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Close Association between Subclinical Atherosclerosis and Pulmonary Function in Middle-Aged Male Smokers

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Aims: Cigarette smoking provokes deleterious influences on cardiovascular and pulmonary systems, although the underlying relationship has not been sufficiently investigated especially in early-stage disease. The present study investigated possible associations between subclinical atherosclerosis and pulmonary function in middle-aged male smokers.

Methods: Male smokers undergoing their periodic health check-up were enrolled in this study (n=3,775, 45±8 years). Pulmonary function was evaluated using spirometry by calculating forced vital capacity (FVC) as a percentage of predicted value (FVC%-predicted), forced expiratory volume in one second (FEV1) as a percentage of predicted value (FEV1%-predicted), and the ratio of FEV1 to FVC (FEV1/FVC). Subclinical atherosclerosis was assessed based on ankle-brachial pressure index (ABI), cardio-ankle vascular index (CAVI), ultrasound examination of the carotid intima-media thickness (IMT), and presence of plaque.

Results: Multivariate regression analysis showed that ABI was positively associated with FVC%-predicted and FEV1%-predicted after adjustment for confounders including smoking intensity, while CAVI or carotid IMT was inversely associated with both. Participants with chronic obstructive pulmonary disease (COPD, n=256) showed reduced ABI and increased CAVI or carotid IMT compared with those without COPD, and participants with carotid plaque had lower pulmonary function than those without plaque. Reduced FEV1/FVC was an independent determinant of carotid plaque and decreased ABI was an independent determinant of COPD, as revealed by logistic regression analysis with the endpoint of carotid plaque presence or a diagnosis of COPD revealed.

Conclusions: Middle-aged male smokers showed a close association between subclinical atherosclerosis and pulmonary function, implying that smoking induced-vascular and pulmonary damage are interacting in early-stage disease.

Key words: Current smoker, Subclinical atherosclerosis, Pulmonary function, Plaque, COPD

1. Introduction

Smoking is a global problem as the major contributor to mortality in non-communicable diseases[1, 2]. Promoting aging and damaging organ systems, cigarette smoke contains various chemical substances, provoking deleterious effects on the human body[1-6]. In the cardiovascular system, smoking induces vascular

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endothelial damage and accelerates the progression of atherosclerosis[7-12]. With its incidence increasing even in individuals with low levels of smoking or smoking with low-tar tobacco, cardiovascular disease is the leading cause of death in many parts of the world[8-11]. Similarly, smoking causes decreased pulmonary function and thus contributes to various pulmonary diseases[1-6]. Further contributing to increased mortality, smoking-induced impairments in the pulmonary system can worsen airflow obstruction, infectious disease, and the incidence of malignant neoplasm including lung cancer[13-16]. High comorbidity rates have also been reported among smokers, although smoking seems to exert harmful effects separately on cardiovascular and pulmonary systems[17, 18]. On the other hand, patients with pulmonary disease, especially chronic obstructive pulmonary disease (COPD), have increased risks of atherosclerotic cardiovascular disease and heart failure than those without[19-24]. Moreover, reduced pulmonary function itself has been associated with progression of atherosclerosis and cardiovascular disease[25-29]. Thus, there may be a close relationship between early-phase vascular and pulmonary dysfunction.

Only habitual smoking has a consistent association with the presence of atherosclerosis, as revealed by our recent investigation of lifestyle and shift work effects on the accumulation of visceral fat and the presence of atherosclerosis in middle-aged male workers[30]. We hypothesized that vascular damage in smokers without cardiovascular disease has a close association with pulmonary dysfunction. In the present study, vascular damage was evaluated by measuring subclinical atherosclerosis using non-invasive examinations, including ankle-brachial pressure index (ABI) and cardio-ankle vascular index (CAVI) as functional indices and carotid intima-media thickness (IMT) as a morphological index. Showing a simple comparison of blood pressure (BP) in the upper and lower extremity, ABI is a physiological parameter while CAVI shows arterial stiffness which is pathologically characterized by decreased arterial elasticity[31-33]. On the other hand, carotid IMT reflects pathological thickening in the vascular wall[34-36].

2. Aim

The present study thus aimed to investigate possible associations between subclinical atherosclerosis and pulmonary function in middle-aged male smokers at a high risk of early atherosclerosis.

3. Methods

The present study enrolled subjects attending their periodic physical check-up. The study was performed in accordance with the principles of the Declaration of Helsinki, and the ethics committees of the Toyota Memorial Hospital approved the protocol. All data used in the analysis were anonymized and opt-out opportunities were provided for participants.

3.1 Subjects

This study screened 15,764 individuals who visited the Health Support Center WELPO in 2008–2009 for a periodic health check-up. The center provides health care for the Toyota Motor Corporation (Toyota, Japan) employees and spouses, and all employees receive annual medical examinations in accordance with the Industrial Safety and Health Law of Japan, with obtained data supplied as medical examination records. Also performed for current smokers and workers exposed to dust were regular examinations of pulmonary function. Of the total screened, 4,496 individuals also underwent pulmonary function testing. Female subjects were excluded since only 44 individuals were current smokers. Among the remaining 4,452 individuals, 3,775 male smokers who completed the questionnaire about smoking history and intensity were enrolled, with their data used for the final analyses.

