Comparison of Utility of Arterial Stiffness Parameters for Predicting Cardiovascular Events in the General Population

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Summary

Several recent studies have suggested that arterial stiffness parameters such as peripheral pulse pressure (PPP), central blood pressure (CBP), and pulse wave velocity (PWV) are more accurate markers than brachial blood pressure for prediction of cardiovascular (CV) events. However, it remains unknown which arterial stiffness parameter is the most useful for predicting CV risk in the general population. Participants in the present study were randomly selected from the 40 to 79 year age group in the general population (n = 973; mean age, 59). PPP was determined in the upper arm with an oscillometric device. CBP was estimated noninvasively by radial pulsatile analysis, and brachial-ankle PWV was measured using a validated automatic device. A follow-up survey assessing the incidence of CV events including CV death was carried out after the baseline study. The mean follow-up duration was 7.8 years. Subjects were divided into quartiles according to PPP, CBP, or PWV. Event-free rates among the PWV quartiles were clearly divergent (P < 0.001); however, the rates among quartiles for the other parameters were not significant. In a multivariate Cox regression model, both the 90th percentile level of PWV (HR = 2.51, 95% CI: 1.21 – 5.22; P = 0.014) and the increase in PWV per one standard deviation (HR = 1.42, 95% CI: 1.06 – 1.90; P = 0.019) were significantly associated with risk of CV events. The area under the curves of the receiver operating characteristics analysis for CV event prediction of PWV was significantly larger than the others (P = 0.002 versus PPP; P = 0.043 versus systolic CBP). The measurement of brachial-ankle PWV is more useful than determination of PPP or CBP for identifying subjects at high risk of CV events within the general population. (Int Heart J 2013; 54: 160-165)

Key words: Blood pressure, Central blood pressure, Pulse pressure, Pulse wave velocity

It has been reported that several types of arterial stiffness parameters are independent predictors apart from brachial blood pressure (BP) levels for cardiovascular (CV) events. Several previous studies have demonstrated that pulse wave velocity (PWV), peripheral pulse pressure (PPP), and central blood pressure (CBP) are useful for evaluation of arterial stiffness and prediction of CV events and mortality in clinical and screening settings. However, a few studies to date have compared the utility of brachial-ankle PWV (baPWV), PPP, and CBP for predicting CV risk in community-based populations. It thus remains uncertain which of the pulsatile hemodynamic measures is the best screening marker for predicting future CV events in the general population. The aim of the present study was to clarify this issue.

Methods

Subjects: Subjects were recruited from the general population aged 40 - 79 years in Higashiyama district of Ichinoseki city, Iwate prefecture, northern Japan. The total population of the district at the time of baseline survey was 8,425 (men, 4,140; women, 4,285) with 4,651 (men, 2,263; women, 2,388) falling within the 40-79 year age bracket. Individuals within this age bracket were invited in a random sex-age stratified manner based on the population characteristics of the district. Invitation letters were sent out to individuals requesting their participation in the study. A total of 1,057 residents (men, 511; women, 546) finally agreed to take part (acceptance rate: 60%). The baseline survey including pulsatile hemodynamic measurements was carried out between April 2002 and November 2003. The protocol was approved by our University Ethics Committee, and written informed consent was obtained from all subjects.

Nineteen subjects were excluded from the analysis due to lack of any arterial stiffness parameters. We also excluded subjects with atrial fibrillation (n = 17), previous myocardial infarction (n = 13), history of stroke (n = 37), and peripheral arterial disease (ankle-brachial pressure index ≤ 0.9; n = 9). The final analysis was thus based on 973 men and women (mean age, 59 ± 11 years; men = 456; women = 517).

Baseline data: Subjects used a self-report questionnaire to document medical history such as hypertension, diabetes, hypercholesterolemia, stroke, angina, and myocardial infarction.
Prescribed drugs were determined by a prescription record or by referring to a pill book. Family history, clinical symptoms, smoking habits, and alcohol intake were also assessed by questionnaire. Body height and weight were measured with participants in bare feet and wearing lightweight clothing. The study also included standard 12-lead ECG recording. For routine laboratory tests, nonfasting blood samples were drawn from the antecubital vein of seated participants and were centrifuged immediately at 1,500 g for 10 minutes and transported to the laboratory (BML, Saitama, Japan) for analysis. Clinical characteristics and baseline arterial stiffness parameters are shown in Table I.

