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Low lung diffusing capacity is associated with high cardio-ankle vascular index in patients with chronic obstructive pulmonary disease

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ABSTRACT

Previous studies have demonstrated that arterial stiffness is independently associated with the severity of pulmonary emphysema observed on computed tomography (CT) in patients with chronic obstructive pulmonary disease (COPD). An inverse correlation exists between emphysema severity on CT image and lung diffusing capacity; however, the relationship between lung diffusing capacity and arterial stiffness in patients with COPD remains unclear. We retrospectively analyzed the data of 30 patients with COPD. Percent predicted diffusing capacity of the lung for carbon monoxide divided by alveolar volume (%DLco/VA) was used as an index of lung diffusing capacity. We used the Goddard score as an index of the severity of pulmonary emphysema on CT image and cardio-ankle vascular index (CAVI) as an index of arterial stiffness. CAVI was inversely correlated with %DLco/VA (r = −0.539, p = 0.002) but not correlated with Goddard score (rs = 0.236, p = 0.209). None of the other respiratory parameters investigated, including forced expiratory volume in the first second (FEV_1), FEV_1/forced vital capacity ratio, and percent predicted FEV_1, were correlated with CAVI. In multiple regression analysis, systolic blood pressure (β = 0.404, p = 0.006), %DLco/VA (β = −0.379, p = 0.012), and modified Borg scale score for dyspnea (β = 0.304, p = 0.033) were significant predictors of CAVI. Lung diffusing capacity is a significant independent predictor of arterial stiffness in patients with COPD. The evaluation of %DLco/VA in patients with COPD might be useful for predicting high CAVI and the development of cardiovascular disease in the future.

Key words: *arterial stiffness*, *chronic obstructive pulmonary disease*, *lung diffusing capacity*, *cardio-ankle vascular index*

INTRODUCTION

Preventing cardiovascular events is very important in the management of patients with chronic obstructive pulmonary disease (COPD) as almost one-third of the deaths in these patients occur due to cardiovascular disease[14,31,40,43]. Studies in recent years have shown that arterial stiffness is a predictor of cardiovascular events[45], and that it is higher in patients with COPD than in healthy subjects[5,9,32,39,44]. In daily clinical practice, pulse wave velocity (PWV) has been used as an index of arterial stiffness[26]. PWV in patients with COPD is positively correlated with age, amount of cigarette smoking, systolic and diastolic blood pressure, mean blood pressure, heart rate, cholesterolemia, glycemia, frequent acute exacerbation of COPD, severity of pulmonary emphysema on computed tomography (CT) image, and physical inactivity[32,39,44]. In contrast, PWV is inversely correlated with forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), six-minute walk distance (6MWD), and left ventricular diastolic function[5,39,44].

Using PWV, McAllister et al. showed that arterial stiffness is independently associated with the severity of pulmonary emphysema on CT image in patients with COPD[32]. Compared to patients with COPD with a low percentage of low attenuation area (LAA%), those with a high LAA% had a poor prognosis and an increased likelihood of respiratory and cardiac disease[25]. These findings suggest a strong link between the severity of pulmonary emphysema on CT image and cardiovascular events in patients with COPD.

In addition to the decline in FEV_1, a decrease in the lung diffusing capacity is another characteristic functional damage in patients with COPD[42]. Based on the fact that lung diffusing capacity is inversely correlated with the severity of pulmonary emphysema on CT image[46], we hypothesized that there might be an inverse correlation between lung diffusing capacity and arterial stiffness in patients with COPD. To our knowledge, the relationship between lung diffusing capacity and arterial stiffness in patients with COPD has not been

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investigated in previous studies, and it is not well understood. We conducted the present study to understand this relationship. We used cardio-ankle vascular index (CAVI) as an index of arterial stiffness, which is based on PWV, because hypertension is a common comorbidity in patients with COPD[16] and CAVI is less affected by blood pressure than by PWV itself[37].

MATERIALS AND METHODS

Subjects

We retrospectively analyzed the clinical data of 30 patients diagnosed with stable COPD at the National Hospital Organization Kure Medical Center and Chugoku Cancer Center from April 2011 to June 2017. The study protocol was approved by our ethics committee.

COPD was diagnosed in patients with a smoking history and airflow limitation indicated by an FEV_1/FVC ratio of < 0.7 after inhalation of a bronchodilator or in those on bronchodilator therapy[20]. Patients who continued cigarette smoking at enrolment were classified as current smokers, and those who had quit cigarette smoking at least one month prior to enrolment were classified as former smokers. The severity of COPD was decided according to the Global Initiative for Chronic Obstructive Lung Disease guideline classification[42].

