High Pulse Wave Velocity Has a Strong Impact on Early Carotid Atherosclerosis in a Japanese General Male Population

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Background: Although there have been several reports on the risk factors associated with intima-media thickness (IMT), many questions remain. The purpose of this study was to investigate the association between IMT and cardiovascular risk factors in a Japanese general population.

Methods and Results: The study group consisted of 1,583 male subjects undergoing routine health checkups. IMT of the common carotid artery was measured by high-resolution ultrasonography. Brachial-ankle pulse wave velocity (baPWV) was measured using an automated device. Univariate analysis demonstrated that carotid IMT significantly associated with age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), baPWV, fasting glucose, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). Multiple logistic regression analysis for carotid atherosclerosis (carotid IMT ≥1.0 mm) was performed using obesity (BMI ≥25.0 kg/m²), high BP (SBP ≥130 mmHg or DBP ≥85 mmHg), dyslipidemia (LDL-C ≥140 mg/dL, TG ≥150 mg/dL, or HDL-C <40 mg/dL), impaired fasting glucose (IFG) (fasting glucose ≥110 g/dL), and high baPWV (≥1,400 cm/s). Carotid atherosclerosis was significantly associated with only high baPWV (OR: 2.22, 95% CI: 1.24–4.17, P<0.01).

Conclusions: High baPWV was a stronger predictor of early carotid atherosclerosis than high BP, dyslipidemia, or IFG in a Japanese general male population.

Key Words: Brachial-ankle pulse wave velocity; Intima-media thickness; Risk factors
Circulation Journal
Vol.81, March 2017

Circulation Journal Vol.81, March 2017

IMT and baPWV elderly subjects. However, there is no report of the relationship between baPWV and IMT in the general population as far as we know.

The purpose of this study was to investigate the association between carotid IMT and cardiovascular risk factors including baPWV in a Japanese general population.

Methods

Study Population

The study group consisted of 1,583 male subjects undergoing routine health checkups. IMT of the common carotid artery was measured by high-resolution ultrasonography. The baPWV and blood pressure (BP) were measured using automated devices. The exclusion criterion of this study was peripheral artery disease or atrial fibrillation. There were no subjects with ankle brachial index <0.9 or >1.4. The protocol used for the study was approved by the institutional review board of Kagoshima University, named the Ethics Committee on Epidemiological Studies, and the approved number of this study was 258. Informed consent was given by all volunteers.

Laboratory Analysis

Blood samples were collected after the subjects had fasted overnight. The serum concentrations of total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting glucose (FG), hemoglobin A1c, uric acid, and creatinine were measured by standard laboratory procedures, while low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald’s equation. LDL-C was not estimated in 8 subjects whose serum TG concentrations were ≥400 mg/dL, as Friedewald’s equation is unreliable in such cases.

Definition of Cardiovascular Risk Factors

Obesity was defined as a body mass index (BMI) ≥25.0 kg/m². High BP was defined as a systolic BP (SBP) ≥130 mmHg, or a diastolic BP (DBP) ≥85 mmHg. Dyslipidemia was identified by LDL-C ≥140 mg/dL, TG ≥150 mg/dL, or HDL-C <40 mg/dL. Impaired FG (IFG) was defined as FG ≥110 mg/dL. Chronic kidney disease (CKD) was evaluated by eGFR using the following equation:

\[ eGFR = 194 \times \frac{\text{Cr}^{-1.094} \times \text{age}^{-0.287}}{1.73^{2}} \text{ (mL/min/1.73 m}^2) \]

CKD was defined as eGFR <60 mL/min/1.73 m².

Measurement of PWV and BP

The baPWV was measured as reported previously and automatically calculated with the use of a Colin Waveform Analyzer (Colin, Komaki, Japan) according to the following equation: baPWV=(D1−D2)/T1, where D1 is the distance from the aortic root to the right ankle, and D2 is the distance from the heart to the right upper arm. These distances were calculated automatically on the basis of the subject’s height. T1 is the time from the onset of the rise in pulse volume record of the right upper arm to the onset of the rise in pulse volume record of the right ankle. BP of the extremity was measured automatically by the Colin Waveform Analyzer when baPWV was measured, and we used the right brachial BP for statistical analysis. baPWV >14.0 m/s is an independent variable for risk stratification by Framingham score and for the discrimination of patients with atherosclerotic cardiovascular disease. Therefore, high baPWV was defined as a baPWV >1,400 cm/s.

