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Clinical Implication of Carotid-Radial Pulse Wave Velocity for Patients with Coronary Artery Disease

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ABSTRACT

Background and Objectives : Arterial stiffness assessed non-invasively with the aortic pulse wave velocity (PWV) has been associated with atherosclerosis in the coronary arteries and also cardiovascular mortality. The aim of this study was to determine whether arterial stiffness may predict the severity of coronary artery disease (CAD). **Subjects and Methods :** We enrolled 106 consecutive, symptomatic patients (males: 71 (67%), mean age: 57.0±10.5 years) who underwent coronary angiography. The extent of the CAD was defined by single or multiple vessel disease according to the number of coronary vessels with a ≥50% narrowing, the lesion type according to the AHA/ACC guidelines, and a modified stenosis scoring system. Arterial stiffness was characterized by measurement of the carotid-radial PWV. In addition, such cardiovascular risk factors as the body mass index, hypertension, smoking, LDL-and HDL-cholesterol, ejection fraction (EF), left ventricle mass index (LVMI), pulse pressure, plasma homocysteine and C-reactive protein (CRP) were evaluated. **Results :** The carotid-radial PWV in multiple vessel CAD was faster than in single vessel CAD and the normal arteries (10.33±1.46 vs. 8.76±1.65 m/sec, respectively, $p<0.001$). On the univariate analysis, the extent of the CAD, as expressed as a modified stenosis score, was associated with the total cholesterol, LDL-cholesterol, the EF and the PWV. However, on the multivariate analysis, the extent of CAD was associated with the carotid-radial PWV ($p<0.001$). **Conclusion :** Arterial stiffness identified by carotid-radial PWV may predict the severity of the CAD after adjusting for other cardiovascular risk factors. **(Korean Circulation J 2006;36:565-572)**

KEY WORDS : Pulse ; Atherosclerosis ; Coronary artery disease.

Introduction

The severity of atherosclerosis in the coronary arteries has been shown to have a positive correlation with the degree of atherosclerosis in the aorta or the other major arterial branches.[1] The mechanical properties of the large arteries are important determinants of the circulatory physiology in both healthy and diseased states. Arterial compliance is related to left ventricular (LV) hypertrophy and the risk for incurring cardiovascular disease events. The loss of arterial compliance has been studied as both a cause and a consequence of vascular disease.[2] A variety of reports have recently shown that arterial stiffness is associated with cardiovascular risk factors,[3][4] as well as cardiovascular morbidity and mortality in older subjects[5] and in patients suffering with hypertension,[6] diabetes,[7] end-stage renal disease[8] and systolic dysfunction.[9]

The population-based Rotterdam study[10] showed that arterial stiffness was strongly associated with atherosclerosis at a variety of sites on the vascular tree. Arterial stiffness can be assessed non-invasively with measuring the pulse wave velocity (PWV). Some authors have reported that PWV may be used as a surrogate of clinical atherosclerosis and as a predictor for the presence of coronary artery disease (CAD).[11][12]

However, there is little data on the relationship between PWV and the extent of CAD as determined by angiography. In addition, the predictive value of PWV for CAD has not been established. Thus, the aim of this study is to evaluate the relationship between carotid-radial PWV and the severity of the CAD.

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Subjects and Methods

Patient population

We prospectively enrolled 106 patients who underwent coronary angiography between January 2004 and March 2005 for the assessment of suspected coronary artery disease. The exclusion criteria were previous myocardial infarction, previous percutaneous coronary intervention, valvular heart disease, cardiomyopathy, sinus node dysfunction, atrial fibrillation, conduction disturbance, known peripheral arterial disorders, diabetes mellitus or impaired renal and/or liver function. Echocardiographic assessment was performed for all patients according to the standards of the American Society of Echocardiography, with measurements of the left ventricular (LV) mass, the left atrium volume and the ejection fraction. All patients were taking antianginal or anti-hypertensive medication before their entry into the study. Vasodilator medications such as nitrate and angiotensin converting enzyme inhibitors, but not such anti-platelet agents as aspirin and clopidogrel, were withdrawn for at least 48 hours before the study. All the patients provided written informed consents before entering the study.