COPD was considered stable in patients who had not experienced any acute exacerbation for at least 3 months. No patient was on long-term oxygen therapy. Because of inadequate rehabilitation staff resources, no patient was on a regular rehabilitation program.

After ascertaining the smoking status and medical history, the height, weight, grade of the modified Medical Research Council (mMRC) dyspnea scale[8], and COPD assessment test score[42] were measured.

Blood examination data

Blood examination data including complete blood count, total cholesterol, blood glucose, glycosylated hemoglobin, and C-reactive protein obtained within the last 3 months were used in the analysis.

Measurement of CAVI

After a 5-minute rest in the supine position, CAVI (standard value < 9.0) was measured using the VaSera® VS-1500 AN vascular screening system (FUKUDA DENSHI Co., Ltd., Tokyo, Japan).

Evaluation of the severity of pulmonary emphysema on CT image

The severity of pulmonary emphysema was evaluated on a high-resolution chest CT image within 3 months before the recruitment. Referring to the study by Goddard and colleagues[22], we evaluated the severity of pulmonary emphysema on CT image by visual assessment. In each CT scan, the LAA% in both upper lung zones at the level of the upper limit of the aortic arch, middle lung zones at the level of the carina, and lower lung zones at the level of 1 to 3 cm above the diaphragm were assessed visually by one pulmonologist blinded to the patient information. When the visually assisted LAA% was 0%, > 0 to ≤ 25%, > 25 to ≤ 50%, > 50 to ≤ 75%, or > 75% to ≤ 100%, the emphysema score was judged as 0, 1, 2, 3, or 4, respectively. A total emphysema score incorporating the two upper, middle, and lower lung zones was expressed as a Goddard score[22] (Table 1).

Lung function tests, including spirometry, measurement of lung volume, and lung diffusing capacity, were performed using lung function testing equipment (CHESTAC-9800®, Chest M.I., Inc., Tokyo, Japan) according to the guidelines of the American Thoracic Society[1]. The predicted values of FVC[6] and vital capacity (VC)[6], and FEV_1[7] were calculated using the formulae mentioned in the previous studies.

Lung volume and lung diffusing capacity were measured before inhaling the bronchodilator. The closed-circuit helium dilution method was used to assess alveolar volume (VA) and lung volume, including functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC), and the ratio of RV to TLC (RV/TLC)[1]. The predicted values of FRC[24], RV[10,23], TLC[36], and RV/TLC[24] were calculated using the formulae mentioned in the previous studies.

The single-breath method was used to assess the diffusing capacity of the lung for carbon monoxide (DLco)[30]. In our hospital, 0.75 liters of washout volume and 1 liters of sample volume of the exhaled gas were collected. However, if FEV_1 was less than 1.5 liters, the washout volume and sample volume of the exhaled gas was decreased to 0.5 liters. DLco was calculated by analysis of the sample gas. DLco/VA was calculated by dividing DLco by VA. The predicted values of DLco[12], DLco/VA[12], and body surface area, which is included in the formula of DLco[18] were calculated using the formulae in the previous studies.

We used percent predicted DLco/VA (%DLco/VA) as an index of lung diffusing capacity in the present study, which was calculated using the following formula:

%DLco/VA (%) = 100 × (the ratio of DLco/VA to the predicted value of DLco/VA)

Similarly, for the other respiratory parameters, the percent predicted parameter (%parameter) was calculated using the following formula:

%parameter (%) = 100 × (the ratio of the value of each parameter to the predicted value of the parameter)

Six-minute walk test (6MWT)

In 29 out of 30 patients, 6MWT was conducted on a different day, within one month of undergoing the lung function test, to evaluate exercise tolerance, according to the guidelines of the American Thoracic Society[4]. The pulse rate and percutaneous arterial oxygen saturation (SpO_2) during the 6MWT were monitored continuously using a pulse oximeter (WristOx$_2$® Model 3150 OEM with Bluetooth® Low Energy; Nonin Medical, Plymouth, MN, USA) and computer software (WristOx$_2$™6MW; Star Product, Tokyo, Japan). The highest pulse rate and the lowest SpO_2 during 6MWT were recorded. The degrees of exertional dyspnea and leg fatigue were evaluated immediately after the termination of 6MWT,

