Brachial-ankle Pulse Wave Velocity as an Index of Central Arterial Stiffness

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Aim: Stiffness of the central arteries plays an important role in the pathophysiology of cardiovascular disease, and pulse wave velocity (PWV) of the aorta has been used as the standard measure of central arterial stiffness. An automated device for brachial-ankle (ba) PWV is available, although information is limited whether baPWV reflects the stiffness of central or peripheral arteries. We therefore addressed this question in the present study.

Methods: The subjects were 2,806 consecutive participants in our non-invasive vascular laboratory, excluding those with an ankle-brachial index (ABI) lower than 0.95. PWV measurements were simultaneously performed using an automated device for the ba, heart-femoral (hf, aorta), heart-carotid (hc), heart-brachial (hb), and femoral-ankle (fa) segments. Correlational analyses were performed (1) among these PWV values, (2) between PWV and individual risk factors, and (3) between PWV and the Framingham risk score (FRS), a surrogate index for integrated cardiovascular risk.

Results: The correlation of baPWV was the highest with hfPWV ($r=0.796$) and the lowest with hcPWV ($r=0.541$). Among the known factors preferentially affecting central arterial stiffness, higher age, diabetes mellitus, and chronic kidney disease (CKD) were also closely associated with increased baPWV. Finally, FRS was more closely correlated with hfPWV ($r=0.613$) and baPWV ($r=0.609$) than with hbPWV ($r=0.523$), hcPWV ($r=0.509$), and faPWV ($r=0.393$).

Conclusion: These results indicate that baPWV is an index of arterial stiffness showing similar characteristics to those of aortic PWV.


Key words: Arterial stiffness, Compliance, Distensibility, Arteriosclerosis, Atherosclerosis

Introduction

Stiffness of the central arteries is an independent predictor of cardiovascular disease (CVD). Pulse wave velocity (PWV) of the aorta is increased in populations at high risk for CVD, such as elderly people\(^1\) and patients with hypertension\(^2\), type 2 diabetes mellitus (T2DM)\(^3\), and chronic kidney disease (CKD)\(^4,5\). Although PWV is affected by ambient blood pressure, aortic PWV predicts mortality from CVD independent of blood pressure and other major risk factors in these populations\(^6-10\).

Although PWV of the aorta has been used as the standard measure for arterial stiffness in Western countries, PWV can be measured in other arterial regions, such as heart-carotid (hc), heart-brachial (hb), and femoral-ankle (fa) segments. In Japan and other Asian countries, brachial-ankle PWV (baPWV) is now widely measured\(^11-16\). Kitahara et al.\(^14\) revealed that increased baPWV is an independent predictor of CVD in hemodialysis patients. A very recent report by Tanka et al.\(^16\) showed that baPWV and carotid-femoral PWV were closely and comparably associated with blood pressure, the Framingham risk score (FRS), and pre-existing CVD. Previous studies\(^17-22\) showed that
the impact of some CVD risk factors and medications on PWV varies among different arterial territories. Also, the association of pre-existing CVD with PWV appears to vary among these regional PWV measurements; therefore, it is an important question whether baPWV is an index of central or peripheral arterial stiffness.

To answer this question, we performed this large cross-sectional study. First, we examined the correlations of baPWV with PWVs of the aorta and other arterial segments. Second, we compared the individual factors associated with baPWV and other PWV measurements. Finally, we evaluated the association of baPWV and other PWV measurements with FRS as a surrogate index for integrated cardiovascular risk.

Subjects and Methods

Subjects

The subjects of this study were participants in our vascular laboratory at Osaka City University Hospital and the Health Promotion Center in Osaka City, Japan. The study was approved by the ethics committee at Osaka City University Graduate School of Medicine, and all subjects gave informed consent. We screened our clinical database for subjects who underwent regional PWV measurements from July 2000 through April 2009, and identified 3,277 consecutive subjects. Among them, 281 were excluded because of the lack of relevant clinical information and/or the presence of arterial fibrillation. Then, 190 subjects with an ankle-brachial index (ABI) less than 0.95 were excluded, because Motobe et al. reported that the accuracy of baPWV measurement was diminished in such subjects. Data of the remaining 2,806 subjects were used for subsequent analyses. Table 1 summarizes the characteristics of the subjects.

