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ORIGINAL ARTICLE

Association between arterial stiffness and pulmonary function in hypertensive patients

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Arterial stiffness, assessed by cardio-ankle vascular index (CAVI), is clinically used to assess arteriosclerosis. Recently, pulmonary age, as determined by pulmonary function test, has been proposed by the Japanese Respiratory Society as a diagnostic measure for chronic obstructive pulmonary disease (COPD). This study aims to examine the association between CAVI and pulmonary function and to elucidate the correlation between vascular stiffness and pulmonary age in hypertensive patients. We enrolled a total of 45 hypertensive patients (70 ± 9 years) who had been taking antihypertensive medications for at least 1 year. Pulmonary function was measured by the percentage of predicted forced vital capacity (FVC) and the ratio of forced expiratory volume in 1 s (FEV_1) to FVC (FEV_1/FVC ratio). Pulmonary age was determined by the equation proposed by the Japanese Respiratory Society. CAVI was measured at the same clinic visit. In the simple correlation analysis CAVI correlated with the FEV_1/FVC ratio ($r=-0.399$, $P=0.007$) and pulmonary age ($r=0.559$, $P<0.001$). Multiple linear regression analysis revealed that CAVI was independently associated with FEV_1/FVC ratio ($\beta=-0.418$, $P=0.014$) and pulmonary age ($\beta=0.514$, $P=0.002$). In addition, CAVI was significantly higher in patients with increased pulmonary age (9.4 ± 1.4) than in those with normal pulmonary age (8.4 ± 0.9) ($P=0.011$). The present study indicates that an increased CAVI is independently associated with reduced pulmonary function and increased pulmonary age. Hypertensive patients with high CAVI may need to be monitored for the progression of COPD.
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INTRODUCTION

Arterial stiffness is attracting attention as an index for assessing arteriosclerosis, as it is an independent predictor of cardiovascular mortality, fatal and non-fatal coronary events, and fatal strokes in hypertensive patients.[1,2] The cardio-ankle vascular index (CAVI) is a new index of arterial stiffness.[3] As the most conspicuous feature of CAVI is a lack of dependence on blood pressure, CAVI has been recently utilized for assessing arterial stiffness in clinical settings.[4] CAVI is high in aging patients and in patients with arteriosclerotic disease, such as coronary artery disease,[5] carotid atherosclerosis[6] and chronic kidney disease,[7] and is related to many coronary risk factors such as hypertension,[8] diabetes,[9] dyslipidemia[9] and smoking.[10] Furthermore, the CAVI decreases with control of diabetes and hypertension, as well as abstention from smoking.[10] These factors suggest that CAVI is a surrogate marker of arteriosclerosis.

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation, which shows reduced forced expiratory volume in 1 s (FEV_1) in pulmonary function tests.[11,12] Recent studies have demonstrated an association between COPD and cardiovascular disease, which accounts for approximately 25 to 50% of mortality.[13–15] Furthermore, recent studies[16–19] have demonstrated the association between pulmonary function and carotid atherosclerosis. These previous studies[16–19] assessed the atherosclerosis by measuring carotid intima-media thickness and plaques. Other previous studies[20,21] have demonstrated the association between pulmonary function and atherosclerosis by measuring arterial stiffness, which was assessed by aortic pulse wave velocity. Although CAVI measures arterial stiffness, CAVI is different from aortic pulse wave velocity as CAVI reflects the stiffness of the aorta, femoral artery and tibial artery as a whole.[22]

Recently, 'pulmonary age' has been proposed by the Japanese Respiratory Society in order to diagnose COPD.[23] Pulmonary age is determined based on the pulmonary function test, including the forced vital capacity (FVC) and FEV_1. Pulmonary age is known to be high in COPD patients.[23] This study aims to examine the association between arterial stiffness assessed by CAVI and pulmonary function in hypertensive patients. Moreover, we seek to elucidate the correlation between pulmonary age assessed by pulmonary function test and vascular stiffness assessed by CAVI in hypertensive patients.

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METHODS

Subjects and protocol

The study subjects were 45 hypertensive outpatients (24 male, 21 female; mean age 70 ± 9 years, range 47–84 years) at Kagawa University Hospital who were diagnosed with hypertension. All had been taking antihypertensive medications for at least 1 year. Hypertension was defined as systolic blood pressure ⩾140 mm Hg and/or diastolic blood pressure ⩾90 mm Hg. Patients on hemodialysis or with a history of heart failure or ischemic heart disease were excluded. Patients with renal impairment, defined by clinically abnormal serum creatinine $>2.0\,mg\,dl^{-1}$, were also excluded. None of the subjects had a history of any atherosclerotic cardiovascular disease or stroke. Blood pressure was determined using the conventional cuff method at the time when the pulmonary function test was performed. Pulmonary function tests were performed for all participants. Before pulmonary function tests, blood examination and measurement of CAVI were performed. Relationships among clinical characteristics, including blood pressure and laboratory data, CAVI and parameters of pulmonary function test, were analyzed. This protocol was approved by the Ethics Committee of Kagawa University. Informed consent was obtained from all participants.