Table 1 Patient characteristics in the two groups stratified by %DLco/VA

	Low-DC group (n = 21)	Normal-DC group (n = 9)	*p* value
Age (years)	73.1 ± 9.7	70.0 ± 8.4	0.405
Gender (male/female)	19/2	8/1	0.965
Height (cm)	161.9 ± 7.1	160.1 ± 9.1	0.556
Weight (kg)	55.8 ± 10.2	58.8 ± 7.0	0.427
Body mass index (kg/m^2)	21.2 ± 3.2	22.9 ± 1.8	0.143
Smoking status (current/former)	5/16	1/8	0.594
Brinkman index	1641.2 ± 953.2	1191.1 ± 636.5	0.207
Grade of the mMRC dyspnea scale	1.6 ± 1.1	0.8 ± 1.1	0.063
CAT score	12.3 ± 7.7	8.2 ± 8.8	0.212
COPD stage (I/II/III/IV)	6/7/8/0	4/5/0/0	0.114
COPD treatment (yes/no)	8/13	4/5	0.790
Heart rate (beats/min)	74.9 ± 13.8	67.2 ± 13.2	0.169
Systolic blood pressure (mmHg)	138.6 ± 19.4	130.8 ± 17.8	0.309
Diastolic blood pressure (mmHg)	86.2 ± 10.5	79.9 ± 7.3	0.111
Mean blood pressure (mmHg)	108.6 ± 14.6	100.9 ± 12.5	0.183
White blood cell count (/μL)	7045.0 ± 1972.3	6300.0 ± 1173.5	0.330
Hemoglobin (g/dL)	13.8 ± 1.6	14.8 ± 0.6	0.079
Total cholesterol (mg/dL)	184.1 ± 38.8	200.3 ± 45.6	0.427
Blood glucose (mg/dL)	129.2 ± 46.3	114.2 ± 19.6	0.453
HbA1c (%)	6.1 ± 0.7	5.7 ± 0.6	0.173
CRP (mg/dL)	0.20 ± 0.17	0.19 ± 0.22	0.895
Goddard score	12.4 ± 5.4	8.0 ± 4.3	0.017*

Data are presented as mean ± standard deviation. DLco: diffusing capacity of the lung for carbon monoxide, VA: alveolar volume, %DLco/VA: percent predicted DLco/VA calculated using the following formula: 100 × (the ratio of DLco/VA to the predicted value of DLco/VA), Low-DC group: low diffusing capacity group with %DLco/VA < 80%, Normal-DC group: normal diffusing capacity group with %DLco/VA ≥ 80%, mMRC: modified Medical Research Council, CAT: chronic obstructive pulmonary disease assessment test, COPD: chronic obstructive pulmonary disease, HbA1c: glycosylated hemoglobin, CRP: C-reactive protein
*$p < 0.05$

using the modified Borg scale[11], which is classified into 12 grades.

The 30 patients with COPD were divided into two groups based on the %DLco/VA.

Since %DLco/VA ≥ 80% is considered as normal in the daily clinical practice, patients with %DLco/VA < 80% were assigned to a low diffusing capacity group (Low-DC group), while those with %DLco/VA ≥ 80% were assigned to a normal diffusing capacity group (Normal-DC group).

Statistical analysis

We compared CAVI and other parameters, including %DLco/VA and Goddard score in each group using one-way analysis of variance or Mann-Whitney U test, as appropriate. Univariate analyses using the Pearson correlation coefficient test or the Spearman rank correlation coefficient test, as appropriate, were performed to investigate the correlations between CAVI and other parameters. Multivariate stepwise regression analysis was performed to investigate independent predictors of CAVI. Mean ± standard deviation was calculated for each parameter, and a *p*-value < 0.05 was considered statistically significant.

RESULTS

Of the 30 patients with COPD, 27 were male, and 3 were female. The mean age was 72.2 ± 9.3 years. Ten patients were in stage I, 12 patients were in stage II, and 8 patients were in stage III of COPD[42]. Only the Low-DC group included patients in stage III (Table 1). Four out of 10 patients in stage I, 6 out of 12 patients in stage II, and 2 out of 8 patients in stage III had received COPD treatment (Table 1).

Twenty-one patients were assigned to the Low-DC group, and 9 were assigned to the Normal-DC group (Tables 1 to 5). Patients in the Low-DC group exhibited a higher mean Goddard score than that of patients in the Normal-DC group (Table 1). There was no significant difference in the prevalence of hypertension, type 2 diabetes, cholesterolemia, ischemic heart disease, stroke, and peripheral arterial disease between the Low-DC group and the Normal-DC group (Table 2). Similarly, the differences between the two groups in the rate of patients under treatment against hypertension, type 2 diabetes, and cholesterolemia were not statistically significant (Table 2).

