Association between Airflow Limitation Severity and Arterial Stiffness as Determined by the Brachial-Ankle Pulse Wave Velocity: A Cross-Sectional Study

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Abstract

Objective Chronic obstructive pulmonary disease (COPD) is often associated with concomitant systemic manifestations and comorbidities, such as cardiovascular disease. There are limited data regarding airflow limitation (AL) and atherosclerosis in Japanese patients, and the potential association between AL and arterial stiffness has not yet been investigated in Japanese patients. Therefore, the purpose of this study was to investigate the association between AL severity and arterial stiffness using the brachial-ankle pulse wave velocity (baPWV).

Methods This cross-sectional study included 1,356 subjects aged 40-79 years without clinical cardiovascular diseases who underwent a comprehensive health screening that included spirometry, the baPWV measurement, and blood sampling during medical check-ups in 2009 at the Japanese Red Cross Kumamoto Health Care Center. AL was defined in accordance with the Global Initiative for COPD criteria (forced expiratory volume in one second / forced vital capacity of < 0.7). A cut-off baPWV value of >1,400 cm/s was used for risk prediction and screening.

Results The average baPWV (SD) results were 1,578.0 (317.9), 1,647.3 (374.4), and 1,747.3 (320.1) cm/s in the patients with a normal pulmonary function, mild AL, and moderate-to-severe AL, respectively (p<0.001). Using logistic regression models adjusted for the age, body mass index, smoking status, hypersensitive C-reactive protein levels, hypertension, hyperglycemia, and dyslipidemia, an increased baPWV (>1,400 cm/s) was significantly associated with moderate-to-severe AL compared with a normal pulmonary function (odds ratio=2.76; 95% confidence intervals, 1.37-5.55; p=0.004).

Conclusion Our results indicated an association between AL and increased arterial stiffness. Arterial stiffness may therefore worsen with an increase in the severity of AL.

Key words: COPD, airflow limitation, arterial stiffness, brachial ankle pulse wave velocity, comorbidity

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide (1-4). COPD often coexists with other diseases (comorbidities) that may have a significant impact on the prognosis (1-6). The comorbidities associated with systemic inflammation (including hypertension and cardiovascular disease) are common among patients with COPD (4-10).

In a cross-sectional study of patients ≥50 years of age, Sin et al. reported an increased incidence of ischemic heart disease in the patients with airflow limitation that ranged from mild to moderate-to-severe (11). Smokers with airflow limitation often have extensive atherosclerosis, suggesting that systemic inflammation in COPD may promote athero-
Figure 1. Flow chart for selecting the subjects with airflow limitation or a normal pulmonary function.

Materials and Methods

Subjects

Fig. 1 demonstrates the flow chart for selecting the subjects with either airflow limitation or a normal pulmonary function. The present study included 1,356 subjects (813 men and 543 women), aged 40-79 years, who underwent routine health check-ups, including both spirometry and baPWV measurements. A total of 25,879 people visited the Japanese Red Cross Kumamoto Health Care Center for standard health check-ups between April 2009 and March 2010. Of these, 2,211 subjects aged 40-79 years underwent a health screening examination that included spirometry, as previously described (15-18), and the optional measurements of baPWV. The health screening examination included interview questionnaires, a physical examination, and blood sampling. The interview questionnaires were conducted by a trained public health nurse to obtain medical history data including medications used, smoking history, and occupation. The non-smokers consisted of those who denied any past or current smoking. The former smokers were those who reported smoking cessation prior to the examination. The current smokers were those who reported smoking at least one cigarette a day. Pack-years were calculated by multiplying the number of years of smoking by the average number of cigarettes smoked per day and dividing it by 20. All of the patients were evaluated by a physician. The subjects with self-reported asthma (n=91) including emphysema (n=1); lung cancer (n=17) including emphysema (n=1) and thoracic surgery (n=14); pulmonary tuberculosis (n=52) including...
## Table 1. The Characteristics of the Study Subjects Based on Pulmonary Function.

| Total n = 1,356 | Normal n=1,184 | Mild airflow limitation n=93 | Moderate-to-severe airflow limitation n=79 | p value |
|----------------|----------------|-----------------------------|-----------------------------------------------|---------|
| Age, yr        | 62.9 (9.8)     | 67.8 (10.2)*                | 65.1 (10.2)                                   | <0.001  |
| Male, %        | 687 (58.0)     | 64 (68.8)                   | 62 (78.5)                                     | <0.001  |
| Height, cm     | 160.9 (8.6)    | 162.2 (8.4)                 | 162.8 (7.6)                                   | 0.063   |
| Weight, kg     | 59.9 (10.9)    | 60.7 (10.3)                 | 61.6 (9.6)                                    | 0.106   |
| BMI, kg/m²     | 23.0 (3.1)     | 22.9 (2.6)                  | 23.2 (2.7)                                    | 0.768   |
| Abdominal circumference, cm | 83.7 (8.4) | 84.5 (7.5) | 84.7 (7.6) | 0.766 |