Definition of Major Risk Factors

Hypertension was diagnosed if the subject had blood pressure of 140/90 mmHg or higher, and/or was taking anti-hypertensive medication. Diabetes mellitus was diagnosed if the subject had a fasting plasma glucose of 126 mg/dL or higher, and/or was taking anti-diabetic medication. Dyslipidemia was diagnosed if the subject had low-density lipoprotein cholesterol of 140 mg/dL or higher, triglyceride of 150 mg/dL or higher, and/or high-density lipoprotein cholesterol lower than 40 mg/dL, and/or was taking lipid-lowering medication. Smoking denotes current smoking. Chronic kidney disease (CKD) was diagnosed if the subject had overt proteinuria and/or a reduced estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m².23-25

Table 1. Characteristics of the subjects and PWV measurements

| Total number of subjects (persons) | 2,806 |
| Age (years) | 60 (53-67) |
| Male sex (%) | 49.3 |
| Smoker (%) | 44.7 |
| Diabetes mellitus (%) | 51.1 |
| Hypertension (%) | 46.6 |
| Dyslipidemia (%) | 70.0 |
| Chronic kidney disease (%) | 27.6 |
| Systolic blood pressure (mmHg) | 127 (115-140) |
| Diastolic blood pressure (mmHg) | 77 (70-84) |
| Fasting plasma glucose (mg/dL) | 107 (95-132) |
| Total cholesterol (mg/dL) | 205 (179-230) |
| Triglycerides (mg/dL) | 108 (79-153) |
| HDL-C (mg/dL) | 53 (43-66) |
| Non-HDL-C (mg/dL) | 148 (124-175) |
| Serum creatinine (mg/dL) | 0.73 (0.60-0.90) |
| eGFR (mL/min/1.73m²) | 74.3 (60.0-88.1) |
| ABI | 1.14 (1.08-1.19) |
| Framingham Risk Score (unit) | 8 (5-11) |
| hf PWV (cm/s) | 1.034 (871-1,231) |
| hc PWV (cm/s) | 998 (799-1,224) |
| hb PWV (cm/s) | 626 (559-705) |
| fa PWV (cm/s) | 1,058 (963-1,150) |
| ba PWV (cm/s) | 1,504 (1,299-1,751) |

Table 1. Characteristics of the subjects and PWV measurements

Number of subjects, percentages, and median (inter-quartile range). Abbreviations: ABI, ankle-brachial pressure index; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; PWV, pulse wave velocity; hf, heart-femoral; hc, heart-carotid; hb, heart-brachial; fa, femoral-ankle; ba, brachial-ankle.

PWV and Blood Pressure Measurements

PWV and blood pressure measurements were performed in the supine position after 5 minutes of bed rest using an automatic waveform analyzer (model BP-203RPE; Colin, Komaki City, Japan) as previously described.20, 22, 25

The ankle-brachial pressure index (ABI) was defined as the ratio of systolic blood pressure (SBP) of the tibial artery to that of the brachial artery. When brachial SBP values differed between right and left sides, the higher value was taken for ABI calculation. The automatic waveform analyzer reports ABI for both sides, and the lower value was used for analysis.

Pressure waveforms of the brachial and tibial arteries were recorded by an oscillometric method using occlusion/sensing cuffs adapted to both arms and ankles. Pressure waveforms of the carotid and femoral arteries were recorded using multielement tonometry sensors placed at the left carotid and left femoral arter-
ies. Electrocardiogram was monitored with electrodes placed on both wrists. Heart sounds S1 and S2 were detected by a microphone set on the left edge of the sternum at the third intercostal space. The waveform analyzer measures time intervals between S2 and the notch of the carotid pulse wave (The), between S2 and the notch of brachial pulse wave (Tbb), between pulse waves of the carotid and femoral arteries (Tcf), between pulse waves of the femoral and tibial (ankle) arteries (Tfa), and between pulse waves of the brachial and ankle arteries (Tba). The sum of The and Tcf gives the time for pulse waves to travel from the heart (aortic orifice) to the femoral artery (Thf). Also, the waveform analyzer estimates the path lengths of the heart-carotid (Dhc), heart-brachial (Dhb), heart-femoral (Dhf), femoral-ankle (Dfa), and heart-ankle segments (Dha) based on the height (HT, in centimeters) using the following formulas: Dhc = 0.2437 × HT − 18.999; Dhb = 0.2195 × HT − 20.734; Dhf = 0.5643 × HT − 18.381; Dfa = 0.2486 × HT + 30.709; Dha = Dhf + Dfa. PWV was calculated for each arterial segment as the path length divided by the corresponding time interval. PWV of the brachial-ankle segment (baPWV) was calculated using the formula: baPWV = (Dha − Dhb)/Tba. Regarding reproducibility, the coefficient of variation was less than 5% for baPWV[11]. In our preliminary study, the coefficients of variation for other regional PWV measurements were 6.0%, 3.3%, 4.9%, 3.3% for hcpPWV, hbPWV, hfPWV, and faPWV, respectively[20]. Since baPWV and faPWV of the right and left sides agreed well (r=0.95 and 0.90, respectively) in the final subjects, excluding those with ABI less than 0.95, the right side values were used in this report. Also, hbPWV indicated the value measured in the right arm.