Angiographic protocol

Selective coronary angiography was performed using the Judkin technique. Each coronary vessel was assessed and a visual estimation of the percent luminal stenosis for each lesion was reported. Multiple projections were acquired to determine the maximal amount of coronary artery luminal narrowing. The severity of CAD was assessed according to the following three factors. The first was a vessel score; this was the number of vessels with significant stenosis (50% or greater reduction in the lumen diameter). The vessel scores ranged from 0 to 3, depending on the number of vessels involved. Left main coronary artery stenosis was scored as a two-vessel disease. The second factor was the lesion type; the characteristics of the most severe lesions among the diseased coronary arteries was assessed according to the AHA/ACC guidelines.[13] The third factor was a modified stenosis score, which has been described previously.[14] Briefly, this was a score with 0, 1, 2 or 3 points, respectively, representing 0% to 30%, 31% to 50%, 51% to 70%, and $\geq$71% diameter stenosis in one to three segments of the three main coronary arteries and in the left main trunk (a total of 10 segments). The scores for each of the ten segments were added together to give a total score out of a theoretical maximum of 30. Therefore, this score places emphasis on the severity of the stenosis while it includes some measure of the extent of the coronary disease. The above three angiographic factors were evaluated by two experts, who were blinded to other patient data.

Biochemical tests

After fasting over night, the venous blood samples were obtained from the patients and the controls from an antecubital vein at the study baseline. The lipid serum levels were measured by routine methods. CRP measurements were performed by the Nephelometer (Dade Behring Inc, Newark, DE, U.S.A.) method. Plasma homocysteine measurements were assessed by employing a fluorescence polarization immunoassay with using the IMx Analyzer (ABBOTT Laboratories, U.S.A.).

Measurement of carotid-radial PWV and the calculated central blood pressure

All the procedures were performed in a controlled environment. The PWV was determined using a semi-automatic device, the Sphygmocor apparatus (ATCOR Medical, Sydney, Australia). In brief, the common carotid artery and radial artery pressure waveforms were recorded non-invasively by using a pressure-sensitive transducer. The two pressure waveforms were then stored in a memory buffer. A preprocessing system automatically analyzed the gain in each waveform and adjusted it for equality of the two signals. When the operator observed a pulse waveform of sufficient quality on the computer screen, digitization was then suspended and calculation of the time delay between the 2 pressure upstrokes was initiated. The distance traveled by the pulse wave was measured manually with a tapeline as the distance between the two recording sites (D), while the pulse transit time (t), which was measured between the feet of the pressure waveforms that were recorded at these different points (the foot-to-foot method), was automatically determined. The PWV was automatically calculated as the PWV=D/t. Measurements were taken over 20 cardiac cycles and when the difference of consecutive mean data during the repeated measurements was less than 0.5 m/sec. The mean data was then used for the final analysis.

The calculated central blood pressure was obtained non-invasively by performing radial artery applanation tonometry and pulse wave analysis.[15] The main principle of this method is based on deriving the a central aortic pressure waveform from the peripheral pressure waveform by using generalized transfer functions. Tonometry of the radial artery was obtained using a high-fidelity strain gauge transducer that was placed on the tip of a pencil-type tonometer (Millar Instruments, Inc, Houston, TX). Analysis of the derived aortic pressure waveforms was done with the Sphygmocor System (ATCOR Medical, Sydney, Australia). Calibration of the peripheral pressure recordings was obtained by measuring the brachial systolic and diastolic blood pressure with a mercury sphygmanometer. Three measurements were performed in each case and the mean value of the systolic and diastolic blood pressure was then calculated.

