Pulse Wave Velocity Predicts Cardiovascular Mortality

Findings From the Hawaii-Los Angeles-Hiroshima Study

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everal prospective studies have focused on the ability to predict cardiovascular risk through measurements of arterial function allowing detection of atherosclerosis status before the occurrence of critical events.1–3 Arterial stiffness can be assessed noninvasively by measuring pulse wave velocity (PWV), and it is therefore possible that PWV measurements, as a marker of aortic stiffness, might help evaluation of individual risk of cardiovascular disease.

Epidemiologic and clinical studies have shown that increased aortic stiffness, determined by PWV, is an independent marker of cardiovascular risk in end-stage renal failure1,4 and hypertensive patients.5,6 Yamashina et al showed that brachial-ankle PWV measurements were significantly higher in coronary artery disease (CAD) patients than non-CAD patients with hypertension, diabetes or dyslipidemia.7 Furthermore, Cruickshank et al showed that aortic PWV was a powerful independent predictor of coronary artery disease mortality in both diabetes and glucose-intolerant subjects.8

To the best of our knowledge, no study has attempted to determine the relationship between PWV measurements and cardiovascular mortality in general populations. We conducted a prospective study on a cohort of 492 Japanese-Americans living in Hawaii that were followed-up for a period of up to 10 years to clarify the importance of PWV measurements in predicting cardiovascular mortality in this population.

Methods

The present study was conducted as a part of the Hawaii-Los Angeles-Hiroshima long-term epidemiologic study on risk factors for cardiovascular disease and diabetes initiated in 1970. The subjects were Japanese inhabitants of Hawaii who were migrants or descendents of migrants. A total of 492 (220 men and 272 women) Japanese-Americans living in Hawaii and aged 40 to 79 years (mean: 63.7±8.8 years) underwent baseline examinations as a part of the Hawaii-Los Angeles-Hiroshima study in 1984, and were followed-up until 1994.

The current study was approved by the ethics committee of Hiroshima University School of Medicine, and all subjects gave informed consent prior to participation.

Definitions

Causes of death were based on reports from the Hawaii State Public Health Bureau. Individual diagnoses were classified by the 9th International Classification of Disease (ICD-9) codes of 1984 to 1994. Cardiovascular disease was defined as the basic cause of death with ICD-9 codes 401-438. Follow-up for mortality was virtually complete.

Measurements

At baseline, all participants were invited to undergo physical examination after an overnight fast. Weight and height were recorded. Blood pressure (BP) was measured in a supine position after a resting period of 15 min by a physician with a mercury sphygmomanometer. Phases I and V of the Korotkoff sounds were determined as systolic and diastolic BP, respectively. When initial BP levels were high (ie, diastolic BP >90 mmHg and/or systolic BP >140 mmHg), BP was remeasured and these levels were reported. Hypertension was defined as a systolic BP...
≥140 mmHg or diastolic BP of ≥90 mmHg; those on medication for high blood pressure were also classified as having hypertension. Body mass index (BMI), calculated as weight (kg)/square of height (m²), was used as a measure of obesity.

Conventional 12-lead resting electrocardiograms (ECG) were taken and interpreted according to the Minnesota code (Mc). Ischemic ECG abnormalities were defined as being present when one of the following conditions was observed: 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2, 5-3, or 7-1. Blood samples were drawn from fasting subjects in the sitting position. Hyperlipidemia was defined as a total cholesterol level of >220 mg/dl. Serum levels of total cholesterol were determined enzymatically with an Autoanalyzer (736-60E, Hitachi, Japan). Blood samples were also drawn for serum glucose and insulin determination at 1 and 2 h after 50 g of oral glucose administration. Diabetes was defined as a fasting serum glucose level of ≥126 mg/dl, 2-h postload serum glucose tolerance test level ≥200 mg/dl, or those receiving medication for diabetes. Glucose levels were determined by glucose oxidase methods. Assays for serum lipids were standardized using Q-PAK Chemistry Control serum 1 and 2 (Technicon Instrument Corp, New York, USA).

**PWV Measurement**

Pulse wave velocity was measured along the descending thoracoabdominal aorta using carotid to femoral artery measurements. Briefly, waveforms were obtained transcuanously over the common carotid artery and right femoral artery using MCG400 (Fukuda Denshi, Tokyo, Japan). One transducer was positioned over the left common carotid artery another over the left femoral artery. Two pressure waves were then recorded, and the PWV was determined as PWV = D/t, in which variable D represents the travel distance between the 2 transducers and t represents the transit time. D was measured on the surface of the body.