Obesity was defined as BMI ≥ 25 kg/m². Hypertension was defined as brachial systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg. Subjects taking antihypertensive drugs were also designated as having hypertension. Hypercholesterolemia was defined as a serum cholesterol concentration ≥ 240 mg/dL and/or the use of antilipidemic medications. Diabetes was interpreted as blood glucose levels ≥ 200 mg/dL in a random blood sample, glycated hemoglobin ≥ 6.5%, and/or use of antidiabetic drugs and/or insulin.

**Arterial stiffness parameters:** Brachial systolic BP and diastolic BP were determined with an automated device (HEM-907, Omron, Tokyo) placed on the right upper arm with the subject seated after resting in a sitting position for at least 5 minutes prior to measurement. Two measurements were obtained, with the mean value used for systolic BP and diastolic BP. PPP was calculated by subtracting diastolic BP from systolic BP.

**BaPWV was measured using a Form PWV/ABI (Colin Co., Komaki, Japan) on all subjects after at least 5 minutes of rest.** This apparatus simultaneously records baPWV, ankle-brachial pressure index, BP in a bilateral upper arm and lower leg, an electrocardiogram, and a phonocardiogram. The time needed to obtain a baPWV value is usually within 5 minutes. BaPWV was calculated according to the following equation: \( \text{baPWV} = (D1-D2)/T \). D1 is the distance between the heart and ankle, D2 is the distance between the heart and brachium, and T is the transit time between the right brachial arterial wave and both arterial tibial waves. The higher of the two baPWV values (from the left or right side) was used for statistical analysis.

CBP was estimated noninvasively using a SphygmoCor radial/aortic transform software module (PWV Medical, Sydney, Australia). Applanation tonometry was performed on the right radial artery. The radial artery was flattened between a handheld micromanometer-tipped probe and the underlying bone. The output of the applanation tonometer was checked on a computer monitor, and when all readings recorded were seen to meet the manufacturer’s quality control standards, 10 seconds of data were fed into the system. Radial blood pressure was calibrated from systolic BP and diastolic BP obtained from an oscillometric brachial arterial cuff system (Form PWV/ABI; Colin, Komaki, Japan). The system then generated an ascending aortic pressure waveform and systolic and diastolic CBP. BaPWV and CBP measurements were performed with the subjects in a supine position and after at least 5 minutes of resting time.

**Outcome data:** A follow-up survey assessing the incidence of CV events including CV death was carried out after the baseline study. A CV event was defined by a composite of stroke, congestive heart failure, myocardial infarction, or CV death including sudden death (from onset to death ≤ 24 hours). Hospital admission events were identified by sending a questionnaire by mail to all subjects every two years (reply rate > 95%). All possible CV event cases were also checked by medical chart review during hospital visits by trained investigators. All-cause deaths and migration were confirmed at local government offices (April 2011).

**Statistical analysis:** As measurements of the above 3 types of arterial stiffness parameters were performed by 4 observers, interobserver and intraobserver reproducibility were evaluated in another set of healthy subjects by the Bland-Altman plot and repeatability coefficient (RC). Subjects were divided into quartiles according to the 3 types of arterial stiffness parameters. The event-free rate from entry into the study was estimated using the Kaplan-Meier method, followed by a trend test (Log rank). The association between baseline arterial stiffness parameters and composite endpoint (new onset of heart failure, acute myocardial infarction, stroke, CV-related death including sudden death) was evaluated. Using a Cox proportional hazards regression model, hazard ratios (HRs) for baPWV above the 90th percentile and increase in baPWV per one-standard deviation with CV events were assessed. In multivariate regression model 1, adjustment factors were sex, age above 65 years, obesity, and the presence or absence of hypertension, diabetes, hypercholesterolemia, and/or current smoking. In model 2, the use of antihypertensive drugs was added to model 1. For analysis of CV events, person-years were censored at the date of CV events, the date of emigration from the study area, the date of death, or the end of the follow-up period, whichever came first. For comparison of the 3 arterial stiffness parameters in terms of overall diagnostic accuracy for CV events, receiver