Statistical analysis

The SPSS 12.0 (SPSS inc., Chicago, Illinois, U.S.A.) statistical software package was used for all calculations. Data are presented as means±standard deviations (SDs) for the continuous variables and as percentages for the categorical data. For the continuous variables, comparisons between the two groups were performed using the unpaired, two-tailed t-test. The categorical data and proportions were analyzed using the Chi-square test. The correlations between the carotid-radial PWV, the cardiovascular risk factors and the severity of the CAD were determined by linear regression analysis; this was followed by multivariate analysis using an Enter multiple regression model. The receiver operating characteristic (ROC) curve analysis was used in order to determine the cut-off value of the carotid-radial PWV to distinguish between simple and severe coronary artery disease at the highest possible sensitivity and specificity levels. $p<0.05$ were considered statistically significant.

Results

Demographic characteristics

The demographic characteristics of the 106 patients are summarized in Table 1. Their mean age was 57.0±10.5 years and 67% of the patients were male. The systolic and diastolic blood pressures were 116.3±16.2 mmHg and 68.7±11.8 mmHg, respectively. 37.7% and 35.8% of the patients had a history of hypertension and smoking, respectively. There was no difference according to age and gender between the patients with and without hypertension. The prevalence of acute coronary syndrome was 48.7%. Abnormalities of the LV structure and function were absent. The mean values for the LV mass index and the left atrial volume index were approximately 110 g/m^2 and 35 mL/m^2, respectively. As an indicator of the LV function, the mean LV ejection fraction based on the echocardiography was 57%, which was within normal limits.

Table 1. Demographic characteristics

Patients number	106
Age (yr)	57.0±10.5
Male (%)	71 (67.0)
BMI (kg/m^2)	24.2±2.5
Peripheral SBP (mmHg)	116.3±16.2
Peripheral DBP (mmHg)	68.7±11.8
Peripheral pulse pr. (mmHg)	47.1±13.6
Hypertension (%)	40 (37.7)
Current smoker (%)	38 (35.8)
LVEF (%)	56.9±11.3
LVMI (g/m^2)	111.8±30.2
LAVI (mL/m^2)	35.1±12.3
Diagnosis	
Stable angina (%)	65 (61.3)
Unstable angina (%)	26 (34.5)
Myocardial infarction (%)	15 (14.2)

Results are presented as means±SDs or as numbers (%). BMI: body mass index, S/DBP: systolic/diastolic blood pressure, Pr: pressure, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, LAVI: left atrial volume index

Clinical and angiographic characteristics

The clinical and angiographic characteristics are summarized in Table 2. The serum CRP and plasma homocysteine levels, which were used as biochemical markers of atherosclerosis, were slightly elevated (0.36±0.78 mg/dL and 14.0±6.2 umol/L, respectively). The calculated systolic and diastolic blood pressures were 104.4±16.7 mmHg and 69.1±11.8 mmHg, respectively. The PWV that was derived from the carotid to the radial arteries was 9.3±1.7 m/sec. For the angiographic characteristics, 79 (74.5%) patients had significant CAD and 39 (36.8%) of these patients had multivessel disease, while 27 (25.5%) had normal arteries with <30% luminal narrowing without any angiographically demonstrated atherosclerotic stenotic lesions. For the patients with significant CAD, the mean number of diseased vessels was 1.65±0.73 per patient. For the lesion types according to the AHA/ACC guidelines, 74 (69.8%) patients had complex lesion that was more than B2/C. There was no difference in age and gender according to the lesion type and the number of diseased vessels. The modified stenosis score that was summed at each coronary artery was 5.55±4.52.

Table 2. Atherosclerotic and angiographic parameters

White cell count (count/mm^3)	7017.4±1967.1
Total cholesterol (mg/dL)	191.0±39.7
LDL-cholesterol (mg/dL)	125.5±36.9
HDL-cholesterol (mg/dL)	42.0±10.0
Serum CRP (mg/dL)	0.36±0.78
Plasma homocysteine (umol/L)	14.0±6.2
Calculated aortic SBP (mmHg)	104.4±16.7
Calculated aortic DBP (mmHg)	69.1±11.8
Calculated aortic pulse pr. (mmHg)	35.0±12.0
Pulse wave velocity (m/sec)	9.3±1.7
Vessel score	
Normal (%)	27 (25.5)
One (%)	40 (37.7)
Two (%)	27 (25.5)
Three (%)	12 (11.3)
Diseased vessels	1.65±0.73 per pt.
Lesion type*	
A/B1	32 (30.2)
B2/C	74 (69.8)
Modified stenosis score	5.55±4.52