**Data Analysis**

The outcome events studied were cardiovascular and all-cause mortality. To assess the reliability of PWV values as a prognostic variable using receiver operating characteristic (ROC) curves, we calculated the sensitivities, specificities, positive predictive values, and negative predictive values in predicting mortality at different cut-off values. Optimal PWV cut-off values were decided from the highest diagnostic accuracy. Survival curves were estimated using the Kaplan-Meier product-limit method and compared by the log-rank test. Cox proportional hazards analysis was used to examine the influence of PWV values on all-cause and cardiovascular mortality. All analyses were performed with JMP 5.1.1 statistical software (SAS Institute Inc, North Carolina, USA). Data are expressed as the mean± SD. A value of p<0.05 was considered significant.

**Results**

**Patient Characteristics**

The patient characteristics are shown in Table 1. In the cohort, PWV values were correlated with age (r=0.60, p<0.0001), systolic BP (r=0.52, p<0.0001), and pulse pressure (r=0.56, p<0.0001). Comparisons of the relationship between PWV values and cardiovascular risk factors revealed that PWV values were significantly higher in subjects with diabetes, ECG abnormalities and hypertension than those without cardiovascular risk factors. We found significant differences in the PWV values between subjects with and without diabetes (10.46±1.78 vs 9.55±1.82 m/s, respectively, p<0.001), those with and without ECG abnormalities (10.53±2.50 vs 9.54±1.67 m/s, respectively, p<0.0001), and those with and without hypertension (10.45±2.08 vs 9.21±1.50 m/s, respectively, p<0.0001).

The optimal cut-off level of the PWV values for predicting cardiovascular mortality was 9.9 m/s with a sensitivity of 93% and specificity of 60% (area under the curve=0.77) (Fig 1A). The optimal cut-off level of the PWV values for predicting all-cause mortality was 9.9 m/s (area under the curve=0.77).

**Fig 1.** Receiver operating characteristic curve (ROC) analysis to determine the best cut-off value of pulse wave velocity (PWV) for cardiovascular mortality (A) and all-cause mortality (B). Area under curves 0.77 and 0.69, respectively.
predicting overall mortality was 9.9 m/s with a sensitivity of 72% and specificity of 62% (area under the curve = 0.69) (Fig 1B).

The cohort was divided into 2 groups according to the PWV values represented in the ROC curve. Overall, 290 individuals had PWV values \( \leq 9.9 \) m/s (lower PWV group), and 202 individuals had PWV values \( > 9.9 \) (higher PWV group). Table 2 shows the comparison of baseline characteristics between the lower PWV group and higher PWV group. Body mass index, systolic BP, serum uric acid level, and triglycerides were significantly increased in the higher PWV group than the lower PWV group, whereas serum high density lipoprotein cholesterol levels were significantly lower in the higher PWV group.

**All-Cause Mortality**

Fig 2 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 between the groups (p<0.0001). Cumulative survival rates at 10 years were 0.959 in the lower PWV group and 0.847 in the higher PWV group.

In the whole population, 43 fatal events occurred. Univariate analysis showed that age, gender, systolic BP, higher PWV values (\( > 9.9 \) m/s) and an increase in PWV of 1 m/s [risk ratio 1.28, 95% confidence intervals (CI): 1.14–1.41, p<0.001] were significantly associated with all-cause mortality, whereas diabetes, hyperlipidemia and ECG abnormalities were not. Multivariate analysis revealed that increasing PWV value was not statistical significant [risk ratio 1.42, 95% CI: 0.96–2.11, p=0.08] (Table 3).

**Cardiovascular Mortality**

Fig 3 shows the event-free probabilities of cardiovascular mortality in the higher and lower PWV groups. The Kaplan-Meier time-to-event curves for death from cardiovascular mortality differed significantly between the groups (p<0.001). Estimated proportions free from cardiovascular death at 10 years were 0.997 in the lower PWV group and 0.932 in the higher PWV group.

Fourteen cardiovascular deaths were documented during the follow-up period. Univariate analysis showed that age, higher PWV values (>9.9 m/s), diabetes and an increase in PWV of 1 m/s (risk ratio 1.35, 95% CI: 1.12–1.57, p<0.01) were significantly associated with cardiovascular mortality, whereas systolic BP, hyperlipidemia and ECG abnormalities were not. Multivariate analysis revealed that the higher PWV values (risk ratio 4.24, 95% CI: 1.39–12.96, p<0.01)
and diabetes (risk ratio 2.27, 95% CI: 1.13–4.54, p<0.05) remained predictors of cardiovascular disease death (Table 4).

