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Relationship of Atherosclerotic Risk Factors with Pulmonary Age and Vascular Age

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Abstract

Background: Different organs undergo different atherosclerotic changes due to aging. This study examined the effects of atherosclerotic risk factors on pulmonary and vascular age.

Methods: Our subjects were 531 persons whose pulmonary and vascular age was measured at our center. First, a correlation between pulmonary age and cardio-ankle vascular index (CAVI), an indicator of vascular age, was examined. Based on mean pulmonary age (60.8) and CAVI (8.53), subjects were divided into four groups (G I: CAVI ≤ 8.5 pulmonary age ≤ 60, G II: CAVI ≥ 8.6 pulmonary age ≤ 60, G III: CAVI ≤ 8.5 pulmonary age ≥ 61, G IV: CAVI ≥ 8.6 pulmonary age ≥ 61). Groups were compared in terms of chronological age, sex, affected atherosclerotic disease (high blood pressure (HBP), dyslipidemia, diabetes mellitus (DM)), blood pressure, low-density lipoprotein cholesterol, triglyceride, high-density lipoprotein cholesterol, fasting blood sugar, HbA1c, waist circumference, bone density, aortic calcification score and smoking score.

Results: A moderate, positive correlation was seen between pulmonary age and CAVI. Comparisons with atherosclerotic risk factors in the four groups revealed: i) HbA1c was associated with increased pulmonary age; ii) diastolic blood pressure and aortic calcification score were associated with increased CAVI; and iii) HBP, dyslipidemia, chronological age and systolic blood pressure were associated with increases in both pulmonary age and CAVI.

Conclusion: Although a correlation was seen between pulmonary and vascular age, it was not particularly high. The present study revealed that this was because atherosclerotic risk factors affect pulmonary and vascular age differently.

Keywords atherosclerotic risk factors, pulmonary age, vascular age, CAVI

Chronic obstructive pulmonary disease (COPD) is a systemic disease[1], and a growing number of studies have reported associations between COPD and atherosclerosis[2–4].

Pulmonary function tests are gaining attention due to the increasing number of patients with COPD[5]. Of all the pulmonary function tests, forced expiratory volume in 1 s (FEV1) shows the best correlation with chronological age[5], and the Japanese Respiratory Society has proposed the use of pulmonary age as an indicator of the degree of aging of the lungs[6]. Arterial stiffness is correlated with risk of cardiovascular lesions[7], and the cardio-ankle vascular index (CAVI) has been drawing attention as a new indicator of arterial stiffness (vascular age) because it is a convenient, non-invasive measure that is independent of blood pressure[8–10].

However, according to studies that have investigated correlations between pulmonary age and CAVI, the degree of correlation is not particularly high[11]. We hypothesized that atherosclerotic risk factors may affect pulmonary and vascular age differently and to verify it, examined the effects of atherosclerotic risk factors on pulmonary age and vascular age.

Methods

Subjects

This study recruited 531 consecutive subjects whose pulmonary age and CAVI were measured at our center between September 1, 2016 and May 31, 2017. Approval for this study was obtained from the Saitama Medical University Hospital Ethics Committee and informed consent was obtained from all participants.

Measurements

The Pulmonary age and CAVI of all subjects were first measured and a correlation was examined. Based on mean pulmonary age (60.8) and CAVI (8.53), subjects were divided into four groups (G I: CAVI ≤ 8.5 pulmonary age ≤ 60, G II: CAVI ≥ 8.6 pulmonary

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age ≤ 60, G III: CAVI ≤ 8.5 pulmonary age ≥ 61, G IV:CAVI ≥ 8.6 pulmonary age ≥ 61), and the groups were compared in terms of qualitative and quantitative atherosclerotic risk factors. Qualitative variables were sex breakdown and affected atherosclerotic disease (high blood pressure (HBP), dyslipidemia, diabetes mellitus (DM)). Quantitative variables were chronological age, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), pulse pressure (PP), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood sugar (FBS), hemoglobin A1c (HbA1c), bone density, aortic calcification score (Ca score) and smoking score. Ca score was determined based on the number of calcified aorta at the ascending aorta, aortic arch, chest descending aorta and abdominal descending aorta, from 0 to 4. The smoking score was 0 for not smoking, 1 for quit smoking and 2 for still smoking.

