



Original Article

Relation between respiratory function and arterial stiffness assessed using brachial-ankle pulse wave velocity in healthy workers

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Abstract. [Purpose] Current studies report that patients with chronic obstructive pulmonary disease (COPD) may also have arteriosclerosis. This study aimed to investigate the relationship between respiratory function and arterial stiffness in healthy workers using the brachial-ankle pulse wave velocity (baPWV). [Subjects and Methods] This study included 104 male Japanese workers without COPD. We collected participant information and measured hemodynamics, body composition, and respiratory function. [Results] In the correlation analysis, baPWV showed a significant positive correlation with age, smoking index, systolic blood pressure, diastolic blood pressure, and heart rate, and a significant negative correlation with height, fat free mass, lower limb muscle mass, forced vital capacity (FVC), and forced expiratory volume in one second (FEV1). In multiple regression analysis using factors other than baPWV and respiratory function as adjustment variables, both FVC and FEV1 showed a significant negative relationship with baPWV ($p=0.009$ and $p=0.027$, respectively). FEV1/FVC was not significantly related to baPWV ($p=0.704$). [Conclusion] The results of this study indicated that FEV1/FVC and the proportion of FEV1 predicted, which are indicators of airflow limitation, are not predictors of baPWV in workers without airflow limitation. However, since baPWV showed a significant negative relationship with FVC and FEV1, the reduction in respiratory function that does not cause airflow limitation, such as FVC or FEV1 decline, may be related to an increase in the risk of arterial stiffness.

Key words: Respiratory function, Arterial stiffness, Worker

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INTRODUCTION

Cardiovascular disease (CVD) is among the leading causes of morbidity and mortality worldwide¹⁻³). The prevention of CVD is an urgent public health issue in Japan as well as other countries around the world. Arterial stiffness can be used as an assessment of the risk of CVD. As one of the methods to measure arterial stiffness, the brachial-ankle pulse wave velocity (baPWV)⁴⁻⁶) can be used to evaluate arteriosclerosis simply by fitting a cuff for blood pressure measurement on the limbs. A meta-analysis of 12 cohort studies confirmed that baPWV was an independent predictor for cardiovascular disease onset⁷).

The risk of arterial stiffness has also been reported in chronic obstructive pulmonary disease (COPD). The prevalence of COPD has increased worldwide⁸), and recent studies have reported that COPD affects not only the lungs but also the whole body^{9, 10}). Ischemic heart disease is highly prevalent among individuals with mild to moderate airflow limitation¹¹).

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Iwamoto et al.¹²⁾ reported that smokers with airflow limitation were observed to have intimal medial thickening in the carotid artery. Thus, patients with COPD may be at high risk of arteriosclerosis¹³⁾. However, no association between respiratory function itself and arterial stiffness has been shown because these studies included patients with airflow limitation. Since the relationship between respiratory function and arteriosclerosis in healthy workers has not been studied, it is unknown whether respiratory function is an influencing factor in preventing arteriosclerosis.

Therefore, the aim of this study was to analyze the relationship between respiratory function and arterial stiffness and to examine whether respiratory function is also an important factor in the prevention of arterial stiffness using baPWV.

SUBJECTS AND METHODS

Respiratory function was measured in 127 male employees of two companies in accordance with the health assessment conducted by Kyushu Rosai Hospital Research Center for the Promotion of Health and Employment Support, in 2015. After having informed participants of the purpose of the study and participant anonymity, written informed consent was obtained from 120 subjects. Nine participants with incomplete self-administered questionnaires, pulmonary disease, or a history of pulmonary disease were excluded. Based on the type of industry according to the International Standard Classification of Occupations (Major Groups)¹⁴⁾, the study cohort comprised the following individuals: legislators, senior official, and managers (n=34); professionals, technicians, and associate professionals (n=25); clerks (n=31); service workers and associate professionals (n=10); craft and related trades workers (n=1); and others (n=10). The study was approved by the Ethics Committee of the Kyushu Nutrition Welfare University, Higashi Chikushi Junior College (No. 1507).

Self-administered questionnaires were used to obtain the following information: age, height, disease under treatment, prevalence of metabolic syndrome (MetS) risk factors (hypertension, dyslipidemia, diabetes, and obesity), smoking habits, drinking habits, and physical activity. Smoking habits were described per the smoking index, which is calculated by multiplying the number of years of smoking by the average number of cigarettes smoked per day. Drinking habits were estimated as the total weekly amount of alcohol consumed (g/week), calculated on the basis of the type and frequency of alcohol. Physical activity was evaluated using the short version of the International Physical Activity Questionnaire (IPAQ) Japanese edition, whose reliability and validity were confirmed in previous studies^{15, 16)}. Physical activity (Mets-mins/week) was calculated using the method developed by Murase et al.¹⁶⁾ The sum of values obtained by multiplying the intensity of the physical activity with the time, according to vigorous, moderate, and walking activity of the exercise in IPAQ, was calculated as the physical activity (Mets-mins/week).