Regarding the lung function parameters, patients in the Low-DC group exhibited lower mean FEV_1/FVC ratio, DLco, DLco/VA and %DLco/VA, and higher mean FRC, RV, %RV, TLC, %TLC, and VA (Tables 3, 4). The mean CAVI was significantly higher in the Low-DC group than in the Normal-DC group (10.5 ± 2.0 vs. 8.4 ± 1.1; $p = 0.006$) (Figure 1).

Regarding the 6MWT results, the differences in the mean 6MWD and the lowest SpO_2 did not reach statistical significance (Table 5). In the Low-DC group, the

Table 2 Prevalence rate of complications and treatment rate in the two groups stratified by %DLco/VA

	Low-DC group (n = 21)	Normal-DC group (n =9)	*p* value
Hypertension (yes/no)	9/12	5/4	0.530
Type 2 diabetes (yes/no)	3/18	1/8	0.818
Cholesterolaemia (yes/no)	6/15	3/6	0.798
Ischemic heart disease (yes/no)	5/16	2/7	0.926
Stroke (yes/no)	1/20	0/9	0.513
Peripheral arterial disease (yes/no)	3/18	0/9	0.240
Antihypertensive drug (yes/no)	9/12	4/5	0.937
Antidiabetic drug (yes/no)	1/20	0/9	0.513
Statin (yes/no)	4/17	1/8	0.599

Data are presented as mean ± standard deviation.
DLco: diffusing capacity of the lung for carbon monoxide, VA: alveolar volume, Low-DC group: low diffusing capacity group with %DLco/VA < 80%, Normal-DC group: normal diffusing capacity group with %DLco/VA ≥ 80
*$p < 0.05$

Table 3 Spirometric parameters in the two groups stratified by %DLco/VA

	Low-DC group (n = 21)	Normal-DC group (n = 9)	*p* value
VC (L)	2.88 ± 0.74	2.94 ± 0.72	0.839
%VC (%)	93.3 ± 20.1	95.2 ± 20.5	0.810
IC (L)	2.00 ± 0.64	2.16 ± 0.58	0.512
FVC (L)	2.73 ± 0.75	2.87 ± 0.70	0.649
%FVC (%)	88.7 ± 21.2	92.7 ± 19.1	0.636
FEV_1 (L)	1.42 ± 0.60	1.71 ± 0.54	0.229
FEV_1/FVC ratio	0.51 ± 0.10	0.59 ± 0.07	0.047*
%FEV_1 (%)	67.9 ± 28.4	78.9 ± 23.4	0.318

Data are presented as mean ± standard deviation.
Note: %parameter (percent predicted parameter) was calculated using the following formula: 100 × (the ratio of the value of each parameter to the predicted value of the parameter).
DLco: diffusing capacity of the lung for carbon monoxide, VA: alveolar volume, Low-DC group: low diffusing capacity group with %DLco/VA < 80%, Normal-DC group: normal diffusing capacity group with %DLco/VA ≥ 80%, VC: vital capacity, IC: inspiratory capacity, FVC: forced vital capacity, FEV_1: forced expiratory volume in the first second
*$p < 0.05$

Table 4 Lung volume and lung diffusing capacity in the two groups stratified by %DLco/VA

	Low-DC group (n = 21)	Normal-DC group (n = 9)	*p* value
FRC (L)	3.82 ± 0.74	3.09 ± 0.53	0.012*
%FRC (%)	108.4 ± 23.0	99.6 ± 34.9	0.418
RV (L)	3.09 ± 0.81	2.28 ± 0.43	0.010*
%RV (%)	181.5 ± 44.9	143.7 ± 30.1	0.029*
TLC (L)	5.89 ± 0.95	5.14 ± 0.64	0.040*
%TLC (%)	116.7 ± 12.0	103.3 ± 11.4	0.009*
RV/TLC (%)	52.3 ± 10.2	44.7 ± 8.2	0.058
%RV/TLC (%)	135.2 ± 31.0	122.5 ± 30.8	0.315
DLco (mL/min/mmHg)	9.69 ± 3.18	16.04 ± 1.86	< 0.001*
VA (L)	4.67 ± 0.78	3.98 ± 0.52	0.024*
DLco/VA (mL/min/mmHg/L)	2.08 ± 0.55	4.07 ± 0.59	< 0.001*
%DLco/VA (%)	48.2 ± 12.0	92.3 ± 10.6	< 0.001*

Data are presented as mean ± standard deviation.
Note: %parameter (percent predicted parameter) was calculated using the following formula: 100 × (the ratio of the value of each parameter to the predicted value of the parameter).
DLco: diffusing capacity of the lung for carbon monoxide, VA: alveolar volume, Low-DC group: low diffusing capacity group with %DLco/VA < 80%, Normal-DC group: normal diffusing capacity group with %DLco/VA ≥ 80%, FRC: functional residual capacity, RV: residual volume, TLC: totallung capacity
*$p < 0.05$

modified Borg scale score for dyspnea was significantly higher than that in the Normal-DC group (Table 5). The modified Borg scale score for leg fatigue in the Low-DC group was higher than that in the Normal-DC group; however, the difference was not statistically significant (Table 5).