Devices used were: i) a spirometer for pulmonary age (Spirosift SP-7710; Fukuda Denshi, Tokyo, Japan); and ii) a vascular screening system for CAVI (VaSera VS-1500N; Fukuda Denshi, Tokyo, Japan).

Statistical analysis

Proportional comparisons among the four groups for qualitative variables were performed using the chi-square test, and this was followed by the Z-test for statistically significant variables. Quantitative variables were expressed as mean ± s.d., and differences among the four groups were compared by one-way analysis of variance (ANOVA), followed by the Bonferroni post hoc test. Values of $p < 0.05$ were considered statistically significant for the chi-square test, ANOVA and Z-test, and values of $p < 0.0083$ were considered significant for the Bonferroni test. SPSS version 24 (IBM, Chicago, IL, USA) was used for the statistical analysis.

Results

Table 1 shows the sex difference between measured qualitative and quantitative variables, and results of comparison.

Correlation between pulmonary age and CAVI

A significant, moderate, positive correlation was evident between pulmonary age and CAVI (pulmonary age = 6.99 × CAVI+1.22 r=0.445 ($p < 0.001$)) (**Fig. 1**).

Comparison of atherosclerotic risk factors among four groups

Table 2 shows the results of the chi-square test for qualitative variables and ANOVA for quantitative variables. Significant differences among the four groups were observed in the following atherosclerotic risk factors: i) qualitative variables (sex breakdown, HBP, dyslipidemia and DM); ii) quantitative variables (chronological age, waist circumference, SBP, DBP, MBP, PP, HDL-C, FBS, HbA1c, Ca score and Smoking score). These factors were used in the next analysis.

Fig. 2-1 and **Fig. 2-2** show the results of the Z-test for qualitative variables and Bonferroni test for quantitative

Table 1. Characteristics of Study Subjects

	Men	Women	*p*
n (%)	321 (60.5%)	210 (39.5%)	<0.001
HBP (%)	123 (38.3%)	49 (23.3%)	0.001
Dyslipidemia (%)	104 (32.4%)	50 (23.8%)	ns
DM (%)	49 (15.3%)	6 (2.9%)	<0.001
Chronological age (years)	63.3 ± 9.9	63.1 ± 3.8	ns
Waist circumference (cm)	85.7 ± 8.4	80.1 ± 8.3	<0.001
SBP (mmHg)	126.5 ± 13.5	120.5 ± 15.0	<0.001
DBP (mmHg)	78.5 ± 9.1	73.9 ± 9.6	<0.001
MBP (mmHg)	110.5 ± 11.4	104.9 ± 12.6	<0.001
PP (mmHg)	48.0 ± 9.0	46.6 ± 10.3	ns
LDL-C (mg/dL)	122.8 ± 29.8	73.9 ± 9.7	0.023
TG (mg/dL)	117.1 ± 76.9	92.7 ± 43.6	<0.001
HDL-C (mg/dL)	58.9 ± 14.5	72.5 ± 16.9	<0.001
FBS (mg/dL)	106.6 ± 21.2	98.0 ± 11.3	<0.001
HbA1c (%)	5.7 ± 0.7	5.5 ± 0.3	<0.001
Bone density (g/cm^2)	0.60 ± 0.09	0.44 ± 0.09	<0.001
Ca score	1.96 ± 1.34	1.67 ± 1.38	ns
Smoking score	0.78 ± 0.67	0.20 ± 0.53	<0.001
Pulmonary age (years)	65.0 ± 18.5	54.4 ± 16.1	<0.001
CAVI	8.8 ± 1.1	8.2 ± 1.1	<0.001

Variables are given as number (%) or mean ± s.d.
HBP: high blood pressure, DM: diabetes mellitus, SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, PP: pulse pressure, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, FBS: fasting blood sugar

