Brachial–Ankle Pulse Wave Velocity is a Simple and Independent Predictor of Prognosis in Patients With Acute Coronary Syndrome

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Background Although a very simple method of measuring brachial–ankle pulse wave velocity (baPWV) has become available in a clinical setting, whether baPWV can predict future cardiovascular events remains uncertain. We examined whether baPWV is a predictor of cardiovascular events in patients with acute coronary syndrome (ACS).

Methods and Results baPWV measurement was performed in 215 consecutive patients with ACS. During the follow-up period (26±10 months), 46 patients experienced post-hospitalization cardiovascular events (18 patients experienced a major event (eg, stroke, re-admission for heart failure or cardiac death), and 28 patients experienced coronary re-intervention). A receiver operating characteristic curve demonstrated that the best cut-off point of a baPWV for predicting a post-hospitalization cardiovascular event was 17.00 m/s and that for predicting a major cardiovascular event was 18.00 m/s. After the adjustment for the conventional risk factors influencing the prognosis, a multivariate Cox proportional hazards model demonstrated that both cut-off points of baPWV had a significant hazard ratio for a post-hospitalization event: 5.47 (2.69–11.09) and for a major cardiovascular event: 9.22 (2.78–30.56).

Conclusions baPWV is a simple predictor of the prognosis of patients with ACS that is independent of conventional risk factors for ACS. (Circ J 2005; 69: 815–822)

Key Words: Acute coronary syndrome; Prognosis; Pulse wave velocity

Pulse wave velocity (PWV), which reflects arterial stiffness, is a predictor of future cardiovascular events in a general population or patients with either hypertension, diabetes mellitus or end-stage renal diseases. The carotid-femoral PWV measurement is known as a conventional method. Recently, brachial–ankle PWV (baPWV) measurement, which is easier to perform than the use of other noninvasive automatic devices and uses pressure cuffs wrapped on the brachium and ankle, has become available in clinical settings. This method can be used to measure PWV in a large number of subjects. baPWV correlates with intima-media thickness of the carotid artery, which is a marker of the severity of atherosclerosis? and a close association between baPWV and aortic PWV has been also demonstrated. However, baPWV measurements include not only the aortic component, but also the muscular arterial component. Therefore, the usefulness of baPWV as a predictor of cardiovascular events has yet to be decisively established.

PWV is a marker related to the severity of atherosclerosis and the increased arterial stiffness (especially aortic stiffness) causes the increased left ventricular afterload and the impaired coronary blood supply. These pathophysiological abnormalities are thought to be involved in the underlying mechanism of influencing the prognosis. Acute coronary syndrome (ACS) is a critical condition and predicting the prognosis of patients with ACS is crucial for their management. Increased aortic stiffness, resulting in the above-mentioned disorders, may have an unfavorable influence on the prognosis of patients with ACS.

The present study was conducted to evaluate the usefulness of this simple baPWV measurement as a marker of predicting the prognosis in a clinical setting. We also examined whether the baPWV measurements can be used to predict the prognosis of patients with ACS.

Methods

Study Population, Follow-up Protocol, Study Endpoints and Endpoint Definitions

Between January 2001 and December 2003, 223 consecutive patients with ACS started their follow-up care in the outpatient cardiology department of the Tokyo Medical University Hospital. All of the patients had been hospitalized for the treatment of ACS between January 2001 and December 2003 and had undergone a coronary angiography procedure to confirm the culprit lesion and an echocardiography examination to assess their left ventricular function. During the patients’ hospitalization for ACS, percutaneous coronary intervention was conducted, if applicable. The baPWV was measured using the oscillometric method within 5 days before their discharge from the hospital.
After their discharge, the patients were asked to visit the cardiology department every month. In the patients who received percutaneous coronary intervention, a stress myocardial scintigraphy was performed 3-6 months after their hospital discharge. If this stress test was positive for ischemia, a second coronary angiography was performed to confirm the severity of the coronary arterial lesions. The number of cardiovascular events occurring within the follow-up period was recorded after a review of all medical records at the end of August 2004. Coronary re-intervention (for restenosis or a new coronary lesion) by percutaneous coronary intervention or coronary bypass surgery for refractory angina, re-infarction, re-admission for congestive heart failure, stroke and cardiac death were defined as post-hospitalization cardiovascular events. Furthermore, among these cardiovascular events, re-infarction, re-admission for congestive heart failure, stroke and cardiac death were defined as major cardiovascular events. Written informed consent was obtained from all patients. The ethical committee of Tokyo Medical University approved all the study protocols.