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and baPWV as indices of arterial stiffness⁹⁾ were measured using a blood pressure pulse wave examination device (form BP-203RPEII, FUKUDA COLIN Co., Ltd., Tokyo, Japan). A manchettes for blood pressure measurement was wound around the limbs with the participant in the supine position. An electrocardiogram clip was attached to both hand joints, and a heart sound microphone was attached near the left border of the fourth intercostal sternum. The stability of the electrocardiogram signal was confirmed before measurement. SBP and DBP adopted the measured values of the right brachium, and baPWV adopted the measured value on the right side.

Body weight, body mass index, waist circumference, percentage of body fat, fat free mass, waist-to-hip ratio, and regional muscle mass were measured using a body composition analyzer (InBody 720, InBody Co., Ltd., Seoul, Korea) by bioelectric impedance analysis. The measurement was carried out in a standing position for approximately 90 seconds. Upper limb muscle mass and lower limb muscle mass were calculated from the results of regional muscle mass.

For visceral fat measurement, a visceral fat measuring device (HDS-2000 DUALSCAN, OMRON HEALTHCARE Co., Ltd., Kyoto, Japan) was used. This instrument measures the visceral fat area (VFA) using the DUAL impedance method and shows a high correlation with measurement using X-ray computed tomography¹⁷⁾. Measurements were obtained in the supine position, and the VFA was measured from the cross-sectional area of the abdomen, fat-free area, and subcutaneous fat area measurements.

Spirometry was performed in accordance with guidelines specified by the Committee of Pulmonary Physiology of the Japanese Respiratory Society¹⁸⁾. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), forced expiratory volume in one second percent (FEV1/FVC) were measured using an electronic spirometer (Autospiro AS-507, MINATO MEDICAL SCIENCE Co., Ltd., Osaka, Japan). The measurement was performed in the sitting position. Predicted FVC and predicted FEV1 were calculated using the equation developed by the Japanese Respiratory Society¹⁹⁾. Participants with FEV1/FVC <70% were considered to have airflow obstructions according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines²⁰⁾. Seven participants with airflow obstruction were excluded, and 104 participants were included in this study.

The relationships among participant information, body composition, respiratory function, and arterial stiffness were analyzed using Spearman's rank correlation coefficient for continuous variables. Two groups, identified in accordance with the prevalence of MetS risk factors, were compared using the Mann-Whitney test. A multiple stepwise linear regression analysis was performed with baPWV as the dependent variable, FVC, FEV1, FEV1/FVC as independent variables, and 24 items, such as participant information, body composition, hemodynamics excluding baPWV, as adjustment factors. Analyses were performed using IBM SPSS Statistics 22.0 (IBM Co., Armonk, NY, USA). P-values less than 0.05 were considered statistically significant.

Table 1. The characteristics of analysis participants

| Variables | N=104 |
|--------------------------------------|---------------------------|
| Participants information | |
| Age (years) | 46.5 (39.5–53) |
| Height (cm) | 171.4 ± 5.4 |
| Presence of MetS risk factors (n, %) | 24 (23.1) |
| Hypertension (n, %) | 11 (10.6) |
| Dyslipidemia (n, %) | 3 (2.9) |
| Diabetes (n, %) | 3 (2.9) |
| Obesity (n, %) | 0 (0) |
| Smoking index | 150.0 (0.0–400.0) |
| Drinking habits (n, %) | 74.0 |
| Alcohol consumption (g/week) | 91.0 (2.5–205.0) |
| Physical activity (Mets-mins/week) | 960.0 (495.0–1637.5) |
| Anthropometry | |
| Body weight (kg) | 71.8 (66.5–81.1) |
| Body mass index (kg/m ²) | 24.8 (22.6–26.7) |
| Waist circumference (cm) | 83.9 (77.7–92.2) |
| Percentage of body fat (%) | 23.4 ± 6.9 |
| Fat-free mass (kg) | 55.5 ± 5.3 |
| Waist-to-hip ratio | 0.85 (0.82–0.90) |
| Upper limb muscle mass (kg) | 6.0 ± 0.8 |
| Lower limb muscle mass (kg) | 18.0 ± 1.9 |
| Trunk muscle mass (kg) | 24.3 ± 2.5 |
| Visceral fat area (cm ²) | 82.2 (63.0–106.5) |
| Hemodynamics | |
| SBP (mmHg) | 131.0 (123.5–140.0) |
| DBP (mmHg) | 79.2 (73.1–87.4) |
| Heart rate (beat/min) | 70.1 ± 12.1 |
| baPWV (cm/sec) | 1,293.0 (1,203.5–1,468.0) |
| Respiratory function | |
| FVC (l) | 4.4 ± 0.6 |
| FVC %predicted | 101.2 ± 10.6 |
| FEV1 (l) | 3.6 ± 0.5 |
| FEV1 %predicted | 96.4 ± 10.1 |
| FEV1/FVC (%) | 82.0 ± 4.7 |
| FEV1/FVC %predicted | 96.0 ± 5.5 |

The values were described as mean ± standard deviation or median (interquartile range 25–75%), for normally and not normally distributed data, respectively. Categorical data were expressed as a frequency and percentage.

