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Mild to Moderate Airflow Obstruction is Closely Associated With the Elevation of Serum Creatinine Levels

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is associated with higher incidence of coronary artery disease (CAD). Nonetheless, COPD and CAD involve overlapping risk factors; therefore, evidence for direct relationship between COPD and CAD is still lacking.

Objectives: 214 patients who underwent respiratory function testing and a computed tomography scan of coronary arteries.

Methods: A retrospective study of the association between COPD and cardiovascular risk factors.

Results: Subjects included 58 patients with COPD and 156 patients without COPD. All COPD patients analyzed had mild to moderate COPD; 38 had Global Initiative for Obstructive Lung Disease (GOLD) Grade I COPD, and 20 had GOLD Grade II COPD. Intergroup comparison of patients with COPD and those without COPD revealed no significant differences in coronary arteriosclerosis by a computed tomography, but serum creatinine levels were significantly elevated in patients with COPD ($p = 0.02$). Independent variables were selected for multivariate analysis using forward selection based on the likelihood ratio test. This analysis indicated that an elevated serum creatinine level was the most important factor that determine an obstructive defect ($p = 0.046$). There was a significant correlation between a decrease in the log-transformed predicted FEV1 and an elevated serum creatinine level ($r = -0.186$, $p = 0.006$).

Conclusion: Mild to moderate airflow obstruction was significantly correlated with elevated serum creatinine levels and could thus be associated with future cardiovascular events.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lungs that is primarily caused by inhalation of and exposure to harmful substances, the most prominent of which is cigarette smoke (1). A respiratory function test will indicate airflow obstruction that does not return to normal. Airflow obstruction is progressive and occurs as a result of the combined interaction of a small-airway disease and parenchymal destruction at varying levels (2). COPD is a leading cause of death and is thought to be associated with arteriosclerosis and its related disorders, such as coronary artery disease (CAD)(3, 4) . There are various hypotheses regarding pathogenesis of COPD and CAD. Patients with COPD are believed to have a 2- to 3-fold higher incidence of cardiovascular events (5), and comorbidity with CAD is a determinant of the prognosis of COPD (6). The presence of an airflow obstruction is reported to be a prognostic factor for CAD, with the same magnitude as serum cholesterol levels, hypertension, and chronic kidney disease (CKD) (7). Recent studies have also reported high prevalence of COPD in CAD (8-11).

CAD and COPD all involve overlapping risk factors, such as smoking. One hypothesis is that smoking triggers an inflammatory response, common to both arteriosclerosis and COPD, in the form of cytokines such as interleukin 6 (IL-6) and IL-8 (5, 6).However, evidence for direct relationship between COPD and CAD is lacking. A computed tomography (CT) scan of the coronary arteries is a minimally invasive and highly precise method for detection of coronary artery arteriosclerosis (12) and calcification, a prognostic factor for cardiovascular disease (13, 14). Thus, individuals who had undergone a coronary artery CT scan and a respiratory function test at approximately the same time served as subjects for the present study. This study tested whether COPD will correlate with findings of the coronary artery CT scan and existing cardiovascular risk factors.

METHODS

Design

This was a retrospective study at a single institution. Subjects were patients who had undergone both a coronary artery CT scan and a respiratory function test within 2 months (between the tests) at the Cardiovascular Medicine Department of Kyoto Medical Center from January 1, 2010 to August 31, 2013. An exclusion criterion was comorbidity (besides COPD) that caused respiratory dysfunction such as interstitial pneumonia. Patients with a current and past experience of acute exacerbation of COPD were also excluded. If a patient was tested multiple times during the period studied, only the initial assessment was analyzed. The subjects were distributed into 2 groups: patients who fulfilled the diagnostic criteria for airflow obstruction in COPD and patients who did not fulfill those criteria. These 2 groups were compared in terms of the risk of coronary artery disease. This study was approved by the Ethics Committee of Kyoto Medical Center.

