



# Relationship between Arterial Stiffness and Blood Pressure Drop During the Sit-to-stand Test in Patients with Diabetes Mellitus

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**Aim:** Patients with orthostatic hypotension (OH) have high arterial stiffness. Patients with diabetes mellitus (DM) often have cardiac autonomic neuropathy that leads to OH; however, whether OH is an indicator of arterial stiffness progression is unclear. We aimed to investigate whether the cardio-ankle vascular index (CAVI) varies between DM patients with and without OH using the sit-to-stand test (STST).

**Methods:** One hundred and fifty-nine patients with DM underwent CAVI assessment and blood pressure (BP) and heart rate change evaluation during the STST. OH was defined as a decline in systolic BP (SBP) and/or diastolic BP of at least 20 mmHg or 10 mmHg, respectively, in the initial and late upright positions compared with that in the sitting position.

**Results:** OH was diagnosed in 42 patients (26.4%). DM patients with OH had significantly higher CAVI ( $9.36 \pm 1.15$  versus  $8.89 \pm 1.18$ ,  $p=0.026$ ) than those without OH. CAVI was significantly inversely correlated with systolic and diastolic BP changes ( $R=-0.347$ ,  $p<0.001$  and  $R=-0.314$ ,  $p<0.001$ , respectively) in the initial upright position. Multivariate regression analysis revealed that age, SBP changes, and low frequency component in the initial upright position were independent determinants of CAVI.

**Conclusion:** Patients with DM having large BP drops occurring when moving from sitting to standing have high arterial stiffness. A significant BP drop during the STST necessitates careful evaluation of advanced arterial stiffness in patient with DM.

**Key words:** Arteriosclerosis, Cardio-ankle vascular stiffness index, Orthostatic hypotension, Diabetes mellitus

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## Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, including the United States,

Europe, and Japan. Previous studies have demonstrated that arteriosclerosis is a key mechanism in the development of CVD, and the degree of arteriosclerosis is a strong surrogate marker for determining the incidence of CVD<sup>1)</sup>.

As a marker for arteriosclerosis, arterial wall thickness is measured by high-resolution B-mode ultrasonography such as carotid intima-media thickness. In addition, arterial stiffness such as carotid-femoral pulse wave velocity (PWV)<sup>2, 3)</sup>, aortic PWV<sup>4, 5)</sup>, and brachial-ankle PWV (baPWV)<sup>6, 7)</sup> have been reported as reliable

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Received: January 21, 2016

Accepted for publication: May 10, 2016

markers for the incidence of CVD and CVD mortality.

Cardio-ankle vascular index (CAVI) is a new index of arterial stiffness that is designed to be essentially independent of blood pressure (BP). CAVI is adjusted for BP based on the stiffness parameter beta and therefore CAVI is reportedly less influenced by BP than baPWV is<sup>8)</sup>. CAVI reflects even a slight-to-moderate extent of carotid atherosclerosis and can be used for the early detection of arteriosclerosis<sup>9-11)</sup>. A recent study revealed that a high CAVI predicts CVD in obese patients<sup>12, 13)</sup>, and a close relationship between arterial stiffness and the various stages of arteriosclerosis progression has been reported<sup>14, 15)</sup>.

Diabetes mellitus (DM), hypertension (HT), dyslipidemia (DL), and smoking are risk factors for CVDs such as stroke and coronary artery disease and are known to cause and accelerate arteriosclerosis<sup>16, 17)</sup>. In arteriosclerotic risk factors, DM is a major risk factor for CVD<sup>18)</sup>. In the evaluation of arteriosclerosis, arterial stiffness indexes such as PWV<sup>19-21)</sup> and CAVI<sup>22)</sup> are reported to increase in patients with DM compared with those in patients without DM.

Patients with orthostatic hypotension (OH) often have high arterial stiffness. OH is defined as a dysfunction in hemodynamic BP regulation during standing. In postural changes, successful rapid responses in the circulatory system are needed to maintain the cerebral flow when changing the posture to the upright position. These responses include appropriate changes in arterial and venous vessel diameters, cardiac output, and skeletal muscle pumps of the lower body<sup>23)</sup>.