Diagnosis and Treatment of ACS and Atherosclerotic Risk Factors

ACS was diagnosed based on the presence of typical ischemic symptoms plus any of the following evidence: either an ST elevation, ST depression, or T wave inversion in 2 or more electrocardiogram leads and the elevation of blood troponin T and creatine kinase levels. In patients who did not have an elevation in these blood markers, the culprit lesion was confirmed by coronary angiography within 48 h after their admission. In patients with an ST elevation, ST depression, or T wave inversion and elevated blood troponin T and creatine kinase levels, an emergency coronary angiography was performed. Percutaneous coronary intervention was also conducted, if applicable. Among these cases, 7 patients initially received thrombolytic therapy, followed by coronary angiography within 48 h and then percutaneous coronary intervention, if applicable. In patients without elevated blood markers, heparin was intravenously infused until the patient underwent coronary angiography (within 48 h after their admission). Percutaneous coronary intervention was then performed, if applicable. When percutaneous coronary intervention was not applicable, the intravenous infusion of heparin was continued until day 3 of hospitalization and then switched to an oral administration. Two patients underwent emergency coronary bypass surgery. Hypertension, dyslipidemia and diabetes mellitus were diagnosed and managed according to the guidelines of the Japanese Society of Hypertension, the Japan Atherosclerosis Society and the Japan Diabetes Society.

Coronary Angiography, Measurement of Fractional Pulse Pressure and Coronary Intervention

Coronary angiography was performed using the standard Judkin’s or Sone’s technique. The results of the coronary angiographies and pressure variables were analyzed using a quantitative coronary angiography technique (Cathcor; Siemens, Munchen, Germany). Significant stenosis of the coronary vessels was defined as a narrowing of greater than 50%. Two experienced angiographers visually assessed all the coronary angiograms. The systolic and diastolic blood pressures in the ascending aorta were obtained using a fluid-filled catheter, and the fractional pulse pressure was calculated (pulse pressure/mean pressure). Percutaneous coronary intervention was performed using standard techniques including, but not limited to, percutaneous transluminal coronary angioplasty, intracoronary stenting and coronary thrombectomy. A successful percutaneous coronary intervention result was defined as a degree of vessel stenosis less than 50% of the luminal diameter.

Echocardiography

An echocardiography examination was performed in each patient on days 3-5 of their hospitalization to assess their left ventricular systolic function. The left ventricular end diastolic and end systolic volumes were determined using 2 and 4 apical views of the chamber, respectively, and the Simpson biplane formula, according to the recommendations of the American Society of Echocardiography. The left ventricular ejection fraction (LVEF) was calculated as [end diastolic minus end systolic volume]/end diastolic volume x100%. The intraobserver and interobserver variabilities in the echocardiographic assessment of the ejection fraction were 5% and 6%, respectively, in our laboratory.

baPWV Measurements Using the Oscillometric Method

After the patients were transferred from the coronary care unit to a general floor of the cardiology department, the measurement of baPWV was conducted at the time when the patients were designated to be discharged from the hospital, and it was performed at the bedside of each patient. After the patient had rested in a supine position for at least 5 min, the baPWV was measured using a volume-plethysmographic apparatus (FORM/ABI; Colin Co Ltd, Komaki, Japan) while the patient was in the same position. This instrument simultaneously records the baPWV and the brachial and ankle blood pressures on the left and right sides, produces an electrocardiogram and records the heart sounds.