Other Measurements
Venous blood was collected into plastic tubes in the morning after an overnight fast. We measured plasma glucose, serum total cholesterol (TC), triglycerides (TG), and creatinine by enzymatic methods using an auto-analyzer. High-density lipoprotein cholesterol (HDL-C) was measured by precipitation. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation to diagnose dyslipidemia, but it was not reported here because 54 subjects had marked elevation of TG >400 mg/dL, which blocked the accurate estimation of LDL-C. We reported Non-HDL-C, which was calculated by subtracting HDL-C from TC, regardless of the TG level. We estimated the glomerular filtration rate (eGFR) according to the formula for Japanese[31]. Proteinuria was determined by a dip-stick method using spot urine samples obtained in the morning. The Framingham risk score (FRS) was calculated as a surrogate index for 10-year risk for coronary heart disease[32].

Statistical Methods
Categorical variables were expressed as a percentage. Continuous variables were summarized as the median (inter-quartile range). Correlation was evaluated by Spearman’s rank correlation method. Multiple regression models were used to analyze associations between PWV and other clinical parameters. P values less than 0.05 was taken as significant. Analyses were performed using StatView 5 (SAS Institute, Cary, NC) for Windows PC.

Results
Correlation of baPWV with Aortic and other Regional PWV Measurements
As shown in Fig. 1, the correlation coefficients of baPWV with hfpPWV, hcpPWV, hbPWV, and faPWV were 0.796, 0.541, 0.581, and 0.705, respectively. The highest correlation was found between baPWV and hfpPWV.

Individual Factors Correlating with PWV
Previous studies[20, 22] identified age, diabetes mellitus, and CKD as the factors preferentially associated with increased PWV of the aorta over other arterial segments. Thus, we examined whether baPWV shared such risk factors with aortic PWV in our subjects. Fig. 2 illustrates the Spearman’s correlation coefficients of the five measurements of PWV with age, diabetes mellitus, CKD, hypertension, dyslipidemia, and smoking. Age, diabetes mellitus, and CKD were more closely associated with hfpPWV than other regional PWVs, and the association with baPWV was comparable to that with hfpPWV. Hypertension was strongly associated with all five measurements of PWV, and the correlation coefficients were comparable between baPWV and hfpPWV. Dyslipidemia showed the highest association with hfpPWV, and the next highest association with baPWV. Smoking was associated with the five PWVs with generally low correlation coefficients.

Independent Factors Associated with baPWV and other PWV Measurements
We performed multiple regression analysis to examine possible differences in the factors independently associated with PWVs of the five arterial segments. The model included age, sex, smoking, diabetes mellitus, hypertension, and CKD as candidate factors. Regarding dyslipidemia, HDL-C, Non-HDL-C, and use
Fig. 1. Correlation of baPWV with other PWV measurements

Spearman’s correlation coefficient ($r$) and level of significance ($p$) are indicated for all subjects ($n=2,806$).

**Abbreviations:** PWV, pulse wave velocity; ba, brachial-ankle; hf, heart-femoral; hc, heart-carotid; hb, heart-brachial; fa, femoral-ankle.

Fig. 2. Risk factor profile of baPWV and other PWV measurements

We calculated Spearman’s correlation coefficient ($r$) and level of significance ($p$) between the five PWV measurements and 6 factors, including age, diabetes, chronic kidney disease (CKD), hypertension, dyslipidemia, and the smoking status. Bars indicate correlation coefficients. **p-values** were less than 0.001 for all.

**Abbreviations:** PWV, pulse wave velocity; ba, brachial-ankle; hf, heart-femoral; hc, heart-carotid; hb, heart-brachial; fa, femoral-ankle.
of lipid-lowering medication were entered into the model (Table 2). We found that age, male sex, diabetes mellitus, and hypertension were commonly significant factors for the five regional PWV measurements. CKD was significantly associated with hPWW, hPWW and baPWV. Although neither HDL-C nor Non-HDL-C was found as an independent factor associated with PWV, the use of lipid-lowering medication was significantly associated with lower faPWV. Smoking was not significantly associated with any of the five PWVs in the multiple regression model.