In everyday clinical practice, the sit-to-stand test (STST) can be easily used to test postural BP changes for the detection of OH. It is a simple procedure and it is safe for elderly subjects.

In community-based, middle-aged, and elderly normotensive subjects, patients with OH assessed by STST had high baPWV<sup>24)</sup>. In patients with DM who are likely to have cardiac autonomic neuropathy leading to OH, it is unclear if OH complications are a sign of significant progression in arterial stiffness.

## Aim

We aimed to investigate whether CAVI varies between DM patients with and without OH using the STST.

## Methods

### Study Participants

From October 2012 to July 2015, we recruited patients who presented to the Kobayashi Medical Clinic in Yokohama, Japan for medical treatment.

Patients included had to be older than 20 years of age and undergoing treatment for DM at the clinic. DM was defined as present if any of the following characteristics was observed: history of physician-diagnosed DM, use of medication for DM, fasting blood glucose concentration of at least 126 mg/dl, or non-fasting blood glucose concentration of at least 200 mg/dl. We excluded participants with a history of the following diseases: coronary heart disease; stroke (including transient ischemic attack); congestive heart failure; peripheral artery disease; arrhythmias, including atrial fibrillation and atrial flutter; neurodegenerative disease, including Parkinson disease; and malignancy. Coronary heart disease included a previous myocardial infarction (defined as a physician-diagnosed myocardial infarction or as a silent myocardial infarction as identified by electrocardiography [ECG]) or a previous coronary revascularization procedure or coronary artery bypass surgery. Peripheral artery disease was defined as an ankle-brachial index <0.9 or a history of revascularization. Atrial fibrillation and flutter were also determined from the baseline ECG. The eligible patients were included in the study. This study was approved by the Ethics Committees of Yokohama City University Hospital, and informed consent was obtained from all subjects (UMIN Clinical Trials Registry: UMIN000009187).

### Study Design

This was a cross-sectional study. Patient characteristics, including demographic data, anthropometric data, BP measurements, laboratory data profiles, medications prescribed, and medical problems, were obtained. Body mass index was calculated as weight (kg) divided by height squared (m<sup>2</sup>). HT was defined as either a resting seated systolic BP (SBP) of at least 140 mmHg, or a diastolic BP (DBP) of at least 90 mmHg, or use of antihypertensive medications. DL was defined as serum concentrations of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides to be  $\geq 140$  mg/dl, <40 mg/dl, and  $\geq 150$  mg/dl, respectively, or if the patient was already being treated with lipid-lowering agents.

### CAVI and Ankle-brachial Index Measurements

CAVI and ankle-brachial index (ABI) were measured using a VaSera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan). The principal underlying CAVI has been described previously<sup>8)</sup>. Cuffs were applied to bilateral upper arms and ankles, with the subjects lying in a supine position and holding their heads along the midline. ECG electrodes were placed on both wrists, and a microphone was placed over the sternum for the detection of heart