The highest baPWV on both sides and the lowest ankle-brachial pressure index value for both sides were determined, and subsequent statistical analyses were performed using these values. The complete methodology has been described elsewhere. All recordings were performed while the patients were under the influence of their regular medications. None of the patients were receiving intravenous medication at the time of the study. Briefly, electrocardiographic electrodes were placed on both wrists and cuffs were wrapped around both arms and ankles. Brachial and post-tibial arterial pressure waveforms obtained by the cuff were connected to a plethysmographic sensor that determines volume pulse form and oscillometric sensor that measures blood pressure, which were wrapped on both arms and ankle, and were stored for 10 s. Sufficient waveform data were obtained in this stored sample. The characteristic points of waveforms were determined automatically according to the phase velocity theory. The components over 5 Hz were stored using a pass filter and the wave front was determined. The time interval between the wave front of brachial waveform and that of ankle waveform was defined as the time interval between brachium and ankle (ΔTba). The distance between sampling points of baPWV was calculated automatically according to the height of the subject. The path length from suprasternal notch to the brachium (Lb) was obtained from superficial measurements and was expressed using the following equation: Lb=0.2195×height of the patient (in cm)-2.0734. The path length from suprasternal notch to ankle (La) was...
has been validated in a previous study.7,8 The interobserver coefficient of variation was 10.0%.7

Calculation of Risk-Prediction Model (Global Registry of Acute Coronary Events Score)

The Global Registry of Acute Coronary Events (GRACE) score, used to predict the prognosis, was calculated based on the patients’ clinical characteristics according to the GRACE risk-prediction model.20 Briefly, the GRACE score was calculated based on the medical history of the patient (age, history of heart failure and/or myocardial infarction), the clinical findings at the time of the initial hospital presentation (heart rate, systolic blood pressure and ST-segment depression), and the clinical findings during hospitalization (renal function, elevation of cardiac enzymes and in-hospital coronary intervention).

Statistics

All data are expressed as the mean ± SD. The statistical analysis was performed using the SPSS software package (SPSS, Chicago, IL, USA). For group comparisons, an unpaired Welch’s t-test or chi-square test was applied. The Cox proportional hazards model was used for the univariate analysis to determine factors significantly associated with a post-hospitalization cardiovascular event or with a major cardiovascular event. A receiver operating characteristic curve analysis was performed to estimate the best baPWV cut-off point for predicting a future post-hospitalization cardiovascular event and for a future major cardiovascular event. The predictive accuracy of the parameters was calculated as the area under the receiver operating characteristic curve. The value with the highest sum of sensitivity and specificity was identified as the cut-off point.
The survival curves were estimated using the Kaplan-Meier method and analyzed using a log-rank test. A multivariate analysis was performed using the Cox proportional hazards model and parameters that had been confirmed as being significantly associated with a post-hospitalization cardiovascular event and with a major cardiovascular event were analyzed using a univariate Cox proportional hazards test. A p-value of <0.05 was considered statistically significant.

**Results**

Among 223 patients, 3 patients were excluded because of factors known to influence PWV: 2 patients with atrial fibrillation and 1 patient with a permanent pacemaker implant. In addition, 5 patients could not determine the maximal plasma creatine kinase level. Therefore, 215 patients were analyzed in the present study. As of the end of August 2004 (mean follow-up periods: 26±10 months), 48 cardiovascular events had been confirmed in 46 patients. Among them, 28 patients required re-interventions, 6 patients were re-admitted to hospital with heart failure, 3 patients had strokes, 2 patients required re-interventions and had heart failure, 2 patients required re-interventions and had strokes, and 5 patients died from cardiac complications. None of the patients in the current study experienced a re-infarction. Thus, 18 patients experienced a major cardiovascular event.

Table 2 Results of Univariate Cox Proportional Hazards Model for Prediction of Post-Hospitalization Cardiovascular Events