Blood examinations

Blood sampling was performed in the morning after a 12-h overnight fast. Plasma total cholesterol, triglyceride, high-density lipoprotein cholesterol, creatinine, high-sensitivity C-reactive protein (hsCRP) and WBC count were measured by standard laboratory techniques. Plasma hsCRP level was measured using a latex particle-enhanced immunoassay with the nephelometry method.

Measurement of CAVI

CAVI was recorded using a VaseraVS-1000 vascular screening system (Fukuda Densi, Tokyo, Japan) with the patient resting in a supine position. The principal underlying CAVI has been described previously.[3] ECG electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum and cuffs were wrapped around both arms and both ankles. Blood pressure was measured after detecting the pulse.

CAVI is determined by the following equation:

$$CAVI = a\{(2\rho/\Delta P)\times \ln(Ps/Pd)PWV^2\}+b,$$

where Ps and Pd are systolic blood pressure and diastolic blood pressure, respectively, PWV is pulse wave velocity from the origin of the aorta to the junction of the tibial artery with the femoral artery, ΔP is Ps–Pd, ρ is blood density and a and b are constants. The equation is derived from Bramwell-Hill's equation and the stiffness parameter β, and CAVI was adjusted for blood pressure based on the stiffness parameter β. Therefore, CAVI reflects the stiffness of the aorta, femoral artery and tibial artery as a whole; theoretically, it is not affected by blood pressure. After automatic measurements, the obtained data were analyzed using VSS-10 software (Fukuda Densi), and the values of right and left CAVI were calculated. The average of the right and left CAVIs was used for analysis. The average coefficient of variation of CAVI in our laboratory was 3.9%, which was sufficiently low for clinical usage and indicated that CAVI had good reproducibility.

Pulmonary function test

Pulmonary function tests were performed using a computed spirometer (DISCOM-21FX, CHEST M.I., Tokyo, Japan). The tests were performed with the subject in a sitting position and with noseclips in place. FVC and FEV_1 from the best tests, as defined by the American Thoracic Society,[24] were recorded. Published prediction equations were used to calculate predicted FVC and FEV_1 for each subject. Percentages of predicted FVC and FEV_1 were calculated. The ratio of FEV_1 to FVC (FEV_1/FVC) was also calculated. Finally, pulmonary age for screening COPD was calculated based on sex, age, height, FVC and FEV_1 of each subject by using the equation proposed by the Japanese Respiratory Society.[23] The obtained pulmonary age divided the subjects into two groups: 20 hypertensive patients with normal pulmonary age, whose pulmonary age was less than or equal to their real age, and 25 hypertensive patients with increased pulmonary age, whose pulmonary age was greater than their real age.

Statistical analysis

Data are expressed as means ± s.d. Statistical analysis was performed using the SPSS software package (SPSS, Chicago, IL, USA). Linear regression analysis was performed to evaluate the association between parameters of the pulmonary function test, CAVI, and other variables. Stepwise multiple regression analysis was performed to identify the independent determinants of the parameters of the pulmonary function test. Comparisons were made between patients with normal and increased pulmonary ages using unpaired *t*-tests for continuous variables and χ^2 analyses for categorical data. Values of $P<0.05$ were considered to indicate statistical significance.

RESULTS

Clinical characteristics of subjects

The clinical and spirometric parameters of the subjects are summarized in Table 1. The percentage (73%) of subjects prescribed calcium channel blockers was highest among those who were also taking antihypertensive drugs. Mean values of systolic (131 ± 14 mm Hg) and diastolic (79 ± 8 mm Hg) blood pressure were not high because the blood pressure of the participants was well controlled.