**Table 1.** Clinical characteristics of the diabetes mellitus participants with or without orthostatic hypotension

	OH ( <i>n</i> =42)	Non-OH ( <i>n</i> =117)	<i>p</i> -value
Male sex (%)	57.1	44.4	0.207
Age (years)	67.9 ± 7.5	67.9 ± 9.3	0.984
Body mass index (kg/m <sup>2</sup> )	24.6 ± 3.3	25.8 ± 4.2	0.102
Systolic blood pressure (mmHg)	144.3 ± 13.9	136.2 ± 16.1	0.004
Diastolic blood pressure (mmHg)	86.7 ± 8.1	81.8 ± 9.1	0.003
Heart rate (bpm)	75.8 ± 11.1	70.4 ± 11.9	0.011
LDL cholesterol (mg/dl)	115.0 ± 29.7	116.4 ± 24.9	0.773
HDL cholesterol (mg/dl)	61.4 ± 14.4	61.6 ± 17.1	0.951
Triglyceride (mg/dl)	126.3 ± 74.2	128.3 ± 72.3	0.881
Creatinine (mg/dl)	0.83 ± 0.27	0.74 ± 0.21	0.025
Fasting blood glucose (mg/dl)	120.1 ± 17.0	117.3 ± 21.6	0.452
HbA1c (%)	6.69 ± 0.61	6.57 ± 0.62	0.441
Albumin (g/dl)	4.48 ± 0.30	4.45 ± 0.29	0.623
Hemoglobin (g/dl)	13.9 ± 1.1	13.6 ± 1.3	0.235
Hypertension (%)	71.4	81.2	0.194
Dyslipidemia (%)	90.5	82.9	0.321
Antihypertensive medication (%)	71.4	72.6	1.000

Data are displayed as mean ± SD or percentage. OH, Orthostatic hypotension; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c.

sounds. The patients rested in this supine position for at least 5 min before monitoring was started. CAVI was calculated using the following formula:  $CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2\} + b$ , where PWV is pulse wave velocity from the origin of the aorta to the junction of the tibial artery with the femoral artery, *Ps* is the SBP, *Pd* is the diastolic blood pressure,  $\Delta P$  is *Ps* – *Pd*,  $\rho$  is blood density, and *a* and *b* are constants. The ABI was calculated as the ratio of the ankle SBP to the brachial SBP.

### Measurement of Postural BP and Heart Rate (HR) Changes

BP, HR, and R-R interval measurements during the sitting and standing positions were performed using the Kiritsu Meijin autonomic reflex, orthostatic tolerance test instrument (Crosswell, Kanagawa, Japan). This device included a BP monitor (TM 2584: A&D Co. Ltd., Tokyo, Japan) and a HR monitor LRR-03 (GMS, Tokyo, Japan). Patients rested for 5 min in a seated position before the postural challenge. Patients assumed a seated position for 2 min, followed by an active standing position for 2 min. BP was evaluated 1 min before standing (sitting position), immediately after standing (initial upright position), and 1 min after standing (late upright position). OH was defined as a decline in SBP of at least 20 mmHg and/or a decline in DBP of at least 10 mmHg at any of the 2 (initial and late) upright positions compared with

that in the sitting position. HR was calculated as the average number of R-R intervals in 1 min. Power spectrum analysis was conducted using the MemCalc method described below; it is based on the variability of the 1-min R-R intervals. The analysis was repeated on a beat-to-beat basis and all results in a 1 min period were averaged and used as representative values.

### Measurement of Autonomic Parameters

Beat-to-beat recording of HR was conducted with the 3-lead ECG in the sitting and upright positions. The majority of previous studies have used spectral techniques based on the fast Fourier transform (FFT). However, FFT is insufficient to estimate the precise power spectral density from short time series data. The MemCalc method<sup>25)</sup> is a new technique for time series analysis. It is a combination of the maximum entropy method for spectral analysis and the non-linear least squares method for fitting analysis. This enabled us to achieve a reliable analysis of the low-frequency component (LF; 0.05–0.15 Hz) and the high-frequency component (HF; 0.15–0.4 Hz) over a minimum interval of 30 s. Time domain analysis and spectral analyses of HR variability using the MemCalc system were performed for each 1-min period during the standing test. HF was used as an index of parasympathetic activity, while LF was used as mixed indices of sympathetic and parasympathetic activity. LF/HF was used as an index of sympathetic activity<sup>26)</sup>.

