ORIGINAL PAPER

Relationship between brachial-ankle pulse wave velocity and invasively measured aortic pulse pressure

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Although brachial-ankle pulse wave velocity (baPWV) has been widely used as an index of arterial stiffness, no consensus exists about whether baPWV can reflect central aortic stiffness. The authors investigated the association between baPWV and invasively measured aortic pulse pressure (APP) in a total of 109 consecutive patients (mean age, 62.3 ± 11.3 years; 67.9% men). Most patients (91%) had obstructive coronary artery disease, and mean baPWV and APP values were 1535 ± 303 cm/s and 66.8 ± 22.5 mm Hg, respectively. In univariate analysis, there was a significant linear correlation between baPWV and APP (r = .635, P < .001). The correlation between baPWV and APP remained significant even after controlling for potential confounders (β = 0.574, P < .001; R^2 = .469). Arterial stiffness measured by baPWV showed a strong positive correlation with invasively measured APP, independent of clinical confounders. Therefore, baPWV can be a good marker of central aortic stiffness.

1 | INTRODUCTION

Aortic pulse pressure (APP), defined as the difference between systolic blood pressure (BP) and reduced diastolic BP of the aorta, is a reliable measure of arterial stiffness of central elastic arteries.[1,2] Previous studies have recognized APP as a surrogate maker of increased risk for cardiovascular morbidity and mortality.[3,4] It has been shown that APP is strongly related to future cardiovascular events and a better predictor of target organ damage compared with peripheral BP.[5-7] Although cardiac catheterization is considered the gold standard to obtain APP,[8,9] it is unsuitable for routine screening of large populations because of its invasiveness, cost, and technical skill.[10] Pulse wave velocity (PWV) is an alternative and noninvasive way to measure arterial stiffness, being widely used in research and clinical fields.[11] Previous studies have shown that PWV is associated with increased morbidity and mortality in various populations, such as individuals with hypertension, diabetes mellitus, and stroke.[12-14] Although carotid-femoral PWV has been considered the standard noninvasive measure of arterial stiffness, the measurement of carotid-femoral PWV is time-consuming and requires considerable operator training as well as the exposure and palpation of the femoral artery.[15] Practically, recently developed brachial-ankle PWV (baPWV) is more feasible than carotid-femoral PWV because it can be simply measured by brachial and tibial arterial wave analyses without exposing the femoral site.[16] More importantly, the value of baPWV has been proven in many clinical studies[17,18] and meta-analysis.[19] Despite the promising results of baPWV, the correlation between baPWV and APP has not yet been fully clarified. Some previous studies evaluated the association of central BP and PWV; however, these studies have limitations because they had a small sample size or the central BP was measured noninvasively.[20,21] Therefore, the aim of this study was to investigate the association between baPWV and invasively measured APP, and to evaluate whether baPWV can reliably reflect central aortic stiffness.

2 | MATERIALS AND METHODS

2.1 | Study population

Between April 2013 and October 2013, 133 consecutive patients who received invasive coronary angiography and baPWV measurement on the same day at Boramae Medical Center (Seoul, Korea) were prospectively recruited. Our study excluded 24 patients with

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acute myocardial infarction, unstable vital signs, ongoing chest pain, pericardial effusion, impaired left ventricular (LV) systolic function (LV ejection fraction <50%), regional wall motion abnormality, significant valvular heart disease (greater than mild degree of regurgitation or stenosis), peripheral artery disease (ankle brachial index <0.9 or >1.4), and nonsinus rhythm on electrocardiography. After such exclusion, 109 patients were finally analyzed in this study. The study protocol was approved by the institutional review board of Boramae Medical Center (Seoul, Korea), and informed consent was obtained from all study participants.