MetS: metabolic syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure; baPWV: brachial-ankle pulse wave velocity; ABI: Ankle Brachial Index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity

RESULTS

The values were described as mean ± standard deviation or median (interquartile range 25–75%) for normally and not normally distributed data, respectively. Categorical data were expressed as frequencies and percentages.

Table 1 shows the participant information, body composition, hemodynamics, and respiratory function of 104 participants.

The correlation between baPWV and participant information, body composition, hemodynamics, and respiratory function are shown in Table 2. A significant positive correlation was found between baPWV and age ($p < 0.01$), smoking index ($p < 0.01$), SBP ($p < 0.01$), DBP ($p < 0.01$), HR ($p < 0.01$), fat-free mass ($p < 0.05$), lower limb muscle mass ($p < 0.01$), FVC ($p < 0.01$), and FEV1 ($p < 0.01$). However, there was no significant correlation between baPWV and other respiratory functions including expiratory flow.

Table 3 shows the relationship between arterial stiffness and MetS risk factor. No significant difference was observed in any factor for baPWV.

Regarding the relation between baPWV and respiratory function, the results of multiple regression analysis with other factors as adjustment variables are shown in Table 4. Both FVC and FEV showed a significant negative correlation with baPWV ($p = 0.009$ and $p = 0.027$, respectively). FEV1/FVC had no significant relationship with baPWV ($p = 0.704$).

Table 2. The correlation coefficient between baPWV and other factors

| | baPWV (cm/sec) |
|--------------------------------------|----------------|
| Age (years) | 0.314** |
| Height (cm) | -0.348** |
| Smoking index | 0.337** |
| Alcohol consumption (g/week) | 0.145 |
| Physical activity (Mets-mins/week) | -0.034 |
| Body weight (kg) | -0.108 |
| Body mass index (kg/m ²) | 0.048 |
| Waist circumference (cm) | 0.024 |
| Percentage of body fat (%) | 0.062 |
| Fat-free mass (kg) | -0.206* |
| Waist-to-hip ratio | 0.086 |
| Upper limb muscle mass (kg) | -0.069 |
| Lower limb muscle mass (kg) | -0.321** |
| Trunk muscle mass (kg) | -0.100 |
| Visceral fat area (cm ²) | 0.144 |
| SBP (mmHg) | 0.504** |
| DBP (mmHg) | 0.511** |
| Heart rate (beat/min) | 0.283** |
| FVC (l) | -0.347** |
| FVC %predicted | -0.158 |
| FEV1 (l) | -0.364** |
| FEV1 %predicted | -0.181 |
| FEV1/FVC (%) | -0.043 |
| FEV1/FVC %predicted | 0.059 |

*p<0.05, **p<0.01

baPWV: brachial-ankle pulse wave velocity; SBP: systolic blood pressure; DBP: diastolic blood pressure; FEV1: forced expiratory volume in one second; FVC: forced vital capacity

Table 3. Relationships between RbPWV and MetS risk factors

| Risk factors | baPWV (cm/sec) Values |
|-------------------------------|---------------------------|
| Hypertension | |
| Yes | 1,385.0 (1,225.5–1,508.0) |
| No | 1,289.0 (1,203.0–1,449.0) |
| Dyslipidemia | |
| Yes | 1,247.0 (1,105.0–1,401.0) |
| No | 1,295.0 (1,204.0–1,457.0) |
| Diabetes | |
| Yes | 1,488.0 (1,388.5–1,568.5) |
| No | 1,291.0 (1,203.0–1,450.0) |
| Presence of MetS risk factors | |
| Yes | 1,296.5 (1,231.0–1,534.0) |
| No | 1,293.0 (1,200.5–1,444.5) |

baPWV: brachial-ankle pulse wave velocity; MetS: metabolic syndrome

Table 4. Multiple regression analysis between baPWV and respiratory function

| | baPWV Coefficient |
|--------------|----------------------|
| FVC (l) | -0.261** |
| FEV1 (l) | -0.219* |
| FEV1/FVC (%) | 0.029 |

*p<0.05, **p<0.01

baPWV: brachial-ankle pulse wave velocity; FEV1: forced expiratory volume in one second; FVC: forced vital capacity
A multivariate logistic regression model adjusted for age, height, presence of MetS risk factors, hypertension, dyslipidemia, diabetes, smoking index, alcohol consumption, physical activity, body weight, body mass index, waist circumference, percentage of body fat, fat-free mass, waist-to-hip ratio, upper limb muscle mass, lower limb muscle mass, trunk muscle mass, visceral fat area, systolic blood pressure, diastolic blood pressure, and heart rate.