Age, systolic and diastolic blood pressure, mean blood pressure, and white blood cell count were positively cor-

Table 5 Results of six-minute walk test in the two groups stratified by %DLco/VA

	Low-DC group (n = 20)	Normal-DC group (n = 9)	*p* value
Six-minute walk distance (m)	406.1 ± 97.4	463.0 ± 97.2	0.157
Lowest SpO_2 (%)	91.1 ± 4.1	94.0 ± 2.6	0.065
Highest pulse rate (beats/min)	107.7 ± 24.4	92.7 ± 20.2	0.121
Modified Borg scale score for dyspnea	4.1 ± 2.2	2.1 ± 1.6	0.018*
Modified Borg scale score for leg fatigue	3.1 ± 2.3	1.4 ± 2.0	0.087

Note: six-minute walk test was conducted in 29 patients with chronic obstructive pulmonary disease.
Data are presented as mean ± standard deviation.
DLco: diffusing capacity of the lung for carbon monoxide, VA: alveolar volume, %DLco/VA: percent predicted DLco/VA calculated using the following formula: 100 × (the ratio of DLco/VA to the predicted value of DLco/VA), Low-DC group: low diffusing capacity group with %DLco/VA < 80%, Normal-DC group: normal diffusing capacity group with %DLco/VA ≥ 80%, SpO_2: percutaneous arterial oxygen saturation
*$p < 0.05$

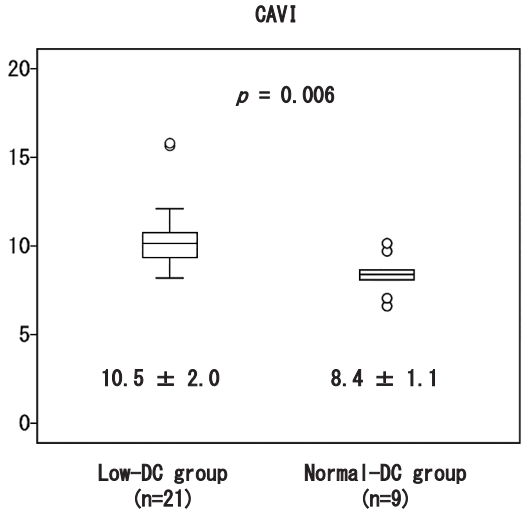

Figure 1 Box-and-whisker plot for the cardio-ankle vascular index (CAVI) in the two groups of patients with chronic obstructive pulmonary disease stratified by the percent predicted diffusing capacity of the lung for carbon monoxide divided by the alveolar volume (%DLco/VA). The low diffusing capacity group (%DLco/VA < 80%; Low-DC group) shows a higher mean CAVI (10.5 ± 2.0) than the normal diffusing capacity group (%DLco/VA ≥ 80%; Normal-DC group; 8.4 ± 1.1; $p = 0.006$).

related with CAVI (Table 6). Although the grade of the mMRC dyspnea scale increased with an increase in the CAVI, this correlation did not reach statistical significance (rs = 0.361, $p = 0.050$) (Table 6). The Goddard score was not significantly correlated with CAVI (rs = 0.236, $p = 0.209$) (Table 6). Similarly, the presence of hypertension, type 2 diabetes, cholesterolemia, or treatment against these complications was not correlated with CAVI (Table 7).

None of the respiratory parameters regarding airflow limitation, i.e., FEV_1, FEV_1/FVC ratio, and $\%FEV_1$ were significantly correlated with CAVI (Table 8). There was an inverse correlation between %DLco/VA and CAVI (r = −0.539, $p = 0.002$) (Table 9, Figure 2). None of the respiratory parameters related to the lung volume were significantly correlated with CAVI (Table 9). Regarding the parameters of 6MWT, the modified Borg scale score for dyspnea was positively correlated with CAVI (rs = 0.548, $p = 0.002$) (Table 10).