Data collection

Information on the patient's history of smoking (number of cigarettes smoked per day, years smoking, and years not smoking) or a lack thereof was obtained via an interview during an outpatient visit. The patient's height and weight were measured and blood pressure was measured in a resting seated position. Information on medication taken (antihypertensive drugs, hypolipidemic agents, hypoglycemic agents, anticholinergics, long-acting β_2 agonists, and inhaled corticosteroids) was also obtained. A blood sample was taken from the forearm prior to the coronary artery CT scan. The blood samples were tested for hemoglobin A1c (HbA1c; %) levels, and serum from the samples was tested for triglyceride (TG; mg/dL), high-density lipoprotein cholesterol (HDL-C; mg/dL), creatinine (Cre; mg/dL), and C-reactive protein (CRP; mg/L) levels.

Spirometry

A CHESTAC-800 spirometer from Chest was used. A forced expiratory volume in 1 second (FEV1) divided by forced vital capacity (FVC) <70% (FEV1/FVC < 70%) was considered to indicate the presence of an airflow obstruction. The predicted FEV1 (%) was calculated on the basis of age, sex, and height.

Coronary artery CT

A 256-slice Brilliance iCT scanner (128 detector rows) was used. After taking a β-blocker, patients received iopamidol 370 mgI/mL as a contrast agent. The patients were injected with 32-50 mL of the contrast agent at a rate of 3.2–5.0 mL/s (potentially varying depending on weight) followed by a normal saline flush to achieve contrast enhancement. Each scan was assessed using curved multiplanar reformation images by an experienced cardiovascular internist at our institution. The coronary artery calcification score (CAC score) was calculated using the Agatston score, and the extent of stenosis was assessed on the basis of the Society of Cardiovascular Computed Tomography (SCCT) guidelines (15). Patients with Grade 4–5 (70% or greater) stenosis were deemed to have coronary artery disease.

Cardio-ankle vascular index (CAVI)

A Va Sera VS-1500 vascular screening system from Fukuda Denshi was used (16, 17). The average CAVI of 2 legs served as the final CAVI.

Statistical analysis

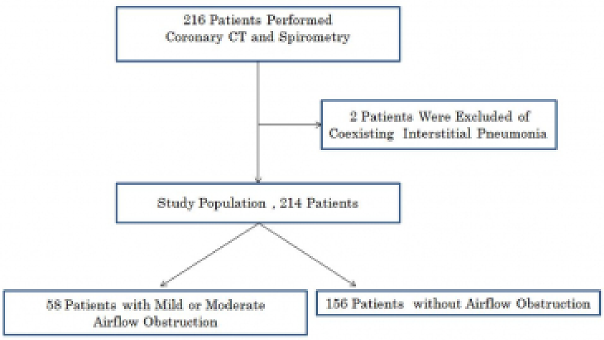
SPSS software, version 14 (SPSS Inc., Chicago, IL) was used. Continuous variables were expressed as mean ± standard deviation (SD), and category data were expressed as the number and percentage of patients in each category. For intergroup comparison, an unpaired t test was used for continuous variables with normal distribution, and Mann–Whitney's U test was used for continuous variables without normal distribution. For variables measured on a nominal scale, either a χ^2 test or Fisher's exact probability test was used. The presence or absence of an airflow obstruction served as a variable criterion in statistical analysis. Univariate and multivariate analyses were performed using logistic regression. We determined odds ratios adjusted for the effects of multiple explanatory variables on the presence of airflow obstruction along with p values and a 95% confidence interval. Forward selection based on the likelihood ratio was used to select independent variables (adjusted for sex) for the multivariate logistic regression analysis. A correlation between 2 continuous variables was assessed by calculating Pearson's correlation coefficient. In all tests, a two-tailed $p < 0.05$ was assumed to indicate statistical significance.