2.2 | Clinical data collection

Demographic characteristics were collected, including age, height (cm), weight (kg), body mass index (kg/m^2), and traditional risk factors including hypertension, diabetes mellitus, dyslipidemia, and smoking status. Hypertension was defined by a history of hypertension or antihypertensive medications. Diabetes mellitus was defined by a history of diabetes mellitus or antidiabetic medications. Dyslipidemia was defined as a history of dyslipidemia or antidyslipidemic medications. Patients who smoked regularly within 12 months were considered current smokers. Information on concomitant vasoactive medications, including calcium channel blockers, β-blockers, renin-angiotensin system blockers, and statins, was collected. Stable angina referred to chest discomfort that occurred reproducibly at a certain level of exertion and was relieved with rest or nitroglycerin.[22] Unstable angina was diagnosed if at least one of the following features was shown: (1) resting chest pain, usually lasting more than 10 minutes; (2) severe and new-onset chest pain; and (3) crescendo-pattern chest discomfort.[23] Venous blood samples for laboratory tests were collected after an overnight fasting of 8 hours, and white blood cell count, hemoglobin, glucose, uric acid, total cholesterol, low- and high-density lipoprotein cholesterol, triglyceride, C-reactive protein, and serum creatinine were measured. Estimated glomerular filtration rate was calculated by the Modification of Diet in Renal Disease equation.[24]

2.3 | Transthoracic echocardiography

Transthoracic echocardiography was performed using a 2.5-MHz probe with commercially available ultrasound systems (Sequoia [Siemens Medical Solutions] or Vivid 7 [GE Medical Systems]). LV ejection fraction was calculated using Simpson's biplane method. LV mass was calculated with a validated formula and indexed to the body surface area.[25] Peak early transmitral filling velocity during early diastole (E) was imaged at the tip of the mitral leaflet from an apical four-chamber view, and color-coded tissue Doppler imaging was applied to the apical four-chamber view to determine mean early (e') velocity at the septal mitral annulus. E/e' was calculated as an index of LV filling pressure. The left atrial volume index was calculated using the biplane method and indexed to body surface area. All measurements represented the average of three consecutive cardiac cycles. Two experienced cardiosonographers performed echocardiography. Correlation coefficients for interobserver agreements were 0.96 and 0.92 for e' and E/e', respectively, in our laboratory.[26]

2.4 | Aortic pressure measurement

Central aortic pressure measurements were made in the ascending aorta using a 5F fluid-filled pigtail catheter with the patient in the supine position before invasive coronary angiography. On the day of invasive aortic pressure measurement, smoking, alcohol drinking, and caffeine consumption were prohibited. Three consecutive beats at full expiration were averaged in each case. Pressure tracing was recorded using a hemodynamic monitoring system (Horizon XVu-hemodynamic monitoring system, Mennen Medical), and systolic BP and diastolic BP values of the central aorta were obtained. Pulse pressure (PP) was calculated as the difference between the peak systolic pressure and the end-diastole pressure. The mean arterial aortic pressure was calculated as 1/3 systolic BP + 2/3 diastolic BP. Invasive coronary angiography was performed according to standardized technique. Obstructive coronary artery disease (CAD) was defined when a major epicardial coronary artery or a branch artery sized ≥2 mm in luminal diameter had >50% diameter stenosis on invasive coronary angiography. The number of arteries with stenosis ≥50% was counted, and the extent of CAD was defined as one-, two-, or three-vessel disease.