Table 6 Univariate analysis between CAVI and patient characteristics

	r/rs	*p* value
Age	0.565	0.001*
Male gender	0.283	0.130
Height	0.143	0.450
Weight	−0.208	0.269
Body mass index	−0.341	0.065
Current smoker	−0.123	0.518
Brinkman index	0.147	0.438
Grade of the mMRC dyspnea scale	0.361	0.050
CAT score	0.261	0.189
COPD stage	0.138	0.466
Existence of COPD treatment	0.075	0.695
Heart rate	0.261	0.164
Systolic blood pressure	0.423	0.020*
Diastolic blood pressure	0.430	0.018*
Mean blood pressure	0.413	0.023*
White blood cell count	0.428	0.023*
Hemoglobin	−0.234	0.231
Total cholesterol	−0.031	0.898
Blood glucose	0.061	0.778
HbA1c	0.253	0.269
CRP	−0.050	0.805
Goddard score	0.236	0.209

CAVI: cardio-ankle vascular index, mMRC: modified Medical Research Council, CAT: chronic obstructive pulmonary disease assessment test, COPD: chronic obstructive pulmonary disease, HbA1c: glycosylated hemoglobin, CRP: C-reactive protein
*$p < 0.05$

We selected the systolic blood pressure for multivariate stepwise regression analysis while omitting the diastolic and mean blood pressures since the systolic blood pressure has been reported as a predictor of CAVI[37]. In addition to the Goddard score, FEV_1/FVC ratio and $\%FEV_1$, we also included the grade of the mMRC dyspnea scale, which exhibited an almost significant correlation with CAVI in the univariate analysis for multivariate stepwise regression analysis (Tables 6, 8). Systolic blood pressure (β = 0.404, $p = 0.006$), %DLco/VA (β = −0.379, $p = 0.012$) and modified Borg scale score for dyspnea (β = 0.304, $p = 0.033$) were significant independent predictors of CAVI (Table 11).

Table 7 Univariate analysis between CAVI and complications and treatments

	rs	*p* value
Hypertension	−0.008	0.968
Type 2 diabetes	0.204	0.279
Cholesterolaemia	−0.181	0.339
Ischemic heart disease	0.333	0.073
Stroke	−0.247	0.188
Peripheral arterial disease	0.289	0.121
Antihypertensive drug	0.105	0.581
Antidiabetic drug	−0.129	0.498
Statin	−0.083	0.664

CAVI: cardio-ankle vascular index

Table 8 Univariate analysis between CAVI and spirometric parameters

	r	*p* value
VC	−0.092	0.627
%VC	−0.058	0.759
IC	−0.176	0.351
FVC	−0.092	0.629
%FVC	−0.056	0.770
FEV_1	−0.218	0.248
FEV_1/FVC ratio	−0.334	0.071
$\%FEV_1$	−0.075	0.695

Note: %parameter (percent predicted parameter) was calculated using the following formula: 100 × (the ratio of the value of each parameter to the predicted value of the parameter).
CAVI: cardio-ankle vascular index, VC: vital capacity, IC: inspiratory capacity, FVC: forced vital capacity, FEV_1: forced expiratory volume in the first second

Table 9 Univariate analysis between CAVI and lung volume and lung diffusing capacity

	r	*p* value
FRC	0.164	0.386
%FRC	−0.240	0.202
RV	0.168	0.374
%RV	0.038	0.841
TLC	0.129	0.496
%TLC	0.079	0.677
RV/TLC	0.124	0.513
%RV/TLC	−0.162	0.392
VA	0.124	0.513
%DLco/VA	−0.539	0.002*

Note: %parameter (percent predicted parameter) was calculated using the following formula: 100 × (the ratio of the value of each parameter to the predicted value of the parameter).
CAVI: cardio-ankle vascular index, FRC: functional residual capacity, RV: residual volume, TLC: total lung capacity, DLco: diffusing capacity of the lung for carbon monoxide, VA: alveolar volume
*$p < 0.05$

DISCUSSION

To the best of our knowledge, this is the first report demonstrating that lung diffusing capacity is an independent predictor of arterial stiffness in patients with COPD. Degradation of the elastic fibers is common in both emphysematous lungs and arterial walls with increased stiffness[21,47]. Given that COPD is a systemic disease,

