Aortic Pulse Wave Velocity Predicts Cardiovascular Mortality in Middle-Aged and Elderly Japanese Men

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Background: Aortic pulse wave velocity (PWV) is widely used as a noninvasive index of arterial stiffness and was used in the present study to investigate the relationship between PWV and cardiovascular mortality in the middle-aged and elderly Japanese population using a longitudinal study design.

Methods and Results: From 1988 to 2003, a total of 3,960 men (50–69 years old at baseline) who underwent medical check-ups and measurement of PWV, which was standardized for diastolic blood pressure, were recruited and divided into 4 groups according to the PWV values. The average follow-up period was 8.2 years. Mortality from all-causes and from cardiovascular disease significantly increased as PWV increased in the entire follow-up period. Multivariate-adjusted relative risks of all-cause and cardiovascular disease mortality for the highest quartile of PWV (>9.0 m/s) were 1.28 (95% confidence interval (CI) 0.97–1.68) and 1.83 (95%CI 1.02–3.29), respectively, compared with the lowest quartile (<7.5 m/s).


Key Words: Aortic pulse wave velocity; Arteriosclerosis; Cardiovascular disease; Mortality

Aortic pulse wave velocity (PWV) is widely used as a noninvasive index of arterial stiffness and is an easy and reproducible method of evaluating arterial stiffness. Pulse wave velocity measurement is widely used as an index of arteriosclerosis because it is very simple, accurate, and reproducible, and thus it can be easily used for the evaluation of cardiovascular risk. Several investigations have been performed using PWV as the index of arteriosclerosis in subjects with hypertension1-3 or end-stage renal disease4-6 and in the elderly aged over 70 years.7 In recent years, epidemiologic studies have been performed in Japanese-Americans living in Hawaiï8 in well-functioning American older adults9 and in a Danish population10. In our center, PWV measurements have been performed since 1987, but to the best of our knowledge, few studies have attempted to determine the relationship between PWV and cardiovascular mortality in a large group of Japanese men. The aim of this study was to determine the association between PWV and all-cause mortality and cardiovascular mortality in a large Japanese population.

Study Population
A total of 5,194 participants, all men aged 50–69 years, underwent a medical check-up, including a 75-g oral glucose tolerance test (OGTT), at Hiroshima Atomic-Bomb Casualty Council Health Management and Promotion Center from January 1988 to December 2003. Of them, 1,130 were excluded because the waveform of the PWV was not able to be measured and 104 participants who had a gastrectomy, were undergoing treatment for diabetes mellitus or were not free of life-threatening illness were also excluded. Consequently, 3,960 men with a mean age of 61±5.5 years were recruited. The average follow-up period was 8.2±3.6 years.

Ethical Considerations
The protocol of this study was approved by the Central Institutional Review Board of our foundation and Hiroshima University. The data of each participant were made anonymous so they could not be identified.

Definitions
Causes of death were ascertained from death certificates. Individual diagnoses were classified according to the 9th International Classification of Disease (ICD-9) codes: cardiovascular disease was defined as the underlying cause of death with ICD-9 codes 401–438.

Measurements
At baseline, all participants underwent a medical check-up including a 75-g OGTT after overnight fast. Body weight and height were recorded. Blood pressure (BP) was measured by a physician with a mercury sphygmomanometer while the subject was seated after resting for 15 min; phases 1 and 5 of the Korotkoff sounds were determined as systolic and diastolic BP, respectively. When the initial BP was high...
PWV Measurement

PWV was measured using an automatic device FCP-4731 with the aid of a pulse wave input box IB-70 (Fukuda DENKI, Tokyo, Japan), according to previous studies. One transducer was positioned over the left common carotid artery and another was placed over the left femoral artery. The device simultaneously recorded the ECG and phonocardiogram (PCG). The PWV was automatically calculated as:

\[
PWV = \frac{D \times 1.3}{t + t_c}
\]

where \(t\) is the time difference in foot between the carotid pulse wave and the femoral pulse wave, \(t_c\) is the time interval from the beginning of the second cardiac sound on the PCG to the incisure of the carotid pulse wave (ie, the transmission time for the pulse to reach the carotid site after the opening of the aortic valve; \(t + t_c\) indicates the time for the pulse wave to travel from the aortic orifice to the femoral site), \(D\) is the superficially measured linear distance from the right parasternal margin of the second intercostal space to the position of the transducer over the left femoral artery. The actual intra-arterial curvilinear distance between the aortic orifice and the femoral site was estimated to be \(D \times 1.3\). The standardization of the measured PWV for diastolic BP was performed in this study. Replicate measures of PWV in 12 subjects revealed a correlation of 0.93 between physicians.