**Discussion**

To the best of our knowledge, the present study is the first report to show increasing PWV values as an important indicator of cardiovascular disease death in Japanese-Americans, independent of confounding variables such as age, gender, ECG abnormalities and other risk factors, during a 10-year follow-up. Several studies have demonstrated relationships between PWV and the prognosis of populations with coronary risk factors: PWV is a powerful independent predictor of mortality in subjects with hypertension, end-stage renal failure, hyperinsulinemia and diabetes and in individuals over 70 years old. We showed that PWV was a major independent predictor of cardiovascular mortality in Japanese-Americans living in Hawaii, who represented the general population. We used PWV as a marker of aortic stiffness. It is known that PWV is an important determinant of both left-ventricular function and coronary blood flow. In addition, as PWV is associated with aortic elasticity and aortic thickness, it might be more suitable for determining the degree of atherosclerosis than pulse pressure. In general, pulse pressure is used as an indicator of cardiovascular disease death in the study population according to pulse wave velocity (PWV) level (lower PWV group: solid line vs higher PWV group: dotted line). Comparisons between survival curves were highly significant (p<0.001).

Table 3. Unadjusted and Multiple-Adjusted Risk Ratios and 95% Confidence Intervals for Cardiovascular Risk Factors to Increasing Risk of All-Cause Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unadjusted risk ratio (95% CI)</th>
<th>p-value</th>
<th>Multiple-adjusted risk ratio* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 year older)</td>
<td>1.11 (1.06–1.16)</td>
<td>&lt;0.0001</td>
<td>1.07 (1.02–1.13)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.46 (1.07–2.00)</td>
<td>&lt;0.05</td>
<td>1.38 (1.01–1.92)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic BP (per 10 mmHg)</td>
<td>1.21 (1.06–1.38)</td>
<td>&lt;0.05</td>
<td>1.00 (0.99–1.02)</td>
<td>0.81</td>
</tr>
<tr>
<td>PWV (&gt;9.9 m/s)</td>
<td>1.28 (1.14–1.42)</td>
<td>&lt;0.0001</td>
<td>1.42 (0.96–2.11)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.53 (0.92–2.56)</td>
<td>0.14</td>
<td>1.23 (0.73–2.07)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.98 (0.73–1.34)</td>
<td>0.90</td>
<td>0.97 (0.71–1.32)</td>
<td>0.83</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>1.28 (0.87–1.78)</td>
<td>0.20</td>
<td>1.15 (0.79–1.67)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, systolic BP, PWV, diabetes, hyperlipidemia, and ECG abnormalities. CI, confidence interval; BP, blood pressure; PWV, pulse wave velocity; ECG, electrocardiogram.

Table 4. Unadjusted and Multiple-Adjusted Risk Ratios and 95% Confidence Intervals for Cardiovascular Risk Factors to Increasing Risk of Cardiovascular Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unadjusted risk ratio (95% CI)</th>
<th>p-value</th>
<th>Multiple-adjusted risk ratio* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 year older)</td>
<td>1.10 (1.02–1.19)</td>
<td>&lt;0.05</td>
<td>1.00 (0.92–1.16)</td>
<td>0.93</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.51 (0.89–2.72)</td>
<td>0.13</td>
<td>1.65 (0.94–3.09)</td>
<td>0.08</td>
</tr>
<tr>
<td>Systolic BP (per 10 mmHg)</td>
<td>1.18 (0.94–1.49)</td>
<td>0.18</td>
<td>1.11 (0.84–1.48)</td>
<td>0.46</td>
</tr>
<tr>
<td>PWV (&gt;9.9 m/s)</td>
<td>4.46 (1.61–12.32)</td>
<td>&lt;0.0001</td>
<td>4.24 (1.39–12.96)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.69 (1.39–5.20)</td>
<td>&lt;0.05</td>
<td>2.27 (1.13–4.54)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.31 (0.76–2.50)</td>
<td>0.34</td>
<td>1.36 (0.77–2.63)</td>
<td>0.30</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>1.21 (0.58–2.17)</td>
<td>0.57</td>
<td>1.08 (0.55–2.13)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, systolic BP, PWV, diabetes, hyperlipidemia, and ECG abnormalities. CI, confidence interval; BP, blood pressure; PWV, pulse wave velocity; ECG, electrocardiogram.
index of aortic stiffness, and recent reports have shown a positive independent association between pulse pressure and cardiovascular mortality. However, the present study did not show that pulse pressure predicts cardiovascular mortality. Pulse pressure, which is a convenient measure of arterial stiffness, might therefore be dependent on the baseline characteristics of the subjects and/or hemodynamic factors such as heart rate, cardiac contractility, and venous pressure. We considered PWV values a more important indicator of future cardiovascular disease death than pulse pressure in general populations.

