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Airflow limitation in smokers is associated with arterial stiffness: The Nagahama Study

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ABSTRACT

Background: Pathophysiological mechanisms of associations between airflow limitation (AL) and arterial stiffness remain unclear. One factor that might affect both AL and arterial stiffness is habitual smoking. The aim of this study is to investigate a possible interaction of smoking on the association between AL and arterial stiffness.

Methods: Study subjects consisted of 8790 apparently healthy community residents. Airflow limitation was defined as a ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity of less than 70%. Brachial-to-ankle pulse wave velocity (baPWV) was used as an index of arterial stiffness. Smoking habit was investigated using a structured questionnaire.

Results: Subjects with AL had significantly higher baPWV (AL 1381 ± 334, control 1261 ± 227 cm/s, $p < 0.001$). In a separate analysis by smoking habit, advanced arterial stiffness in AL was observed only in smokers (non-smokers: AL 1300 ± 220, control 1260 ± 218; smokers: AL 1436 ± 384, control 1264 ± 243 cm/s). Other clinical features of subjects with AL were older age; increased plasma hsCRP levels; and a high prevalence of male sex, hypertension, and smoking experience. Multiple linear regression analysis adjusted for these covariates identified the smoking × AL interaction as an independent determinant of baPWV ($\beta = 0.066$, $p < 0.001$). Conversely, baPWV was an independent determinant of AL in current and past smokers, but not in never smokers.

Conclusions: AL arising from cigarette smoking, but not AL in non-smokers, was associated with arterial stiffness in a general population independently of established risk factors. Measurement of subclinical arterial change in smokers may be useful in identifying persons at risk for AL.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health burden, reportedly responsible for approximately 25% of deaths from ischemic heart disease [1], and forecast to be the third-leading cause of death in 2020, after ischemic heart disease and cerebrovascular disease [2]. In general populations, airflow limitation, as assessed by forced expiratory volume in 1 s (FEV_1), is associated with the incidence of cardiovascular diseases including stroke [3], myocardial infarction [4], and heart failure [5]. Further, persons with comorbid hypertension or diabetes with airflow limitation have a further risk for adverse outcomes of hospitalization and mortality [6].

The mechanism by which airflow limitation increases cardiovascular diseases (CVD) has not been precisely determined. Although these pathologies share several risk factors, systemic inflammation, represented by elevated plasma levels of C-reactive protein (CRP) [7], might be a key factor in this comorbidity [8]. The co-occurrence of CVD in persons with reduced pulmonary function is more directly explained by a second factor, arteriosclerotic

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vascular change [9]. Several studies have reported atherosclerotic vascular changes and arterial stiffening in subjects with COPD [10,11], and atherosclerosis is known to be associated with an increased risk of cerebral disease [12], coronary artery disease, and total mortality [13]. In general populations, two studies have reported a direct association between airflow limitation and subclinical vascular changes [14,15]. The MESA lung study [14] reported greater carotid arterial thickness in subjects with reduced FEV_1, while the ARIC study [15] reported increased carotid arterial thickness and also decreased ankle-brachial index in subjects with lower FEV_1.

Smoking is an established risk factor for reduced pulmonary function [16]. Habitual smoking, even of low-tar cigarettes, also increases risks for CVD and mortality [17,18] through the initiation and progression of atherothrombotic vascular change [19]. It is therefore hypothesized that smokers with airflow limitation show synergistically greater arteriosclerotic vascular change. If smoking habit were involved in the relationship between airflow limitation and changes in vasculature, this would be a clue in elucidating the pathophysiological mechanisms of atherosclerotic progression in persons with airflow limitation.

Given this background, we investigated cross-sectional interrelationships between airflow limitation and habitual smoking on arterial stiffness in a large-scale general population sample.

2. Materials and methods

2.1. Study subjects

The study subjects consisted of 8790 participants of the Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience (The Nagahama Study). The Nagahama Study cohort was recruited from the general population living in Nagahama City, a largely rural city of 125,000 inhabitants in Shiga Prefecture, located in the center of Japan. Among 9804 total study participants recruited from 2008 to 2010, the study enrolled persons who were free from any symptomatic cardiovascular diseases, whose fasting plasma and urine samples were available, and who were not receiving treatment for COPD or asthma. Cigarette smoking habit and the medical history of each person was investigated using a structured questionnaire. Past smoking was defined as smoking at any time prior to baseline measurement. Smoking intensity (pack-year) for every age decade was obtained by the questionnaire and life-time exposure to cigarette smoke was expressed by the Brinkman index. All study procedures were approved by the ethics committee of Kyoto University Graduate School of Medicine. Signed informed consent was obtained from all participants.