2.5 | baPWV measurement

The baPWV values were measured noninvasively using an automated wave form analyzer (VP-1000, Colin Co. Ltd,).[27] After approximately 5 minutes of rest in a temperature-controlled and quiet environment, patients were studied in the supine position. All of the regular medications were permitted, but smoking, alcohol drinking, and caffeine consumption were prohibited on the day of examination. Briefly, volume plethysmography was used to measure the arterial pulse wave at the brachial and tibial arteries, simultaneously recording BP, heart rate, and heart sound. The time delay (Qt, seconds) was measured by the transmission time between the respective rise (foot) in the brachial and tibial pressure wave (foot-to-foot duration), and the distance was automatically calculated from the patient's height and a fixed regression equation. L1 was the distance from the heart to the ankle and L2 was the distance from the heart to the arm; each were calculated as: L1 = 0.2195 × H − 2.0734, L2 = 0.5643 × H − 18.381. Then, PWV was calculated as (L1–L2)/Qt. When measurements were obtained from both extremities, the average value of the left and right measurements was chosen for analysis. In order to get precise brachial BP data, all clothing that covered the location of cuff placement was removed. The appropriate cuff size was selected based on the patient's arm circumference. The brachial artery was palpated in the antecubital fossa to locate the point to place the cuff. The lower end of the cuff was 2 to 3 cm above the antecubital fossa. A minimum of two readings was taken at intervals of at least 1 minute, and the average of those readings was used as the patient's BP. If there was a > 5 mm Hg difference between the first and second readings, an additional reading was

obtained, and then the average of these multiple readings was used. All the measurements were made by the same experienced operator blinded to all of the clinical data. The intraobserver coefficient of variation for baPWV measurement was 0.949 (95% confidence interval [CI], 0.911–0.971) in our laboratory and Bland-Altman plot is shown in Figure S1.

2.6 | Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables are expressed as percentages. Univariate associations between two continuous variables were assessed using bivariate Pearson's correlation analysis. Scatter plots were used for the demonstration of linear correlations between two continuous variables. Multivariable linear regression analysis was subsequently applied to examine independent relationships between baPWV and APP. Age, height, heart rate, estimated glomerular filtration rate, e' velocity, and left atrial volume index were controlled in this multivariable analyses. To examine multicollinearity in a linear regression model, the variance inflation factor was used. All VIF values were less than three in our multivariable analysis, suggesting that there was no significant multicollinearity problem. For comparison of the correlation coefficients between APP and brachial PP, a Fisher r-to-z transformation was used. A P value <.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 20.0 (IBM).

3 | RESULTS

3.1 | Baseline clinical characteristics

The baseline characteristics of the total 109 patients are shown in Table 1. The mean age was 62.3 ± 11.3 years, and there were 67.9% men. A total of 66.1%, 23.9%, and 40.4% of patients had hypertension, diabetes mellitus, and dyslipidemia, respectively, and 29.4% of the patients were current smokers. About half of the patients (51.4%) were diagnosed with unstable angina. Blood test results and echocardiographic findings were within the normal range. A total of 26.6%, 20.2%, 53.2%, and 56.0% of patients took calcium channel blockers, β-blockers, renin-angiotensin system blockers, and statins, respectively. Invasive coronary angiography revealed that 91.7% of patients had obstructive CAD, where 21.1%, 33.9%, and 36.7% had one-vessel, two-vessel, and three-vessel disease, respectively.

Measurements of hemodynamic parameters and baPWV of the study patients are shown in Table 2. Mean values of central APP and baPWV were 66.8 ± 22.5 mm Hg and 1535 ± 303 cm/s, respectively.

3.2 | Correlation between APP and baPWV

The linear associations of baPWV values with various demographic parameters, laboratory findings, and echocardiographic/hemodynamic measurements are shown in Table 3. Results showed that baPWV had significant correlations with age, height, estimated glomerular