**FRS in Association with baPWV and other PWV Measurements**

Fig. 3 shows the correlation of FRS with baPWV and PWV of the four arterial segments. The correlation coefficient was highest for hPWW (r=0.613) and lowest for faPWV (r=0.393). The correlation coefficient of baPWV (r=0.609) was comparable to that of hPWW.

**Discussion**

Since the measurement of baPWV includes both central and peripheral arteries, some researchers may take it as an index of peripheral rather than central arteries. We addressed the question of whether baPWV is an index of stiffness of the central or peripheral arteries using a large database in our non-invasive vascular laboratory. The results indicated that baPWV had the highest correlation with hPWW as compared with hPWW, hPWW and faPWV. Furthermore, baPWV and hPWW shared higher age, diabetes mellitus, and CKD as risk factors. Finally, FRS showed similarly close associations with aortic PWV and baPWV. These results indicate that baPWV has properties of central rather than peripheral arterial stiffness.

Several studies have also addressed this issue previously. Yamashina et al. 13 examined the correlation between baPWV and aortic PWV, which was directly measured using a catheter tip with a pressure manometer during coronary angiography in 41 patients with coronary artery disease, showing a very close correlation between the two methods (r=0.87). Sugawara et al. 33 measured baPWV, aortic PWV, and faPWV in 409 healthy adults aged 18–76 years, and showed that baPWV was closely correlated with both aortic PWV (r=0.76) and faPWV (r=0.76), but aortic PWV explained most of the total variance of baPWV in their cross-sectional and longitudinal studies. Tanaka et al. 16 recently examined the correlation between baPWV and carotid-femoral PWV, another measure of aortic PWV in 2,287 subjects, and found a high correlation between the two (r=0.73). Our results are consistent with these studies, and further revealed that baPWV showed a higher correlation with aortic PWV than it did with other regional PWV measurements.

We 20, 22 previously found that higher age, diabetes mellitus, and CKD were preferentially associated with central over peripheral arterial PWV. In the present study, we compared the associations between age and the five PWVs, and found that hPWW and ba PWV showed the highest and next highest correlation coefficients with age, respectively. Also, hPWW and baPWV showed comparably high correlation coefficients with diabetes mellitus and with CKD. These results showed that aortic PWV and baPWV shared a similar risk factor profile.

Tanaka et al. 16 compared the association of FRS with aortic PWV and baPWV, and found that these
two measurements showed comparable associations with FRS, a surrogate risk index for coronary heart disease. We made a similar comparison among the five PWV measurements, and the results were in agreement with the report by Tanaka et al.16 Also, we showed that FRS correlated significantly, but to a lesser extent, with hbPWV, hcPWV, and faPWV. These data suggest that the risk for CVD is more closely associated with central than peripheral arterial stiffness, and that baPWV reflects the integrated risk for CVD to a similar extent as aortic PWV.

We noticed an inverse association between the use of lipid-lowering medications and faPWV in multiple regression analysis. This was not likely due to the presence of obstructive disease in the leg arteries among subjects receiving lipid-lowering drugs, because we excluded those with ABI less than 0.95. In our subjects treated with lipid-lowering medications (n=795), 648 patients were on statin treatment. PWV of the leg arteries, but not of the central arteries, showed a significant decrease during longitudinal observations with simvastatin19 or atorvastatin21. Although the present finding was based on cross-sectional analysis, the observed inverse association between lipid-lowering medication and faPWV is in good agreement with longitudinal studies.

There are several limitations in this study. First, we used FRS as a surrogate index for cardiovascular risk. The results would have been more relevant if the subjects had been followed up longitudinally for future CVD events, and the risk for CVD directly calculated. Second, because of the cross-sectional nature of the study, the observed associations between PWV and other clinical parameters do not necessarily indicate a causal relationship. Third, we are not completely sure whether the results apply to other populations, although the sample size is relatively large. In particular, care should be taken in the interpretation of baPWV among subjects with reduced ABI. In such subjects, baPWV is decreased and does not accurately reflect central arterial stiffness12,20.

In conclusion, this study provides further information showing that baPWV correlated best with aortic PWV among the five PWV measurements. Because
of the high correlation, its risk factor profile, and the close association with the surrogate index for CVD risk, baPWV appears an index of central rather than peripheral arterial PWV. Although baPWV is affected by peripheral arterial disease and blood pressure at the time of measurement, it may serve as a convenient and easy-to-measure tool for the assessment for central arterial stiffness if appropriately applied.

References

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