2.2. Pulmonary function

Pulmonary function was measured by a forced vital capacity (FVC) maneuver on a computed spirometer with automated quality checks (SP-350 COPD, Fukuda Denshi Co., Ltd., Tokyo, Japan). Airflow limitation was defined as a ratio of forced expiratory volume in 1 s (FEV_1) to FVC of less than 70%. The severity of airflow limitation was graded by the ratio of FEV_1 to FEV_1 predicted value as <50%, severe; 50%–80%, moderate; and ≥80%, mild. FEV_1 predicted value was calculated using the following formulas according to a guideline from the Japan Respiratory Society: males, $0.036 \times \text{height} - 0.028 \times \text{age} - 1.178$; females, $0.022 \times \text{height} - 0.022 \times \text{age} - 0.005$. Pulmonary function was measured by trained and certified medical technologists according to a standardized protocol.

2.3. Evaluation of arterial stiffness

baPWV was used as an index of arterial stiffness. To measure baPWV, cuffs were applied to both brachia and ankles, and all blood pressures were measured simultaneously by a cuff-oscillometric method (Vasera-1500, Fukuda Denshi). The pulse volume waveforms were also recorded simultaneously using a plethysmographic sensor connected to the cuffs. baPWV was calculated from the time interval between the wave fronts of the brachial and ankle waveforms, and the path length from the brachia to ankle ($0.597 \times \text{height} + 14.4014$) [20]. Co-linearity of baPWV with a cfPWV, a standard measure of arterial stiffness, has been reported elsewhere [21], though some portions of baPWV may be determined by peripheral arterial stiffness [22].

2.4. Evaluation of risk factors

Plasma markers were measured using peripheral blood obtained after fasting. The homeostasis model assessment index for insulin resistance (HOMA-IR; [insulin (μU/ml) × glucose (mg/dl)]/405) was used as an index of insulin resistance. Kidney function was evaluated by estimated glomerular filtration rate (eGFR) calculated from serum creatinine levels using the following formula: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female). Chronic kidney disease (CKD) was defined as eGFR <60 ml/min/1.73 m^2, or urinary albumin ≥30 mg/day. Hypertension was defined as any or all of systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of antihypertensive drugs. Type 2 diabetes was defined as a fasting blood glucose level ≥126 mg/dl or use of antihyperglycemic drugs.

2.5. Statistical analysis

Values are mean ± standard deviation. Group differences in numeric and categorical variables were assessed by analysis of variance (ANOVA) or a chi-squared test. Post-hoc analysis comparing group differences was done using Tukey's test. Factors independently associated with baPWV were analyzed by multiple linear regression analysis. Multiple logistic regression analysis was used to calculate odds ratio for airflow limitation, and high baPWV in this regression model was defined as baPWV faster than 1395 cm/s (4th quartile). p values less than 0.05 were considered to indicate statistical significance.

3. Results

Mean baPWV was 1265 ± 232 cm/s baPWV was significantly higher in males (male, 1321 ± 252; females, 1238 ± 217 cm/s, $p < 0.001$), and positively associated with age ($r = 0.648$, $p < 0.001$) and systolic BP ($r = 0.626$, $p < 0.001$). eGFR was inversely associated with baPWV ($r = -0.318$, $p < 0.001$), and subjects with CKD showed markedly higher baPWV (CKD, 1392 ± 268; normal renal function, 1245 ± 215, $p < 0.001$). In contrast, HOMA-IR and high-sensitive C reactive protein (hsCRP) showed only weak associations with baPWV (HOMA-IR, $r = 0.167$, $p < 0.001$; hsCRP, $r = 0.255$, $p < 0.001$).

Table 1 shows associations between airflow limitation and atherosclerotic risk factors. Subjects with airflow limitation (FEV_1/FVC <0.7) were significantly older and had a higher prevalence of male sex, hypertension, and smoking experience. Because the frequency of airflow limitation was significantly higher in current (8.0%) and past (4.7%) smokers than in never smokers (2.1%) ($p < 0.001$), we pooled current ($n = 1218$) and past smokers ($n = 1782$) to increase statistical power. Plasma inflammatory marker (hsCRP) and total cholesterol were also significantly associated with pulmonary function. In contrast, no clear relationships were seen for diabetic parameters or renal function.