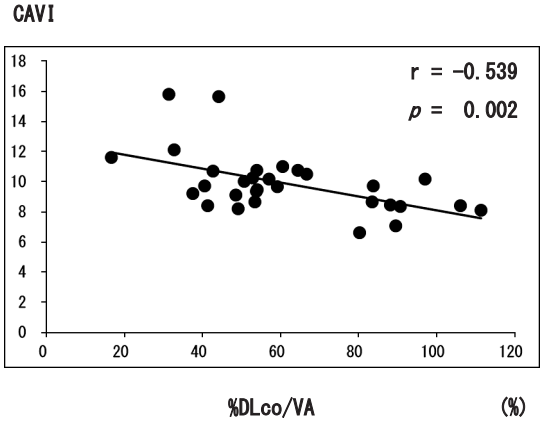

Figure 2 Scattergram showing an inverse correlation between the percent predicted diffusing capacity of the lung for carbon monoxide divided by alveolar volume (%DLco/VA) and cardio-ankle vascular index (CAVI) (r = −0.539, *p* = 0.002).

Table 10 Univariate analysis between CAVI and six-minute walk test parameters

	r/rs	*p* value
Six-minute walk distance	−0.171	0.376
Lowest SpO_2	−0.294	0.121
Highest pulse rate	0.265	0.165
Modified Borg scale score for dyspnea	0.548	0.002*
Modified Borg scale score for leg fatigue	0.196	0.357

Note: six-minute walk test was conducted in 29 patients with chronic obstructive pulmonary disease.
CAVI: cardio-ankle vascular index, SpO_2: percutaneous arterial oxygen saturation
*$p < 0.05$

Table 11 Multivariate stepwise regression analysis for predictors of CAVI

$R^2 = 0.647$	β	*p* value
Age	0.148	0.311
Grade of the mMRC dyspnea scale	0.041	0.803
Systolic blood pressure	0.404	0.006*
White blood cell count	−0.133	0.438
Goddard score	−0.057	0.743
FEV_1/FVC ratio	−0.143	0.319
$\%FEV_1$	−0.003	0.984
%DLco/VA	−0.379	0.012*
Modified Borg scale score for dyspnea	0.304	0.033*

CAVI: cardio-ankle vascular index, R^2: determination coefficient, β: standardized regression coefficient, mMRC: modified Medical Research Council, FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, DLco: diffusing capacity of the lung for carbon monoxide, VA: alveolar volume, %DLco/VA: percent predicted DLco/VA calculated using the following formula: 100 × (the ratio of DLco/VA to the predicted value of DLco/VA)
*$p < 0.05$

the degradation of elastic fibers, in which matrix metalloproteinases are known to play a primary role[3,19,29,47], is a possible explanation for the correlation between decreased lung diffusing capacity and increased arterial stiffness.

In patients with COPD, lung diffusing capacity decreases due to the reduction of contact between alveoli and capillary vessels due to the destruction of alveoli in the emphysematous area[46]. Pulmonary emphysema is classified into subgroups according to the distribution area, i.e., centrilobular emphysema, panlobular emphysema, and paraseptal emphysema, which varies among patients with COPD[41]. In addition, the extent of capillary vessel destruction associated with emphysematous change varies, and its estimation on CT is difficult[48]. The heterogeneity of emphysematous changes might explain the variation in the values of lung diffusing capacity in patients with COPD, having the same total emphysematous area, and why only %DLco/VA but not Goddard score was a predictor of CAVI in the present study.

Modified Borg scale score for dyspnea was another independent predictor of CAVI in the present study[11]. In patients with COPD, low lung diffusing capacity and increased ventilation-perfusion mismatch induced by airflow limitation might lead to lowering of SpO_2 on exertion. Although the respiratory rate increases to prevent or correct this exertional desaturation, air trapping occurs in the lung because of the airflow limitation. As a result, the FRC gradually increases, and dynamic hyperinflation occurs, accompanied by an increase in the intrinsic positive end-expiratory pressure. This leads to difficulty in negative pressure breathing and increased inspiratory effort, which in turn leads to exertional dyspnea in patients with COPD[34]. We speculated that exertional dyspnea would strengthen the sympathetic nerve activation, and this sympathetic over-activation is another possible reason for the strong link between COPD and arterial stiffness.

It is well known that cigarette smoking is a common cause of COPD and atherosclerosis[38]. Iwamoto et al. showed that compared with current or former smokers without airflow limitation, those with airflow limitation have more advanced atherosclerosis[27]. Since atherosclerosis increases the value of CAVI[2,37], the results of several studies demonstrating that FEV_1 or COPD stage was a predictor of arterial stiffness in patients with COPD is reasonable[5,44]. However, airflow limitation can occur without a decrease in the lung diffusing capacity in patients with COPD with less emphysematous change and more obstructive bronchiolitis. The heterogeneity in the distribution of emphysema might also affect the degree of airflow limitation[35]. Thus, we considered it rational that the degree of airflow limitation is not proportionate to the progression of emphysematous change or decrease in the lung diffusing capacity. This is also a possible explanation for the weaker association between CAVI and parameters regarding airflow limitation than that between CAVI and lung diffusing capacity.