RESULTS

Of the 216 patients who underwent a coronary artery CT scan and a respiratory function test at approximately the same time, 2 had interstitial lung disease that was apparent on images. These patients were excluded from analysis; thus, ultimately there were 214 subjects (Fig. 1). The mean age of these 214 patients was 70.3 ± 9.0 years, and 131 of the patients were male (61.2%). Patients included 75 never-smokers (35.0%), 83 ex-smokers (38.8%), and 53 current smokers (24.8%). The reason for undergoing the coronary artery CT scan was to screen for coronary artery disease in 144 patients with cardiovascular risk factors (67.3%) because subjective symptoms and electrocardiogram abnormalities were noted in 70 (32.7%) and 4 patients (1.9%), respectively.

Figure 1

A Flow Diagram of the Study Population



Results of intergroup comparison regarding the presence or absence of an obstructive defect are shown in Table 1. Fifty-eight patients (27.1%) were found to have an obstructive defect according to a respiratory function test, whereas 156 (72.9%) were found to have no obstructive defects. Of the patients found to have an obstructive defect, 38 (65.5%) had Global Initiative for Obstructive Lung Disease (GOLD Grade I (FEV1 ≥80% predicted) COPD, 20 (34.5%) had GOLD Grade II (FEV1 ≤50%–<80% predicted) COPD, and none (0%) had GOLD Grade 3 or 4 (FEV1 <50% predicted) COPD. Of the patients who had an airflow obstruction, 24.6% were never-smokers. This proportion is in line with the findings of the Burden of Obstructive Lung Disease (BOLD) study, which reported that 23.3% of patients with moderate COPD are never-smokers (18). Among the patients with airflow obstruction, never-smokers were significantly older than ex-smokers/current smokers (78.6 ± 6.9 vs. 71.9 ± 6.8, $p = 0.002$). Intergroup comparison regarding the presence or absence of an obstructive defect revealed no significant differences in terms of coronary artery disease, the total CAC score, CAVI, serum cholesterol, or the blood HbA1c levels. Nonetheless, patients with an obstructive defect were significantly older ($p = 0.003$), were more likely to be males ($p = 0.003$), had low BMI ($p < 0.001$), and had significantly elevated serum creatinine levels ($p = 0.004$).

Table 1

Patients Characteristics

	FEV_1 / FVC < 70 (n = 58)	FEV_1 / FVC >= 70 (n = 156)	*P - value*
Sex , % male	78	55	0.003 [1]
Age , years	74 ± 8	70 ± 9	0.003 [2]
Smoking			0.100 *
Never , %	25	40	
Ex , %	49	36	
Current , %	26	25	
BMI , kg / m^2	23.3 ± 2.7	25.4 ± 4.0	<0.001 †
Pack-years	42.0 ± 36.4	30.1 ± 25.0	<0.001
SBP , mmHg	134 ± 16	131 ± 18	0.4 †
DBP , mmHg	74 ± 12	74 ± 12	0.9 †
HbA1c , %	6.1 ± 1.0	6.2 ± 0.9	0.07 [3]
LDL-C , mg / dl	102 ± 26	108 ± 30	0.2 †
HDL-C , mg / dl	60 ± 17	60 ± 24	0.2 †
TG , mg / dl	135 ± 70	136 ± 75	0.9 ‡
Cre , mg / dl	0.91 ± 0.28	0.80 ± 0.21	0.004 ‡
CRP , mg / l	0.21 ± 0.53	0.30 ± 1.03	0.4 ‡
CAVI_ave	9.0 ± 1.7	8.7 ± 1.2	0.07 †
FEV_1 , L	1.9 ± 0.6	2.3 ± 0.6	<0.001 †
FEV_1 % predicted	90.7 ± 21.3	114.5 ± 21.5	<0.001 †
CAD ,%	47	48	0.8 *
total CAC	378.6 ± 567.4	330.3 ± 712.7	0.5 ‡
Agents, n (%)			
Antihypertensive Drug	43 (74.1)	119 (76.3)	0.7 *
Antihyperlipidemic Agent	25 (43.1)	80 (51.3)	0.3 *
Antidiabetes drug	12 (20.7)	30 (19.2)	0.8 *
Insulin	2 (3.4)	14 (9.0)	0.2 [4]
LABA	4 (6.9)	2 (1.3)	0.05 §
Anticholinergenic Agent	2 (3.4)	1 (0.6)	0.2 §
ICS	4 (6.9)	2 (1.3)	0.05 §