Statistical Analysis

PWV was examined using quartiles, with the lowest quartile serving as the reference category. Quartiles were defined as follows: quartile 1 (Q1), 5.5–7.4 m/s; quartile 2 (Q2), 7.5–8.1 m/s; quartile 3 (Q3), 8.2–8.9 m/s; quartile 4 (Q4), 9.0–14.7 m/s. For proportions, we used the \(Z\) statistic with Bonferroni correction of the probability values, if appropriate. One-way ANOVA with Tukey’s test for multiple comparisons was used to examine differences between mean values in the quartiles. The outcome events studied were cardiovascular mortality and all-cause mortality. The Kaplan-Meier method was used to estimate the unadjusted survival curves for the 4 PWV groups. The log-rank test was used to compare the unadjusted survival curves. Cox proportional hazards analysis was used to assess the association between PWV quartiles and study outcomes. Hazard ratios (relative risk) and 95% confidence intervals (CI) are reported. All variables related to either PWV or outcome measures were considered in the multivariate analysis. All analyses were performed in this study. Replicate measures of PWV in 12 subjects revealed a correlation of 0.93 between physicians.

Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Quartile 1 (n=934)</th>
<th>Quartile 2 (n=1,024)</th>
<th>Quartile 3 (n=948)</th>
<th>Quartile 4 (n=1,054)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.0±5.5</td>
<td>61.0±5.2</td>
<td>61.5±5.2</td>
<td>63.4±4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136.8±18.6</td>
<td>134.2±17.9</td>
<td>137.3±18.3</td>
<td>143.3±18.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.3±10.9</td>
<td>80.7±10.7</td>
<td>81.6±10.0</td>
<td>82.7±10.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>55.5±13.4</td>
<td>53.7±12.8</td>
<td>55.7±12.8</td>
<td>60.6±14.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>7.0±0.4</td>
<td>7.8±0.2</td>
<td>8.5±0.2</td>
<td>9.9±0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4±2.8</td>
<td>23.4±3.0</td>
<td>23.5±2.9</td>
<td>23.7±2.9</td>
<td>0.100</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>212.5±40.1</td>
<td>213.8±36.0</td>
<td>211.8±34.8</td>
<td>215.4±37.3</td>
<td>0.130</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>135.5±100.6</td>
<td>147.1±99.7</td>
<td>147.8±98.0</td>
<td>158.4±105.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>60.2±16.9</td>
<td>57.9±15.4</td>
<td>57.4±15.8</td>
<td>56.9±16.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>106.3±25.2</td>
<td>107.6±24.1</td>
<td>110.9±29.0</td>
<td>113.5±29.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>58.2</td>
<td>59.7</td>
<td>57.4</td>
<td>58.2</td>
<td>0.762</td>
</tr>
<tr>
<td>ECG abnormality (%)</td>
<td>7.5</td>
<td>7.1</td>
<td>7.9</td>
<td>12.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HT (%)</td>
<td>28.5</td>
<td>34.8</td>
<td>40.1</td>
<td>53.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>18.8</td>
<td>21.9</td>
<td>27.7</td>
<td>32.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD. Abbreviations see in Table 1.
performed with SAS version 8.2 for windows (SAS Institute Inc, NC, USA). Data are expressed as the mean±SD. A value of P<0.05 was considered significant.