Results are presented as means±SDs or as numbers (%). *: lesion type determined by AHA/ACC guidelines, L/HDL: low/high density lipoprotein, CRP: C-reactive protein, S/DBP: systolic/diastolic blood pressure, Pr: pressure, Pt: patient

Traditional atherosclerotic risk factors and the carotid-radial PWV

Among the cardiovascular risk factors measured in our study, the age, peripheral systolic blood pressure, calculated aortic systolic pressure and LV ejection fraction were statistically related to the carotid-radial PWV ($p<0.05$) (Fig. 1). The carotid-radial PWV of the patients with hypertension was significantly increased compared to that of the patients without hypertension (9.94 ± 1.59 vs. 8.97 ± 1.75 m/sec, respectively, $p<0.05$). In addition, the carotid-radial PWV of the males was significantly increased compared to that of the females (9.65 ± 0.81 vs. 8.69 ± 1.43 m/sec, respectively, $p<0.05$) (Fig. 2). However, the carotid-radial PWV was not related to other

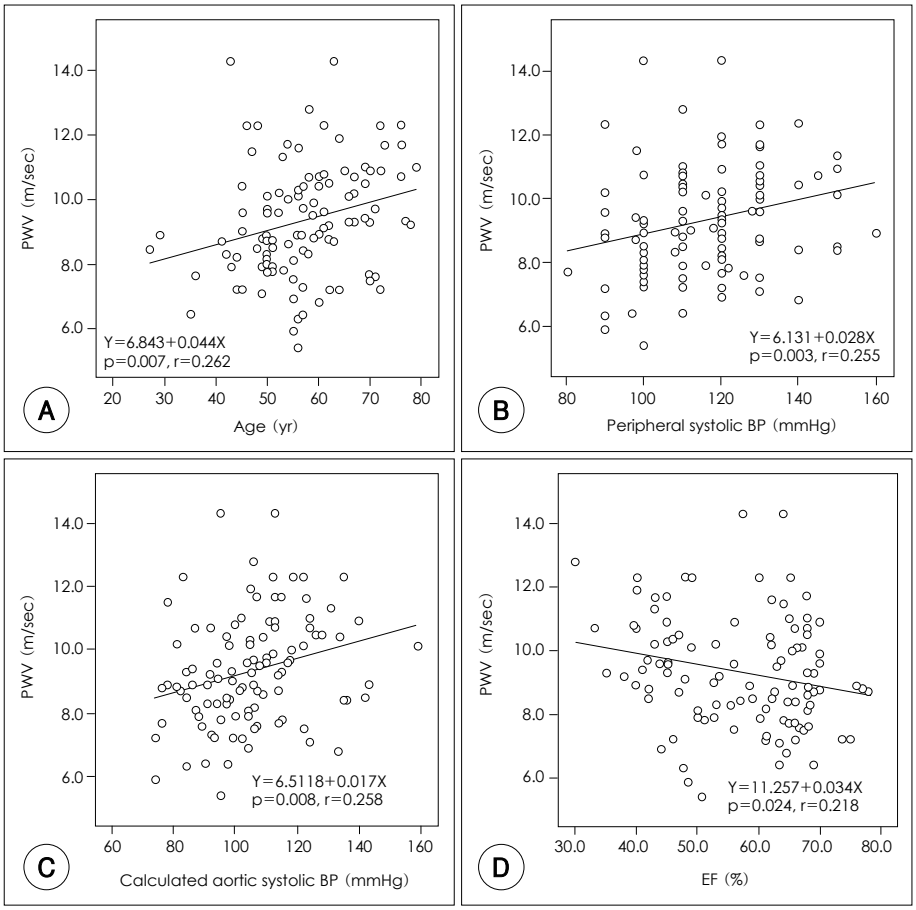

Fig. 1. Atherosclerotic risk factors and carotid-radial pulse wave velocity (PWV). Age (A), the peripheral (B) and the calculated (C) systolic blood pressure (BP) had a positive correlation with PWV (D) ($p<0.05$). Also, the left ventricular ejection fraction (EF) had a negative correlation with the carotid-radial PWV ($p<0.05$). However, there was no different between the other traditional risk factors such as the presence of smoking, pulse pressure, LDL cholesterol, C-reactive protein and plasma homocysteine and PWV.