Data are present as mean ± SD. FEV_1 / FVC=forced expiratory expiratory volume in 1 second /forced vital capacity; SBP=systolic blood pressure; DBP=diastolic blood pressure; HDL=high-density lipoprotein; LDL=low-density lipoprotein; CAVI=cardio-ankle vascular index; FEV_1= forced expiratory volume in 1s.; CAD=coronary artery disease, CAD was defined as 70% =< stenosis in Coronary CT; CAC=coronary artery calcification; LABA=long-acting beta-agonist; ICS=inhaled corticoid

Results of sex-adjusted logistic regression analysis of the presence of an obstructive defect are shown in Table 2. Systolic blood pressure, the blood HbA1c level, serum LDL-C, TG, creatinine, and CRP levels, the average CAVI, and the total CAC score served as explanatory variables to examine the association between COPD and cardiovascular risk factors. Univariate analysis using logistic regression indicated that elevated serum creatinine levels significantly correlated (OR = 4.80, $p = 0.02$) with the presence of an obstructive defect. Moreover, independent variables were selected for multivariate analysis using forward selection based on the likelihood ratio. This analysis indicated that an elevated serum creatinine level was the most important factor that determines an obstructive defect (OR = 1.16, $p = 0.046$). In addition, there was a significant correlation ($r = -0.186$, $p = 0.006$) between a decrease in the log-transformed predicted FEV1 and elevated serum creatinine levels (Fig. 2).

Table 2

Independent Determinants of Airflow Obstruction

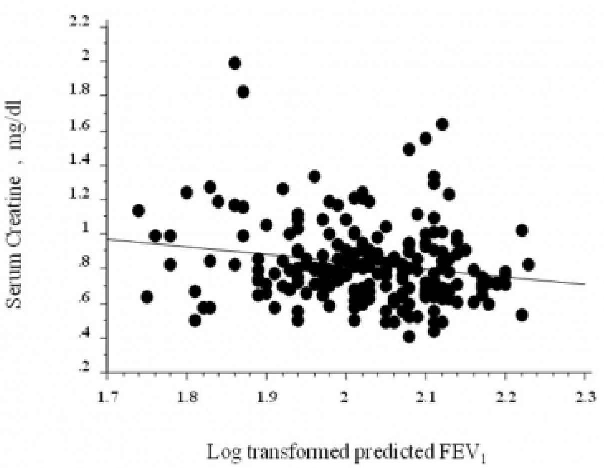
	Univariate (gender adjusted)				Multivariate (gender adjusted)			
	OR	95% CI		*P-value*	OR	95% CI		*P-value*
SBP, per 10mmHg	1.06	0.89	1.26	0.50				
HbA1c, per 0.1%	0.98	0.95	1.02	0.30				
LDL-C, per 10mg/dl	0.93	0.83	1.04	0.18				
HDL-C, per10mg/dl	1.03	0.90	1.18	0.64				
TG, per 10mg / dl	1.00	0.96	1.04	0.84				
Cre, per 0.1 mg/dl	4.80	1.02	1.34	0.02	1.16	1.00	1.34	0.046
CRP, per 0.1 mg/l	1.17	0.98	1.04	0.56				
CAVI ave, per 0.1	1.01	0.99	1.04	0.29				
CAC[total], per 10	1.00	1.00	1.00	0.86				

See Table 1 legend for expansion of abbreviations.
OR=Odds Ratio, 95% CI= 95 % Confidence Interval

There is a significant inverse association between log-transformed predicted FEV1 (%) and serum creatinine (mg/dL; r = –0.186, p = 0.006).

