Impact of Airflow Limitation on Carotid Atherosclerosis in Coronary Artery Disease Patients

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Key Words

Airflow limitation · Smoking habit · Atherosclerosis

Abstract

Background: Both airflow limitation and smoking are established cardiovascular risk factors. However, their interaction as risk factors for the development of atherosclerosis in coronary artery disease patients remains unclear. **Objectives:** To evaluate the effect of the interaction between airflow limitation and smoking status on the severity of carotid atherosclerosis. **Methods:** We categorized the 234 enrolled patients with coronary artery disease into four groups: never-smokers with normal pulmonary function (group A), never-smokers with airflow limitation (group B), ever-smokers with normal pulmonary function (group C), and ever-smokers with airflow limitation (group D). **Results:** The prevalence of airflow limitation in the enrolled patients was 23.1% (ever-smokers: 15.8%, never-smokers: 7.3%). The prevalence of severe carotid atherosclerosis was 28.2, 29.4, 41.3, and 45.9%, respectively, in the four groups (group D vs. group A, $p = 0.035$). Even after multivariate adjusting for con-

founding factors, ever-smokers with airflow limitation were independently associated with severe carotid atherosclerosis (odds ratio 2.89, 95% confidence interval, 1.19–7.00, $p = 0.019$). **Conclusions:** Ever-smokers with airflow limitation were significantly associated with severe carotid atherosclerosis among patients with coronary artery disease. These findings also provide additional insight into the correlation between airflow limitation and poor cardiovascular clinical outcomes.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality [1, 2]. Furthermore, it is predicted to become the third leading cause of death worldwide by 2020 [3, 4]. Recently, COPD has been recognized as a systemic disease; many patients with COPD have comorbidities that may have a significant impact on their quality of life and their prognosis [5, 6]. In particular, cardiovascular disease (CVD) is a major co-

morbidity in COPD and probably both the most frequent and the most important disease coexisting with COPD [7]. Although smoking is the main risk factor for COPD, it was recently recognized that approximately one fourth to one third of subjects with COPD are never-smokers [8–10]. In addition, it was reported that risk factors for airflow limitation differ between smokers and never-smokers [11]. However, few studies have evaluated the relationship between airflow limitation and atherosclerotic status in both smokers and never-smokers. Therefore, the aim of this study was to evaluate the effect of the interaction between airflow limitation and smoking status on the severity of carotid atherosclerosis in coronary artery disease (CAD) patients.

Methods

Study Design and Subjects

From April 2012 to December 2013, a total of 234 patients with stable CAD were enrolled in this study from the Nagoya University Hospital. Stable CAD was defined as stable angina pectoris and a previous myocardial infarction. All the subjects underwent spirometry and carotid ultrasonography. Exclusion criteria were as follows: patients who had respiratory diseases other than COPD as determined by chest radiogram and pulmonary function tests, those who had experienced clinical cerebrovascular events within 3 months before screening, and those who had undergone previous carotid artery stenting. The local Institutional Ethics Committee of Nagoya University Hospital approved the study protocol. All the patients provided written informed consent. After an overnight fast of 12 h, blood samples were obtained from all the patients. The body mass index was calculated as body weight divided by height squared (kg/m^2). The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) study equation modified with the Japanese coefficient ($0.741 \times \text{MDRD}$) [12].

Definitions

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of current antihypertensive medication. Diabetes mellitus was defined as the use of any antihyperglycemic medication or a glycosylated hemoglobin concentration $\geq 6.5\%$ (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dl, high-density lipoprotein cholesterol < 40 mg/dl, triglycerides ≥ 150 mg/dl, or receiving lipid-lowering therapy. Enrolled patients also completed a medical history questionnaire including questions about their smoking status and smoking history. Current smokers were defined as those who declared that they were actively smoking at all available examinations. Past smokers were defined as those who declared that they had not been smoking during the last year in one of the examinations. Current or past smokers were classified as ever-smokers. Never-smokers were defined as those who had never smoked before or during the study. Pack-years were calculated as the number of packs of cigarettes smoked per day multiplied by the number of years during which the patient had smoked.

Fig. 1. Prevalence of airflow limitation in patients with CAD. Of 234 patients with CAD, a total of 54 (23.1%) patients had airflow limitation. Nine (3.8%) patients were previously diagnosed and treated for airflow limitation. An additional 45 (19.3%) were newly diagnosed with airflow limitation by spirometry.