| Table I. Clinical Characteristics and Quartile Ranges of Each Arterial Stiffness Parameter |
|------------------------------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| Number of subjects                 | 973             | Age (years)    | 59 ± 11        | Elderly (age ≥ 65 years) | 37%           | Sex (M/F)      | 456 / 517       | Obesity         | 36%            | Systolic blood pressure (mmHg) | 127 ± 19   | Diastolic blood pressure (mmHg) | 72 ± 12    | Hypertension | 44%           | Use of antihypertensive drugs | 29%     | Hypercholesterolemia | 18%     | Diabetes     | 8%        | Current smoking | 22% |
| baPWV (m/second)                   |                 | Q1             | 9.1 – 13.0     | Q2              | 13.0 – 14.5    | Q3             | 14.5 – 16.6    | Q4             | 16.7 – 27.0    | Systolic CBP (mmHg)                  | 83 – 107  | Diastolic CBP (mmHg)                  | 108 – 118 | Hypertension | 44%           | Use of antihypertensive drugs | 29%     | Hypercholesterolemia | 18%     | Diabetes     | 8%        | Current smoking | 22% |
| PPP (mmHg)                         |                 | Q1             | 18 – 42        | Q2              | 43 – 48        | Q3             | 49 – 55        | Q4             | 56 – 188       | baPWV indicates brachial-ankle pulse wave velocity; CBP, central blood pressure; PPP, peripheral pulse pressure; and Q, quartile. |
operating characteristic (ROC) curves were constructed and area under the curve (AUC) and 95% confidence intervals (CI) for each ROC curve were calculated. Statistical analyses were performed using SPSS (Version 11.0.1 J, Illinois) or Medicalc (Version 12.3.0, Belgium) software. Data are shown as the mean ± standard deviation. A significant difference was defined as $P < 0.05$.

**RESULTS**

**Cohort characteristics:** The mean age of the subjects was 59 years and the percentage of elderly (≥ 65 years) was 37%. The male to female ratio was 1.0:1.1. The mean brachial systolic BP and diastolic BP were 127 mmHg and 72 mmHg, respectively. The incidence of risk factors was: obesity 36%, hypertension 44%, antihypertensive drug use 29%, hypercholesterolemia 18%, diabetes mellitus 8%, and current smoking 22%.

**Reproducibility:** The reproducibility of baPWV has been reported previously. In terms of systolic CBP, mean interobserver and intraobserver differences determined by Bland-Altman plots were 1.1 mmHg and 0.27 mmHg, respectively. Differences between the two measurements ranged mostly within ± 2 standard deviations from the mean. Reproducibility coefficient (RC) was defined as: $(RC)^2 = 1.96 \times \sqrt{\frac{\sum D_i^2}{(n-1)}}$, where “$D_i$” is the difference between two measurements and “$n$” is the number of subjects. The interobserver and intraobserver RC for systolic CBP were 2.6 mmHg and 1.4 mmHg, respectively. These suggest an acceptable level of reproducibility of CBP measurement in the present study.

**Arterial stiffness parameters and CV events:** The cohorts were followed for 7,619 person-years. Composite CV events during the follow-up period (mean = 7.8 years) were found in 37 cases in the cohort. The number of CV events per 1,000 person-years was 4.9. The Kaplan-Meier curves for CV event-free rate according to quartile levels of PPP, systolic CBP, and baPWV in the cohort are shown in Figure 1. The CV event-free rate was significantly lower in the highest baPWV quartile ($P = 0.0001$ by log-rank test). The baseline characteristics of the quartile group of PWV are shown in Table II. However, for PPP and systolic CBP, no significant differences in the event-free ratio were found among the quartiles (Figure 1).

In a multivariate adjustment of the Cox regression model (Table III), there was a significant association between the 90 percentile level of baPWV (categorical variable) and CV events (HR = 2.51, 95% CI = 1.21 – 5.22; $P = 0.014$). Also, the association between the increase in baPWV per one standard deviation (continuous variable) and CV events remained

![Figure 1](image-url)
ARTERIAL STIFFNESS AND CARDIOVASCULAR EVENTS

The present study has demonstrated that, in an apparently healthy population, increased baPWV is related to an elevated risk of future CV events, while this relationship does not hold for other arterial stiffness parameters such as PPP and CBP. The observed relationship between baPWV and CV events remained significant after adjustment for several established CV risk factors. In addition, the overall predictive ability of baPWV was superior to the other parameters. These observations suggest that baPWV is the most useful arterial stiffness parameter for predicting CV events compared to other popular pulsatile hemodynamic measures in a screening setting.

