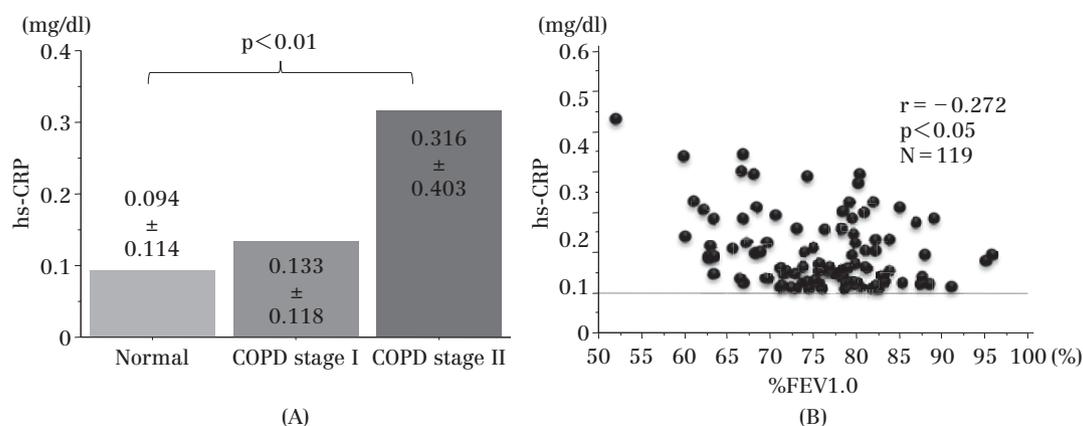


Fig. 3 (A) Association of hs-CRP with COPD stage, (B) Association of hs-CRP with %FEV1.0. %FEV1.0: percent predicted forced expiratory volume in 1 second, hs-CRP: high-sensitivity C-reactive protein, COPD: chronic obstructive pulmonary disease

Table 3 Multiple regression analysis with stepwise backward elimination: Association between %FEV1.0 and indicators of atherosclerosis

Independent variable	Regression coefficient	Standard error	t-value	p-value
hs-CRP	-20.703	7.350	-2.817	0.0061
eGFR	0.332	0.120	2.758	0.0072
CAVI	-1.770	0.838	-2.113	0.0377
Hypertension: {0 (-), 1 (+)}	6.801	4.032	1.687	0.0955
Smoking: {0 (-), 1 (+)}	-0.894	1.700	-0.526	0.6004
Dyslipidemia: {0 (-), 1 (+)}	-0.714	1.800	-0.397	0.6926
Diabetes mellitus: {0 (-), 1 (+)}	0.282	1.890	0.149	0.8816
Plaque score	0.028	0.217	0.131	0.8958

Variables not accepted were age, body mass index, and number of atherosclerotic risk factors.

%FEV1.0: percent predicted forced expiratory volume in 1 second, hs-CRP: high sensitivity C-reactive protein, eGFR: estimated glomerular filtration rate, CAVI: cardio-ankle vascular index

Relationship between arteriosclerotic indexes and %FEV1.0

Regression analysis was performed to investigate associations of %FEV1.0 with arteriosclerosis indexes and revealed inverse correlations with hs-CRP and CAVI and a positive correlation with eGFR. However, no significant correlation was observed between %FEV1.0 and PS (Table 3).

Discussion

The definition of COPD has changed over time. In guidelines developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which were revised in 2006,¹⁴⁾ COPD is defined as a preventable, treatable disease with some significant extrapulmonary effects that may contribute to disease severity in individual patients. Its pulmonary component is characterized by airflow limita-

tion that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lung to noxious particles or gases.

Smoking is the most important factor among the noxious particles and gases that affect the lungs. It was reported that about 20% of smokers develop COPD and that more than 90% of patients with COPD are smokers. In the present study, 28% of smokers had COPD, which is consistent with previous reports, whereas only 69% of COPD patients were smokers, which is lower than in previous studies. This discrepancy could be due to the fact that bronchodilator inhalation was not performed during pulmonary function testing, which may have resulted in overdiagnosis of COPD. In addition, COPD was rather mild among the present patients, and air pollution (which could result in diverse exposures to noxious particles and gases) and subse-

quent changes in patient susceptibility were not analyzed. Buist et al.¹⁵⁾ noted in an international study that although age and smoking status are important risk factors for COPD they do not fully explain variation in COPD prevalence and that other factors may contribute to prevalence.

Although COPD can be defined as continuous abnormal inflammation occurring in local areas of the lungs, it also involves systemic inflammation and has been referred to as chronic systemic inflammatory syndrome.¹⁶⁾ In fact, inflammatory mediators reflecting systemic inflammation, such as hs-CRP, fibrinogen, and tumor necrosis factor, are elevated even during the stable phase of COPD.^{14,17-19)} In the present study, hs-CRP was closely associated with COPD stage and %FEV1.0, which is used to diagnose COPD, and thus reflects COPD severity. With regard to the correlation between CRP and pulmonary function, Man et al.²⁰⁾ reported that CRP was associated with an accelerated decline in FEV 1.0. In contrast, Pinto-Plata et al.²¹⁾ found no association between selected pulmonary function test measurements and CRP in COPD patients.

Analysis of the relationship between COPD and arteriosclerotic risk factors showed that DM and multiple risk factors were closely associated with COPD. Mita et al.¹⁸⁾ reported that increased active oxygen in COPD is associated with DM, suggesting that an abnormal hs-CRP level in COPD has adverse effects on insulin level and insulin resistance, which may worsen diabetes.