Association between parameters of pulmonary function test and other variables

Linear regression analysis was performed to examine the relationship between parameters of the pulmonary function test and other variables in all subjects (Tables 2, 3, 4, and 5). The percentage of predicted

Table 1 Clinical characteristics of the patients

Number (male/female)	45 (24/21)
Age (years)	69.6 ± 9.4
BMI ($kg\,m^{-2}$)	24.2 ± 3.4
Diabetes mellitus (*n* (%))	8 (18)
Dyslipidemia (*n* (%))	17 (38)
Current smoker (*n* (%))	7 (16)
Antihypertensive drugs	
ARB/ACEI (*n* (%))	24 (53)
CCB (*n* (%))	33 (73)
β-Blockers (*n* (%))	13 (29)
Diuretics (*n* (%))	7 (16)
Systolic BP (mm Hg)	131 ± 14
Diastolic BP (mm Hg)	79 ± 8
Heart rate (beats per min)	63 ± 10
Total cholesterol ($mg\,dl^{-1}$)	195 ± 28
HDL cholesterol ($mg\,dl^{-1}$)	52 ± 12
Triglycerides ($mg\,dl^{-1}$)	137 ± 78
Hemoglobin ($g\,dl^{-1}$)	13.1 ± 1.6
Creatinine ($mg\,dl^{-1}$)	0.75 ± 0.21
White cell count (cells per μl)	5894 ± 1665
hsCRP ($mg\,dl^{-1}$)	0.17 ± 0.19
CAVI	9.0 ± 1.3
Pulmonary function	
FVC (l)	2.70 ± 0.71
Percentage of predicted FVC (%)	96.9 ± 16.0
FEV_1 (l)	2.12 ± 0.63
Percentage of predicted FEV_1 (%)	106.8 ± 22.6
FEV_1/FVC ratio	78.5 ± 9.9
Pulmonary age (years)	74.2 ± 17.4

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; CCB, calcium channel blockers; FEV_1, forced expiratory volume in 1 s; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Table 2 Correlations between clinical parameters and the percentage of predicted FVC

	Univariate		*Multivariate*	
	r	P *value*	β	P *value*
Age	−0.319	0.032	—	NS
BMI	−0.068	NS	—	NS
Diabetes mellitus	−0.115	NS	—	NS
Dyslipidemia	−0.032	NS	—	NS
Current smoker	−0.024	NS	—	NS
Antihypertensive drugs				
ARB/ACEI	0.083	NS	—	NS
CCB	−0.237	NS	—	NS
β-Blockers	−0.231	NS	—	NS
Diuretics	0.092	NS	—	NS
Systolic BP	−0.197	NS	—	NS
Diastolic BP	−0.140	NS	—	NS
Heart rate	0.049	NS	—	NS
Total cholesterol	0.267	NS	—	NS
HDL cholesterol	0.261	NS	—	NS
Triglycerides	−0.020	NS	—	NS
Hemoglobin	0.153	NS	—	NS
Creatinine	−0.013	NS	—	NS
White cell count	−0.092	NS	—	NS
hsCRP	−0.346	0.023	−0.360	0.036
CAVI	−0.338	0.023	—	NS

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; CCB, calcium channel blockers; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Table 3 Correlations between clinical parameters and the percentage of predicted FEV_1

	Univariate		*Multivariate*	
	r	P *value*	β	P *value*
Age	0.045	NS	—	NS
BMI	−0.069	NS	—	NS
Diabetes mellitus	−0.216	NS	—	NS
Dyslipidemia	−0.075	NS	—	NS
Current smoker	−0.118	NS	—	NS
Antihypertensive drugs				
ARB/ACEI	−0.222	NS	—	NS
CCB	−0.077	NS	—	NS
β-Blockers	−0.141	NS	—	NS
Diuretics	0.064	NS	—	NS
Systolic BP	−0.242	NS	—	NS
Diastolic BP	−0.378	0.011	−0.354	0.037
Heart rate	−0.048	NS	—	NS
Total cholesterol	0.202	NS	—	NS
HDL cholesterol	0.174	NS	—	NS
Triglycerides	−0.056	NS	—	NS
Hemoglobin	−0.003	NS	—	NS
Creatinine	−0.083	NS	—	NS
White cell count	−0.208	NS	—	NS
hsCRP	−0.178	NS	—	NS
CAVI	−0.239	NS	—	NS

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; CCB, calcium channel blockers; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

FVC correlated with age ($r=-0.319$, $P=0.032$), hsCRP ($r=-0.346$, $P=0.023$) and CAVI ($r=-0.338$, $P=0.023$) by linear regression analysis. Stepwise multiple regression analysis indicated that hsCRP ($\beta=-0.360$, $P=0.036$) was independently associated with the percentage of predicted FVC (Table 2).

The percentage of predicted FEV_1 correlated with diastolic blood pressure ($r=-0.378$, $P=0.011$) by linear regression analysis. Stepwise multiple regression analysis indicated that diastolic blood pressure ($\beta=-0.354$, $P=0.037$) was independently associated with percentage of predicted FEV_1 (Table 3).