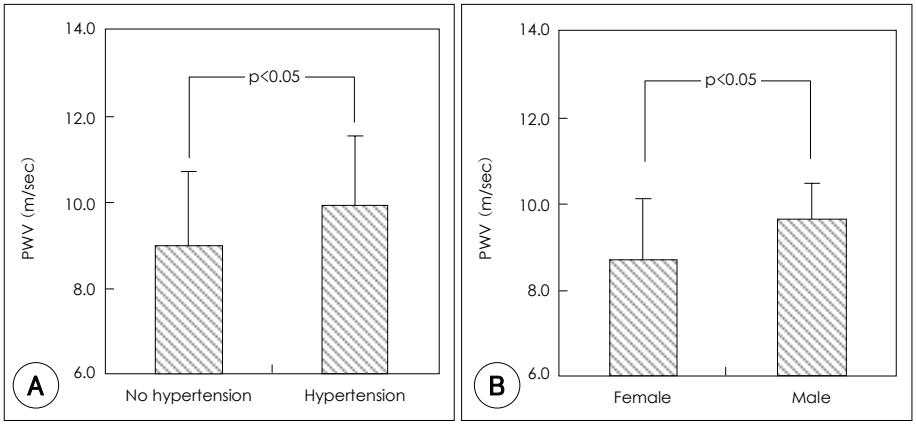

Fig. 2. Hypertension, gender and the carotid-radial pulse wave velocity (PWV). The carotid-radial PWV was significantly increased in the patients with hypertension (A) and in the patients who were male (B) ($p<0.05$).

traditional risk factors such as the presence of smoking, pulse pressure, the levels of total cholesterol and LDL cholesterol, serum CRP or plasma homocysteine, as well as the presence of a clinical diagnosis such as stable angina and acute coronary syndrome (9.22±1.89 vs. 9.52±1.49 m/sec, respectively, p=NS) (Table 3).

Relationships among the parameters of the extent of the CAD

When we compared the three parameters concerning the extent of the CAD, the modified stenosis score for the more complex lesions (B2/C) was significantly higher than that for the simple lesion (A/B1) according to the lesion type as determined with using the AHA/ACC guidelines (9.55±1.59 vs. 8.97±1.75 m/sec, respectively, p<0.05) (Fig. 3). Furthermore, the higher the vessel score, the higher was the modified stenosis score. Thus, the modified stenosis score, which was very precise in evaluating the extent of the CAD, was strongly related to the other two methods.

Carotid-radial PWV and extent of the CAD

In regard to the lesion types as determined with using the AHA/ACC guidelines, the carotid-radial PWV was higher in the complex lesions (B2/C) than in the simple lesions (A/B1) (p<0.05) (Fig. 4). For the vessel score, for values >50% diameter stenosis, the carotid-radial PWV was significantly increased with a high vessel score (p<0.05). When the vessel scores were divided into simple (normal or single vessel disease) and severe (multiple vessel disease of more than two vessels) CAD, the cut-off value for the carotid-radial PWV to differentiate between the groups was 9.05 m/sec; this score allowed a sensitivity of 85% and a specificity of 67% (Fig. 5). For the modified stenosis score, the carotid-radial PWV that was measured non-invasively had a positive correlation to the modified stenosis score that was measured invasively by coronary angiography (p<0.001) (Fig. 6).

