Orthostatic Blood Pressure Changes and Subclinical Markers of Atherosclerosis

Maasa Takahashi,1 Nobuyuki Miyai,1 Shiori Nagano,1 Miyoko Utsumi,1 Mayumi Oka,1 Mio Yamamoto,1 Mitsuru Shiba,1 Yuji Uematsu,1 Yoshiko Nishimura,1 Tatsuya Takeshita,2 and Mikio Arita1

BACKGROUND
Using a simple standing-up test in normotensive subjects, we evaluated orthostatic upright postural blood pressure (BP) changes and autonomic nervous function, as well as the relationship between orthostatic BP changes and subclinical markers of atherosclerosis.

METHODS
A total of 515 normotensive subjects aged 35–75 years (58.4 ± 10.0 years) were enrolled. We measured body mass index (BMI), systolic BP (SBP) and diastolic BP (DBP), serum lipids, hemoglobin A1c (HbA1c), high-sensitivity C-reactive protein (hs-CRP), and urinary albumin-to-creatinine ratio. Brachial to ankle pulse wave velocity (baPWV) and carotid mean intima-media thickness (IMT) were measured. Participants underwent a simple standing-up test involving sitting then standing for 2 minutes each, followed again by sitting. To evaluate autonomic fluctuations, we calculated the coefficient of variation of the R-R interval, the ratio of low to high frequency heart rate variability (LF/HF), and the coefficient of component variance of high frequency.

RESULTS
SBP and DBP decreased when standing, with a reduction of SBP when changing position of −8.0 ± 10.2 mm Hg. Orthostatic hypotension (OH) produced a significantly higher SBP than without OH. The baPWV was significantly higher in OH than in without OH. Stepwise regression analysis adjusted for age, sex, BMI, baseline SBP, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting glucose, HbA1c, hs-CRP, IMT, late systolic peak of the pressure wave form (SBP2), and baPWV confirmed that baPWV, SBP2, and triglycerides were independently related to orthostatic BP changes. Multiple regression analyses showed that a decrease in SBP as well as baseline SBP, age, BMI, and fasting glucose were independent determinants of PWV.

CONCLUSIONS
We have shown that increased arterial stiffness was associated with OH during a standing-up test. Arterial stiffness may contribute to greater BP responses to postural changes from standing.

Keywords: arterial stiffness; arterial wave reflection; blood pressure; hypertension; orthostatic hypotension.
doi:10.1093/ajh/hpu301

Risk factors including age, cigarette smoking, hypertension, diabetes mellitus, and hyperlipidemia.1

Orthostatic hypotension (OH) occurs in approximately 5% of middle-aged adults in community-based studies.1–3 In elderly adults, the prevalence of OH is 16.2%,6 and increases further with age.7,8 Emerging evidence suggests that orthostatic BP changes are associated with poor cardiovascular outcomes due to stroke5 and coronary heart disease.9,10 Recently, measurement of upright BP, a simple maneuver, has shown that increased systolic BP (SBP) upon standing may provide a novel predictor of masked hypertension.11 Additionally, subjects with OH may display significantly more atherosclerosis

Standing produces a pooling of blood in the peripheral circulation.1 This shift in compartmentalization reduces cardiac return to the heart and, consequently, stroke volume and cardiac output. Nonetheless, under normal conditions, assuming an upright posture does not result in major changes in blood pressure (BP) due to complex integration of autonomic, circulatory, and neurohumoral responses.2

Orthostatic hypotension (OH) occurs in approximately 5% of middle-aged adults in community-based studies.1–3 In elderly adults, the prevalence of OH is 16.2%,6 and increases further with age.7,8 Emerging evidence suggests that orthostatic BP changes are associated with poor cardiovascular outcomes due to stroke5 and coronary heart disease.9,10 Recently, measurement of upright BP, a simple maneuver, has shown that increased systolic BP (SBP) upon standing may provide a novel predictor of masked hypertension.11 Additionally, subjects with OH may display significantly more atherosclerosis

REFERENCES

1. School of Health and Nursing Sciences, Wakayama Medical University, Wakayama City, Wakayama, Japan.
2. Department of Public Health, Wakayama Medical University, Wakayama City, Wakayama, Japan.