Figure 2

The Correlation between Serum Creatinine and Predicted FEV1 (%)



DISCUSSION

This study did not include patients with severe airflow obstruction or patients with a history of acute exacerbation of COPD. A direct correlation between mild to moderate airflow obstruction and coronary artery stenosis or calcification was not evident. Nonetheless, a close association between mild to moderate airflow obstruction and elevated serum creatinine levels was noted. A significant inverse correlation between the log-transformed predicted FEV1 and serum creatinine levels was evident (r = –0.186, p = 0.006).

Assessment of the extent of coronary artery stenosis using coronary artery CT scans is highly precise (19) and minimally invasive; therefore, coronary artery CT scans are increasingly being performed to screen for CAD among patients with cardiovascular risk factors. However, few of the current studies found any correlation between the extent of airflow obstruction and the extent of coronary artery stenosis or calcification. The finding that COPD is closely associated with arteriosclerosis (4) has been previously reported. Studies have suggested that COPD is associated with asymptomatic atherosclerosis (20), pulse wave velocity (21), and pericardial fat (22). However, most of these studies have analyzed patients with severe airflow obstruction or subjective symptoms, and patients diagnosed based on imaging without a pulmonary function test. Many patients with severe COPD have problems in multiple organs, and acute exacerbation of COPD worsens thickening of the coronary artery walls (23). Recent study reported that the elevation of coronary artery calcification score is a prognostic factor of COPD(24). Accordingly, acute exacerbation of COPD and cardiovascular disease may have overlapping pathogenesis. No previous study has examined the association between mild to moderate airflow obstruction and cardiovascular risk factors; in contrast, none of the patients enrolled in the study had severe COPD.

In addition, a significant correlation between the extent of airflow obstruction and elevated serum creatinine levels is evident in our results. One study did report that smoking is a risk factor for CKD (25), but few studies have examined the association between the extent of airflow obstruction and CKD. A study by Chandra et al. reported that there is no correlation between the estimated glomerular filtration rate (eGFR) and FEV1 (26). Another study, however, reported that microalbuminuria is a useful indicator of emphysematous changes in the lungs (27), and might be a prognostic factor of COPD(28). Among patients who have undergone a vascular surgery, those with COPD exhibit diminished kidney function, and a study reported that the prevalence of CKD increases with severity of COPD (29). CKD causes an increase in inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF-) (30, 31). IL-6 and TNF- cause endothelial cell injury and can trigger myocardial infarction (30). Thus, CKD is a significant risk factor for CAD (32, 33). The cytokines that trigger inflammation are reported to be induced by mild to moderate airflow obstruction. The cytokines that are triggered both by CKD and by COPD may be linked to the occurrence of a future cardiovascular event.

The limitations of the current study are as follows. First, subjects were 214 patients who underwent a coronary artery CT scan and respiratory function test; thus, the sample size was relatively small. In addition, a drug challenge test was not conducted as part of the assessment of respiratory function. Excluding bronchial asthma by assessing the reversibility of airflow obstruction was not possible. In addition, many of the patients with COPD in the current study were elderly and had a low body mass index, presumably indicating that they had low muscle mass. Assessing the eGFR using the Cockcroft–Gault (34) and Modification of Diet in Renal Disease Study equations (35) would have proven difficult in these patients.

In the future, a prospective observational study of patients with COPD should clarify the relationship among COPD, CKD and CAD. Moreover, the question of whether therapeutic interventions for COPD result in the prevention of cardiovascular events needs to be addressed.

CONCLUSIONS

A direct correlation between mild to moderate airflow obstruction and the extent of coronary artery stenosis or calcification was not noted. However, mild to moderate airflow obstruction was associated with elevated serum creatinine levels, which may be associated with the future occurrence of a cardiovascular event. Therefore, this hypothesis needs to be verified by future prospective studies.

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