Table 1. Characteristics of the Japanese Male Subjects (n=1,583)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56±10</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166±6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67±10</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>24±3</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>146±136</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>55±14</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>131±33</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>109±22</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.3±0.7</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8±0.3</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>78±15</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.0±1.2</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>125±17</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80±11</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>29</td>
</tr>
<tr>
<td>baPWV (cm/s)</td>
<td>1,531±328</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.78±0.13</td>
</tr>
</tbody>
</table>

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

Table 2. Univariate Linear Regression Analysis of IMT With Risk Factors

<table>
<thead>
<tr>
<th>Variables</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.427</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.137</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TG</td>
<td>−0.080</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−0.038</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.063</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fasting blood sugar</td>
<td>0.117</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP</td>
<td>0.286</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP</td>
<td>0.093</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>eGFR</td>
<td>−0.133</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking history</td>
<td>−0.070</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>baPWV</td>
<td>0.360</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI, body mass index; NS, not significant. Other abbreviations as in Table 1.

Figure 1. Relationship between intima-media thickness (IMT) and brachial-ankle pulse wave velocity (baPWV) in a general Japanese male population (n=1,583).
Age and baPWV showed stronger correlations with carotid IMT than did the other variables (Figure 1). Multiple regression analysis was performed using IMT as the dependent variable, and conventional atherosclerotic risk factors, such as age, BMI, TG, HDL-C, LDL-C, fasting blood sugar, SBP, DBP, eGFR, smoking history and baPWV as independent variables. This revealed that IMT was independently related to age, BMI, TG, LDL-C, FBS, SBP, smoking history and baPWV (Table 3).

In addition, multiple logistic regression analysis for carotid atherosclerosis, defined as carotid IMT ≥1.0 mm, was performed using obesity, high BP, dyslipidemia, IFG, CKD, smoking history, and high baPWV (≥1,400 cm/s). After adjustment for age, carotid atherosclerosis was significantly associated with only high baPWV (odds ratio (OR): 2.22, 95% confidence interval (CI): 1.24–4.17, P<0.01) (Table 4).

Figure 2 shows the receiver-operator characteristics curve between baPWV or SBP and carotid atherosclerosis (carotid IMT ≥1.0 mm). The area under the curve was 0.73, and the sensitivity and specificity were 0.64 and 0.73, respectively, at baPWV=1,626 cm/s. When SBP was 128 mmHg, the area under the curve was 0.68, and the respective sensitivity and specificity were 0.70 and 0.60.

### Measurement of IMT
IMT imaging of the common carotid artery was performed using high-resolution B-mode ultrasonography (Vivid 7, GE Ultrasound, Solingen, Germany) with a 10-MHz linear array transducer. Bifurcation of the common carotid artery was confirmed, and IMT was measured from the far wall of the distal common carotid arteries over the distance to within 10 mm proximal to the bifurcation. Three points on the bilateral common carotid arteries without plaque were measured, and IMT was defined as the mean IMT value of the left and right common carotid arteries.

### Statistical Analysis
Data are expressed as mean ± SD. The relationship between continuous variables was analyzed by linear regression analysis. The independence of the association between variables was tested by multiple regression analysis. Statistical analyses were performed with JMP pro 11, while calculation of the partial contribution ratio (partial $R^2$) in multiple regression analysis was performed with SPSS version 23. P<0.05 was considered statistically significant.

### Results
The clinical characteristics of the subjects are shown in Table 1. Mean values for age, BMI, SBP, DBP, baPWV and IMT were 56±10 years, 24±3 kg/m², 125±17 mmHg, 80±11 mmHg, 1,531±328 cm/s and 0.78±0.13 mm, respectively.

Univariate analysis demonstrated that carotid IMT was significantly associated with age, BMI, SBP, DBP, baPWV, FG, LDL-C, TG, eGFR, and smoking history (Table 2).
IMT and baPWV

IMT and baPWV

In addition, after adjustment for age and sex, carotid atherosclerosis was significantly associated with high baPWV, but not with obesity, dyslipidemia, IFG, smoking history, presence of CKD or high BP. Furthermore, baPWV is a more useful index for predicting IMT than high BP because the OR of a high baPWV was high compared with that of a high BP, and the area under the curve of baPWV had a high value compared with that of SBP.