Table II. Baseline Characteristics of Quartile Group of PWV

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>243</td>
<td>244</td>
<td>243</td>
<td>243</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>87/156</td>
<td>129/115</td>
<td>119/124</td>
<td>121/122</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51±8</td>
<td>56±10</td>
<td>62±10</td>
<td>68±8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Elderly (age ≥ 65 years)</td>
<td>10%</td>
<td>25%</td>
<td>44%</td>
<td>68%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (%)</td>
<td>23.9±3.4</td>
<td>24.1±3.1</td>
<td>24.3±3.1</td>
<td>24.1±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>113±12</td>
<td>123±15</td>
<td>129±15</td>
<td>141±20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>67±10</td>
<td>73±11</td>
<td>74±12</td>
<td>77±13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12%</td>
<td>32%</td>
<td>32%</td>
<td>32%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>16%</td>
<td>18%</td>
<td>17%</td>
<td>21%</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3%</td>
<td>6%</td>
<td>10%</td>
<td>12%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current smoking</td>
<td>24%</td>
<td>25%</td>
<td>21%</td>
<td>21%</td>
<td>NS</td>
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</tbody>
</table>

Table III. Multivariate Cox Regression Analysis of the Association Between baPWV and CV Events

<table>
<thead>
<tr>
<th></th>
<th>Adjusted hazard ratio for baPWV above 90th percentile</th>
<th>Adjusted hazard ratio per 1SD increment in baPWV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Model 1</td>
<td>2.51</td>
<td>1.21 - 5.22</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.98</td>
<td>1.24 - 5.37</td>
</tr>
</tbody>
</table>

Hazard ratios (HRs) were adjusted for sex, age above 65, obesity, hypertension, diabetes, hypercholesterolemia, and current smoking (model 1), and model 1 plus use of antihypertensive drugs (model 2).

Figure 2. Comparison of receiver operating characteristics curves of PPP, systolic CBP, and baPWV for prediction of CV events in the general population.

Discussion

The present study has demonstrated that, in an apparently healthy population, increased baPWV is related to an elevated risk of future CV events, while this relationship does not hold for other arterial stiffness parameters such as PPP and CBP. The observed relationship between baPWV and CV events remained significant after adjustment for several established CV risk factors. In addition, the overall predictive ability of baPWV was superior to the other parameters. These observations suggest that baPWV is the most useful arterial stiffness parameter for predicting CV events compared to other popular pulsatile hemodynamic measures in a screening setting.

Few studies have compared the utility of various noninvasive arterial stiffness parameters for the stratifying risk of CV events in the general population. Mitchell, et al reported that an increase in carotid-femoral PWV was significantly associated with increased risk for CV events, however, this degree of clinical utility was not found for other arterial stiffness parameters such as the augmentation index and CBP obtained by tonometry on carotid pressure. This observation may be in agreement with the present results, however, the methodologies used to measure PWV in previous studies differed from ours. The present instrument may be simpler in that it requires wrapping of blood pressure cuffs around upper and lower extremities without exposing the inguinal area during the acquisition of pressure waveforms.

Despite the lack of sufficient evidence concerning the association between baPWV and CV events, Tsuchikura, et al have shown that heart-femoral PWV, the most reliable predictor for CV events, was principally correlated with baPWV but not with other types of PWV (heart-carotid, heart-brachial, femoral-ankle) in subjects undergoing vascular examination. In addition, the relationship between baPWV and an established CV (Framingham risk score) was optimal in these pa-
tients. Similarly, in a community-based population, Tanaka, et al found a significant and potent relationship between baPWV and carotid-femoral PWV, and that the Framingham risk score was more closely correlated with baPWV than carotid-femoral PWV. They also suggested a procedural advantage may exist for baPWV apparatus especially in a population screening setting due to the simplicity of measurement without use of a pressure transducer and Doppler probe for the target vessels.