The FEV_1/FVC ratio correlated with age ($r=-0.332$, $P=0.026$) and CAVI ($r=-0.399$, $P=0.007$) by linear regression analysis. Stepwise multiple regression analysis indicated that CAVI ($\beta=-0.418$, $P=0.014$) was independently associated with the FEV_1/FVC ratio (Table 4).

The pulmonary age correlated with age ($r=0.553$, $P<0.001$), hsCRP ($r=0.314$, $P=0.040$) and CAVI ($r=0.559$, $P<0.001$) by linear regression analysis. Stepwise multiple regression analysis indicated that CAVI ($\beta=0.514$, $P=0.002$) was independently associated with pulmonary age (Table 5).

Comparisons of CAVI between hypertensive patients with normal and increased pulmonary age

The clinical parameters and CAVI were compared between patients with normal and increased pulmonary age (Table 6). The CAVI and hsCRP were significantly higher in patients with increased pulmonary age (9.4 ± 1.4 and $0.22 \pm 0.23\,mg\,dl^{-1}$) than in those with normal pulmonary age (8.4 ± 0.9 and $0.10 \pm 0.11\,mg\,dl^{-1}$) ($P=0.011$ and 0.045, respectively).

DISCUSSION

Pulmonary function assessed by spirometry can differentiate between restrictive and obstructive defects of ventilator function.[25] Restrictive ventilatory defects are characterized by decreased FVC. By contrast, obstructive ventilatory defects are characterized by decreased FEV_1/FVC ratio. This study presents data regarding the relationships between CAVI and pulmonary function in treated hypertensive patients who have been receiving antihypertensive drugs for at least 1 year. The data led us to the following conclusions. First, increased CAVI was not associated with decreased FVC, reflecting a restrictive ventilatory defect, but was associated with a decreased FEV_1/FVC ratio reflecting an obstructive ventilatory defect. Second, CAVI was an independent predictor of pulmonary age. Finally, hypertensive patients with increased pulmonary age, who have reduced pulmonary function, show increased CAVI values and increased hsCRP levels.

Our data suggest that hypertensive patients with increased arterial stiffness, as assessed by elevated CAVI, may have a risk of COPD. Some previous studies[16–19] have demonstrated that airflow limitation with decreased predicted FEV_1 was associated with atherosclerosis. However, the atherosclerosis in the previous studies was assessed by carotid intima-media thickness and plaque. Our data provide new information regarding the association between obstructive ventilatory defects and increased arterial stiffness.

Table 4 Correlations between clinical parameters and FEV_1/FVC ratio

	Univariate		*Multivariate*	
	r	P *value*	β	P *value*
Age	−0.332	0.026	—	NS
BMI	0.211	NS	—	NS
Diabetes mellitus	−0.188	NS	—	NS
Dyslipidemia	0.139	NS	—	NS
Current smoker	0.160	NS	—	NS
Antihypertensive drugs				
ARB/ACEI	−0.204	NS	—	NS
CCB	0.011	NS	—	NS
β-Blockers	0.070	NS	—	NS
Diuretics	0.145	NS	—	NS
Systolic BP	−0.228	NS	—	NS
Diastolic BP	−0.226	NS	—	NS
Heart rate	−0.125	NS	—	NS
Total cholesterol	0.184	NS	—	NS
HDL cholesterol	0.051	NS	—	NS
Triglycerides	0.239	NS	—	NS
Hemoglobin	−0.079	NS	—	NS
Creatinine	−0.300	NS	—	NS
White cell count	−0.296	NS	—	NS
hsCRP	−0.031	NS	—	NS
CAVI	−0.399	0.007	−0.418	0.014

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; CCB, calcium channel blockers; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Table 5 Correlations between clinical parameters and pulmonary age

	Univariate		*Multivariate*	
	r	P *value*	β	P *value*
Age	0.553	<0.001	—	NS
BMI	−0.096	NS	—	NS
Diabetes mellitus	0.078	NS	—	NS
Dyslipidemia	−0.112	NS	—	NS
Current smoker	−0.063	NS	—	NS
Antihypertensive drugs				
ARB/ACEI	−0.096	NS	—	NS
CCB	0.190	NS	—	NS
β-Blockers	0.168	NS	—	NS
Diuretics	−0.238	NS	—	NS
Systolic BP	0.291	NS	—	NS
Diastolic BP	0.138	NS	—	NS
Heart rate	−0.041	NS	—	NS
Total cholesterol	−0.195	NS	—	NS
HDL cholesterol	−0.141	NS	—	NS
Triglycerides	−0.061	NS	—	NS
Hemoglobin	−0.178	NS	—	NS
Creatinine	0.157	NS	—	NS
White cell count	0.229	NS	—	NS
hsCRP	0.314	0.040	—	NS
CAVI	0.559	<0.001	0.514	0.002