Table 3. Correlation between PWV and the cardiovascular risk factors

	p
Age	0.007
Peripheral SBP	0.008
Calculated SBP	0.008
Peripheral PP	0.236
Calculated PP	0.088
LVEF	0.024
Total cholesterol	0.520
LDL cholesterol	0.678
CRP	0.836
Plasma homocysteine	0.375

PWV: pulse wave velocity, SBP: systolic blood pressure, PP: pulse pressure, LVEF: left ventricular ejection fraction, LDL: low density lipoprotein, CRP: C-reactive protein

Predictor of the extent of the CAD

On the univariate regression analysis, the extent of the CAD expressed as the modified stenosis score was associated with the total cholesterol, the LDL-cholesterol, the LV ejection fraction and PWV (Table 4). However, on the multivariate regression analysis, after adjusting for the total cholesterol, the LDL-cholesterol, the LV ejection fraction, the PWV and the other traditional cardiovascular risk factors such as gender, age, presence of hypertension, the HDL-cholesterol and LV mass index and the extent of the CAD, as expressed as a modified stenosis score, was associated with the carotid-radial PWV (p<0.001) (Table 4).

Discussion

In the present study, we observed a strong and independent association between the manifestations of increased arterial stiffness, as derived from the noninvasive carotid-radial PWV, and the extent of the CAD, as assessed by invasive coronary angiography.

Increased arterial stiffness is associated with several

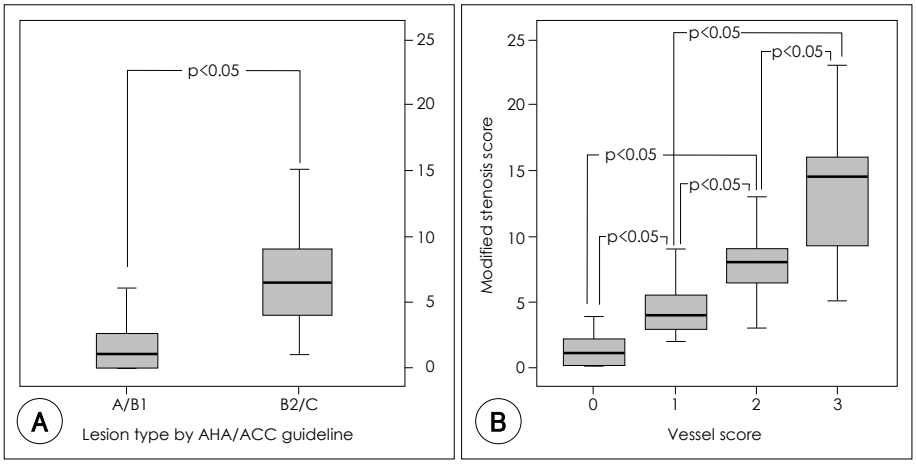

Fig. 3. The relationship among the parameters for assessing the extent of coronary artery disease. The modified stenosis score was significantly related to the lesion type as determined by the AHA/ACC guidelines (A) and the vessel score (B) (p<0.05).

cardiovascular risk factors, including age, hypertension and diabetes mellitus. Ohmori et al.[16] have also reported a positive correlation between age and the PWV value. Asmar et al.[17] have reported that the two major determinates of PWV were the patient's age and the systolic blood pressure, which were correlated with a positive PWV. This finding is consistent with the results of our study, which showed that the patient's age and systolic blood pressure were significantly related to PWV. Thus, the age-related decrease in arterial distensibility has been described to be a consequence of an increased ratio of the collagen to elastin and the qualitative wall thickness, as well as atherosclerosis.[18] The functional and structural changes in the arterial wall with increasing age influence the reactivity of arteries and this accelerate the atherogenic process.[19]

Certain biochemical markers, including the CRP and possibly homocysteine or LDL particles, may allow additional discrimination of the cardiovascular risk among otherwise apparently healthy individuals. In our study population, CRP and homocysteine were distributed equally according to the stenosis score among the patients suffering with CAD; the total cholesterol and LDL-cholesterol were accounted for in the univariate analysis. This discrepancy might have been the result of the small number of study patients.