**Table 2.** Blood pressure and heart rate during postural change in the diabetes mellitus patients with or without orthostatic hypotension

	OH (n=42)	Non-OH (n=117)	p-value
SBP in sitting position (mmHg)	144.3 ± 13.9	136.2 ± 16.1	0.004
SBP in initial upright position (mmHg)	121.9 ± 13.4	132.5 ± 16.3	< 0.001
SBP in late upright position (mmHg)	132.2 ± 15.4	137.4 ± 17.5	0.088
SBP change in initial upright position (mmHg)	-22.4 ± 9.2	-3.7 ± 8.8	< 0.001
SBP change in late upright position (mmHg)	-12.1 ± 12.4	1.3 ± 9.4	< 0.001
DBP in sitting position (mmHg)	89.8 ± 12.1	82.2 ± 9.4	0.003
DBP in initial upright position (mmHg)	81.0 ± 12.1	81.2 ± 9.4	0.146
DBP in late upright position (mmHg)	82.0 ± 10.0	82.4 ± 9.8	0.822
DBP change in initial upright position (mmHg)	-8.3 ± 6.1	-0.9 ± 4.2	< 0.001
DBP change in late upright position (mmHg)	-4.6 ± 6.3	0.6 ± 4.5	< 0.001
HR in sitting position (mmHg)	75.8 ± 11.1	70.4 ± 11.9	0.011
HR in initial upright position (mmHg)	80.8 ± 11.3	74.8 ± 12.2	0.006
HR in late upright position (mmHg)	81.3 ± 11.9	75.1 ± 12.1	0.004
HR change in initial upright position (mmHg)	5.0 ± 3.1	4.3 ± 2.7	0.212
HR change in late upright position (mmHg)	5.5 ± 4.0	4.8 ± 3.3	0.266

Data are displayed as mean ± SD. OH, Orthostatic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

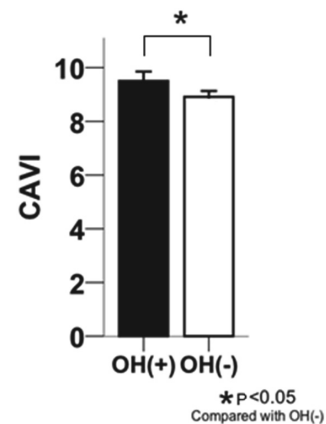
### Statistical Analysis

Values are expressed as the mean ± standard deviation, frequency, and percentages. Student's *t*-test was used to compare continuous variables and the  $\chi^2$ -test and Fisher's exact test were used to test for differences between categorical variables. Spearman's correlation coefficient was calculated to evaluate the relationship among parameters. HF and LF indexes were log-transformed (logHF and logLF) prior to analysis due to skewness. All statistical analyses were carried out using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA), and a *p*-value of less than 0.05 was considered to indicate statistical significance.

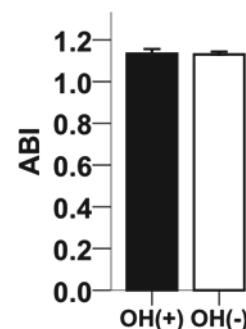
### Results

In total, 159 patients with DM were evaluated. The average SBP in the sitting position, initial upright position, and late upright position was 138.3 ± 15.9 mmHg, 129.7 ± 16.2 mmHg, and 136.1 ± 17.0 mmHg, respectively. The average DBP in the sitting position, initial upright position, and late upright position was 83.1 ± 9.1 mmHg, 80.2 ± 9.4 mmHg, and 82.3 ± 9.8 mmHg, respectively. OH was diagnosed in 42 patients (26.4%). The clinical characteristics of patients with DM are shown according to the presence or absence of OH in **Table 1**. Patients with OH had significantly higher SBP, DBP, HR, and serum creatinine levels than those without OH. **Table 2** shows the BP and HR measurements during the postural changes.