The associations between IMT and risk factors for atherosclerosis, such as hypertension, metabolic syndrome and diabetes mellitus, have been reported previously. With regard to hypertension, it is clear that BP is an independent risk factor for carotid atherosclerosis. Matsui et al reported that the maximum home SBP was significantly associated with left ventricular mass index and IMT, and assessment of the maximum home SBP may increase the predictive value of hypertensive target organ damage in the heart and arteries. It has been reported that the metabolic syndrome is associated with progression of early carotid atherosclerosis in the general population and with subclinical atherosclerosis. However, the association between IMT and the HbA1c value or the severity of diabetes mellitus is controversial. Although Selvin et al showed a significant association between HbA1c and IMT in 2,060 diabetic patients, Temelkova-Kurktschiev et al reported no significant correlation between HbA1c and IMT after adjustment for sex and age in newly detected type 2 diabetic subjects. In the present study, carotid atherosclerosis was significantly associated with high baPWV and high BP, but not with obesity, dyslipidemia or IFG, and high baPWV strongly related with carotid atherosclerosis in comparison with high BP. In addition, baPWV is a simple and noninvasive examination that could be useful to detect early atherosclerosis in the clinical setting and in general populations.

Although carotid-femoral PWV (cfPWV) is widely considered to be the most established index of arterial stiffness, the baPWV is a simple, noninvasive, and automatic method that can evaluate arterial stiffness, and closely correlates with aortic PWV. cfPWV showed a positive association with IMT in elderly patients, with a correlation coefficient of 0.322. In our study, baPWV had a significant association with carotid IMT, with a similar correlation coefficient (r=0.353). Therefore, it is suggested that baPWV, like cfPWV, is a useful index of early-stage atherosclerosis.

We reported that baPWV was more dependent on BP compared with CAVI. However, in the present study, we adjusted the BP, including SBP and DBP, and revealed that baPWV was a predictor of carotid atherosclerosis, which was independent of BP. These results suggested high baPWV as an independent predictor of carotid atherosclerosis.

IMT is considered to be a parameter of structural change in atherosclerosis whereas baPWV can be evaluated as an arterial functional distensibility. There are several studies that report the mechanism of how PWV affects atherosclerosis. Dao et al reported that increased arterial stiffness leads to increased SBP and decreased DBP, and promotes vascular remodeling. Furthermore, increased luminal pressure stimulates excessive collagen production, and these molecular changes lead to a doubling or tripling of the IMT. On the other hand, we demonstrated that baPWV correlated with IMT independent of classical risk factors such as high BP. There may be a new mechanism for baPWV accelerating worsening of the IMT.

In a meta-analysis, it was found that an increase in baPWV of 1 m/s corresponds to increases of 12% in total cardiovascular events, 13% in cardiovascular deaths, and 6% in all-cause deaths. Several studies have reported the cutoff value of baPWV for cardiovascular disease. In patients with acute coronary syndrome, the cutoff value for predicting a post-hospitalization cardiovascular event was 1,700 cm/s, and that for predicting a major cardiovascular event was 1,800 cm/s. In hypertensive patients, a value of 1,750 cm/s is an appropriate cutoff value for predicting the onset of stroke, cardiovascular disease, stroke and cardiovascular disease, and total death.
baPWV is a risk factor for re-admission or cardiac death of heart failure patients and the cutoff value is 1,750 cm/s. In addition, Lee et al demonstrated that baPWV was useful for estimating the risk of cardiovascular events in patients with suspected or known coronary artery disease, and the cutoff value was 1,790 cm/s. On the other hand, the present study demonstrated that the cutoff value of baPWV to predict carotid atherosclerosis in a general male population was 1,626 cm/s. In addition, when the cutoff value of baPWV was >1,600 cm/s, the sensitivity and specificity were 0.65 and 0.68, respectively. These results are similar to those with a baPWV >1,626 cm/s. Therefore, we propose that baPWV >1,600 cm/s is the screening value for early atherosclerosis in the general population. If baPWV is >1,600 cm/s in the general male population, we recommend further examinations including carotid ultrasonography.

Study Limitations
First, it was a cross-sectional study. Therefore, a prospective longitudinal study is needed to confirm the relation between baPWV and IMT in the general population. Second, baPWV cannot be measured accurately in patients with aortic valve stenosis, peripheral arterial disease, or atrial fibrillation. Therefore, subjects with peripheral arterial disease or atrial fibrillation were excluded. Third, we did not have detailed data on alcohol intake and medication because detailed declaration was lacking in the questionnaire used in this study.

Conclusions
For the first time, a high baPWV value has been revealed as a stronger predictor of early carotid atherosclerosis than high BP, dyslipidemia, or IFG in a Japanese general male population.

Disclosures
The authors have no conflicts of interest to declare.

References