After overnight fasting, systolic and diastolic BP was measured using a validated oscillometric technique in a seated position, and participants underwent measurements of body height and weight using an automated BF-220 instrument (Tanita, Tokyo, Japan). Blood samples were taken from the antecubital vein in the morning for laboratory measurements, while ABI, CAVI, and carotid IMT were measured to assess subclinical atherosclerosis. To evaluate peripheral artery disease or arterial stiffness, ABI and CAVI were measured in a supine position, followed by ultrasound examination to measure carotid IMT. Expressed as the Brinkman index (a product of smoking years and number of cigarettes per day), a self-reported questionnaire regarding smoking history, duration, and frequency (number per day) was used to assess smoking intensity. Individuals taking antihypertensive medications or with a systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg were defined as having hypertension[37]. Individuals taking lipid-lowering medications or with high-density lipoprotein cholesterol (HDL-C) levels <40 mg/dL, low-density lipoprotein cholesterol (LDL-C) levels ≥ 140 mg/dL, or triglycerides ≥ 150 mg/dL were defined as having dyslipidemia[38]. Individuals taking blood glucose-lower-

ing medication or presenting a fasting blood glucose (FBG) level ≥ 126 mg/dL were defined as having diabetes[39].

3.2 Biochemical Analysis

Standard laboratory assays were used for performance of biochemical tests including determination of total cholesterol, LDL-C, HDL-C, triglycerides, creatinine, and FBG, as previously described[40]. Concentrations of glycated hemoglobin A1c (HbA1c) were measured by high-performance liquid chromatography and expressed according to the National Glycohemoglobin Standardization Program.

3.3 Assessment of Arterial Stiffness and Ankle-Brachial Pressure Index

Arterial stiffness was assessed by CAVI using a Vasera VS-1000 automatic system (Fukuda Denshi, Tokyo, Japan), as previously described[41] and after resting in the supine position. Electrocardiogram electrodes and a microphone were placed on both wrists and on the sternum to detect heart sounds. Cuffs were wrapped around both upper arms and both ankles. Cardio-ankle pulse wave velocity (PWV) was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the difference between when the time the pulse waves were transmitted to the brachium and when they were transmitted to the ankle, combined with the time difference between the second heart sound on the phonocardiogram and that on the notch of the brachial pulse wave. CAVI is expressed as the stiffness parameter β according to the following equation: $CAVI = a[2\rho/pp \times [\ln Ps/Pd] PWV^2] + b$ (where a, b, constants; ρ, blood density; PP, pulse pressure; Ps, systolic pressure; and Ps, diastolic pressure). The mean CAVI from left and right parts of the body was used for analysis, and, theoretically, BP does not affect the CAVI measurement. Simultaneously, ABI was calculated bilaterally as the ratio of systolic BP in each ankle to systolic BP in the higher BP side of the arm using the apparatus. Among the obtained bilateral ABI values, those of the lower side were adopted for analyses.

3.4 Assessment of Carotid Artery IMT and Plaque Presence

Carotid artery IMT was assessed by ultrasound using the Aplio 500 device (Cannon Medical Systems, Otawara, Japan), as previously described[40]. All estimations of carotid IMT and plaque were performed by well-trained clinical laboratory technicians who were blinded to other clinical information. Common carotid artery (CCA) IMT and presence of plaque were evaluated manually using a 7.5MHz frequency probe, with all participants in the supine position. CCA IMT was measured in the far wall at ~20 mm from the carotid bifurcation using recorded images of the carotid artery, with the mean IMT from both sides used for analysis[34, 35]. Carotid plaque, a representative of subclinical atherosclerosis, was identified as elevated lesions with a maximal thickness ≥ 1.1 mm, and having a point of inflection on the surface of the intima-media complex in the CCA, carotid bulb, and internal carotid artery.

3.5 Assessment of Pulmonary Function

Pulmonary function was assessed by standard spirometric techniques using the Spiro Shift SP-770 COPD device (Fukuda denshi, Tokyo, Japan). Spirometry measured forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), with the obtained data evaluated by calculating FVC as a percentage of predicted value (FVC%-predicted), FEV1 as a percentage of predicted value (FEV1%-predicted), and the ratio of FEV1 to FVC (FEV1/FVC). In terms of pulmonary disease, participants showing a FEV1/FVC of less than 70% were diagnosed as having COPD, which, according to the definition of Global Initiative for Chronic Obstructive Lung Disease (GOLD), is representative of common pulmonary disease[42].

3.6 Statistical Analysis

Data were analyzed using SPSS Statistics 19 (IBM Corp., Chicago, IL, USA). Data with a normal distribution are expressed as mean ± standard deviation. Univariate and multivariate regression analyses were performed as appropriate. Comparisons of the categorical variables were analyzed by Chi-square tests. Logistic regression analyses were also performed to determine the independent variables. Receiver operating characteristics (ROC) curve analysis was performed to determine the cut-off level, area under the curve (AUC) with 95% confidence interval (CI), sensitivity, and specificity. A two-tailed $p < 0.05$ value was considered significant.