TABLE 1 Clinical characteristics of study patients

Characteristic	Value (n = 109)
Age, y	62.3 ± 11.3
Male sex	74 (67.9)
Height, cm	162 ± 8
Weight, kg	65.4 ± 10.9
Body mass index, kg/m^2	24.5 ± 3.0
Brachial SBP, mm Hg	123 ± 17
Brachial DBP, mm Hg	71 ± 9
Heart rate, beats per min	67.0 ± 12.9
Traditional risk factors	
Hypertension	72 (66.1)
Diabetes mellitus	26 (23.9)
Dyslipidemia	44 (40.4)
Current smoking	32 (29.4)
Clinical diagnosis	
Stable angina	53 (48.6)
Unstable angina	56 (51.4)
Laboratory findings	
White blood cell count, per μL	7112 ± 2231
Hemoglobin, g/dL	13.4 ± 62.3
Uric acid, mg/dL	5.44 ± 1.51
Total cholesterol, mg/dL	160 ± 44
Low-density lipoprotein cholesterol, mg/dL	100 ± 46
High-density lipoprotein cholesterol, mg/dL	47.3 ± 13.6
Triglyceride, mg/dL	121 ± 64
Estimated glomerular filtration rate, mL/min/1.73 m^2	82.5 ± 19.7
C-reactive protein, mg/dL	0.32 ± 0.88
Echocardiographic findings	
Left ventricular ejection fraction, %	65.3 ± 6.9
Left ventricular mass index, g/m^2	99.4 ± 24.5
e' velocity, cm/s	6.08 ± 1.81
E/e'	11.3 ± 4.5
Left atrial volume index, mL/m^2	29.6 ± 11.2
Tricuspid regurgitation maximal velocity, m/s	2.35 ± 0.35
Concomitant medications	
Calcium channel blocker	29 (26.0)
β-Blocker	45 (41.3)
Renin-angiotensin system blocker	58 (53.2)
Statin	61 (56.0)
Findings of coronary angiography	
Insignificant	9 (8.3)
One-vessel disease	23 (21.1)
Two-vessel disease	37 (33.9)
Three-vessel disease	40 (36.7)

Values are expressed as number (percentage) or mean ± standard deviation.

TABLE 2 Measures of central aortic pressures and brachial-ankle pulse wave velocity

Measure	Value (n = 109)
Measures of central hemodynamics	
Central aortic systolic BP, mm Hg	143 ± 26
Central aortic diastolic BP, mm Hg	75.7 ± 14.2
Central aortic pulse pressure, mm Hg	66.8 ± 22.6
Central aortic mean BP, mm Hg	98.0 ± 15.6
Brachial-ankle pulse wave velocity, cm/s	1535 ± 303

Abbreviation: BP, blood pressure.
Values are expressed as mean ± standard deviation.

filtration rate, and diastolic indices including e', E/e', left atrial volume index, and BP profiles. Among these factors, APP showed the strongest correlation with baPWV (r = .635 [95% CI, 0.508–0.735]; R^2 = .404, P < .001). Although there was a significant correlation between baPWV and brachial PP (r = .441 [95% CI, 0.278–0.581]; R^2 = .210, P < .001), the correlation power was stronger between baPWV and APP, which met statistical significance (P = .044; Figure). Additionally, we performed analysis using the higher value of the left and right baPWV measurements (baPWV$_{max}$) instead of using the average value. The linear associations of baPWV$_{max}$ values with various parameters are shown in Table S1. APP showed strong correlation with baPWV$_{max}$ (r = .582 [95% CI, 0.442–0.694]; R^2 = .339, P < .001), which was stronger than the correlation between baPWV$_{max}$ and brachial PP (r = .458 [95% CI, 0.281–0.604]; R^2 = .209, P < .001) (Figure S2).

A multiple linear regression model was constructed to evaluate the independent association of baPWV and APP after including potential confounders, such as age, height, heart rate, estimated glomerular filtration rate, e' velocity, and left atrial volume index. The model showed fair explanation (R^2 = .469), while the association between baPWV and APP remained significant even after controlling for confounders (β = 0.574, P < .001).

4 | DISCUSSION

The current study showed that baPWV had a good linear correlation with invasively measured APP. This correlation between baPWV and APP remained significant even after controlling for potential clinical confounders. This finding supports that baPWV can be used as a useful surrogate marker of central aortic stiffness.