For Permissions, please email: journals.permissions@oup.com

© American Journal of Hypertension, Ltd 2015. All rights reserved.

Initially submitted July 8, 2014; date of first revision August 3, 2014; accepted for publication December 19, 2014; online publication February 11, 2015.
We also investigated the relationship between orthostatic BP changes and subclinical markers of atherosclerosis.

**METHODS**

**Study subjects**

Participants were residents of 3 communities in western Japan participating in a health evaluation conducted during 2012 through 2013. A total of 515 subjects (212 men and 303 women), aged 35–75 years (mean age: 58.4 ± 10.0 years), were evaluated. Subjects were excluded if they had hypertension (BP ≥ 140/90 mm Hg or on antihypertensive agents); diabetes mellitus (fasting glucose ≥ 126 mg/dl and/or hemoglobin A1c (HbA1c) ≥ 6.5%); autonomic failure, or taking anti-Parkinsonian medications; or had missing data.

All participants were informed of the study's aims and provided informed consent prior to the examination and was approved by the Ethical Committee of Wakayama Medical University.

**General examination**

We measured patients’ height and weight following a standard protocol to calculate body mass index (BMI). With the patient in seated position, upper arm SBP and diastolic BP (DBP) were measured by the same investigator using an automated oscillometric BP device (HEM-907; Omron, Kyoto, Japan) with appropriate cuff size. Morning blood samples were collected from an antecubital vein after an overnight fast to measure triglyceride, total cholesterol, high- and low-density lipoprotein cholesterol, fasting glucose, and HbA1c levels. A standardized questionnaire was administered to evaluate each subject’s smoking status, regular exercise habits, and medication use.

**Subclinical markers of atherosclerosis**

A noninvasive automatic device (form PWV/ABI; Omron) was used to measure brachial to ankle pulse wave velocity (baPWV) during a standard electrocardiogram measurement. The mean of the right and left baPWV was used for analysis.

Arterial pulse waveforms of the radial artery were measured noninvasively with an automated tonometric system (HEM-9000AI; Omron). This measurement was conducted with the tonometer probe fastened to the right wrist while the BP cuff was wrapped around the left arm. The radial arterial waveforms were used to calculate the late peak systolic pressure wave form (SBP2).

**Ultrasoundographic examination**

Carotid atherosclerosis was determined using a B-mode ultrasound machine (GM-72P00A; Panasonic, Kanagawa, Japan) equipped with an 8.5-MHz linear scan type B-mode probe. All subjects were kept in the supine position. The thickness of the intima-media thickness (IMT) was measured from the far wall of the bilateral common carotid artery 10 mm proximal to the carotid bifurcation, where thickness is most clearly depicted. The mean value of the area was calculated for each side and the mean IMT was used for further analyses. If a carotid artery plaque was identified, the carotid IMT was measured outside of that site. Average values of both the right and left arteries from each segment were used for analyses with the aid of a software program providing the average thickness of the IMT complex on the left and right side of the common carotid artery. The images were measured in an automated analyzing system, composed of 4 automated settings (Auto ROI, Auto Trigger, Auto IMT, and Auto Freeze) based on ultrasound echo signal processing. High-sensitivity C-reactive protein (hs-CRP) level was determined using a specific kit (LZ test, EIKEN CRP-HG; EIKEN CHEMICAL, Tochigi, Japan) using the latex agglutination method (TBA-200FR NEO; TOSHIBA, Tochigi, Japan) equipped with an 8.5-MHz linear scan type B-mode probe. All subjects were kept in the supine position. The ultrasonic examination was performed using a specific kit (LZ test, EIKEN CRP-HG; EIKEN CHEMICAL, Tochigi, Japan) using the latex agglutination method (TBA-200FR NEO; TOSHIBA, Tochigi, Japan).
Figure 1. Changes in BP, PR, and autonomic nervous function during standing-up test in OH(+) and OH(−) groups. Values represent means ± SEM. (a, b) SBP and DBP decreased when changing position from sitting to standing and increased while maintaining an upright position. (c) Increasing PR during the test was observed. (d, f) CVRR and CCVHF were significantly lower in upright position. (e) LF/HF significantly increased after standing up. *P < 0.05, **P < 0.01, ***P < 0.001. Abbreviations: BP, blood pressure; CCVHF, coefficient of component variance of high-frequency power; CVRR, coefficient of variation of the R-R interval; DBP, diastolic blood pressure; LF/HF, ratio of low to high frequency heart rate variability; OH, orthostatic hypotension; PR, pulse rate; SBP, systolic blood pressure.