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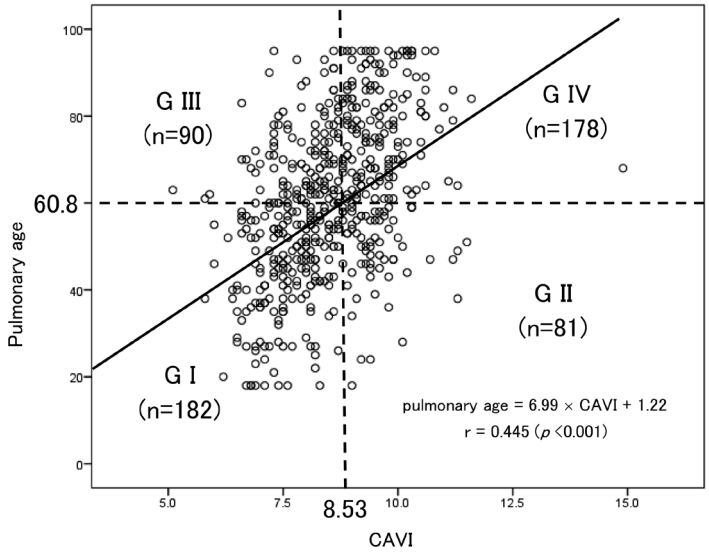

Fig.1. Correlation of Pulmonary Age and CAVI in Subjects Divided into 4 Groups by Mean of Pulmonary Age and CAVI
60.8: mean of pulmonary age; 8.53: mean of CAVI. A significant, moderate, positive correlation was evident between pulmonary age and CAVI (pulmonary age = 6.99 × CAVI+1.22 r=0.445 (p <0.001)). Subjects were divided into four groups based on the means of the parameters (pulmonary age: 60.8 years; CAVI: 8.53).

Table 2. Comparison of Atherosclerotic Risk Factors Among Four Groups

	G I (*n*=182)	G II (*n*=81)	G III (*n*=90)	G IV (*n*=178)	*p*
Sex breakdown: Men (%)	79 (43.4%)	47 (58.0%)	57 (63.3%)	138 (77.5%)	<0.001
HBP (%)	24 (13.2%)	27 (33.3%)	34 (37.8%)	88 (49.4%)	<0.001
Dyslipidemia (%)	33 (18.1%)	29 (35.8%)	31 (34.4%)	62 (34.8%)	<0.006
DM (%)	6 (3.3%)	7 (8.6%)	10 (11.1%)	33 (18.5%)	<0.001
Chronological age (years)	55.7 ± 8.8	66.0 ± 6.1	62.6 ± 9.1	70.0 ± 6.7	<0.001
Waist circumference (cm)	81.6 ± 8.6	83.8 ± 6.8	84.7 ± 10.7	84.7 ± 8.3	0.003
SBP (mmHg)	117.8 ± 13.9	128.3 ± 12.7	126.0 ± 14.2	127.6 ± 13.5	<0.001
DBP (mmHg)	74.3 ± 10.2	78.4 ± 8.4	78.1 ± 8.7	77.6 ± 9.4	0.001
MBP (mmHg)	103.3 ± 12.3	111.7 ± 10.2	110.0 ± 11.8	110.9 ± 11.4	<0.001
PP (mmHg)	43.5 ± 7.4	49.9 ± 10.9	47.9 ± 9.5	50.1 ± 9.7	<0.001
LDL-C (mg/dL)	126.6 ± 28.6	129.4 ± 29.9	126.3 ± 31.4	121.0 ± 28.2	ns
TG (mg/dL)	104.4 ± 91.2	108.5 ± 39.0	111.8 ± 61.8	107.9 ± 47.1	ns
HDL-C (mg/dL)	68.5 ± 18.3	63.0 ± 15.4	62.7 ± 15.3	61.3 ± 16.0	<0.001
FBS (mg/dL)	98.7 ± 18.3	101.6 ± 10.5	105.2 ± 21.4	107.5 ± 18.7	<0.001
HbA1c (%)	5.5 ± 0.5	5.5 ± 0.3	5.7 ± 0.7	5.8 ± 0.6	<0.001
Bone density (g/cm^2)	0.52 ± 0.10	0.44 ± 0.11	0.54 ± 0.15	0.51 ± 0.12	ns
Ca score	1.2 ± 1.2	1.9 ± 1.3	1.3 ± 1.2	2.6 ± 1.2	<0.001
Smoking score	0.54 ± 0.74	0.37 ± 0.56	0.52 ± 0.62	0.66 ± 0.67	0.016

Variables are given as number (%) or mean ± s.d.
HBP: high blood pressure, DM: diabetes mellitus, SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, PP: pulse pressure, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, FBS: fasting blood sugar

variables, respectively.