APP is a composite of a forward-traveling wave generated by LV ejection, and a backward-traveling reflected wave arising from the site of impedance mismatch.[1] Although brachial BP is widely used in routine clinical assessment and known to be associated with future cardiovascular risk,[28] recent evidence suggests that APP measurements are more accurate in predicting future cardiovascular events.[6,29] As central arteries are directly connected to vital organs, such as the heart, brain, and kidney, APP represents the true load imposed on these organs

TABLE 3 Simple linear correlations between baPWV and various clinical parameters

Parameter	Correlation coefficient (95% confidence interval)	
	With baPWV	With central aortic pulse pressure
baPWV	–	0.635* (0.508–0.735)
Central aortic pulse pressure	0.635* (0.508–0.735)	–
Age	0.577** (0.436–0.670)	0.511** (0.357–0.638)
Brachial pulse pressure	0.441** (0.276–0.581)	0.699** (0.578–0.790)
E/e'	0.371** (0.197–0.523)	0.368** (0.193–0.520)
Central aortic SBP	0.369** (0.194–0.521)	0.754** (0.659–0.825)
Brachial SBP	0.305** (0.124–0.466)	0.678** (0.551–0.774)
Left ventricular mass index	0.302** (0.121–0.464)	0.153 (−0.043 to 0.337)
Left atrial volume index	0.226* (0.082–0.463)	0.186 (−0.015 to 0.373)
Tricuspid regurgitation maximal velocity	0.204 (−0.033 to 0.419)	0.318** (0.090–0.515)
Left ventricular ejection fraction	0.055 (−0.135–0.241)	0.312** (0.132–0.472)
Heart rate, beats per min	−0.002 (−0.190 to 0.186)	−0.053 (−0.243 to 0.137)
Brachial DBP	−0.097 (−0.280 to 0.093)	0.124 (−0.081 to 0.319)
Central aortic DBP	−0.174 (−0.351 to 0.015)	−0.085 (−0.269 to 0.105)
White blood cell count	−0.188 (−0.363 to 0.000)	−0.325** (−0.484 to 0.146)
Height	−0.258* (−0.426 to 0.074)	−0.310** (−0.471 to 0.129)
eGFR	−0.317** (−0.477 to 0.137)	−0.351** (−0.476 to 0.123)
e' velocity	−0.369** (−0.521 to 0.194)	−0.349** (−0.504 to 0.172)

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
Parameters were arranged by the direction of association and effect size for the correlation with brachial-ankle pulse wave velocity (baPWV) (from the most positive association to most negative association).
*P < .05.
**P < .001.

and influences the local flow into these vital organs.[6] Indeed, previous studies have shown that APP is a predictor of end-stage renal disease, microvascular damage in the brain, and hypertensive heart disease.[30,31]

FIGURE 1 Linear correlation (A) between brachial-ankle pulse wave velocity and invasively measured aortic pulse pressure, and (B) between brachial-ankle pulse wave velocity and brachial pulse pressure
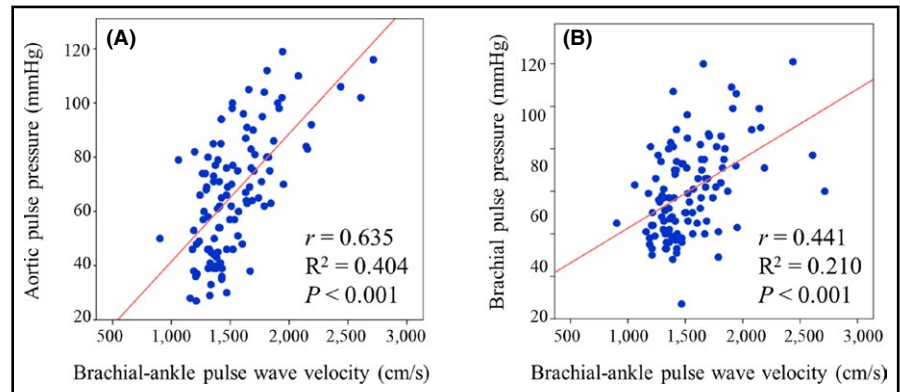
TABLE 4 Independent association between PWV and central aortic pulse pressure