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
<th>Wald Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.01–1.06)</td>
<td>&lt;0.05</td>
<td>5.97</td>
</tr>
<tr>
<td>Gender</td>
<td>0.61 (0.33–1.14)</td>
<td>NS</td>
<td>2.38</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.92 (0.83–1.01)</td>
<td>NS</td>
<td>3.65</td>
</tr>
<tr>
<td>CRP</td>
<td>0.99 (0.92–1.06)</td>
<td>NS</td>
<td>0.05</td>
</tr>
<tr>
<td>maxCK</td>
<td>1.00 (0.98–1.02)</td>
<td>NS</td>
<td>0.11</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.97 (0.95–0.99)</td>
<td>&lt;0.05</td>
<td>6.00</td>
</tr>
<tr>
<td>UAP/MI</td>
<td>0.87 (0.48–1.56)</td>
<td>NS</td>
<td>0.23</td>
</tr>
<tr>
<td>Killip ≥ II</td>
<td>1.58 (0.32–4.00)</td>
<td>NS</td>
<td>0.93</td>
</tr>
<tr>
<td>No. of diseased arteries</td>
<td>1.09 (0.76–1.56)</td>
<td>NS</td>
<td>0.19</td>
</tr>
<tr>
<td>PPf</td>
<td>8.78 (1.47–52.49)</td>
<td>&lt;0.05</td>
<td>5.76</td>
</tr>
<tr>
<td>PWVmax</td>
<td>1.18 (1.12–1.24)</td>
<td>&lt;0.01</td>
<td>43.5</td>
</tr>
<tr>
<td>ABI &lt; 0.9</td>
<td>1.74 (0.81–3.73)</td>
<td>NS</td>
<td>2.02</td>
</tr>
<tr>
<td>GRACE score</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.05</td>
<td>5.12</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.76 (0.42–1.39)</td>
<td>NS</td>
<td>0.79</td>
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<tr>
<td>Hypertension</td>
<td>1.44 (0.74–2.78)</td>
<td>NS</td>
<td>1.17</td>
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<tr>
<td>Dyslipidemia</td>
<td>1.35 (0.75–2.44)</td>
<td>NS</td>
<td>0.98</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.23 (1.24–4.01)</td>
<td>&lt;0.01</td>
<td>7.14</td>
</tr>
</tbody>
</table>

CI, confidence interval; Age, age at the time of admission; CRP, plasma level of C-reactive protein on the first day of admission; maxCK, maximal plasma creatine kinase level; LVEF, left ventricular ejection fraction; UAP/MI, patients with unstable angina/patients with acute myocardial infarction; Killip ≥ II, patients with a clinical severity of greater than Killip’s stage II; PPf, fractional pulse pressure; PWVmax, highest brachial-ankle pulse wave velocity value on both sides; ABI < 0.9, patients whose lowest brachial-ankle pressure index was <0.9; GRACE score, calculated risk prediction score based on the GRACE study protocol.

Fig 1. Receiver operating characteristic curve for estimating the best brachial-ankle pulse wave velocity (PWV) cut point for predicting post-hospitalized cardiovascular events in patients with acute coronary syndrome (ACS).

Fig 2. Kaplan-Meier curve showing the cumulative event-free probability from post-hospitalized cardiovascular events. PWV, pulse wave velocity.
Such variables in patients who experienced a major cardiovascular event were also shown in Table 1. The LVEF was lower and the age, fractional pulse pressure, baPWV, GRACE score and prevalence of diabetes mellitus were higher in patients who experienced a post-hospitalization cardiovascular event than in those who did not. These differences (except fractional pulse pressure) were also observed between the patients who experienced a major cardiovascular event and those who did not. In addition, the prevalence of patients with a clinical severity greater than Killip’s stage II was also higher in these patients.

The univariate Cox hazards proportional model demonstrated that the age at the time of admission, LVEF, GRACE score, presence of diabetes mellitus and baPWV were significantly associated with post-hospitalization cardiovascular event (Table 3).

For a major cardiovascular event, the univariate Cox hazards proportional model demonstrated that the age at the time of admission, LVEF, GRACE score, presence of patients with a clinical severity greater than Killip’s stage II, the presence of diabetes mellitus and baPWV were significantly associated with major cardiovascular events (Table 4). The receiver operating characteristic curve analysis demonstrated that a baPWV of 18.00 m/s was the best cut-off point for predicting a future major cardiovascular event (area under curve =0.89, sensitivity =89%, specificity =74%) (Fig 3). The Kaplan-Meier analysis demonstrated that patients with a baPWV of 18.00 m/s or higher had a significantly higher prevalence of major cardiovascular events during the follow-up period (p<0.01) (Fig 4). The multivariate Cox proportional hazards model demonstrated that a baPWV of 18.00 m/s or higher was a significant and independent predictor of a major cardiovascular event (Table 5).

Discussion

The clinical characteristics of patients obtained at the time of their hospital admission to receive treatment for ACS provide valuable information regarding prognosis, and several risk-prediction models for differing outcomes of ACS have been reported.20–22 Recently, the GRACE study protocol...
The present study demonstrated, for the first time, that baPWV is a useful predictor of the prognosis of patients with ACS (the best cut-off point of a baPWV for predicting a post-hospitalization cardiovascular event was 17.00 m/s and that for predicting a major cardiovascular event was 18.00 m/s) that is independent of the GRACE risk prediction model, maximal creatine kinase level and the LVEF.