4. Results

A total of 3,775 male smokers aged 35 to 59 years were enrolled in the study (**Table 1**). The number of participants (percentage of total) with hypertension, dyslipidemia, and diabetes mellitus was 856 (22.7%), 1,907 (50.5%), and 318 (8.4%), respectively, with 256 participants (6.8% of total) fulfilling the definition of COPD. Obtained parameters in the examination of atherosclerosis (ABI, CAVI, and carotid IMT) and pulmonary functions (FVC%-pre-

Table 1. Subject characteristics

Variable	Total subjects (n = 3,775)	Subjects without COPD (n = 3,519)	Subjects with COPD (n = 256)	p value
Age (years)	45.2 ± 7.5	44.9 ± 7.4	50.3 ± 7.2	< 0.0001
Body mass index (kg/m^2)	23.3 ± 3.3	23.3 ± 3.3	22.4 ± 3.1	< 0.0001
Systolic BP (mmHg)	120 ± 15	119 ± 15	122 ± 5	< 0.05
Diastolic BP (mmHg)	76 ± 10	76 ± 10	77 ± 9	0.375
Creatinine (mg/dL)	0.79 ± 0.12	0.79 ± 0.12	0.78 ± 0.11	0.067
HDL-C (mg/dL)	56.1 ± 14.7	56.1 ± 14.6	57.3 ± 14.7	0.167
LDL-C (mg/dL)	121.6 ± 31.5	121.9 ± 31.6	117.6 ± 29.7	< 0.05
Triglyceride (mg/dL)	139.4 ± 101.1	139.0 ± 99.9	145.4 ± 115.9	0.330
FBG (mg/dL)	96.3 ± 17.3	96.2 ± 17.3	97.7 ± 17.2	0.184
HbA1c (%)	5.75 ± 0.61	5.74 ± 0.62	5.80 ± 0.54	0.133
Indices of smoking intensity				
Smoking duration (years)	25.0 ± 7.4	24.7 ± 7.3	29.4 ± 7.0	< 0.0001
Number of cigarettes smoked per day	18.3 ± 9.2	18.2 ± 9.1	19.8 ± 9.9	< 0.01
Brinkman index	466 ± 282	457 ± 277	586 ± 329	< 0.0001
Parameters of pulmonary function				
FVC%-predicted (%)	108.0 ± 13.9	107.8 ± 13.7	109.9 ± 16.6	< 0.05
FEV1%-predicted (%)	87.9 ± 11.2	88.9 ± 10.5	74.0 ± 12.2	< 0.0001
FEV1/FVC (%)	79.7 ± 6.7	80.8 ± 5.3	64.7 ± 4.8	< 0.0001
Examination of atherosclerosis				
ABI	1.11 ± 0.07	1.11 ± 0.07	1.10 ± 0.07	< 0.01
CAVI	7.42 ± 0.79	7.40 ± 0.78	7.72 ± 0.83	< 0.0001
Carotid IMT (mm)	0.565 ± 0.113	0.563 ± 0.112	0.600 ± 0.117	< 0.0001
Complication and past history				
Hypertension, n (%)	856 (22.7)	782 (22.2)	74 (28.9)	< 0.05
Dyslipidemia, n (%)	1907 (50.5)	1769 (50.3)	138 (53.9)	0.261
Diabetes mellitus, n (%)	318 (8.4)	294 (8.4)	24 (9.4)	0.571
Obesity, n (%)	956 (25.6)	919 (26.1)	46 (18.0)	< 0.0001

Data are presented as the mean ± standard deviation or as n (%).
BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; FVC, forced vital capacity; FVC%-predicted, FVC as a percentage of predicted value; FEV1, forced expiratory volume in 1 second; FEV1%-predicted, FEV1 as a percentage of predicted value; ABI, ankle-brachial pressure index; CAVI, cardio-ankle vascular index; IMT, intima-media thickness; COPD, chronic obstructive pulmonary disease.
Percent predicted values were 100 × observed/predicted values.
Obesity was diagnosed by body mass index ≥ 25 kg/m^2.

dicted, FEV1%-predicted, and FEV1/FVC) showed nearly normal distributions with the median value of 1.11, 7.35, 0.550 mm, 107.6%, 88.2%, and 80.2%, respectively **(Supplementary Fig. 1)**. Participants with COPD also had decreased ABI and increased CAVI or carotid IMT compared with those without. The mean values of smoking duration, number of cigarettes smoked per day, and Brinkman index were 25 years, 18.3/day, and 466, respectively, with all values showing significant inverse correlations with each index of pulmonary function **(Table 2)**. Univariate and multivariate regression analyses showed that ABI was positively associated with FVC%-predicted and FEV1%-predicted after adjustment for potential confounders including the Brinkman index for smoking intensity; in contrast, CAVI and mean carotid IMT were inversely associated with FVC%-predicted and FEV1%-predicted **(Tables 2 and 3)**.

Among the enrolled total participants, 713 participants (18.9% of total) had carotid plaque. Participants with carotid plaque had reduced pulmonary function and showed decreased ABI and increased CAVI or carotid IMT compared to those without **(Fig. 1)**. That the reduced FEV1/FVC was an independent determinant of carotid plaque after adjustment for potential confounders including the Brinkman index **(Table 4)** was revealed by logistic regression analysis with the endpoint of carotid plaque. On the other hand, logistic regression analysis with the endpoint of COPD diagnosis revealed that decreased

Table 2. Univariate regression analysis of factors possibly associated with indices of pulmonary function in total subjects (n=3,775)

Variable	FVC%-predicted		FEV1%-predicted		FEV1/FVC	
	Coefficient (r)	p value	Coefficient (r)	p value	Coefficient (r)	p value
Indices of smoking intensity						
Smoking duration (years)	-0.073	<0.0001	-0.103	<0.0001	-0.261	<0.0001
Number of cigarettes smoked per day	-0.072	<0.0001	-0.096	<0.0001	-0.061	<0.001
Brinkman index	-0.099	<0.0001	-0.137	<0.0001	-0.179	<0.0001
Examination of atherosclerosis						
ABI	0.057	<0.001	0.059	<0.001	0.011	0.505
CAVI	-0.080	<0.0001	-0.098	<0.0001	-0.146	<0.0001
Carotid IMT (mm)	-0.099	<0.001	-0.121	<0.01	-0.137	<0.0001

FVC, forced vital capacity; FVC%-predicted, FVC as a percentage of predicted value; FEV1, forced expiratory volume in 1 second; FEV1%-predicted, FEV1 as a percentage of predicted value; ABI, ankle-brachial pressure index; CAVI, cardio-ankle vascular index; IMT, intima-media thickness.
Percent predicted values were 100 × observed/predicted values.