Figure 2. Orthostatic blood pressure changes during standing-up test. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
A spot routine urinalysis was obtained in the morning before the medical examination.

**Simple standing-up test**

After 5 minutes of resting in a quiet, temperature-controlled room, the subjects performed a simple standing test involving sitting for 2 minutes, followed by standing erect for 2 minutes, and then sitting for 1 minute. During the test, brachial BP and pulse rate were measured every minute oscillometrically with a BP device (Circlemates; Crosswell, Kanagawa, Japan).

OH was defined as a decrease in SBP ≥20 mm Hg or a decrease in DBP ≥10 mm Hg when changing positions from sitting to standing 16; heart rate was determined from the R-R interval recorded electrocardiographically. To evaluate autonomic fluctuations, we calculated the following parameters: the coefficient of variation of the R-R interval, ratio of low to high frequency heart rate variability (LF/HF), and the coefficient of component variance of high frequency as an indicator of parasympathetic function 17,18.

**Statistical analysis**

Data analyses were performed by SPSS 16.0 for Windows (SPSS Software, Inc., Chicago, IL). Significant differences between the study subgroups were determined by Student’s t-test or the Chi-square test. Univariate 1-way analysis of covariance was used to test for differences in markers of atherosclerosis between those with and without OH. Multivariate regression analyses were performed to investigate significant determinants of PWV. A decrease in SBP as well as the following recognized clinically-relevant factors were entered into the model as explanatory variables: age, sex, BMI, SBP, triglyceride, total cholesterol, HDL-C, LDL-C, fasting glucose, and HbA1c. All data were expressed as mean ± SD unless otherwise stated. Those variables showing skewed distribution were logarithmically transformed before statistical analysis. A P value of <0.05 on a 2-tailed test was considered to be statistical significance.

**RESULTS**

Table 1 provides clinical and biochemical characteristics of the study population. Figure 1 presents the variations of hemodynamic and autonomic nervous function parameters induced by postural changes in OH(+) and OH(−) groups during the simple standing-up test. SBP and DBP decreased when changing positions and from sitting to standing, increasing while maintaining the upright position. Pulse rate increased while standing. Coefficient of variation of the R-R interval and LF/HF significantly increased at standing and decreased upright position. SBP reductions from sitting to standing ranged between −4.9 and 10 mm Hg, with a mean of −8.0 ± 10.2 mm Hg. OH was found in 81 (15.7%) of subjects.

**Table 2.** Clinical characteristics of normotensive subjects by presence of orthostatic hypotension

<table>
<thead>
<tr>
<th>Variables</th>
<th>OH(+) (n = 434)</th>
<th>OH(−) (n = 81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.3 ± 10.1</td>
<td>59.0 ± 9.6</td>
<td>0.597</td>
</tr>
<tr>
<td>Male, %</td>
<td>40.6</td>
<td>40.7</td>
<td>0.975</td>
</tr>
<tr>
<td>Change in SBP, mm Hg</td>
<td>−4.7 ± 7.1</td>
<td>−19.2 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in DBP, mm Hg</td>
<td>−1.6 ± 3.8</td>
<td>−10.3 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.9 ± 3.0</td>
<td>21.7 ± 2.8</td>
<td>0.681</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>115.0 ± 12.7</td>
<td>120.0 ± 11.8</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>70.0 ± 8.6</td>
<td>71.5 ± 8.2</td>
<td>0.147</td>
</tr>
<tr>
<td>PR, bpm</td>
<td>67.3 ± 9.2</td>
<td>70.9 ± 11.9</td>
<td>0.002</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>113.6 ± 78.5</td>
<td>101.4 ± 47.6</td>
<td>0.176</td>
</tr>
<tr>
<td>TC, mg/dl</td>
<td>211.2 ± 36.2</td>
<td>211.9 ± 32.0</td>
<td>0.868</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>67.2 ± 16.6</td>
<td>69.4 ± 15.9</td>
<td>0.260</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>125.2 ± 32.3</td>
<td>123.5 ± 27.3</td>
<td>0.650</td>
</tr>
<tr>
<td>FBS, mg/dl</td>
<td>90.9 ± 8.9</td>
<td>92.6 ± 8.7</td>
<td>0.107</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.3 ± 0.3</td>
<td>5.3 ± 0.3</td>
<td>0.171</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>13.1</td>
<td>13.6</td>
<td>0.913</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>15.9</td>
<td>14.8</td>
<td>0.806</td>
</tr>
<tr>
<td>Regular exercise, %</td>
<td>59.0</td>
<td>59.3</td>
<td>0.963</td>
</tr>
</tbody>
</table>