In terms of sex breakdown, men predominated in the high pulmonary age group (G I vs G III $p < 0.05$, G II vs. G IV $p < 0.05$). HbA1c was significantly higher in G IV than in G II ($p = 0.008$). DBP was significantly higher in G II than in G I ($p = 0.007$), and a significant difference in Ca scores was evident between G III and G IV ($p < 0.001$). HBP (G II vs. G III $p < 0.05$, G I vs. G III $p < 0.05$), dyslipidemia (G I vs. G II $p < 0.05$, G I vs. G III $p < 0.05$), chronological age (G I vs. G II $p < 0.001$, G I vs. G III p < 0.001), SBP (G I vs. G II $p < 0.001$, G I vs. G III $p < 0.001$), MBP (G I vs. G II $p < 0.001$, G I vs. G III $p < 0.001$) and PP (G I vs. G II $p < 0.001$, G I vs. G III $p < 0.001$) were significantly higher in G II and G III than in G I.

Discussion

Decreased pulmonary function and arterial stiffness are factors associated with atherosclerosis with a common background[12]. Both COPD and CAVI have associations with atherosclerosis and studies have reported the involvement of inflammatory responses and

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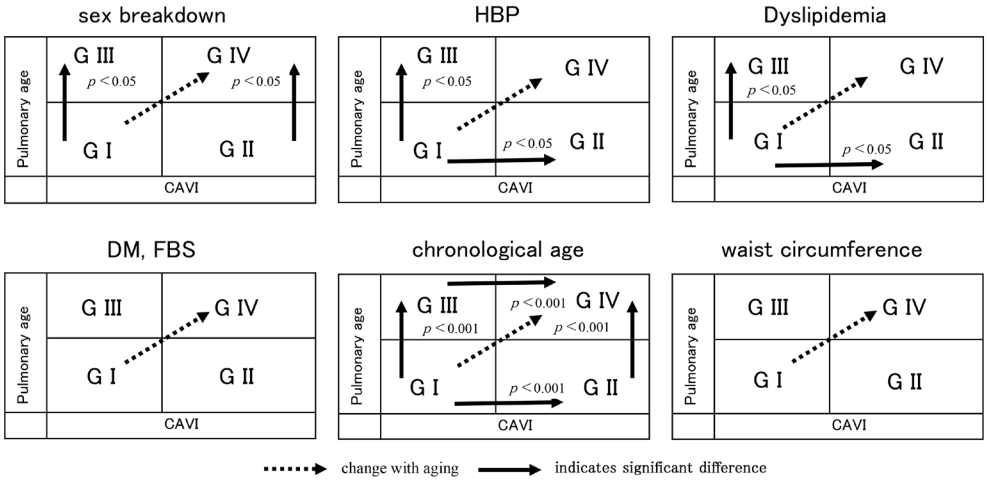

Fig.2-1. Comparison of Atherosclerotic Risk Factors Among Four Groups

Comparison of sex breakdown, HBP, Dyslipidemia, DM, FBS, chronological age and waist circumference among the four groups. In terms of sex breakdown, men predominated in the high pulmonary age groups. HBP, dyslipidemia and chronological age were significantly higher in G II and G III than in G I.