Table 3. Multivariate regression analysis of relationships between atherosclerosis and pulmonary function in total subjects (=3,775)

Variable	FVC%-predicted		FEV1%-predicted		FEV1/FVC	
	Coefficient (β)	p value	Coefficient (β)	p value	Coefficient (β)	p value
ABI						
Unadjusted	0.057	<0.001	0.059	<0.001	0.011	0.505
Adjusted Model 1	0.071	<0.0001	0.069	<0.0001	0.012	0.426
Adjusted Model 2	0.066	<0.0001	0.064	<0.0001	0.012	0.434
Adjusted Model 3	0.066	<0.0001	0.063	<0.0001	0.012	0.457
CAVI						
Unadjusted	-0.080	<0.0001	-0.096	<0.0001	-0.146	<0.0001
Adjusted Model 1	-0.087	<0.0001	-0.081	<0.0001	0.029	0.114
Adjusted Model 2	-0.071	<0.001	-0.065	<0.01	0.029	0.130
Adjusted Model 3	-0.071	<0.001	-0.065	<0.001	0.029	0.131
Carotid IMT (mm)						
Unadjusted	-0.099	<0.0001	-0.121	<0.0001	-0.137	<0.0001
Adjusted Model 1	-0.059	<0.01	-0.081	<0.0001	-0.022	0.203
Adjusted Model 2	-0.053	<0.01	-0.079	<0.0001	-0.027	0.121
Adjusted Model 3	-0.052	<0.01	-0.077	<0.0001	-0.026	0.136

FVC, forced vital capacity; FVC%-predicted, FVC as a percentage of predicted value; FEV1, forced expiratory volume in 1 second; FEV1%-predicted, FEV1 as a percentage of predicted value; ABI, ankle-brachial pressure index; CAVI, cardio-ankle vascular index; IMT, intima-media thickness.
Percent predicted values were 100 × observed/predicted values.
Adjusted Model 1 was adjusted for age and body mass index.
Adjusted Model 2 was further adjusted for systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, and creatinine.
Adjusted Model 3 was further adjusted for the Brinkman index.

ABI was an independent determinant of COPD **(Table 5)**.

Finally, the effects of coincident COPD and carotid plaque were investigated, with 76 of the 3,775 enrolled participants receiving a combined diagnosis. ROC curve analysis performed to discriminate those participants using ABI, CAVI, and carotid IMT indicated cut-off levels of 1.09 (AUC 0.599, 95% CI 0.583-0.615, p<0.01), 7.70 (AUC 0.747, 95% CI 0.732-0.760, p<0.0001), and 0.55 mm (AUC 0.740, 95% CI 0.725-0.754, p<0.0001), respectively, in middle-aged smokers **(Fig. 2)**. To evaluate the impacts of smoking intensity on the coincidence of COPD and carotid plaque, the other ROC curve analyses were performed using Brinkman index, CAVI, and carotid IMT. The AUC values of Brinkman index and