In fact, several cohort studies have examined the utility of baPWV without comparisons for other arterial stiffness parameters for events risk stratification. Turin, et al reported that the relative risk of all-cause death in subjects with the top tertile of baPWV was 6.8 times higher than that in subjects with the lowest tertile in a community-based population. In an elderly Japanese population, the hazard ratio of CV mortality in a group with baPWV above the median was elevated 10-fold compared to the lower baPWV group. A recent meta-analysis has suggested that the pooled relative risk for total CV events and all-cause mortality in subjects with higher baPWV was several times higher than that in subjects with lower baPWV. However, no longitudinal cohort studies have compared the prognostic utility of baPWV with different types of arterial stiffness parameters for CV events in a community-based population. In this regard, the present study has suggested for the first time baPWV is an important CV event marker to compare with other noninvasive arterial stiffness markers in the general population.

Several population-based cohort studies conducted in US and European populations have demonstrated that PPP is an effective hemodynamic parameter for predicting coronary heart disease, especially in the elderly. However, the feasibility of PPP for predicting CV events has yet to be established in other ethnic groups such as Asian populations where the prevalence of stroke is higher than that of coronary artery disease. Miura, et al have reported that the utility of PPP for predicting risk of stroke or myocardial infarction was lower than peripheral systolic BP in any age-group in the general Japanese population. Using ambulatory 24-hour BP monitoring, Inoue, et al compared the utility of 4 BP indices (PPP, systolic BP, diastolic BP, and mean BP) for CV event prediction, and found that PPP was the weakest predictor of stroke in the general population living in northeast Japan where stroke is a more dominant type of CV event than coronary artery disease.

A number of studies suggest closer correlation between end-organ damage and central BP than peripheral BP, and central BP may provide additional prognostic information regarding CV risk. Pini, et al compared the predictive abilities for CV event incidence and mortality among CBP, brachial BP or PPP in a population aged over 65 years. They suggested the superiority of CBP over the other two blood pressure markers after adjustment for several confounding factors. However, the present study could not confirm the association between CBP and CV risk in our general population. The discrepancy may be due to differences in methodology for acquisition of CBP levels; in the present study CBP was obtained from a tonometry system (SphygmoCor) on the radial artery, whereas in the previous studies CBP was acquired from the carotid artery.

**Limitations of the present study:** First, the number of CV events during the follow-up was relatively low in the present low-risk population. However, despite this shortage, we found a significant relationship between an increase in baPWV and CV event risk. This may indicate that baPWV measurement is an important tool for evaluating CV event risk beyond brachial BP measurement or noninvasive measurement of CBP in clinical and screening settings. Second, as one of the aims of this study was to examine the utility of several types of arterial stiffness parameters for stratifying CV risk in routine screening situations, subjects taking antihypertensive drugs were not excluded from the study. It has been demonstrated that antihypertensive drugs, particularly the renin-angiotensin-aldosterone inhibitors, decrease baPWV as well as other arterial stiffness parameters. However, the relationship between baPWV and CV events did not change significantly when the variable of ‘yes or no’ for antihypertensive drugs was included in the Cox regression model (Table II). Third, the present study did not include the results of the augmentation index, another popular arterial stiffness parameter, simultaneously obtained from the apparatus used. This was due to the poor reproducibility of measurement in our preliminary study (>10%). In addition, Millasseau, et al reported that aortic augmentation index values obtained from radial artery tonometry using transfer functions were questionable, especially in healthy subjects. Lastly, the cutoff level of baPWV to identify subjects at high risk for future CV events has yet to be established in community-based screening. The present study suggests 15.1 m/second of baPWV is the threshold for predicting CV events based on the results of ROC analysis in this relatively low risk cohort. This value may be somewhat lower compared to those of previous reports in patients with hypertension or having various risks of atherosclerosis. These previous studies have suggested that the threshold level of baPWV was approximately 17 m/second. In this regard, further studies recruiting a large number of subjects may be needed to clarify the sex- and age-dependent thresholds of the arterial stiffness parameters for improving CV event prediction in the general population.

In conclusion, measurement of baPWV is more useful than determination of PPP or CBP for selecting subjects at high risk of CV events in the general population.

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**References**