In this study, data on hs-CRP level showed that systemic inflammation was higher in patients than in controls. In addition, there was a good correlation between %FEV1.0 and hs-CRP. The presence of systemic inflammation may explain why patients with COPD have an increased risk of developing type 2 DM. Some aspects of inflammation can predict DM development, while fibrinogen, circulating white blood cell count, and lower serum albumin predict development of type 2 DM. Furthermore, patients with type 2 DM have increased circulating levels of inflammatory mediators, which are also risk factors for cardiovascular events. DM is independently associated with reduced lung function, which together with obesity could further worsen COPD. The complex interaction between smoking and obesity in the development of chronic comorbidities has been previously reviewed.²²⁾

We found a correlation between COPD stage and multiple risk factors. COPD is no longer considered a disease only of the lungs. It is associated with a variety of systemic consequences, most notably systemic inflammation (which

influences many tissues and organs), and with risk factors of arteriosclerosis such as high blood pressure, DM, and dyslipidemia. The origin of systemic inflammation in COPD is unknown, although several potential mechanisms have been proposed.²³⁾

The present study cannot determine whether arteriosclerotic risk factors influence COPD or if COPD is caused by multiple risk factors. However, some reports suggest that COPD is an independent risk factor for arteriosclerosis development,^{1,17,18)} and use of statins and angiotensin receptor blockers in patients with COPD reduces the incidence of cardiovascular diseases and improves prognosis.^{24,25)} These findings indicate that COPD has an important role in arteriosclerosis.

We found that all the investigated indexes of arteriosclerosis (eGFR, PS, and CAVI) were associated with COPD severity. Regression analysis of the association of %FEV 1.0 with each index showed a correlation with eGFR and CAVI but not with PS, perhaps because PS is a parameter used for morphologic evaluation, whereas eGFR and CAVI evaluate functional capacity. Tounian et al.^{26,27)} reported that arterial stiffness was significantly higher and vascular endothelial function was significantly lower, but IMT was unchanged, which suggests that, as compared with increased IMT (and PS), arterial stiffness and vascular endothelial dysfunction might represent an earlier stage in arteriosclerosis development.

Sabit et al.²⁸⁾ used PWV to evaluate the association between COPD and vascular elasticity and found that PWV reflected COPD stage. PWV is useful for predicting arteriosclerosis; however, its clinical use is problematic because PWV itself essentially depends on blood pressure. CAVI was developed to overcome this disadvantage and essentially reflects the stiffness of the aorta and femoral and tibial arteries. Unlike PWV, CAVI is independent of blood pressure. Several reports have shown the usefulness of CAVI in detecting arteriosclerotic disease.⁷⁻⁹⁾

We used CAVI to assess the relation with COPD stage, and our results were consistent with those reported by Sabit et al, which showed that arterial stiffness reflects COPD stage. Sabit et al.²⁸⁾ evaluated patients with mild-to-very severe airway obstruction; however, our patients had only mild or moderate airway obstruction. The inverse correlation between FEV1.0, an indicator of pulmonary function in COPD, and arterial stiffness suggests that arterial stiffness is affected in early COPD.

This study had limitations. The small number of pa-

tients with stage II COPD limited statistical power. Second, because bronchodilator inhalation was not performed during pulmonary function testing, there is a possibility of overdiagnosis. Finally, this study only enrolled outpatients with cardiovascular disease.

Conclusion

Early COPD was closely associated with markers and risk factors for arteriosclerosis. These findings suggest that COPD has an important role in arteriosclerosis among patients with early COPD without respiratory symptoms.

This study was performed with the assistance of comedical staff working in clinical physiology.

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呼吸器症状の無い早期慢性閉塞性肺疾患と動脈硬化の関係

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要約

目的: 慢性閉塞性肺疾患 (chronic obstructive pulmonary disease : COPD) が動脈硬化に及ぼす影響を検討する。

対象および方法: 呼吸器症状の無い連続 126 例を対象に 1 秒率と %1 秒量により COPD のステージ分類を行った。動脈硬化危険因子として喫煙、高血圧、糖尿病および脂質異常症を考慮し、これら 4 因子のうち 3 因子以上を有する症例を動脈硬化の多危険因子合併例 (multiple risk factor : MRF) とし検討した。動脈硬化の指標として estimated glomerular filtration rate (eGFR)、頸動脈エコーによるプラークスコア (plaque score : PS) および cardio-ankle vascular index (CAVI) を用いた。さらに炎症マーカーであり、かつ動脈硬化促進因子でもある高感度 C 反応性蛋白 (high-sensitivity C reactive protein : h-CRP) と COPD との関係を検討した。

結果: 126 例のうち呼吸機能正常例は 87 例であり、32 例 (25%) が COPD と診断された。COPD の内訳はステージ I が 22 例、II が 10 例であり、III 以上の重症例はなかった。呼吸機能正常例を対照とし比較検討すると MRF、eGFR、PS、CAVI および hs-CRP はともに COPD のステージが上昇するに従い増悪し、COPD ステージ II との間に有意差を認めた。特に hs-CRP は %1 秒量との間に負の相関を示し、%1 秒量を目的変数、動脈硬化指標を説明変数とする重回帰解析では hs-CRP が最も強い説明変数であった。

結論: COPD は呼吸器症状に乏しい早期より動脈硬化因子および動脈硬化指標の異常をきたしており、特に hs-CRP とのかかわりが強いことから炎症に基づく動脈硬化の促進に関わっていることが示された。

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