

主論文の要旨

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

〔冠動脈疾患患者における閉塞性肺機能障害と頸動脈硬化との関連〕

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## **Introduction**

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. Furthermore, it is predicted to become the third leading cause of death worldwide by 2020. 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. In particular, cardiovascular disease (CVD) is a major comorbidity in COPD and is probably both the most frequent and the most important disease coexisting with COPD. 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. In addition, it was reported that risk factors of airflow limitation differ between smokers and never-smokers. 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 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, or 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 ( $\text{kg}/\text{m}^2$ ). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation modified with the Japanese coefficient ( $0.741 \times \text{MDRD}$ ).

### *Statistical analysis*

With regard to continuous variables, all normally distributed data were expressed as mean  $\pm$  standard deviation (SD). Variables that were not normally distributed were expressed as median (interquartile range). Categorical variables were expressed as numbers (percentages). Continuous variables were compared using one-way analysis of variance. Categorical variables were compared using the chi-square 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, IL, USA).

## **Results**

### *Baseline characteristics*

A total of 234 subjects enrolled in this study. Figure 1 shows the prevalence of airflow limitation among 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 enrolled patients into four groups: Group A, never-smokers with normal pulmonary function; Group B, never-smokers with airflow limitation; Group C, ever-smokers with normal pulmonary function; and Group D; ever-smokers with airflow limitation. Table 1 shows the differences in baseline clinical characteristics across 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. Figure 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 was significantly associated with severe carotid atherosclerosis in patients with coronary artery disease. 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 presence of airflow limitation is a risk factor for more advanced atherosclerosis and subsequent CVD events in CAD patients.

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 under-diagnosis 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.

From 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 test to smoking status may be of value in the risk stratification of patients with coronary artery disease.

Our present study also demonstrated that prevalence of severe carotid atherosclerosis was not significantly different between normal pulmonary function and airflow limitation in never-smokers 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.

### **Conclusion**

We demonstrated that ever-smokers with airflow limitation were significantly associated with severe carotid atherosclerosis in patients with coronary artery disease. These findings may also provide additional insight into the correlation between airflow limitation and poor cardiovascular clinical outcomes.