Pulmonary Function Testing

Pulmonary function tests were performed for all the subjects, without bronchodilators, and using a computed spirometer (DISCOM-21FX, CHEST M.I. Inc., Tokyo, Japan). The protocol for lung function measurements conformed to the American Thoracic Society's recommendations [13]. Airflow limitation compatible with COPD was defined according to the lower limit of normal method. A forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio below the lower 5th percentile of healthy reference groups established the diagnosis of COPD [14].

Carotid Ultrasonography

Ultrasonography of the bilateral common carotid artery, carotid bifurcation, and internal carotid artery was performed using a high-resolution carotid ultrasound system with a 7.5-MHz linear array transducer (Prosound $\alpha 10$; Hitachi ALOKA Medical, Tokyo, Japan). Intima-media thickness (IMT) is defined as the distance from the leading edge of the first echogenic line to that of the second. The first line represents the lumen-intima interface, and the second line represents the collagen-containing upper layer of the adventitia. Maximum IMT is defined as the maximal IMT of several sites in the bilateral carotid arteries [15, 16]. To assess the severity of carotid atherosclerosis, a plaque score (PS) was calculated by summing all plaque thickness measurements of 8 segments, as proposed by Handa et al. [17]. The severity of PS was classified as normal, mild, moderate, or severe if the total PS was < 1.1 , 1.1 – 5.0 , 5.1 – 10.0 , or > 10.0 , respectively. All the measurements were performed by a trained physician who was blinded to the patients' clinical information.

Statistical Analysis

With regard to continuous variables, all normally distributed data were expressed as mean $\pm$ standard deviation. Variables that were not normally distributed were expressed as median (inter-

Table 1. Baseline characteristics

	Never-smokers		Ever-smokers		p
	normal (n = 71)	airflow limitation (n = 17)	normal (n = 109)	airflow limitation (n = 37)	
Men	34 (48)	9 (53)	103 (94)	31 (84)	<0.001
Age, years	70.2±10.3	71.5±8.7	69.3±7.3	69.2±7.9	0.74
Body mass index	23.6±3.6	23.0±4.9	23.5±3.1	22.6±3.2	0.50
Hypertension	57 (80)	12 (71)	86 (79)	29 (78)	0.86
Diabetes	23 (32)	10 (59)	50 (46)	15 (41)	0.15
Smoking status					<0.001
Past smoker	0	0	69 (63)	17 (46)	
Current smoker	0	0	40 (37)	20 (54)	
Pack-year history	0	0	41 (24–65)	44 (29–69)	<0.001
Total cholesterol, mg/dl	186.9±35.3	182.4±40.6	170.5±34.6	166.4±34.1	0.010
LDL cholesterol, mg/dl	104.9±31.7	101.5±31.8	96.8±30.2	97.3±35.0	0.40
HDL cholesterol, mg/dl	51.7±14.7	50.5±16.5	45.1±10.4	44.9±13.2	0.012
Triglycerides, mg/dl	135.6±74.7	141.3±79.4	149.6±85.6	128.1±72.1	0.47
Fasting glucose, mg/dl	112.7±41.2	145.4±69.9	118.1±35.8	113.3±36.5	0.33
Hemoglobin A1c, %	6.3±0.9	6.9±1.3	6.4±1.0	6.3±0.8	0.24
eGFR, ml/min/1.73 m ²	68.1±22.6	63.6±16.5	65.1±21.3	69.9±26.5	0.60
ACE-I or ARB	40 (56)	12 (71)	64 (59)	23 (62)	0.74
Beta-blockers	26 (37)	4 (24)	27 (25)	12 (32)	0.33
Statins	53 (75)	13 (76)	75 (69)	26 (70)	0.85
Antidiabetic drugs	15 (21)	4 (24)	34 (31)	10 (27)	0.49

Data are presented as n (%), mean ± standard deviation or median (interquartile range).

LDL = Low-density lipoprotein; HDL = high-density lipoprotein; eGFR = estimated glomerular filtration rate; ACE = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers.

quartile range). Categorical variables were expressed as numbers (percentages). Continuous variables were compared using one-way analysis of variance. Categorical variables were compared using the χ^2 test. To obtain independent predictors of severe carotid atherosclerosis, multiple logistic regression analyses were performed. A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 18.0 for Windows (SPSS, Inc., Chicago, Ill., USA).