As shown in **Fig. 1a**, DM patients with OH had



**Fig. 1a.** Comparison of arterial stiffness assessed by CAVI between diabetes mellitus patients with and without OH



**Fig. 1b.** Comparison of ABI between patients with diabetes mellitus with and without OH

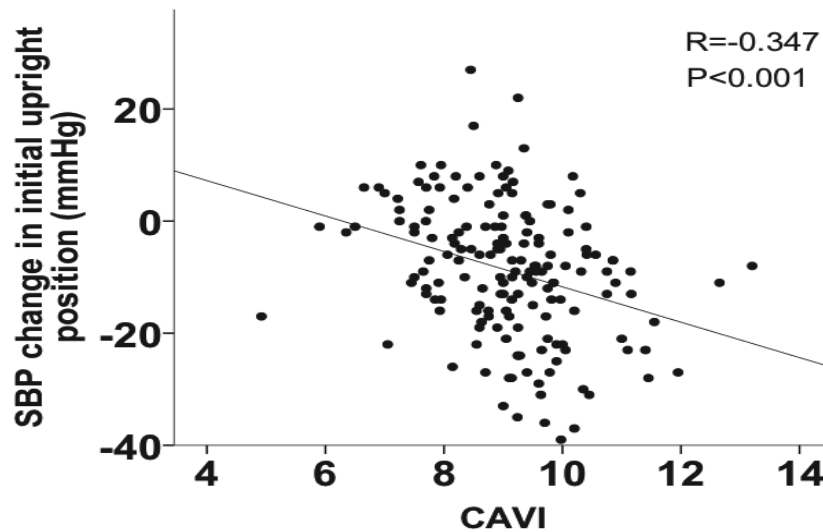


Fig. 2a. Correlation between CAVI and SBP change in initial upright position

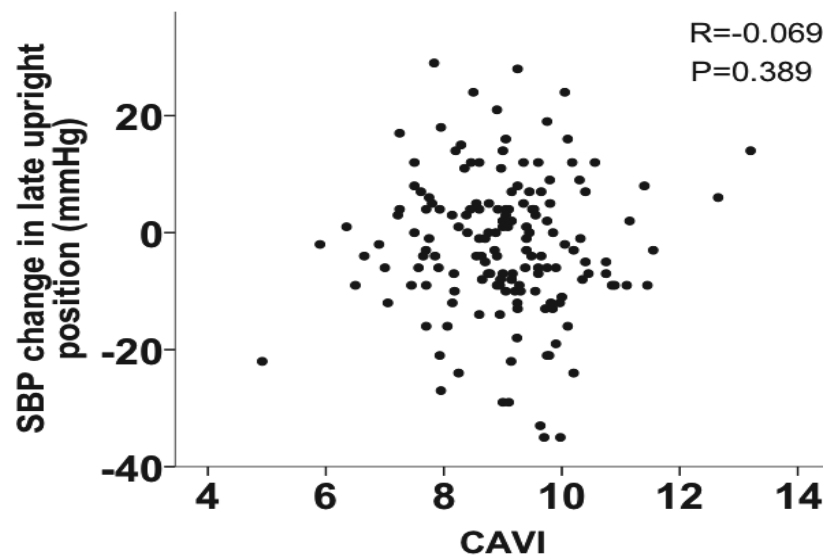


Fig. 2b. Correlation between CAVI and SBP change in late upright position

significantly higher CAVI ( $9.36 \pm 1.15$  versus  $8.89 \pm 1.18$ ,  $p = 0.026$ ) than those without OH had. There were no differences in ABI measurements between DM patients with and without OH ( $1.14 \pm 0.07$  versus  $1.13 \pm 0.07$ ,  $p = 0.408$ , Fig. 1b).

As shown in Fig. 2a and 2b, there was a significant negative correlation between CAVI and SBP change in the initial upright position ( $R = -0.347$ ,  $p < 0.001$ ), whereas there was no significant correlation between CAVI and SBP change in the late upright position ( $R = -0.069$ ,  $p = 0.389$ ).

As shown in Fig. 2c and 2d, there was a significant negative correlation between CAVI and DBP

change in the initial upright position ( $R = -0.314$ ,  $p < 0.001$ ), whereas there was no significant correlation between CAVI and DBP change in the late upright position ( $R = -0.119$ ,  $p = 0.136$ ).

The HR variability parameters of patients with DM are shown in Table 3. DM patients with OH showed a significantly lower logHF change in the late upright position than those without OH. Concerning cardiac autonomic activity and CAVI, there were significant inverse correlations between CAVI and both logLF and logHF in the sitting position, logLF in the initial upright position, and both logLF and logHF in the late upright position (Table 4).