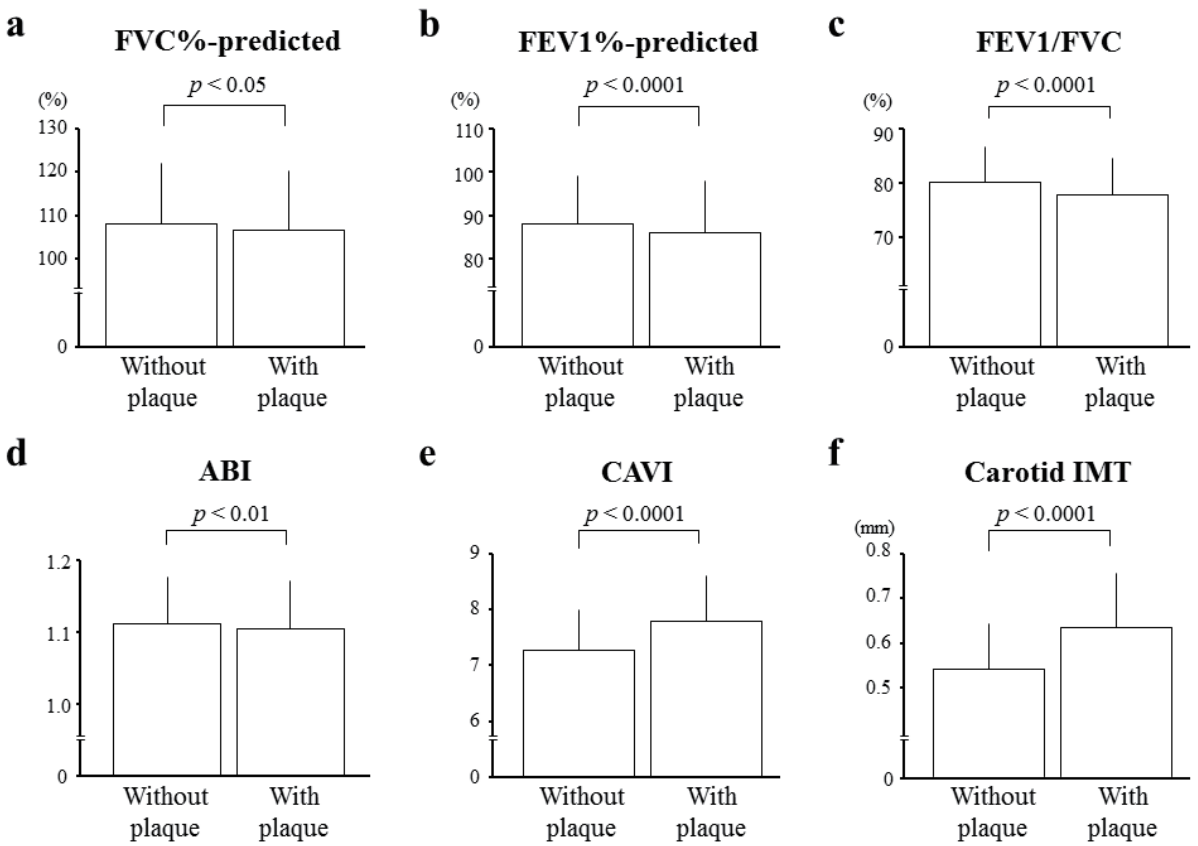

Fig. 1.

Impacts of carotid plaque on: a) forced vital capacity (FVC) as a percentage of predicted value (FVC%-predicted); b) forced expiratory volume in 1 second (FEV1) as a percentage of predicted value (FEV1%-predicted); c) the ratio of FEV1 to FVC (FEV1/FVC); d) ankle-brachial pressure index (ABI); e) cardio-ankle vascular index (CAVI); and f) carotid intima-media thickness (IMT).

Brinkman index with CAVI or carotid IMT were 0.695 (95% CI 0.638-0.752, $p<0.0001$), 0.772 (95% CI 0.720-0.824, $p<0.0001$), or 0.774 (95% CI 0.726-0.821, $p<0.0001$), respectively **(Fig. 3)**.

5. Discussion

The main findings of the present study are that: (i) participants with COPD showed lower ABI and higher CAVI or carotid IMT than those without COPD, while participants with carotid plaque had reduced pulmonary function compared to those without; and (ii) ABI was positively associated with FVC%-predicted and FEV1%-predicted after adjustment for confounders including smoking intensity, while CAVI or mean carotid IMT was inversely associated; and (iii) reduced FEV1/FVC was an independent determinant of carotid plaque and decreased ABI was an independent determinant of COPD. Overall, although these relationships were not uniform among the parameters of vascular and respiratory functions, a close association was confirmed between subclinical atherosclerosis and pulmonary function in middle-aged smokers. These findings indicate that smoking-induced vascular and pulmonary dysfunctions might affect each other in early-stage disease.

In general, ABI, CAVI, and carotid IMT measurements are performed to examine peripheral artery disease, arterial stiffness, and progression of atherosclerosis[31, 32, 34, 35]. In the present study, we assessed subclinical atherosclerosis using ABI and CAVI as indices of vascular function, and carotid IMT and plaque as indices of morphological atherosclerosis. A combination of examinations increases accuracy of the diagnostic value and a non-invasive nature of examination is quite important and useful in such an epidemiologic study, although each measurement used in the present study is not a perfect one to evaluate atherosclerosis. We here analyzed associations between the parameters of subclinical atherosclerosis and pulmonary function and investigated the relationships of these parameters based on presence of COPD indicating common pul-

Table 4. Logistic regression analysis investigating possible association of pulmonary function with the presence of carotid plaque in total subjects (n=3,775)

Variable	Carotid plaque presence (n=713)		
	Odds ratio	95% confidence interval	p value
FVC%-predicted (%)			
Unadjusted	0.992	0.987 – 0.998	<0.05
Adjusted Model 1	0.999	0.992 – 1.005	0.651
Adjusted Model 2	1.001	0.995 – 1.008	0.677
Adjusted Model 3	1.002	0.996 – 1.009	0.519
FEV1%-predicted (%)			
Unadjusted	0.985	0.978 – 0.992	<0.0001
Adjusted Model 1	0.993	0.986 – 1.001	0.087
Adjusted Model 2	0.996	0.988 – 1.004	0.277
Adjusted Model 3	0.997	0.989 – 1.005	0.401
FEV1/FVC (%)			
Unadjusted	0.951	0.940 – 0.963	<0.0001
Adjusted Model 1	0.986	0.973 – 0.999	<0.05
Adjusted Model 2	0.984	0.970 – 0.997	<0.05
Adjusted Model 3	0.985	0.972 – 0.999	<0.05

FVC, forced vital capacity; FVC%-predicted, FVC as a percentage of predicted value; FEV1, forced expiratory volume in 1 second; FEV1%-predicted, FEV1 as a percentage of predicted value.
Percent predicted values were 100 × observed/predicted values.
Analysis endpoint was presence of plaque, identified as elevated lesions with a maximum thickness ≥ 1.1 mm and point of inflection on the surface of the intima-media complex.
Adjusted Model 1 was adjusted for age and body mass index.
Adjusted Model 2 was further adjusted for systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, and creatinine.
Adjusted Model 3 was further adjusted for the Brinkman index.

