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Original article

Low forced expiratory volume in one second is associated with the history of acute coronary syndrome in patients with organic coronary stenosis

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ABSTRACT

Background: Chronic obstructive pulmonary disease often coexists with cardiovascular diseases and airflow limitation has been known as a risk of cardiovascular death. However, the association between airflow limitation and the history of acute coronary syndrome (ACS) in patients with coronary stenosis remains to be determined.

Methods: Study subjects were 271 consecutive patients (age: 70.6 ± 9.5 years, sex: 200 males) who underwent coronary angiography and in whom organic coronary stenosis was detected. We collected spirometric data from those patients and investigated the association of the pulmonary function and the history of ACS. We also compared the prevalence of airflow limitation of the present subjects with Japanese epidemiological data that had been previously published.

Results: Multivariate analysis with multiple logistic regression analysis showed that the reduced forced expiratory volume in one second ($FEV_{1.0}$) less than 80% of predicted value was significantly associated with a history of ACS (odds ratio: 2.81, 95% CI: 1.27–6.20, $p < 0.02$) independently of age, sex, body mass index, and classic coronary risk factors including smoking habit, diabetes mellitus, hypertension, and dyslipidemia. Furthermore, the airflow limitation was more prevalent in the present subjects than in the Japanese general population (25.8% vs. 10.9%, $p < 0.05$).

Conclusions: Reduced $FEV_{1.0}$ is associated with a history of ACS in patients with coronary arterial stenosis irrespective of any coronary risk factors. Airflow limitation is more prevalent in patients with coronary stenosis than in the general population.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular death by two or three times, and half of them die from cardiovascular events [1–5]. Reduced forced expiratory volume in one second ($FEV_{1.0}$) has been known to be a risk of cardiovascular death [6–8]. From the viewpoint of coronary artery disease (CAD), coexistent COPD has a negative impact on acute-phase and long-term prognosis [9–13]. Although

COPD and CAD share some risk factors such as smoking habits, advanced age, sedentary life style, and male sex, it cannot fully explain the high incidence of cardiovascular events in COPD [6]. Chronic systemic inflammation and increased oxidative stress are assumed as the underlying possible mechanisms by which COPD links to cardiovascular death [14–18]. Since chronic inflammation and increased oxidative stress play pivotal roles in the progression of atherosclerosis [19,20], it is possible that in patients with coronary atherosclerosis, the concomitant airway inflammation with airflow limitation accelerates plaque growth and enhances plaque instability, leading to plaque rupture and the occurrence of acute coronary syndrome (ACS) [21]. Animal studies have shown that airway inflammation caused by air pollution particulate matters accelerates atherosclerosis in systemic arteries [22,23]. And so it is plausible that the airflow limitation detected by spirometry is associated with the occurrence of ACS in patients

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with atherosclerotic burdens. As far as we know, however, there is no report that coexistence of airflow limitation is systematically investigated in patients with organic coronary stenosis. Accordingly, we tested the hypothesis that in patients with organic coronary stenosis confirmed with coronary angiogram, coexistent airflow limitation detected by spirometry is associated with a history of ACS. We also compared the prevalence of spirometric abnormality in the present study subjects with Japanese epidemiological data to elucidate whether airflow limitation is more prevalent in CAD patients than in the general population.

Methods

Two hundred ninety one patients who consecutively underwent coronary angiogram in Tohoku Rosai Hospital from April 1st, 2008 through December 31st, 2012, and in whom organic coronary stenoses (>75%) in major coronary branches were detected at least in one site were included in the present study.

Classic risk factors were evaluated for those subjects. The definition of each risk factor was as follows. Smoking habit: to have cigarette smoking habit within 5 years (self-reported). Diabetes mellitus: to be diagnosed as having diabetes mellitus or glucose intolerance validated with medical records, or to be prescribed with antidiabetic agents. Hypertension: to be clinically diagnosed as having hypertension validated with medical records, or to be prescribed with antihypertensive agents. Dyslipidemia: to be clinically diagnosed as having dyslipidemia, hyperlipidemia, or hypercholesterolemia validated with medical records, or to be prescribed with drugs for dyslipidemia. The history of ACS was investigated by questioning to the patients whether they had ever been diagnosed as having acute myocardial infarction, unstable angina, or ACS, and the diagnosis was validated by referring to the medical records, when they were available.