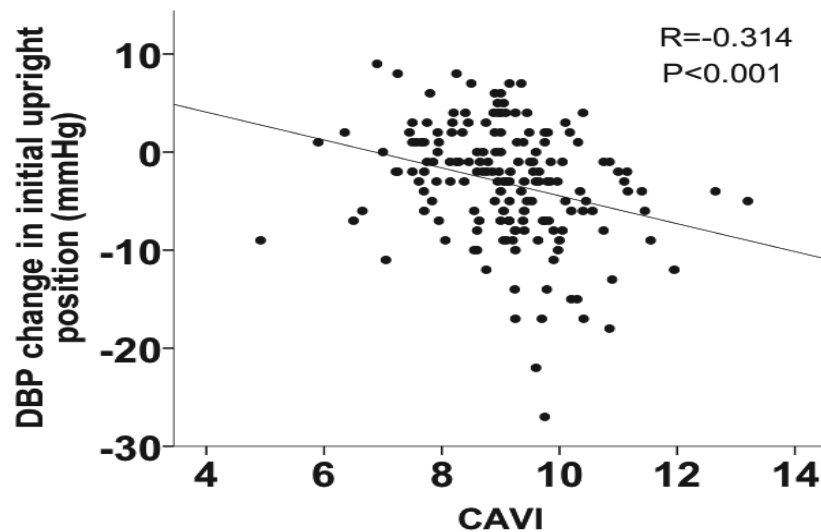


Fig. 2c. Correlation between CAVI and diastolic blood pressure change in initial upright position

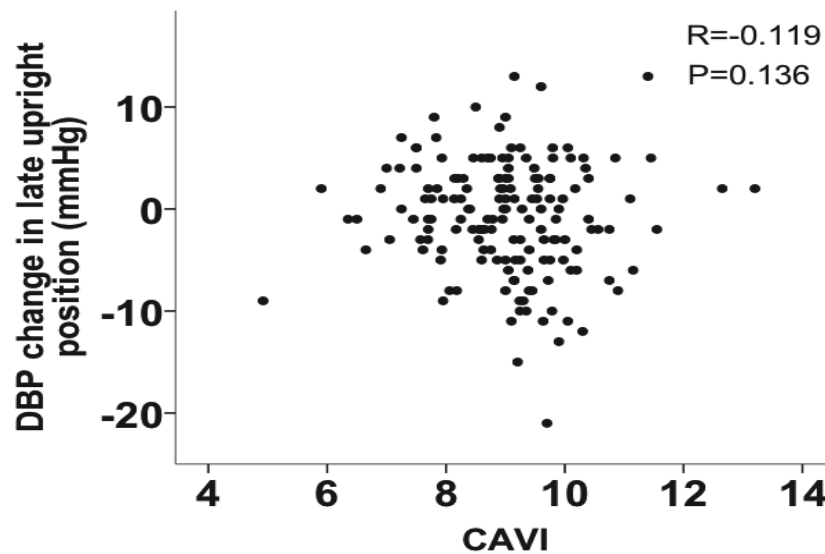


Fig. 2d. Correlation between CAVI and diastolic blood pressure change in late upright position

Stepwise multivariate regression analysis revealed that age, SBP change in the initial upright position, and logLF in the initial upright position were independent determinants of CAVI ( $R^2 = 0.384$ , **Table 5**). When logHF in the initial upright position and LF/HF in the initial upright position, instead of logLF in the initial upright position, were entered one-by-one in the multivariate regression analysis, SBP change in the initial upright position remained a significant determinant ( $p = 0.010$ ,  $p = 0.010$ , respectively).