DISCUSSION

Among various diseases related to aging, COPD has a high incidence among the elderly²¹). It has been suggested that systemic inflammation associated with COPD has an adverse effect not only on the lungs but also on the vascular system^{11–13}). Therefore, the risk of cardiovascular disease may increase with the onset of COPD. However, the relationship between respiratory function and hemodynamics in healthy volunteers who do not develop COPD is not clear, and the causal relationship between respiratory function and arterial stiffness has not been studied. In this study, we aimed to examine the relationship between arterial stiffness and expiratory flow in labor generations without airflow restriction.

In workers without airflow limitation, baPWV, an index of arterial stiffness, was found to have a significantly negative relationship between FVC and FEV1 in this study. This implies that it is related to the progression of arterial stiffness and decreased respiratory function. However, FEV1/FVC or the proportion of FEV1 predicted, which is the standard indicator of COPD severity per the GOLD classification, cannot be a predictor of baPWV. Oda et al.¹³) reported that baPWV increased significantly in subjects with strong airflow restriction, which are applicable to stages II to IV in the GOLD severity classification, compared to healthy subjects without airflow limitation. They also reported that there was a significant negative relationship between FEV1% predicted and baPWV. McAllister et al.²²) reported that baPWV increases if the severity of emphysema is high or FEV1% predicted is low in COPD patients. These studies on individuals with airflow limitation show that the risk of arterial stiffness may increase with decreased expiratory flow.

However, the reason the baPWV increases with the airflow limitation is not clearly understood yet. Inflammatory cytokines such as tumor necrosis factor (TNF)- α , which is responsible for systemic inflammation, and inflammatory markers such as C-reactive protein, leukocytes, and fibrinogens are elevated in subjects with chronic airflow limitation^{9, 23}). As a potential pathomechanism, the “spill-over” hypothesis suggests that chronic inflammation of the lung local region spreads throughout

the body²⁴). Systemic inflammation accompanying COPD that may adversely affect the vascular system is expected; it has been reported that systemic inflammation in COPD may increase the risk of arteriosclerosis²⁵). We did not obtain a relationship between baPWV and the indicator of airflow limitation in this study. Since we could not investigate the treatment of COPD in this study, we excluded those with FEV1/FVC less than 70% to completely exclude those with COPD. Thus, the distribution of values of FEV1/FVC was narrowly restricted, so there is a possibility that there was no significant difference. However, decreased respiratory function without airflow disturbance, such as FVC and FEV1 decrease, may possibly be related to the increase in the risk of arterial stiffness. Further studies are necessary to elucidate this mechanism.

In the univariate analysis in this study group, baPWV was correlated with lower limb muscle mass and smoking index as well as age, height, and hemodynamics. With aging, the hardness of the artery increases owing to changes in the content and properties of the elastic fiber, which is largely responsible for the hardness of the arterial wall, an increase in which increases pulse wave velocity^{26, 27}). In addition, baPWV has been associated with blood pressure and heart rate. It can be inferred that hemodynamics is a major influence factor because blood pressure rises and arterial tightness decreases vascular elastic modulus^{27–29}). For lower limb muscle mass, Ochi et al.³⁰) revealed that the cross-sectional area of the quadriceps muscles corrected for body weight has a very significant negative correlation with baPWV among men. Tanimoto et al.³¹) showed that lower limb muscle mass decreases greatly, especially with age. Therefore, health prevention that focuses on lower limb muscle mass may be necessary to prevent arterial stiffness. Regarding the relationship between the smoking index and baPWV, a prospective prior study³²) reported that continuous smoking promotes the progression of arterial stiffness. Thus, we wish to consider not only the smoking index but also the effect of passive smoke.

There are several limitations associated this study. First, this is a cross-sectional study. A prospective longitudinal study is required for the study of the relationship between respiratory function and arterial stiffness for individuals without airflow restriction. Second, we have not studied smoking habits in detail. It is necessary to consider whether smoking habits are present or not, including the period of smoking cessation.

In conclusion, we aimed to examine the relationship between arterial stiffness and expiratory flow in laboring individuals without airflow restriction. The results of this study show that FEV1/FVC or the proportion of FEV1 predicted, which are indicators of airflow limitation, cannot be predictors of baPWV, which is an index of arterial stiffness in workers without airflow limitation. However, baPWV showed a significant negative relationship with FVC and FEV1. The reduction in respiratory function, which does not extend to airflow disturbance such as FVC or FEV1 decline, may be related to the increase in the risk of arterial stiffness.

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