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; CCB, calcium channel blockers; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Table 6 Comparison of clinical parameters between hypertensive patients with increased and normal pulmonary ages

	Normal pulmonary age (n=20)	*Increased pulmonary age (n=25)*	P *value*
Age (years)	67.5 ± 8.2	71.3 ± 10.1	NS
BMI	24.5 ± 3.4	24.0 ± 3.5	NS
Diabetes mellitus (%)	15	20	NS
Dyslipidemia	45	33	NS
Current smoker (%)	10	20	NS
Antihypertensive drugs			
ARB/ACEI (%)	55	52	NS
CCB (%)	70	76	NS
β-Blockers (%)	20	36	NS
Diuretics (%)	22	11	NS
Systolic BP (mm Hg)	127 ± 11	135 ± 15	NS
Diastolic BP (mm Hg)	77 ± 5	81 ± 10	NS
Heart rate (beats per min)	64 ± 10	63 ± 11	NS
Total cholesterol ($mg\,dl^{-1}$)	200 ± 25	190 ± 31	NS
HDL cholesterol ($mg\,dl^{-1}$)	54 ± 15	50 ± 9	NS
Triglycerides ($mg\,dl^{-1}$)	148 ± 104	127 ± 43	NS
Hemoglobin ($g\,dl^{-1}$)	13.3 ± 1.5	13.0 ± 1.8	NS
Creatinine ($mg\,dl^{-1}$)	0.73 ± 0.22	0.77 ± 0.20	NS
White cell count (cells per μl)	5872 ± 1548	5916 ± 1814	NS
hsCRP ($mg\,dl^{-1}$)	0.10 ± 0.11	0.22 ± 0.23	0.045
CAVI	8.4 ± 0.9	9.4 ± 1.4	0.011

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; CCB, calcium channel blockers; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Recently, COPD has been recognized as a systemic disease,[26,27] and the association between COPD and cardiovascular disease has received attention.[28] COPD is characterized by chronic airflow limitation from an inappropriate and excessive inflammatory response of the lungs to respiratory pollutants, mainly tobacco smoking.[29] Recent studies have suggested that an important clue to the mechanism linking increased cardiovascular disease and COPD is persistent low-grade systemic inflammation as indicated by elevated levels of CRP observed in patients with COPD.[30,31] CRP levels are associated with cardiovascular risk in the general population [32,33] and poor prognosis in patients with COPD.[34] Various studies have found CRP has a causal role in atherosclerosis,[35,36] metabolic syndrome,[37] coronary heart disease and ischemic heart failure.[38] Thus, CRP has been increasingly investigated as a promising therapeutic target for the prevention of cardiovascular disease.[39] Our data regarding high-sensitivity CRP (hsCRP) are in agreement with these previous studies.[30–39] Actually, hypertensive patients with increased pulmonary age showed increased hsCRP and CAVI compared with those with normal pulmonary age (Table 6). Therefore, low-grade systemic inflammation may have led to an association between arterial stiffness and pulmonary function in the present study.

Several limitations exist in the present study. First, both CAVI and pulmonary function are influenced by aging. Therefore, we performed stepwise multiple regression analysis to identify the independent determinants of the parameters of the pulmonary function test and found that increased CAVI was an independent determinant of FEV_1/FVC ratio (Table 4). However, the present study is limited by relatively small sample size of the patients. Further studies, including larger

numbers of patients, are needed to confirm that increased CAVI is an independent determinant of pulmonary function. Second, the majority of patients in the present study did not show severe pulmonary dysfunction, which was assessed by the percentage of predicted FVC, percentage of predicted FEV_1 and FEV1/FVC ratio (Table 1). Further studies, including larger numbers of patients with more severe pulmonary dysfunction, are needed to validate the association between CAVI and pulmonary function.

In conclusion, increased arterial stiffness is associated with reduced pulmonary function, which is assessed by FEV_1/FVC ratio, in hypertensive patients. Arterial stiffness, as assessed by CAVI, is correlated with pulmonary age, which has been proposed by the Japanese Respiratory Society as a measure to detect early-stage COPD. Therefore, hypertensive patients with high CAVI may be paid extra attention to monitor the progression of COPD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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