Results

Baseline Characteristics

A total of 234 subjects were enrolled in this study. Figure 1 shows the prevalence of airflow limitation among the enrolled subjects. A total of 54 (23.1%) patients had airflow limitation. Surprisingly, 45 patients were newly diagnosed with airflow limitation by spirometry.

To evaluate the interaction between airflow limitation and smoking status, we further categorized the enrolled patients into four groups: never-smokers with normal pulmonary function (group A); never-smokers with air-

flow limitation (group B); ever-smokers with normal pulmonary function (group C), and ever-smokers with airflow limitation (group D). Table 1 shows the differences in baseline clinical characteristics across the four groups. There were significant differences in the number of males and in the lipid profiles among the four groups, in addition to the expected differences in the smoking status. However, other variables such as prevalence of hypertension and diabetes were comparable among the four groups.

Combined Effects of Airflow Limitation and Smoking Status

Table 2 shows data for pulmonary function tests and carotid ultrasonographies among the four groups. There were significant differences in carotid PS among the four groups (7.2 ± 5.4 , 7.7 ± 3.9 , 9.4 ± 6.0 , and $9.9 \pm 5.6\%$, respectively; p for trend = 0.035). In addition, ever-smokers with comorbid airflow limitations were significantly associated with severe carotid atherosclerosis in comparison with never-smokers with normal pulmonary func-

Table 2. Data from spirometry and carotid ultrasonography

	Never-smokers		Ever-smokers		p
	normal (n = 71)	airflow limitation (n = 17)	normal (n = 109)	airflow limitation (n = 37)	
FVC, l	2.96±0.95	2.24±0.67	3.53±0.65	2.63±0.76	<0.001
FEV ₁ , l	2.28±0.79	1.62±0.47	2.58±0.49	1.72±0.52	<0.001
Predicted FEV ₁ , %	115.2±16.4	76.7±12.1	110.5±14.9	75.3±13.0	<0.001
FEV ₁ :FVC ratio	0.77±0.09	0.74±0.13	0.74±0.09	0.67±0.14	0.004
Maximum IMT, mm	2.19±0.92	2.38±0.82	2.53±1.03	2.65±0.96	0.067
PS	7.2±5.4	7.7±3.9	9.4±6.0	9.9±5.6	0.035
PS severity					0.097
Normal (<1.1)	7 (11)	1 (6)	5 (5)	0 (0)	
Mild (1.1–5)	24 (33)	3 (18)	20 (18)	8 (22)	
Moderate (5.1–10)	20 (28)	8 (47)	39 (36)	11 (30)	
Severe (>10)	20 (28)	5 (29)	45 (41)	18 (48)	

Data are presented as mean ± standard deviation or n (%).

FVC = Forced vital capacity.

Table 3. Simple and multiple logistic regression analyses for severe carotid atherosclerosis

Variables	Simple regression			Multiple regression		
	OR	95% CI	p	OR	95% CI	p
Men	1.57	0.83–2.97	0.16			
Age (years)	1.04	1.00–1.07	0.030	1.04	1.01–1.08	0.026
Body mass index	1.01	0.94–1.09	0.78			
Hypertension	2.10	1.05–4.18	0.035	1.80	0.86–3.75	0.12
Diabetes mellitus	1.54	0.91–2.61	0.11			
eGFR (ml/min/1.73 m ²)	0.98	0.96–0.99	<0.001	0.98	0.97–0.99	0.002
HDL cholesterol (mg/dl)	0.99	0.97–1.01	0.26			
LDL cholesterol (mg/dl)	1.00	0.99–1.01	0.91			
Never-smokers, normal PFT	Ref.			Ref.		
Never-smokers, airflow limitation	1.06	0.33–3.40	0.92	1.02	0.31–3.38	0.98
Ever-smokers, normal PFT	1.79	0.94–3.41	0.075	1.89	0.96–3.72	0.066
Ever-smokers, airflow limitation	2.42	1.06–5.52	0.036	2.89	1.19–7.00	0.019

OR = Odds ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PFT = pulmonary function test.

tion (group A, 28.2%; group B, 29.4%; group C, 41.3%; group D, 45.9%; group D vs. group A, $p = 0.035$; fig. 2). After multivariable adjustment for cardiovascular risk factors, ever-smokers with airflow limitation were significantly more likely to have severe carotid atherosclerosis compared with never-smokers with normal pulmonary function (odds ratio 2.89, 95% confidence interval, 1.19–7.00, $p = 0.019$; table 3).