Table 5. Logistic regression analysis of the association between atherosclerosis examination and the presence of chronic obstructive pulmonary disease in total subjects (n=3,775)

Variable	Diagnosis of COPD (n=256)		
	Odds ratio	95% confidence interval	p value
ABI (per 0.01)			
Unadjusted	0.974	0.956 – 0.993	<0.01
Adjusted Model 1	0.977	0.958 – 0.997	<0.05
Adjusted Model 2	0.978	0.958 – 0.998	<0.05
Adjusted Model 3	0.978	0.959 – 0.998	<0.05
CAVI (per 1.0)			
Unadjusted	1.617	1.391 – 1.879	<0.0001
Adjusted Model 1	0.976	0.812 – 1.172	0.791
Adjusted Model 2	0.930	0.767 – 1.128	0.460
Adjusted Model 3	0.926	0.763 – 1.125	0.439
Carotid IMT (per 0.1 mm)			
Unadjusted	1.304	1.178 – 1.444	<0.0001
Adjusted Model 1	1.070	0.951 – 1.204	0.259
Adjusted Model 2	2.120	0.638 – 7.038	0.224
Adjusted Model 3	2.104	0.763 – 7.019	0.226

COPD, chronic obstructive pulmonary disease; ABI, ankle-brachial pressure index; CAVI, cardio-ankle vascular index; IMT, intima-media thickness.
Endpoint of analysis was diagnosis of COPD, which was diagnosed by forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) less than 0.7.
Adjusted Model 1 was adjusted for age and body mass index.
Adjusted Model 2 was further adjusted for systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, and creatinine.
Adjusted Model 3 was further adjusted for the Brinkman index.

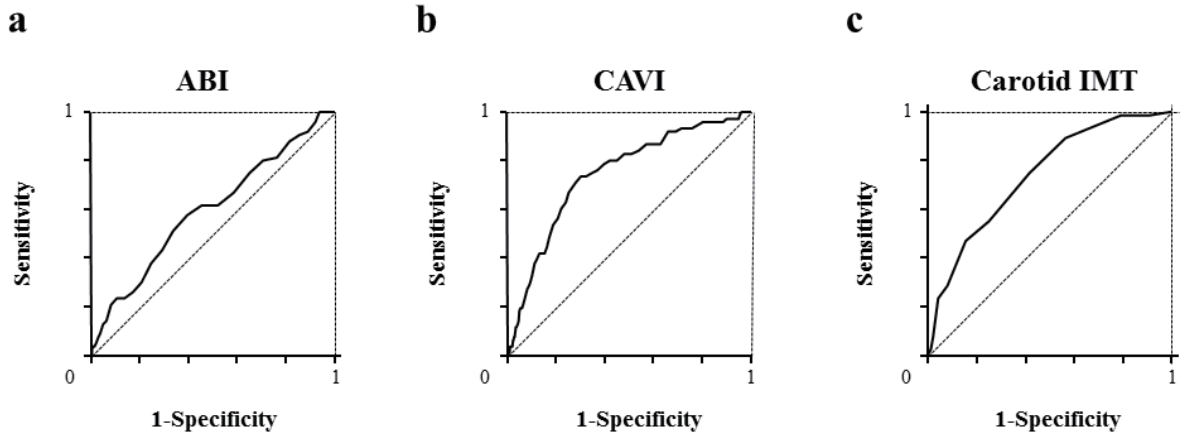

Fig. 2. Receiver operating characteristics curve analyses to determine the cut-off levels in atherosclerosis examinations for the presence of both chronic obstructive pulmonary disease (COPD) and carotid plaque in middle-aged smokers

a. The cut-off level, sensitivity, and specificity of ankle-brachial pressure index (ABI) for the presence of both COPD and carotid plaque were 1.09 (area under the curve: AUC 0.599, 95% confidence interval: CI 0.583-0.615, $p<0.01$), 0.579 (95% CI 0.460-0.691), and 0.604 (95% CI 0.588-0.620), respectively.
b. The cut-off level, sensitivity, and specificity of cardio-ankle vascular index (CAVI) for the presence of both COPD and carotid plaque were 7.70 (AUC 0.747, 95% CI 0.732-0.760, $p<0.0001$), 0.737 (95% CI 0.623-0.831), and 0.700 (95% CI 0.685-0.715), respectively.
c. The cut-off level, sensitivity, and specificity of carotid intima-media thickness (IMT) for the presence of both COPD and carotid plaque were 0.55 mm (AUC 0.740, 95% CI 0.725-0.754, $p<0.0001$), 0.750 (95% CI 0.637-0.842), and 0.582 (95% CI 0.566-0.598), respectively.