### Pulmonary Function

|                      | Normal      | Mild         | Moderate-to-severe | p value |
|----------------------|-------------|--------------|--------------------|---------|
| FEV₁, mL             | 2,493.6 (583.7) | 2,255.1 (518.6)* | 1,812.5 (295.3)**## | <0.001  |
| FVC, mL              | 3,187.6 (741.7) | 3,433.9 (775.8)* | 2,970.3 (575.6)**## | 0.002   |
| FEV₁/FVC, %          | 78.4 (4.9)  | 65.8 (3.2)**  | 61.0 (6.9)**##     | <0.001  |
| FEV₁% predicted, %   | 101.2 (12.9)| 90.8 (7.9)**  | 67.4 (10.4)**##    | <0.001  |

### Smoking status, n (%)

- Non smoker (n=799): 722 (61.0) 46 (49.5) 31 (39.2)
- Former smoker (n=380): 320 (27.0) 29 (31.2) 31 (39.2)
- Current smoker (n=167): 142 (12.0) 18 (19.4) 17 (21.5) 0.001

### Pack-years

11.6 (18.7) 16.5 (22.7) 24.5 (29.4) <0.001

### Labo data

|                      | Normal       | Mild         | Moderate-to-severe | p value |
|----------------------|--------------|--------------|--------------------|---------|
| hsCRP (mg/L)         | 0.110 (0.288) | 0.100 (0.154) | 0.147 (0.213)      | 0.497   |
| White blood cell count (×10³/μL) | 5.10 (1.28) | 5.55 (1.35)** | 5.68 (1.20)**      | <0.001  |
| Triglycerides (mg/dL) | 109.4 (64.7) | 118.4 (61.4) | 117.7 (59.8)       | 0.062   |
| HDL-cholesterol (mg/dL) | 67.3 (16.9) | 64.8 (16.1) | 64.7 (17.4)        | 0.173   |
| LDL-cholesterol (mg/dL) | 120.8 (27.4) | 117.2 (23.8) | 111.6 (26.0)       | 0.273   |
| Fasting glucose (mg/dL) | 103.2 (20.2) | 100.1 (13.9) | 99.7 (12.9)        | 0.550   |
| Systolic blood pressure (mmHg) | 124.0 (17.0) | 122.5 (15.1) | 127.3 (14.3)       | 0.532   |
| Diastolic blood pressure (mmHg) | 73.7 (11.0) | 70.4 (9.9)*  | 71.4 (10.2)        | 0.006   |

### Clinical information, n (%)

- Hypertension: 650 (54.9) 49 (52.7) 51 (64.6) 0.215
- Hyperglycemia: 65 (5.5) 8 (8.6) 3 (3.8) 0.351
- Dyslipidemia: 331 (28.0) 38 (40.9) 28 (35.4) 0.014

### Brachial-ankle PWV (cm/sec)

1,578.0 (317.9) 1,647.3 (374.4) 1,747.3 (320.1)** <0.001

Data presented are mean (SD) unless otherwise stated.

| p value | p value | p value |
|---------|---------|---------|
| <0.05   | <0.01   | <0.01   |

*Definition of abbreviations: FEV₁: Forced expiratory volume in one second, FVC: Forced vital capacity, % predicted: percentage of the predicted value, HDL: high-density lipoprotein, hsCRP: hypersensitivity C-reactive protein, PWV: Pulse Wave Velocity, Pack-years: (number of cigarettes smoked per day × number of years smoked) / 20

Airflow limitation was defined as FEV₁/FVC<0.7.

Analysis of variance (ANOVA) or Kruskal-Wallis test were used to assess the difference in characteristics by the category of airflow limitation. Subsequent analysis of differences between subgroups was performed using the Scheffe’s test. Chi-square test was performed for categorical variables.

Hypertension: antihypertensive medication use, or systolic blood pressure ≥130 mmHg, or diastolic blood pressure ≥85 mmHg.

Hyperglycemia: blood glucose-lowering medication use, or elevated fasting glucose >110 mg/dL.