Discussion

In the present study, we showed that ever-smokers with airflow limitation were significantly associated with severe carotid atherosclerosis among patients with CAD. The relationship between these two factors was found to be independent of each other after adjustment for traditional risk factors. Thus, these findings suggest that the

Fig. 2. Combined effects of airflow limitation and habitual smoking on severe carotid atherosclerosis. Ever-smokers with comorbid airflow limitations were significantly associated with severe carotid atherosclerosis in comparison with never-smokers with normal pulmonary function (group A, 28.2%; group B, 29.4%; group C, 41.3%; group D, 45.9%; group D vs. group A, $p = 0.035$).

presence of airflow limitation is a risk factor for more advanced atherosclerosis and subsequent CVD events in CAD patients.

It is generally accepted that CVD is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD. In addition, several studies have reported that the prevalence of COPD is high among patients with ischemic heart disease [18, 19]. As reported recently, it is clear that the loss of lung function is more accelerated in the early phase of COPD than in the late phase [20–22]. However, the National Health and Nutrition Examination Survey study reported that the early phase of COPD is usually asymptomatic; only 60% of patients with moderately impaired lung function complained of symptoms [23]. In the present study, we found that approximately 23.1% of the enrolled patients had airflow limitation. Moreover, a large majority (83.3%) of these patients had not been diagnosed. Lack of recognition and underdiagnosis of COPD may be one of the biggest problems for these patients and could adversely affect their prognosis and quality of life. It is important to perform pulmonary function tests to determine who is at risk for advanced atherosclerosis. Our findings may also provide additional insight into the

correlation between airflow limitation and poor cardiovascular clinical outcomes.

Several recent studies have demonstrated that the synergistic effects of airflow limitation and smoking experience are associated with more advanced atherosclerosis. Iwamoto et al. [24] demonstrated a greater carotid IMT and a greater carotid PS in smokers with airflow limitation but not in smokers with normal pulmonary function in a case-control study. In addition, the Nagahama study with 8,790 subjects from the general population also suggested that the association between airflow limitation and arterial stiffness is rather prominent in smokers [25]. Furthermore, a longitudinal study revealed that the combination of reduced FEV₁ and smoking exposure are better predictors of future cardiovascular mortality than serum cholesterol levels [26]. In the present study, we found that the presence of smoking experience alone was not significantly related to an increase in carotid atherosclerosis. However, compared with never-smokers with normal pulmonary function, subjects with both airflow limitation and smoking experience were significantly associated with severe carotid atherosclerosis. The addition of pulmonary function tests to smoking status may be of value in the risk stratification of patients with CAD.

Although cigarette smoking is widely accepted as the principal risk factor for COPD, it is now recognized that never-smokers may account for between one fourth and one third of all COPD patients [8–10]. Several recent studies have demonstrated that risk factors for airflow limitation differ in smokers and never-smokers [11]. Air pollution [27, 28], environmental tobacco smoke [29, 30], low socioeconomic status [31], and a prior diagnosis of asthma [32, 33] have been shown to be linked to an increased risk for COPD among never-smokers. In addition, Young et al. [26] have shown an association between low FEV₁ and cardiovascular events in never-smokers. However, the atherosclerotic risk and status in this population are not yet well defined. Our present study also demonstrated that the prevalence of severe carotid atherosclerosis was not significantly different between normal pulmonary function and airflow limitation in the never-smoker group. The basis of this non-smoker association is not fully understood. Thus, more investigations are required to identify a mechanism and an optimal treatment strategy for COPD in never-smokers.

Several limitations of the study should be considered. First, it was an observational analysis conducted in a single center and included a relatively small sample. In par-

ticular, never-smokers with COPD are a minority. Second, the subjects with airflow limitation in the present study could not be precisely identified as having COPD. Because we did not perform post-bronchodilator pulmonary function tests, our study may have overestimated the prevalence of subjects with airflow limitation. However, these patients most likely had COPD because we excluded the possibility of other respiratory diseases through self-reported diagnoses, identification of symptoms, examination of medical records, and chest radiograms. Finally, we were not able to acquire personal data such as exposure to passive smoking, socioeconomic status, and occupational environment.

In conclusion, we demonstrated that ever-smokers with airflow limitation were significantly associated with severe carotid atherosclerosis among patients with CAD. These findings may also provide additional insight into the correlation between airflow limitation and poor cardiovascular clinical outcomes.

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