Aortic stiffness, rather than muscular arterial stiffness, is more closely associated with coronary outcome. The carotid-femoral PWV is a noninvasive marker that is closely related to arterial stiffness and several studies have reported its usefulness as a predictor of future cardiovascular events. The measurement of baPWV, however, is a relatively new technique, but this method has been demonstrated to be valid and reproducible? Although baPWV reflects arterial stiffness in the central and peripheral arteries, it is closely correlated with aortic arterial stiffness measured using a catheter tip with a pressure manometer. Comparing baPWV with carotid-femoral PWV as tools to be used in general practice, baPWV measurements do not require a specialized technique and the examiner only has to wrap cuffs on the brachium and ankle. To measure the carotid-femoral PWV, however, a special technician is required and the femoral area must be exposed. Thus, the simplicity of the baPWV measurement technique is a major advantage.

Pulse pressure is a related marker of arterial stiffness, and some population studies have demonstrated that a wide pulse pressure is an independent risk factor of a cardiovascular event as well as a predictor of restenosis after percutaneous coronary intervention. Cardiac systolic function is another major determinant of pulse pressure. Cardiac function is impaired in most patients with ACS. The present study confirmed that the baPWV, rather than the fractional pulse pressure, had a significant hazards ratio not only for the prediction of post-hospitalized cardiovascular events, but also for that of a major cardiovascular event.

The current study has some limitations. First, we could not evaluate the underlying mechanisms contributing to increased arterial stiffness to influence the prognosis of patients with ACS. Our speculated mechanisms are outlined as follows. For heart failure and cardiac death, it is well noted that increased arterial stiffness (especially aortic stiffness) directly increases the left ventricular afterload and impairs the coronary blood supply via a reduction in the diastolic blood pressure level. In addition, our previous study produced a simple model for clinical use. In addition, the extent of myocardial damage (maximal creatine kinase level), the LVEF and B-type natriuretic peptide have been shown to be clinically useful predictors of prognosis. The present study demonstrated, for the first time, that baPWV is a useful predictor of the prognosis of patients with ACS (the best cut-off point of a baPWV for predicting a post-hospitalization cardiovascular event was 17.00 m/s and that for predicting a major cardiovascular event was 18.00 m/s) that is independent of the GRACE risk prediction model, maximal creatine kinase level and the LVEF.

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study demonstrated a significant positive association between increased arterial stiffness and impaired cardiac diastolic function? This interaction amplifies cardiac diastolic dysfunction and increases cardiac energy cost; these disorders harm cardiac performance in high-risk subjects. Another proposed mechanism is in regards to the coronary blood supply seems to increase the risk of the cerebral vasculature. In addition, the increased amplitude of pulse pressure caused by increased arterial stiffness may thicken the extra and intra-cranial arterial wall and produce the development of plaques. Finally, these phenomena may induce plaque rupture. For restenosis, increased arterial stiffness (including aortic and muscular arterial components) may directly act as an atherogenic factor via lowering wall shear stress and the impairment of the coronary blood supply seems to increase the risk of coronary restenosis after percutaneous coronary intervention.

Second, a lack of aortic PWV measurements as a control was a major limitation of the present study. The predictions of the baPWV and carotid-femoral PWV measurement techniques should be compared with regards to the prognosis of patients with ACS.

Third, the number of patients in the current study was relatively small and the duration of follow-up period was also relatively short. While LVEF is a major determinant for the prognosis, the shortness of the follow-up period in the study might influence the deterioration of the significance of the LVEF as a risk for prognosis, at least in part. The results of the present study should therefore be confirmed by using a larger number of patients and a long-term follow-up period. Most of the patients in the present study received percutaneous coronary intervention, and the usefulness of baPWV as a predictor of the prognosis of patients with ACS who have not received percutaneous coronary intervention is also required.

In conclusion, baPWV is a simple predictor of the prognosis of patients with ACS that is independent of the influence of conventional risk factors on the prognosis of patients with ACS. A baPWV of 17.00 m/s or higher seems to indicate a risk of a post-hospitalization cardiovascular event. Furthermore, a baPWV of 18.00 m/s or higher seems to indicate a risk of a major cardiovascular event.

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