Dyslipidemia; medication use, or triglycerides ≥150 mg/dL, or HDL-C < 40 mg/dL, or LDL-C > 140mg/dL.

The subjects with forced expiratory volume in one second / forced vital capacity (FEV₁/FVC) >70% and FEV₁ <80% of predicted (n=93) were excluded from this study. Ultimately, a total of 1,356 subjects without clinical cardiovascular diseases, asthma, or other respiratory diseases were assessed (Fig. 1, Table 1). None of the subjects were diagnosed with COPD or had been receiving treatment for COPD among the subjects with airflow limitation in the present study.

All the participants in the present study gave their informed consent to undergo a screening examination. Our research protocol was approved by the Human Ethics Committee of Kumamoto University and the Japanese Red Cross Kumamoto Health Care Center.
**Anthropometry**

The height and weight of each patient were measured, and the body mass index (BMI) was calculated as the weight (kg) divided by the height (m²).

**Pulmonary function tests**

Spirometry was performed using an electronic spirometer (DISCOM-21 FX: CHEST MI, Tokyo, Japan), as previously described (15-18), using equipment and quality criteria which complied with international recommendations (19). Reversibility tests were not performed for the present study and the classifications were based on the pre-bronchodilator levels. In accordance with the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines, we used a FEV₁/FVC ratio of <70% to define airflow limitation (1).

The predicted values were determined from the prediction equations published by the Japanese Respiratory Society (JRS) (20): men, 0.036×height (cm) -0.028×age-1.178; women, 0.022×height (cm)-0.022×age-0.005. The criteria used for the COPD staging were as follows: Stage I (mild COPD): FEV₁/FVC<70% and FEV₁ ≥80% of predicted; Stage II (moderate COPD): FEV₁/FVC<70% and 50%≤ FEV₁<80% of predicted; Stage III (severe COPD): FEV₁/FVC<70% and 30%≤ FEV₁<50% of predicted; and Stage IV (very severe COPD): FEV₁/FVC<70% and FEV₁ <30% of predicted. The subjects were divided into three groups: including a control group (normal pulmonary function), GOLD Stage I (mild AL), and GOLD Stage II-IV (very severe AL). The subjects with a normal pulmonary function were defined as FEV₁/FVC>70% and FEV₁ >80% of predicted values.

**Arterial stiffness as determined by baPWV**

baPWV is a useful and safe noninvasive method for assessing arterial stiffness (13) which may be used as a measure of health in various conditions. The baPWV can be obtained by simply wrapping the four extremities with blood pressure cuffs and can be easily used to screen a large number of subjects (13). In the present study, the baPWV was measured while the subject was in the supine position, after at least 5 min of rest, using an automated device (form PWV/ABI; Omron Colin, Komaki, Japan) as previously described (13). For the analysis, we used the average of two measurements. A cut-off baPWV value of >1,400 cm/s was used for risk prediction and screening (14).

**Laboratory measurements**

Following an overnight fast, blood samples were obtained to measure the serum levels of routine medical check-up indicators, including triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting glucose, and hypersensitivity C-reactive protein (hsCRP), as previously described (18). The hsCRP levels were measured using a high-sensitivity latex assay.

**Clinical information**

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained nurses using an automated digital sphygmomanometer (HEM-904; Omron, Kyoto, Japan) placed on the upper arm at heart height, while the subject was seated, following 5 minutes of rest. Hypertension was defined as antihypertensive medication use, a systolic blood pressure of ≥130 mmHg, or diastolic blood pressure of ≥85 mmHg. Hyperglycemia was defined as blood glucose-lowering medication use, or a fasting serum glucose level of ≥110 mg/dL. Dyslipidemia was defined as medication use, triglycerides of ≥150 mg/dL, HDL-C of <40 mg/dL, or LDL-C of >140 mg/dL.

**Statistical analysis**

The results are given as the means (SD). The results for the subjects with airflow limitation and a normal pulmonary function were compared using an analysis of variance (ANOVA), the Kruskal-Wallis test for continuous variables, or the Chi-square test for categorical variables. The post-hoc Scheffe’s test was used to assess the difference in characteristics according to the pulmonary function status. A multivariate logistic regression model adjusted for the age, BMI, hsCRP, smoking status, hypertension, hyperglycemia, and dyslipidemia was used to assess the relationship between the airflow limitation severity and the prevalence of increased baPWV (>1,400 cm/s). The significance of the correlations was evaluated by determining Spearman’s rank correlation coefficients. A p value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed using the IBM SPSS statistical package for Windows, version 20.0 (IBM Co., New York, USA).