## Discussion

In the present study, patients with DM underwent the measurement of arterial stiffness by CAVI, and measurements of BP and cardiac autonomic activity during the STST. DM patients with OH showed more advanced arterial stiffness than DM patients without OH. Postural drop in SBP during the simple STST is independently associated with CAVI level in patients with DM. Our study suggests that a postural drop in BP during the simple STST is clinically effective in determining arterial stiffness progression in

**Table 3.** Heart rate variability parameters of the diabetes mellitus patients with or without orthostatic hypotension

	OH ( <i>n</i> = 42)	Non-OH ( <i>n</i> = 117)	<i>p</i> -value
logLF in sitting position	1.85 ± 0.57	1.99 ± 0.55	0.163
logLF in initial upright position	2.14 ± 0.42	2.23 ± 0.49	0.288
logLF in late upright position	1.72 ± 0.51	1.88 ± 0.51	0.086
logLF change in initial upright position	0.29 ± 0.42	0.24 ± 0.42	0.549
logLF change in late upright position	−0.14 ± 0.44	−0.13 ± 0.46	0.946
logHF in sitting position	1.82 ± 0.59	1.85 ± 0.55	0.736
logHF in initial upright position	1.72 ± 0.56	1.88 ± 0.52	0.084
logHF in late upright position	1.45 ± 0.66	1.67 ± 0.57	0.053
logHF change in initial upright position	−0.08 ± 0.31	0.03 ± 0.34	0.060
logHF change in late upright position	−0.35 ± 0.52	−0.20 ± 0.35	0.047
LF/HF in sitting position	2.36 ± 2.63	3.06 ± 5.27	0.410
LF/HF in initial upright position	6.72 ± 10.3	4.70 ± 7.43	0.176
LF/HF in late upright position	3.57 ± 4.19	3.13 ± 5.80	0.650
LF/HF change in initial upright position	4.36 ± 10.05	1.63 ± 6.89	0.055
LF/HF change in late upright position	1.21 ± 3.97	0.07 ± 3.95	0.109

logLF, logHF and LF/HF are displayed as mean ± SD. OH, Orthostatic hypotension; LF, low frequency component; HF, high frequency component.

**Table 4.** Correlation between cardio-ankle vascular index and heart rate variability parameters

	R	<i>p</i> -value
logLF in sitting position	−0.216	0.006
logLF in initial upright position	−0.237	0.003
logLF in late upright position	−0.202	0.014
logLF change in initial upright position	−0.011	0.892
logLF change in late upright position	0.006	0.941
logHF in sitting position	−0.244	0.002
logHF in initial upright position	−0.148	0.062
logHF in late upright position	−0.178	0.027
logHF change in initial upright position	0.159	0.056
logHF change in late upright position	0.053	0.536
LF/HF in sitting position	−0.034	0.671
LF/HF in initial upright position	0.059	0.459
LF/HF in late upright position	0.010	0.904
LF/HF change in initial upright position	0.047	0.575
LF/HF change in late upright position	0.036	0.666

*P*-values are for correlation coefficients. R, correlation coefficient; LF, low frequency component; HF, high frequency component.

patients with DM.

Arterial stiffness is caused and affected by many clinical factors including aging, DM, DL, HT, smoking, and inflammation<sup>13</sup>. A drop in SBP during the STST was independently associated with arterial stiffness after adjustment for related factors; this adjustment showed that the association was not influenced by confounding factors. A BP drop during the STST necessitates a careful evaluation of CVD risk.

Patients with DM are at a high risk of severe arterial stiffness and cardiac autonomic neuropathy<sup>20</sup>. Arterial stiffness<sup>6</sup> and cardiac autonomic dysfunction<sup>27</sup> in patients with DM are known to significantly affect prognosis. Cardiac autonomic neuropathy can be evaluated by spectral analysis of HR variability<sup>28</sup>. Our study showed that an orthostatic BP drop was independently related to CAVI after adjustment for HR variability parameters. The results implied that

**Table 5.** Stepwise multiple regression analysis for variables independently associated with cardio-ankle vascular index

	B	SE	$\beta$	P-value
Age (years)	0.070	0.014	0.458	< 0.001
SBP change in initial upright position (mmHg)	-0.028	0.009	-0.273	0.003
log LF in initial upright position	-0.631	0.263	-0.218	0.019

Variables used in the models were age, gender, body mass index, SBP, heart rate, triglyceride, HDL cholesterol, LDL cholesterol, fasting glucose, hemoglobin A1c, creatinine, logLF in initial upright position, and SBP change in initial upright position.