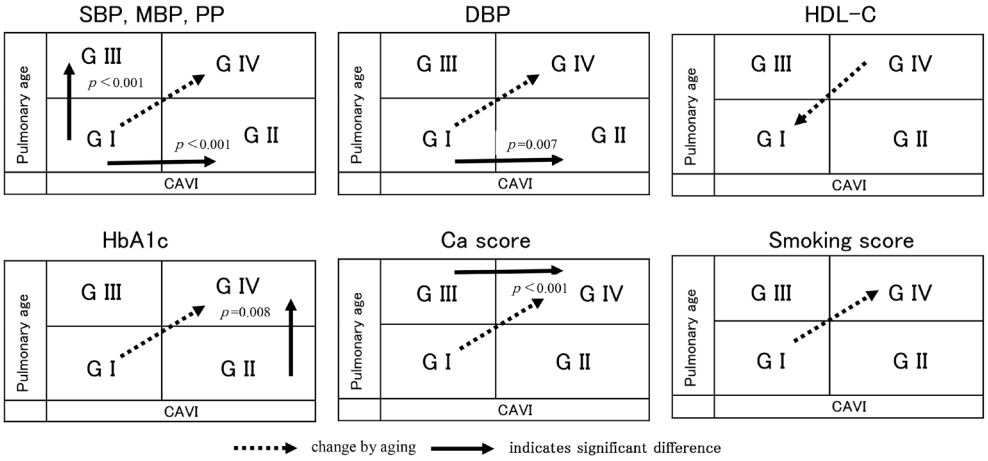

Fig.2-2. Comparison of Atherosclerotic Risk Factors Among Four Groups

Comparison of SBP, MBP, PP, DBP, HDL-C, HbA1c, Ca score and Smoking score among the four groups. HbA1c was significantly higher in G IV than in G II. DBP was significantly higher in G II than in G I. Ca score was significantly higher in G IV than in G III. SBP, MBP and PP were significantly higher in G II and G III than in G I.

high-sensitivity CRP (hs-CRP) as common factors[13–15]. However, in a study examining the degree of correlation between pulmonary age and CAVI in hypertensive patients, the correlation coefficient was not particularly high (r = 0.559)[5], similarly to our finding (r = 0.445). One reason may be that atherosclerotic risk factors affect pulmonary and vascular age differently.

Factors increasing pulmonary age

This study showed that HbA1c was a factor associated with increased pulmonary age. Previous studies have shown that HbA1c is an exacerbating factor for COPD[16,17], but mechanisms remain unclear. Since HbA1c exhibits seasonal variation[18], this may be related to seasonal exacerbations in COPD patients. Further studies are clearly warranted.

Factors increasing CAVI

The present study found that DBP and Ca score were factors associated with increased CAVI. In general, DBP increases with age until about 50 years old, and thereafter likely declines as PP increases[19]. In our study, a significant increase in DBP was seen in G II. The mean age in G I was 55.7 ± 8.8 years, compared to 66.0 ± 6.1 years in G II. The mean age of G II was significantly higher than that of G III (62.6 ± 9.1 years), but in G II, DBP had not declined despite the high age. In other words, peripheral vascular resistance had increased more than age and this was believed to be involved in the increase in CAVI.

Chronological age, HBP, dyslipidemia, DM and smoking are factors known to be associated with aortic calcification[20]. Also, increased afterload from an elevated

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central aortic blood pressure due to wave reflection is thought to be involved in the calcification of the aortic arch, rather than systemic blood pressure[21]. An increase in afterload may be associated with an increase in CAVI, but the mechanisms underlying the development of aortic calcification may vary depending on the site.

Factors that increase both pulmonary age and CAVI

This study identified HBP, SBP, MBP, PP and dyslipidemia as factors associated with increases in both pulmonary age and CAVI.

In a study of patients with hypertension, 20% of them had COPD as a complication and approximately 30% of COPD patients had hypertension[22]. In other words, hypertension appears to be a factor associated with increased pulmonary age. While CAVI is unaffected by blood pressure, patients with hypertension are known to exhibit a high CAVI[23], and hypertension is thus a factor associated with increased CAVI.

Lipid-lowering therapy with statins is effective not only in heart failure, but also in COPD[24], and dyslipidemia is thus believed to be a factor associated with increased prevalence of COPD. Dyslipidemia is almost certainly a factor that increases CAVI, since a positive correlation has been observed between serum lipid levels and CAVI in patients with hypertension[25], and CAVI is high in dyslipidemia patients[26].

Study limitations

The sex breakdown in this study may have affected our results. Men tended to have higher levels for many atherosclerotic risk factors other than chronological age (**Table 1**). In future studies, we will need to increase the number of subjects to improve examinations in terms of sex. The association of pulmonary age and smoking score were slightly short ($p = 0.009$) of the level of significance. There may have been a problem in how the smoking score was defined, and this will have to be looked at in future studies.

Conclusions

Although a correlation was seen between pulmonary and vascular age, it was not particularly high. One plausible explanation is that atherosclerotic risk factors may have different effects on pulmonary and vascular age.

This study was presented orally at the plenary session of the 58th Scientific Meeting of the Japanese Society of Ningen Dock (August 2017 Omiya).

Conflict of Interest

There are no conflicts of interest to declare concerning this study.

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