Systolic blood pressure was another independent predictor of CAVI in this study, which is consistent with the finding of a previous study by Shirai et al.[37]. Although the change in CAVI associated with that in systolic blood pressure might be small in each patient, it is reasonable to conclude that there might be a positive correlation between systolic blood pressure and CAVI in the broader population. Sympathetic over-activation in patients with COPD can be another possible explanation for the strong direct relationship between blood pressure and CAVI[44]. In addition, atherosclerosis, arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis induced by sustained elevations in blood pressure increase the CAVI in hypertensive patients[2,37]. Considering that hypertension is a common comorbidity in patients with COPD[16], good control of hypertension in these patients might delay the progression of arterial stiffness and reduce the risk of future cardiovascular events.

Dransfield et al. showed that arterial stiffness improves by inhaled therapy using a combination of inhaled corticosteroid and long-acting β_2-adrenergic receptor agonist (ICS/LABA) in patients with COPD with high PWV (> 10.9 m/s)[17]. In the TORCH study, cardiovascular adverse events were significantly lower in patients with COPD treated with ICS/LABA than in those treated with placebo[13]. From these results, it is reasonable to expect that an improvement in arterial stiffness by ICS/LABA treatment would reduce the risk of cardiovascular disease in patients with COPD. It is known that patients with COPD exhibit progressive vessel endothelial dysfunction[15]. Endothelium-dependent vasodilation due to systemic stimulation of the endothelial nitric oxide synthesis by inhalation of β_2-adrenergic receptor agonist is considered as the underlying mechanism for improvement in the arterial stiffness[17,28]. In addition, reduction of systemic inflammation, which leads to atherosclerosis, by ICS might also contribute to the improvement in arterial stiffness[17]. Improvement in the lung function parameters would decrease sympathetic nerve activation by improving exertional desaturation, dynamic hyperinflation, and exertional dyspnea. This might be another possible mechanism for the improvement in arterial stiffness by inhaled therapy.

A previous study showed that in patients with COPD with low %DLco/VA, %DLco/VA itself and FEV_1 tend to develop a rapid annual decline[33]. Considering that an acceleration of degradation of the elastic fibers probably leads to the decline in %DLco/VA, it is possible that arterial stiffness deteriorates more rapidly in patients with COPD with low %DLco/VA. In addition, arterial stiffness might deteriorate year-on-year due to the exacerbation of exertional desaturation induced by the decline in %DLco/VA and FEV_1, resulting in an increase in sympathetic nerve activation. From this perspective, while the difference in CAVI between patients with COPD with low %DLco/VA and those with normal %DLco/VA was relatively small in this cross-sectional study (Figures 1, 2), it is possible that the difference in arterial stiffness between the two groups indicated by CAVI might increase with time. Thus, the risk of future cardiovascular disease in patients with COPD with low %DLco/VA

might accordingly increase.

The present study has several limitations. First, the sample size was small. Second, healthy subjects were not included. Third, the method of diagnosing COPD was heterogeneous. Fourth, the severity of pulmonary emphysema on CT image was not scored by multiple pulmonologists for objective assessments. Fifth, we could not evaluate the severity of pulmonary emphysema on CT image by quantifying the LAA%. Although it is relatively easy to measure the Goddard score in the course of routine medical care, this is a semi-quantitative evaluation with inter-individual differences. Hence, it might be inferior to the method of LAA% measurement using the computer software, in terms of quantitative assessment[25,46]. In large-population studies, different methods for measuring the severity of pulmonary emphysema might lead to different results. Finally, since VA was not measured using body plethysmography, the accuracy of VA values might have been underestimated, especially in patients with COPD with severe bullous emphysema, which does not play a role in airflow exchange.

In conclusion, the results in the present study showed that low %DLco/VA is an independent predictor of high CAVI in patients with COPD. Clinicians should recognize patients with COPD with low %DLco/VA as a patient subgroup that is likely to have high CAVI and develop cardiovascular disease in the future. Early medical interventions for this subgroup might slow the progression of arterial stiffness. We believe that the evaluation of %DLco/VA has clinical significance in that it is useful for the early detection of this patient subgroup and improvement in their prognosis.

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Conflict of interest

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