Results

Baseline Characteristics of the Participants

The characteristics of the participants are shown in Table 1. Average age at baseline examination was 61.0 years, and PWV values ranged from 5.5 m/s to 14.7 m/s, with a mean of 8.3 m/s and median of 8.2 m/s. In this population, PWV significantly correlated with age (r=0.34, P<0.0001), systolic BP (r=0.25, P<0.0001), diastolic BP (r=0.09, P<0.001), pulse pressure (r=0.28, P<0.001), BMI (r=0.03, P<0.05), fasting plasma glucose level (r=0.12, P<0.0001), 2-h plasma glucose level (r=0.17, P<0.0001), HDL-cholesterol level (r=–0.075, P<0.0001) and triglyceride level (r=0.094, P<0.0001).

The baseline characteristics of the subjects in each PWV quartile are shown in Table 2. BP, triglycerides and other covariates associated with arteriosclerosis significantly increased and HDL-cholesterol levels decreased as the PWV value increased.

Cardiovascular Mortality

All-Cause Mortality

Over an average follow-up of 8.2 years (32,416 person-years accrued), 499 deaths occurred, including 241 deaths from cancer and 123 from cardiovascular diseases. Mortality rates per 1,000 person-years are shown in Table 3. The mortality rate of all causes of death for Q4 was significantly higher than that for Q1. Figure 1 shows the probabilities of overall survival according to the PWV values. The Kaplan-Meier time-to-event curves for death from all causes differed significantly among the 4 groups over the entire follow-up period (P<0.0001). Univariate analysis revealed that the risk ratio of all-cause mortality for Q3 was 1.50 (95%CI 1.15–1.95, P<0.01) and for Q4 it was 2.11 (95%CI 1.65–2.71, P<0.0001), using Q1 as the reference. Multivariate analysis adjusted for age, BMI, pulse pressure, fasting plasma glucose level, HDL-cholesterol, triglycerides, current smoking habit and ECG abnormality showed that the risk ratio was 1.28 (95%CI 0.97–1.68, P=0.07) for the highest group (Q4) compared with the lowest (Q1) group as the reference (Table 4).

Cardiovascular Mortality

Figure 2 shows the event-free probabilities of cardio-

![Figure 1. Survival curves from all-cause mortality in the study population according to pulse wave velocity (PWV) quartiles (Q). Comparison among survival curves was highly significant (P<0.0001).]
vascular mortality in the 4 groups. The Kaplan-Meier time-to-event curves for death from cardiovascular mortality differed significantly among them (P<0.0001). During the follow-up period, the number of cardiovascular deaths increased as the PWV level increased. The mortality rates for Q1 and Q4 were 2.19 and 6.26 per 1,000 person-years, respectively. The mortality for Q4 was 3-fold higher than that for Q1. In the Cox proportional model, univariate analysis revealed that the risk ratio of cardiovascular mortality for Q3 was 2.05 (95%CI 1.16–3.63, P<0.05) and for Q4 it was 3.06 (95% CI 1.79–5.25) using the Q1 group as the reference. Using multivariate analysis, the risk ratio for Q4 was 1.83 (95%CI 1.02–3.29, P<0.05), which was adjusted for age, BMI, pulse pressure, fasting plasma glucose, HDL-cholesterol, triglycerides, current smoking habit and ECG abnormality and was significantly higher than that of the reference (Q1) (Table 5).
in Q4, the cut-off level of PWV 9.0 m/s in clinical use seem to be appropriate.

This evidence-based review confirms PWV as a robust and important indicator of cardiovascular disease and supports its important role in routine investigation in clinical practice.

Study Limitation
The definition of the cause of death was determined from information on death certificates, and therefore the proportion of patients with cardiovascular disease may have been underestimated. Information about heart rates23–25 and medications for hypertension or dyslipidemia, which are associated with arteriosclerosis, was not available in this study.

Further examination is needed to clarify the progression of cardiovascular mortality in terms of differences in lifestyles, the effects of medication26 and gender, and to compare other new methodologies such as brachial–ankle PWV27,28 and CAVI (Cardio-Ankle Vascular Index)29–31

Conclusion
The present study has shown that increased PWV values were significantly associated with cardiovascular disease mortality in a Japanese male population. Those patients who had PWV values >9.0 m/s had a higher risk of mortality from all causes of death, as well as cardiovascular-related death. Further epidemiologic studies and therapeutic trials are required to evaluate these findings. We believe that aortic PWV should be used as an index in daily clinical practice.

References