**Results**

**Study population characteristics**

Table 1 shows the characteristics of the study subjects based on their pulmonary function status. The numbers of subjects with normal pulmonary function, mild airflow limitation, and moderate-to-severe airflow limitation were 1,184, 93, and 79, respectively. In the present study, none of the subjects demonstrated very severe airflow limitation. Among the non-smokers (n=799), 9.6% (77/799) fulfilled the criteria for airflow limitation, 5.8% (46/799) met the criteria for mild airflow limitation, and 3.9% (31/799) met the criteria for moderate-to-severe airflow limitation. The non-smokers comprised 44.8% (77/172) of all the subjects with airflow limitation: 49.5% (46/93) of all the subjects with mild airflow limitation and 39.2% (31/79) of all the subjects with moderate-to-severe airflow limitation. Significant differences in the pulmonary function status were found with regard to age, sex, smoking status, pack-years, white blood cell count, and dyslipidemia (Table 1).
For the subjects with a normal pulmonary function, mild airflow limitation, and moderate-to-severe airflow limitation, the mean baPWV (SD) values were 1,578.0 (317.9), 1,647.3 (374.4), and 1,747.3 (320.1) cm/s, respectively (p < 0.001; Table 1, Fig. 2).

**Correlation between baPWV and FEV$_1$ % predicted**

There was a weak negative correlation between baPWV and FEV$_1$ (% predicted) in the subjects with airflow limitation (n = 172, r=-0.155; p = 0.042; Fig. 3).

**Odds ratio for the prevalence of increased baPWV**

Using logistic regression models adjusted for age, BMI, smoking status, hsCRP, hypertension, hyperglycemia, and dyslipidemia, an increased baPWV (>1,400 cm/s) was significantly associated with moderate-to-severe airflow limitation compared with a normal pulmonary function (odds ratio = 2.76; 95% confidence intervals: 1.37-5.55, p=0.004). No significant association was found between the subjects with a normal pulmonary function and those subjects with mild airflow limitation (Table 2).

**Discussion**

In the present study, we demonstrated that arterial stiffness determined by the baPWV values in the subjects with moderate-to-severe airflow limitation was significantly greater than in the control subjects with a normal pulmonary function. We found negative correlations between the baPWV levels and FEV$_1$ % predicted levels. An increased baPWV (>1,400 cm/s) was significantly associated with moderate-to-severe airflow limitation compared with a normal pulmonary function after adjusting for age, BMI, hsCRP, smoking status, hypertension, hyperglycemia, and dyslipidemia. These results suggested an association between airflow limitation and arterial stiffness and these findings may be predictive of increased arterial stiffness in the patients with moderate-to-severe airflow limitation.

The currently available data regarding the severity of airflow limitation and atherosclerosis measured by the baPWV, especially in Japanese subjects, are limited. Our results were consistent with previous reports, which have shown a relationship between COPD, pulmonary function and arterial stiffness. Mills et al. demonstrated that the patients with COPD had increased arterial stiffness compared with age- and smoking-matched controls (21). Bhatt et al. demonstrated that the aortic PWV values may be an important predictor of CVD for the patients with COPD (22). In a review by Maclay et al. (23) of men without cardiovascular disease, a relationship between reduced pulmonary function and increased PWV was found, independent of the traditional risk factors for cardiovascular disease, such as smoking, hypercholesterolemia, and hypertension (24). In these studies, however, carotid femoral pulse wave velocity (cfPWV) was used for assessing arterial stiffness. In the present study, we used the baPWV measurements to assess arterial stiffness. Compared with the cfPWV determination, the baPWV assessment includes the smaller arteries (13). The baPWV reflects the properties of the lower limb arteries and the aorta. Yamashina et al. found that an increased baPWV (>1,400 cm/s) could be used to distinguish patients with stroke or coronary heart disease, independently of the conventional atherosclerotic risk factors for both genders in a Japanese population (14). In a recently published paper, Tabara et al. showed that airflow limitation in smokers was associated with arterial stiffness as measured by the baPWV (25).