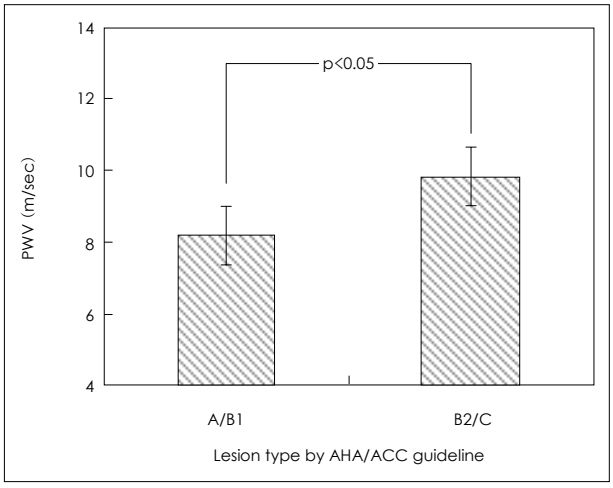

Fig. 4. The lesion type and carotid-radial pulse wave velocity (PWV). The carotid-radial PWV of the more complex lesions (B2/C lesion type) was significantly more increased than that of the simple lesions (A/B1 lesion type) ($p<0.05$).

There have been several reports on the relationship between the PWV and various biochemical markers. Kullo et al.[20] reported that CRP, a marker for systemic inflammation, was related to the measurement of arterial wave reflection and stiffness in asymptomatic subjects from the community. Bortolotto et al.[21] have suggested that both the PWV and the homocysteine levels were significantly elevated in the presence of cardiovascular disease in hypertensive populations. Our findings showed that CRP and homocysteine levels were not related to the carotid-radial PWV. This discrepancy of the C-reactive protein and homocysteine levels might have been the result of the small number of study patients who were treated with antihypertensive medication. There continues to be conflicting reports on the association of the PWV and the lipid profile. Cameron et al.[22] have reported that increased LDL cholesterol levels are associated with the aortic PWV. Conversely, Benetos et al.[23] have found no significant correlation between the total plasma cholesterol level and the aortic PWV.

Atherosclerosis refers to the concentric hyaline thickening of the arterial and arteriolar walls.[24] As atherosclerosis progresses, the tunica media thickens and the tunica intima becomes rigid, and this reduces the arterial elasticity.[25] Reduced arterial distensibility has been shown to be associated with atherosclerotic events. Thus, an increased aortic PWV is strongly associated with the presence and extent of atherosclerosis and it constitutes a potent marker and predictor of the cardiovascular risk, including CAD.[26] In the Rotterdam study,[10] van Popele et al. reported that arterial stiffness was strongly associated with atherosclerosis at a variety of sites on the vascular tree. Our findings showed similar results in that

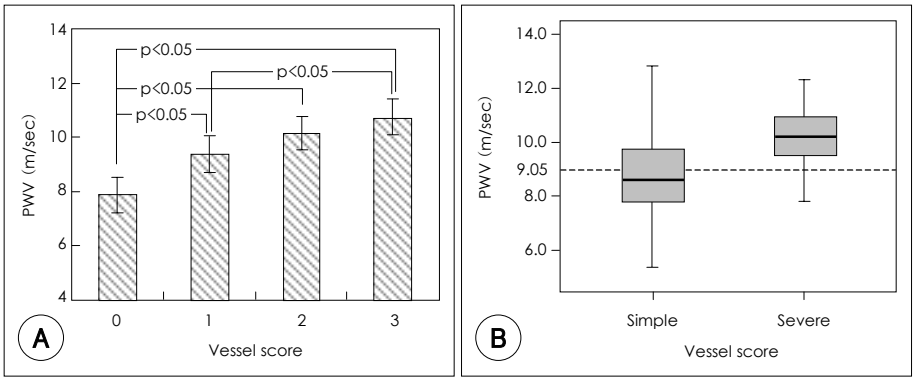

Fig. 5. Vessel score and the carotid-radial pulse wave velocity (PWV). A: the carotid-radial PWV was significantly increased as the vessel score, with >50% diameter stenosis, became higher with a stepladder appearance ($p<0.05$). B: the vessel scores were divided into the simple (normal or single vessel disease) and severe (multiple vessel disease of more than two vessels) coronary artery disease, and the cut-off value for the carotid-radial PWV for differentiating between the two groups was 9.05 m/sec, with a sensitivity of 85% and a specificity of 67%.