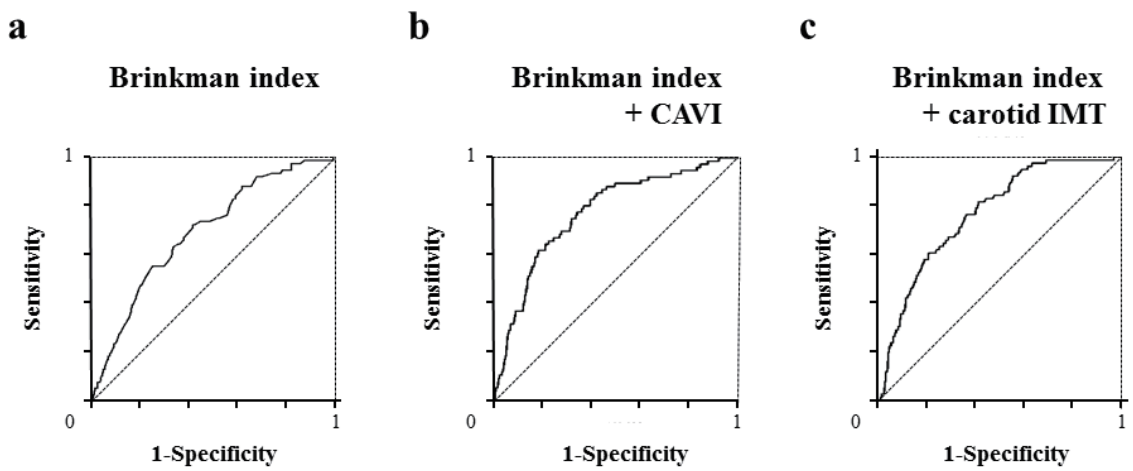

Fig. 3. Receiver operating characteristics curve analyses to evaluate the diagnostic impacts of smoking intensity on the presence of both chronic obstructive pulmonary disease (COPD) and carotid plaque in middle-aged smokers

a. The area under the curves (AUC) value of Brinkman index for the presence of both COPD and carotid plaque were 0.695 (95% confidence interval: CI 0.638-0.752, $p<0.0001$).
b. The AUC value of cardio-ankle vascular index (CAVI) with Brinkman index for the presence of both COPD and carotid plaque were 0.772 (95% CI 0.720-0.824, $p<0.0001$).
c. The AUC value of carotid intima-media thickness (IMT) with Brinkman index for the presence of both COPD and carotid plaque were 0.774 (95% CI 0.726-0.821, $p<0.0001$).

monary disease, and the presence of carotid plaque representing subclinical atherosclerosis. COPD is a pulmonary disease showing airflow limitation, and the main cause of COPD is cigarette smoking[22-24]. As previously reported, participants with COPD had lower ABI, higher CAVI, and increased carotid IMT than those without COPD, showing the possibly lower prevalence of COPD compared to participants in the previous reports, and possibly reflecting the narrow and relatively young age range of 35-59 years for participants enrolled in this study[42, 43]. The present study showed that low-ABI alone was an independent

determinant of COPD by logistic regression analysis and that only reduced FEV1/FVC was an independent determinant of carotid plaque, although previous studies significantly associated increased PWV and IMT with airflow limitation[18, 44, 45]. The prevalence of COPD, age distribution, and sample size may be backgrounds that discrepancies can be attributed to. Indeed, smokers in the present study were younger and numbered about twice as many as those in the previous study[42-45]. In addition, the ABI value shown in the present study ranged from 0.90 to 1.34 within the normal reference range, despite an ABI value of < 0.9 indicating peripheral artery stenosis in the lower extremities and a value of >1.4 implying peripheral artery disease with advanced calcification[32]. On the other hand, when the factors were analyzed as continuous variables, CAVI and carotid IMT were inversely associated with FVC%-predicted and FEV1%-predicted by multivariate regression analysis, compared to ABI being positively associated. Interestingly, where this could indicate that strong associations between parameters of vascular and pulmonary function are initiated in early-stage atherosclerosis among relatively young participants prior to the diagnosis of COPD, these results are consistent with a previous report investigating older participants by multivariate regression analysis[27].

Although detailed mechanisms underlying such pathways have not been clarified, common pathways involved in the impairment of vascular and pulmonary function might exist. Among the possibilities, systemic inflammation and oxidative stress are frequently reported as common components underlying the onset of cardiovascular disease and pulmonary disease[13, 14, 46-50]. We also previously reported that oxidative stress or inflammation was associated with vascular damage and arterial stiffness[51-53]. The harmful influences of smoking appear to occur similarly in cases of low-dose or low-intensity smoking[7-9], with smoking being one of the strongest origins of oxidative stress and inflammatory substances causing vascular and pulmonary damage[7, 8, 18, 23]. Indeed, all participants enrolled in the present study were current smokers. A decrease of elasticity in both arterial walls and pulmonary parenchymal tissues is another possible pathway for the impaired vascular and pulmonary function, as previously reported by Duprez *et al.*[54], although these authors also considered the underlying mechanism of decreased elasticity as inflammatory outcomes or physiological changes for aging. Thus, the vascular and pulmonary impairment might also simultaneously arise.