The present study focused on the possible associations between the severity of airflow limitation and arterial stiffness as assessed by the baPWV measurements and revealed that
arterial stiffness increases with an increase in the severity of airflow limitation. McAllister et al. demonstrated that the degree of arterial stiffness was related to greater disease severity as indicated by the FEV1 results (26). They further showed that arterial stiffness increases with increased severity of airflow limitation. McAllister et al. demonstrated that the degree of arterial stiffness was related to greater disease severity as indicated by the FEV1 results (26). The mechanism(s) by which arterial stiffness increases in the patients with COPD and increased with more severe airflow limitation is unknown, as is the mechanism of the pathogenesis underlying the relationship between airflow limitation and elevated baPWV levels. In a previous study by Sabit et al., the PWV values were found to be associated with the IL-6 levels; the authors postulated that the increased systemic inflammation observed in COPD may have been responsible for the observed increases in arterial stiffness (28). In a review by Maclay et al. (23), COPD was found to be associated with the systemic elastin degradation that resulted in increased arterial stiffness, and consequently increased cardiovascular risk. McAllister et al. reported pathological changes in the distal aorta to be a more likely explanation for the association between pulmonary function and aortic stiffness than the changes in the proximal aorta (29). Further studies are required to elucidate these mechanisms.

In this study population, we observed airflow limitation in 9.6% of the non-smokers; 5.8% with mild airflow limitation and 3.9% with moderate-to-severe airflow limitation. We also observed that 44.8% of the subjects with airflow limitation were non-smokers. Lamprecht et al. reported that 12.2% of the non-smokers had airflow limitation and 27.7% of the subjects with airflow limitation were non-smokers (30). The risk factors for COPD in the non-smokers included age, education, occupational exposure, environmental tobacco smoke exposure, exposure to smoke from biomass fuels, childhood respiratory diseases, and BMI alterations (30). More detailed studies are required to elucidate the risk factors for COPD in non-smokers in Japan.

There are several limitations associated with the present study. First, we did not use reversibility testing as our Institutional Review Board considered it unacceptable in the absence of a high suspicion of disease. Therefore, the subjects with airflow limitation may have included subjects with a post-bronchodilator FEV1/FVC ratio greater than 70%. This limitation has also been reported in a previous study by Iwamoto et al. (12). Our study excluded any subjects who had ever received a diagnosis of asthma or other respiratory diseases. Therefore, the subjects with airflow limitation could possibly have COPD. A modified GOLD definition that omits bronchodilation has become widely adopted by population-based epidemiological studies (2). Second, this was a cross-sectional study. Therefore, large-scale prospective studies are needed to further confirm these findings. Third, 2,211 subjects aged 40-79 years had both baPWV and pulmonary function tests among 25,879 subjects who visited the Japanese Red Cross Kumamoto Health Care Center, because baPWV was provided as an optional examination. Some selection bias may therefore be present. Despite these limitations, we found an association between the severity of airflow limitation and increased arterial stiffness.

### Conclusion

In conclusion, we herein observed that the subjects without cardiovascular disease, diagnosed with asthma, or other respiratory diseases and those who had moderate-to-severe airflow limitation had increased arterial stiffness. Therefore, efforts aimed at the earlier detection of airflow limitation and the identification of increased arterial stiffness (subclinical atherosclerosis) may become integral for the prevention of cardiovascular disease in patients with COPD.

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**Table 2. Prevalence of Increased baPWV (>1,400 cm/sec) between Subjects with AL(mild), AL(moderate-severe) and Normal Pulmonary Function.**

| baPWV (>1,400 cm/sec) | Crude | Adjusted |
|-----------------------|-------|----------|
|                       | n     | %       | OR (95%CI) | p value | OR (95%CI) | p value |
| Normal n=1,184        | 405   | 65.7    | 1 (ref)    |         | 1 (ref)    |         |
| AL (mild) n=93        | 24    | 64.9    | 1.27 0.79 2.06 0.328 |         | 1.09 0.65 1.82 0.755 |         |
| AL (moderate-severe) n=79 | 42    | 85.7    | 3.05 1.55 5.99 0.001 |         | 2.76 1.37 5.55 0.004 |         |

**Definition of abbreviations:** n: number, OR: Odds ratio, CI: Confidence Interval, AL: Airflow Limitation, baPWV: brachial-ankle Pulse Wave Velocity

Airflow limitation (AL) was defined as FEV1/FVC ratio <0.7. Subjects with systolic blood pressure ≥130mmHg or diastolic blood ≥85mmHg or those using antihypertensive drugs were considered to have hypertension. Subjects with fasting serum glucose levels >110mg/dl, or those with blood glucose-lowering medication use were considered to have hyperglycemia. Subjects with triglyceride >150mg/dl, or LDL-C >80mg/dl, or LDL-C >140mg/dl, or those with dyslipidemia medication were considered to have dyslipidemia.

A multivariate logistic regression model adjusted for age, smoking habits, body mass index (BMI), hs-CRP, hypertension, hyperglycemia, and dyslipidemia.
The authors state that they have no Conflict of Interest (COI).

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