Values represent mean ± SD or percentage. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OH, orthostatic hypotension; PR, pulse rate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

**Figure 3** presents the comparisons of subclinical markers of atherosclerosis in those with and without OH. PWV was significantly higher in the OH group even after adjustment for age, sex, and baseline SBP. A significant difference between the 2 groups was also found in SBP2, but this did not remain significant after adjustment for the above covariates.

We subsequently investigated which variables were most robustly related to orthostatic SBP and DBP (Table 3). Subsequent stepwise regression analyses revealed that baPWV and SBP2 was associated with change in SBP, while PWV and log triglyceride was associated with change in DBP. A multiple regression analyses were performed to determine the factors significantly associated with the baPWV after adjustment for age, SBP, and pulse rate (Table 4). Upright changes in SBP, as well as age, SBP, pulse rate, BMI, log triglyceride levels, and fasting glucose levels were found to be independent determinants of baPWV.

**DISCUSSION**

The results of this study demonstrate that orthostatic BP changes are significantly associated with baPWV, SBP2, and triglycerides. Patients with OH also had a significantly higher baPWV. In addition, SBP decrease was found to be a significant determinant for baPWV on multiple regression...
analysis. These data suggest that BP in individuals with OH may have been influenced by vascular changes and may be a marker in evaluating cardiovascular disease risk among otherwise healthy individuals.

Previous studies have shown that the risk of OH increased exponentially with age, and that its prevalence may be greater in elderly subjects. The occurrence of OH related to aging seems to relate mainly to 3 factors: (i) structural and functional changes in the circulatory system itself; (ii) autonomic function; and (iii) probable impaired skeletal muscle pump function. Other studies confirm this observation even in middle-aged individuals. In the present study, age was not significantly different between those with and without OH. This may be due to the fewer number of middle-aged individuals in our study.

OH is more often found in hypertensive subjects with autonomic dysfunction, which may contribute to dizziness, falls, syncope, and coronary heart disease. It is therefore unsurprising that in our study, orthostatic BP decreased and autonomic nervous function indices decreased in subjects with erect position, findings which are in accordance with previous studies. This corroborates the idea that occurs in individuals with neurohumoral factors regulating circulating blood volume and autonomic dysfunction.

Individuals with cardiovascular disease demonstrated a blunted heart rate and ejection time response to upright posture. These circulatory changes relate to less compliant vessels contributing to impaired vasoconstriction and the baroreflex mechanism. In this study, orthostatic changes SBP and DBP significantly related to baPWV and SBP2. These data suggested that the orthostatic changes of BP correlated with arterial stiffness and might be influenced by a posture dysfunction.
In the present study, the associations of OH with urinary albumin-to-creatinine ratio and hs-CRP were not clearly demonstrated. Several studies have reported that urinary albumin-to-creatinine ratio and hs-CRP are useful as the markers of endothelial dysfunction atherosclerosis and are associated with end-organ damage and cardiovascular disease events.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) Indeed, several studies have demonstrated that urinary albumin-to-creatinine ratio and hs-CRP are markers of endothelial dysfunction atherosclerosis.