In the present study cohort, the higher PWV group had a higher tendency of all-cause mortality, but this difference was not statistically significant (risk ratio 1.42, 95% CI: 0.96–2.11, p=0.08). A total of 43 deaths occurred during the follow-up; 27 as a result of cancer. A large study population would indicate if PWV values are related to all-cause death.

As a recent topic, diastolic ventricular dysfunction was important for cardiovascular mortality. Redfield et al emphasized the usefulness of Doppler parameters of ventricular diastolic dysfunction with marked increases in all-cause mortality in the community. Carotid arterial intima-media thickness (IMT) is also recognized as an important risk factor for cardiovascular mortality. Kobayashi et al showed that increased IMT was correlated with increased PWV values and both were associated with a higher prevalence of atherosclerotic disease. We could not evaluate these factors in the present study, therefore, further investigation is required to assess the associations between cardiovascular mortality and ventricular diastolic dysfunction and IMT.

Our previous study demonstrated that diabetes was a powerful indicator of cardiovascular disease death in 927 Japanese-Americans living in Hawaii and also demonstrated that individuals with diabetes were more prone to have complications with other risk factors. Some studies have indicated that individuals with diabetes were more likely to have multiple risk factors for coronary heart disease than those without. Otherwise, in subjects with diabetes, glycosylation of collagen and elastin, and an accumulation of advanced glycosylation end-products has been shown to increase vessel stiffness. In the present study, PWV values were significantly higher in subjects with diabetes than those without. Hyperlipidemia was not related to cardiovascular mortality in the present study. First, the ages of the cohort in the current study were higher than in other studies. Second, as hyperlipidemia was partially associated with other cardiovascular risk factors such as hypertension and obesity, subjects with hyperlipidemia were strictly treated for hypertension and received advice to reduce fat intake in their diet.

Hara et al showed that the PWV values of Japanese-Americans in Hawaii were greater than those of the Japanese living in Japan, and increased PWV was correlated with risk factors of atherosclerosis. A Westernized lifestyle may play an important role in increased PWV. Westernization of eating habits is considered to be causes of the increase in atherosclerosis and a rise of cardiovascular mortality. Therefore, it is important to compare PWV with the Japanese people living in Japan and Japanese-Americans living in Hawaii. However, we could not compare the PWV values between the Japanese living in Japan and Japanese-Americans in Hawaii in the present study. Further examination is needed to clarify the progression of cardiovascular mortality in terms of differences of lifestyles.

Study Limitations

Causes of death were based on reports from the Hawaii State Public Health Bureau. Although a significant proportion of patients had confirmed cardiovascular disease, this value was probably underestimated, and asymptomatic myocardial ischemia or cerebrovascular disease death remained unapparent. We could not investigate the cardiovascular events (ie, non-fatal myocardial infarction, aortic disease, or stroke) in the cohort.

Information about anti-hypertensive or anti-hyperlipidemic agents was not available for the cohort. Angiotensin-converting enzyme (ACE) inhibitor improves the properties of the large arteries, and several studies on high-risk populations have shown that ACE inhibitors have a favorable prognostic effect; reducing death rates and cardiovascular complications.

Further examinations are therefore required to clarify more precisely the relationships between cardiovascular events and mortality. Recently, the new instruments used in PWV measurements are more convenient. Pulse wave velocity measurement should be implicated for the evaluation of future cardiovascular disease death or events in subjects with coronary risk factors or healthy populations.

Conclusion

The present study found that increased PWV values were related to cardiovascular mortality in Japanese-Americans in Hawaii. Subjects with PWV values >9.9 m/s had a higher risk of mortality from cardiovascular disease. Further epidemiologic studies and therapeutic trials are needed to extend these findings to other populations.

Acknowledgements

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References