Adjusted  $R^2=0.384$ ,  $F$  value = 16.183,  $P<0.001$ .

Abbreviations: B, partial regression coefficient;  $\beta$ , standardized partial regression coefficient; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

arterial stiffness is involved in the postural BP regulation in patients with DM independent of cardiac autonomic activity. Our finding is consistent with that reported in non-DM populations<sup>24, 29</sup>, and supports the contribution of arterial stiffness to OH development, even in patients with DM.

Our analysis showed the inverse relationships between LF components and CAVI. The LF component is considered to represent baroreceptor activity<sup>30</sup>. Baroreceptors are located inside the arterial wall and are triggered by stretch. Arterial stiffness may hamper stretch, reduce baroreceptor sensitivity, and contribute to a drop in postural BP<sup>31</sup>. Our results infer that arterial stiffness may affect the function of baroreceptors in the carotid artery and aorta, similar to previous reports<sup>32, 33</sup>.

An initial BP drop during the STST was associated with CAVI levels; a late BP drop was not. The pathophysiology of the initial BP drop is believed to be a temporal mismatch between cardiac output and vascular resistance and does not necessarily result in classic OH<sup>34</sup>. Inadequate cardiac output during postural change may be due to arterial stiffness because this stiffness may impair the buffering effect of the large artery during BP fluctuations<sup>35</sup>. Our results suggested that arterial stiffness is likely to result in an initial orthostatic BP drop and that this drop may be a more sensitive marker for arteriosclerosis than subsequent postural BP drops.

Increasing evidence has shown that arterial stiffness is a strong predictor for morbidity<sup>12</sup> and mortality<sup>6, 7</sup>. The evaluation of arterial stiffness is necessary to provide adequate care for patients at risk for CVD. However, dedicated equipment and space and elaborate efforts are needed to measure arterial stiffness. The STST, a simple and easily performed method, may have many advantages for evaluating the progress of arterial stiffness in routine clinical practice.

STST load represents a physiologic challenge that usually occurs in daily life<sup>36</sup>. Detection of OH by STST may be necessary to assess the risk of falling,

especially in high-risk populations such as the elderly. However, the load of the STST is generally considered to be less than that of the supine-to-stand test. Therefore, OH detected by STST may be a more severe pathological condition. If OH is detected by STST, the patient may need further examination for arteriosclerosis and the appropriate medical management.

This study has limitations that should be taken into account when interpreting the results. First, the cross-sectional design may have limited our ability to infer a causal relationship between arterial stiffness and OH in patients with DM. Second, in the protocol for OH detection in this study, BP change after standing was traced for a relatively short period. Therefore, any OH-associated BP drops that occurred outside of this tracing period would not have been detected. However, patients with OH diagnosed by the STST showed increased arterial stiffness, suggesting that the STST has clinical implications for the management of arteriosclerosis.

## Conclusion

The results of this study using CAVI measurements and the STST method indicate that patients with DM that experience large BP drops have high arterial stiffness. In patients with DM, a postural BP drop from sitting to standing may be partially attributed to arterial stiffness. A large postural drop in BP during the STST needs careful examination of advanced arterial stiffness in patients with DM.

## Acknowledgements

We wish to thank the entire staff of the Kobayashi Medical Clinic for their measurement of the CAVI and the postural hemodynamic changes, and their assistance in recruiting participants. We also appreciate the assistance of Mr. Hiroto Tomita, Ms. Shoko Niida, and Mr. Taiki Matsubayashi in this study.



## Notice of Grant Support

No funding was received for this study.

## Conflict of Interests

The authors declare that they have no conflicts of interest.

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