Spirometry was performed under standardized conditions using DISCOM-21 FXII (Chest M.I., Inc., Tokyo, Japan) within one month of the implementation of coronary angiogram. FEV_{1,0} and forced vital capacity (FVC) were measured. Spirometry was performed at least three times, and the best values were taken as data. The machine was calibrated daily. To obtain satisfactory loop recordings, spirometry was repeated up to four times, and the highest FEV_{1,0} and FVC values were used for analysis. No bronchodilators were used during the spirometry because they could have adverse effects on some patients with myocardial ischemia such as tachycardic or arrhythmogenic effects. In 20 patients, spirometric data could not be obtained because of death ($n=5$), transfer to other hospitals ($n=5$), poor general condition ($n=3$), neuromuscular disorders ($n=3$), dementia ($n=3$), or tracheostomy ($n=1$), and they were excluded from the data set. Informed consent for this study was obtained from each patient, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review board.

To elucidate whether airflow limitation is more prevalent in subjects with organic coronary stenosis than the general population, we compared the prevalence of abnormal FEV_{1,0}/FVC in the present study with that in a Japanese epidemiological study, Nippon COPD Epidemiology Study (NICE Study) [24]. In that study, spirometry was performed in the general population (age > 40 years, $n=2343$, male: 1125, female: 1218).

Continuous variables are expressed with means \pm standard deviation, and categorical variables were summarized as frequencies and percentage. Comparisons between two groups were performed with Student's *t* test for continuous variables and with the chi-square analysis for categorical variables. Comparison between the present data and the Japanese epidemiological data (NICE Study) was performed with the normal distribution analysis or the binomial

distribution analysis appropriately. Multivariate analyses were performed with multiple logistic regression analysis to test whether the spirometric abnormalities (FVC less than 80% of predictive value, FEV_{1,0} less than 80% of predictive value, and FEV_{1,0}/FVC less than 70%) are independent variables which associate with the history of ACS by adjusting age, sex, body mass index (BMI), and classic risk factors (smoking habit, diabetes mellitus, hypertension, and dyslipidemia) as confounding factors. Odds ratios and 95% confidence intervals were calculated. Values of *p* less than 0.05 were accepted for statistical significance. Statistical analyses were performed with IBM SPSS® version 22 (IBM, Inc., New York, NY, USA).

Results

There were 106 cases with ACS history and they consisted of 74 cases of myocardial infarction (M/F: 56/18), and 32 cases of unstable angina (M/F: 26/6). Of these ACS patients, 88 cases were treated with percutaneous coronary intervention, 10 cases were treated with coronary bypass surgery, and 10 cases were medically treated. Demographic and clinical data of the study patients with and without history of ACS are shown in Table 1. Univariate analysis showed that patients with ACS had higher incidence of low value of FVC (<80% of predicted value) and low value of FEV_{1,0} (<80% of predicted value). Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were taken more often in patients with a history of ACS than ones without it.

Multivariate analysis showed that the history of ACS is significantly associated with low FEV_{1,0} independent of age, sex, body mass index, and classic coronary risk factors including smoking habit, hypertension, diabetes mellitus, and dyslipidemia (Table 2).

All of the present spirometric data are shown in Fig. 1. The filled symbols represent the patients with clinical diagnosis of COPD. There were 45, 23, and 2 patients with airflow limitation in the stage of Global Initiative for Chronic Obstructive Lung Disease (GOLD) I, II, and III, respectively. Eighty four percent of patients in GOLD 1 stage (38 out of 45 patients), 61% of GOLD 2 stage (14 out of 23 patients), and one patient out of two patients in GOLD 3 stage were not diagnosed as having COPD.

The comparison of the present spirometric data with the Japanese epidemiological study (NICE Study) is shown in Table 3. Airflow limitation defined by the low FEV_{1,0}/FVC (<70%) was more prevalent in the present subjects compared with the Japanese general population in either sex. When subjects were stratified by age, prevalence of airflow limitation tended to be higher in the present study subjects in any age group, but the statistical significance was attained in the age of sixties.

Discussion

In the present study, we found several important findings. First, in patients with organic coronary stenosis, low FEV_{1,0} is associated with a history of ACS independently of age, sex, body mass index, and classic coronary risk factors. Second, airflow limitation is more prevalent in patients with coronary stenosis compared with the general population. Third, comorbidity of COPD is frequently overlooked in patients with CAD.

We have shown that reduced FEV_{1,0} associates with the occurrence ACS independently of classic risk factors. It is in line with epidemiological evidence that reduced FEV_{1,0} is a marker for cardiovascular mortality [6]. Sin et al. [6] have shown that the lowest quintile for FEV_{1,0} had 5.65 of the relative risk for mortality of ischemic heart diseases compared with the highest quintile. The increased incidence of ACS may account for the large proportion of cardiovascular death in COPD. Earlier studies have demonstrated the relationship between airflow limitation and atherosclerotic

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