Factor	β	95% CI	P Value	VIF
baPWV	0.574	0.027–0.055	<.001	1.531
Age	0.024	−0.474 to 0.573	.851	2.495
Height	−0.156	−1.004 to 0.120	.121	1.531
eGFR	−0.082	−0.327 to 0.141	.432	1.670
Heart rate	−0.112	−0.531 to 0.091	.163	1.161
e' velocity	−0.011	−0.277 to 0.249	.915	1.699
LA volume index	−0.043	−0.431 to 0.261	.625	1.173

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CI, confidence interval; eGFR, estimated glomerular filtration rate; LA, left atrial; PWV, pulse wave velocity; VIF, variance inflation factors.

Cardiac catheterization is the most accurate method for measuring APP; however, it is difficult to use this invasive method in our daily clinical practice. Current studies have reported that noninvasive radial artery tonometry can estimate APP. However, these methods are operator-dependent, showing a range of errors, which limit its accuracy.[8] Still, direct intra-arterial measurement is considered the gold standard.[9] In this context, our results deserve clinical attention because invasive techniques, such as cardiac catheterization, are employed for more accurate and reliable measurement of APP.

Although baPWV has been widely used as a measure of arterial stiffness, some critics have suggested that baPWV may not reflect pure central aortic stiffness because it is measured at the peripheral extremities.[32] Also, it is known that baPWV is more affected by peripheral artery diseases and BP at the time of measurement, compared with APP.[33] In our study, however, baPWV showed a stronger correlation with APP than brachial PP. In addition, various studies have proven the predictive value of baPWV in cardiovascular events, which implies its association with central arterial stiffness.[16-18] To date, few studies have evaluated the correlation between baPWV and APP. A study conducted by Jung and colleagues[20] demonstrated that baPWV was associated with APP in patients with type 2 diabetes mellitus ($r = .531$, $P < .001$). Sueta and associates[21] evaluated the association of APP with PWV in patients with CAD ($r = .91$, $P < .001$). Yamashina and researchers[34] studied the correlation between aortic PWV and baPWV in 41 patients and showed excellent correlations between these values

($r = .87$, $P < .01$). However, Sueta and colleagues[19] used mathematical transformation to calculate APP rather than cardiac catheterization, and Yamashina and associates[34] conducted their study on a small population without adjustment for confounding factors. Compared with these studies, our study showed strengths because we used invasively measured APP and performed multivariable analysis.

4.1 | Clinical implications

Considering the prognostic value of APP in future cardiovascular events,[5-7] a noninvasively measured indicator of APP could provide valuable information on the prediction of patients' risk to clinicians. Our results showed that baPWV may be a good candidate for such purpose. In our study, it was found that baPWV can be a reliable marker for central aortic stiffness, which was measured by invasive method. With its simplicity and reproducibility,[35] baPWV may be a good method to estimate APP in clinical practice, especially in the mass screening of large populations.

4.2 | Study limitations

This study has several limitations. First, patients undergoing elective invasive coronary angiography were enrolled, which may have been associated with potential selection bias. Second, not all confounders were controlled as a result of the relatively small study sample size. Third, APP and baPWV were not measured simultaneously. However, we tried to minimize variability of various factors that could influence test results by performing both measurements on the same working day. Finally, clinical outcomes were not evaluated in our study. Large-scale studies with long-term follow-up are needed to solve these issues.

5 | CONCLUSIONS

This study demonstrated a linear correlation between baPWV and invasively measured APP, with strong correlation power, in patients undergoing invasive coronary angiography. Our findings suggest that baPWV can be a good surrogate marker of central aortic stiffness. Further large-scale studies with a longitudinal clinical follow-up design are needed to confirm our results.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.