To reduce the effects of subsequent cardiovascular complications, the early identification of subgroups who may be more likely to develop early atherosclerotic changes is important. In this study of apparently healthy people, OH occurred in 81 (15.7%) subjects, similar to findings from a previous study demonstrating an 18.2% prevalence of OH.\(^7\) In addition, we also demonstrated that arterial stiffness was significantly associated with OH, thereby implicating abnormal vascular function as a contributing factor in orthostatic BP changes.

This study, however, has certain limitations. First, subjects underwent a low-load standing-up test with a relatively short resting time. Therefore, it is possible that the test was an underestimation of true prevalence. Second, these cross-sectional data revealed associations between orthostatic BP, autonomic nervous function, and subclinical atherosclerosis markers. Although increased arterial stiffness and/or impaired endothelial function may be novel mechanisms contributing to OH,\(^8\)\(^9\) other explanations may be possible. Further studies relating to the indices we have employed to long-term risk identification are necessary.

**CONCLUSION**

The results of this study have shown that increased arterial stiffness may be associated with orthostatic OH during a simple standing-up test. Briefly, arterial stiffness may contribute to greater BP responses to sitting-to-standing postural changes.

**ACKNOWLEDGMENTS**

We thank the staff of the Divisions of Health and Welfare of Minabe, Katsuragi, and Kamitonda towns for their cooperation in this study. We also thank Dr Edward D. Frohlich and Dr Gautam A. Deshpande for their important contributions. This study was supported by a Gran-in Aid for Scientific Research (JSPS25350894 to M.A.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

**DISCLOSURE**

The authors declared no conflict of interest.

**REFERENCES**


**Table 3.** Stepwise multiple regression analysis for orthostatic changes in SBP and DBP

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic change in SBPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV</td>
<td>−0.007</td>
<td>0.002</td>
<td>−0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP2</td>
<td>−0.082</td>
<td>0.032</td>
<td>−0.127</td>
<td>0.011</td>
</tr>
<tr>
<td>Orthostatic change in DBPb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV</td>
<td>−0.004</td>
<td>0.001</td>
<td>−0.202</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG(log)</td>
<td>2.089</td>
<td>0.985</td>
<td>0.093</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*Variables entered in the models were age, sex, BMI, SBP, SBP2, HR, TG, TC, HDL-C, LDL-C, fasting glucose, and HbA1c.*

Abbreviations: β, standardized partial regression coefficient; B, partial regression coefficient; baPWV, brachial to ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SBP2, late systolic peak of the pressure wave-form; TC, total cholesterol; TG, triglycerides.

---

**Table 4.** Stepwise multiple regression analysis for variables independently associated with baPWV

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>8.114</td>
<td>0.723</td>
<td>0.412</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, year</td>
<td>7.157</td>
<td>0.875</td>
<td>0.289</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Orthostatic change in SBP, mm Hg</td>
<td>−3.614</td>
<td>0.964</td>
<td>−0.135</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>136.775</td>
<td>41.402</td>
<td>0.119</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>−9.961</td>
<td>3.139</td>
<td>−0.118</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>3.246</td>
<td>1.055</td>
<td>0.115</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Variables entered in the models were age, sex, BMI, SBP, HR, TG, TC, HDL-C, LDL-C, fasting glucose, HbA1c, and change in SBP. Adjusted R² = 0.371, F value = 44.335, P < 0.001.*

Abbreviations: β, standardized partial regression coefficient; B, partial regression coefficient; baPWV, brachial to ankle pulse wave velocity; BMI, body mass index; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

In our study, baPWV was greater in the OH group in normotensive individuals. The baPWV is one functional marker of cardiovascular wall changes which may be related to arterial elastic properties. The baPWV has been useful in predicting stroke and coronary artery disease.\(^22\)\(^23\)\(^24\) Activation of carotid and aortic baroreceptors initiates the baroreflex response regulating the sympathetically/parasympathetic and cardiovascular response. These baroreceptors are located inside the arterial wall and are triggered by stretching, arterial stiffness may interfere with its activation, thereby explaining the altered baroreceptor sensitivity.\(^25\)\(^26\) In addition, central BP may be considered a better cardiovascular marker than conventional cuff brachial BP.\(^27\) Central BP and baPWV are markers relating to arterial stiffness.\(^28\)\(^29\) These alterations may be due to OH reflecting arterial stiffness.