The dual complications of concurrent COPD and carotid plaque were observed in only 2.0% of total subjects, while the prevalence of COPD in participants with carotid plaque was 10.7% and the presence of carotid plaque in participants with COPD was 29.7%. These latter proportions were greater than those observed in total participants, suggesting that COPD and atherosclerosis are, at least partially, based on similar pathophysiology. The AUC value for CAVI showed the greatest value (0.747) among the measured indices followed by that for carotid IMT (0.740). On the other hand, the AUC value of ABI was lower than that of CAVI or carotid IMT. Detailed mechanisms are not clear, but the results might have been influenced by the narrow distribution of the ABI value (from 0.90 to 1.34) and the small difference of ABI values between participants with a combination of COPD and carotid plaque and others (1.11 vs 1.08) . The obtained cut-off levels were also of slightly higher value than the normal limit, implying that subclinical atherosclerosis and destruction of pulmonary tissue might silently progress in smokers. Adding the Brinkman index to evaluate the impact of smoking intensity on the combined diagnosis of COPD and carotid plaque showed a slight increase of AUC values. These findings support the concept that smokers should be followed up carefully and recommended to give up smoking even if still relatively young with only early-stage atherosclerosis. Discriminating participants with a combination of COPD and carotid plaque by simple examination using CAVI would be clinically meaningful, since pulmonary function testing is not routine for asymptomatic participants. Although the results were based on data obtained from older participants with hypertension, the importance of CAVI for detecting reduced pulmonary function was also reported previously[55]. In addition, the present study enrolled relatively younger individuals, who might have early atherosclerosis, but included only 22.7% hypertensives. Thus, despite the obtained results being similar, the characteristics of the enrolled participants were quite different, reinforcing the usefulness of CAVI for detecting both COPD and carotid plaque.

The findings of the present study should be interpreted with caution as the study has several limitations. Firstly, the study was a cross-sectional study of participants with a heterogeneous background. Secondly, ex-smokers or non-smokers were not investigated, with the results limited to current smokers only. Thirdly, the causal relationship underlying any identified associations was not investigated in this study. Finally, parameters reflecting oxidative stress or inflammation were not evaluated. Further investigations with a longitudinal design including past smokers and non-smokers are therefore necessary for definite conclusions to be drawn.

6. Conclusions

In conclusion, the findings of this study revealed a close association between subclinical atherosclerosis and pulmonary function in middle-aged male smokers at risk of early atherosclerosis. These findings imply that smoking-related vascular and pulmonary dysfunctions are interacting with each other in early-stage disease, and that measuring CAVI in this participant group might be useful for early detection of both carotid plaque and COPD.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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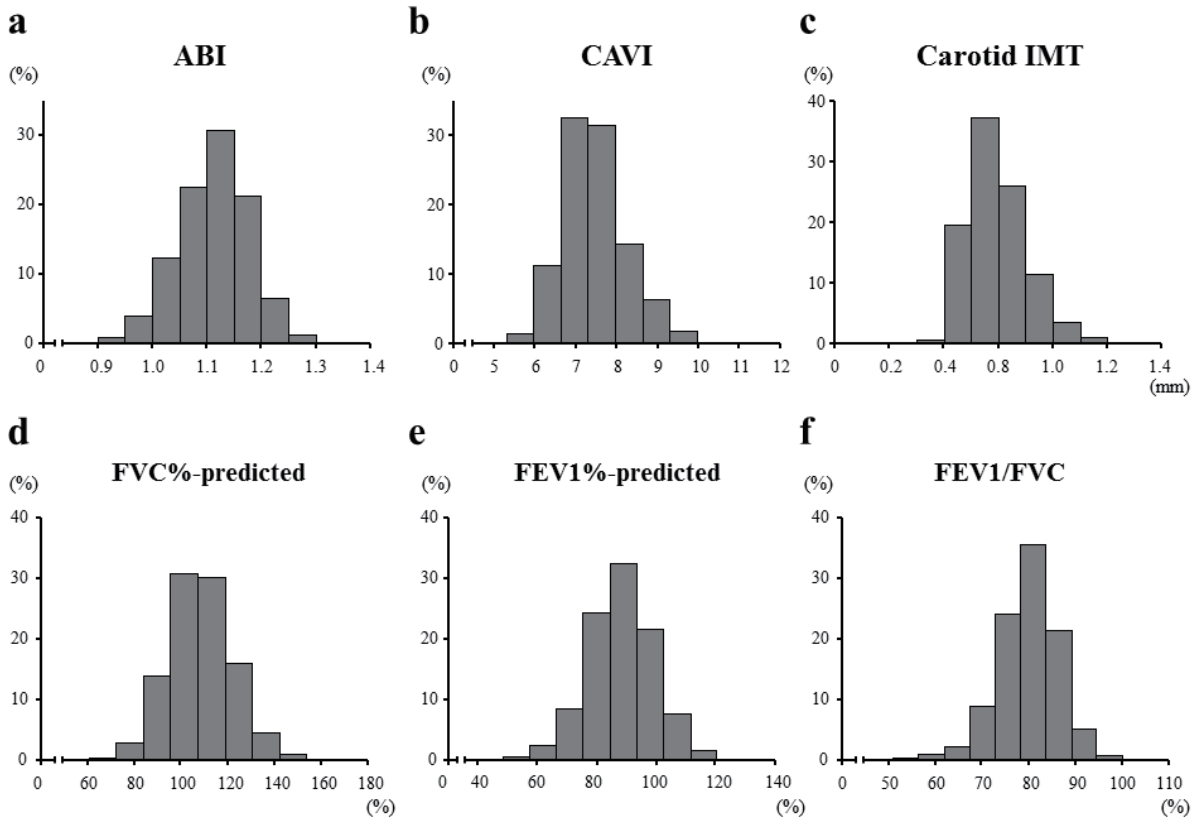

Supplemental Fig.1

Distribution of a) ankle-brachial pressure index (ABI), b) cardio-ankle vascular index (CAVI), c) carotid intima-media thickness (IMT), d) forced vital capacity (FVC) as a percentage of predicted value (FVC%-predicted), e) forced expiratory volume in 1 second (FEV1) as a percentage of predicted value (FEV1%-predicted), f) the ratio of FEV1 to FVC (FEV1/FVC).