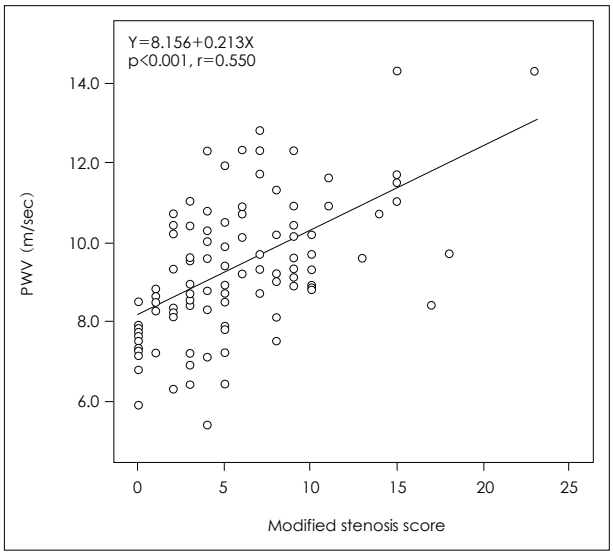

Fig. 6. The modified stenosis score and the carotid-radial pulse wave velocity (PWV). The modified stenosis score that was measured invasively by coronary angiography had a positive correlation to the carotid-radial PWV that was measured non-invasively ($p<0.001$).

Table 4. Univariate regression analysis of the modified stenosis score as a dependent variable

Independent variable	B	R	p
Gender (female 0, male 1)	1.585	0.166	0.089
Age	0.066	0.153	0.118
BMI	0.099	0.056	0.571
Peripheral SBP	0.031	0.109	0.265
Calculated aortic SBP	0.029	0.107	0.273
Presence of smoking	0.952	0.102	0.300
Presence of hypertension	1.691	0.182	0.061
Total cholesterol	0.029	0.252	0.009
HDL cholesterol	-0.085	-0.187	0.054
LDL cholesterol	0.026	0.215	0.027
Plasma homocysteine	-0.015	-0.018	0.885
C-reactive protein	0.593	0.099	0.342
LVEF	-0.094	-0.234	0.016
LVMI	0.024	0.150	0.105
PWV	1.422	0.055	0.000

B: unstandardized coefficient, BMI: body mass index, SBP: systolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, PWV: pulse wave velocity

the severity of the CAD was explained by the PWV after adjusting for several cardiovascular risk factors in the multivariate regression analysis.

The PWV might provide a sensitive technique for assessing changes in the pulsatile arterial function that can serve as a marker for atherosclerotic change in the coronary vessels. Syeda et al.[27] have reported that patients with multivessel disease had a significant reduction in small arterial elasticity. We also found that the PWV was higher in patients with multiple vessel CAD than in those patients with single vessel CAD. The receiver operating characteristic curve analysis revealed a cut-off value of 9.05 m/sec for multiple vessel CAD with a sensitivity of 85% and a specificity of 67%.

Table 5. Multivariate regression analysis of modified stenosis score as a dependent variable

Independent variable	Standardized coefficient	p	95% CI
Gender (female 0, male 1)	0.012	0.897	-1.702, 1.941
Age	0.016	0.871	-0.075, 0.088
Presence of hypertension	0.086	0.341	-0.859, 2.461
Total cholesterol	0.254	0.140	-0.010, 0.068
HDL cholesterol	-0.131	0.139	-0.140, 0.020
LDL cholesterol	0.020	0.905	-0.038, 0.043
LVEF	-0.139	0.135	-0.129, 0.018
LVMI	0.081	0.340	-0.013, 0.038
PWV	0.436	0.000	0.635, 1.633

CI: confidential interval, HDL: high density lipoprotein, LDL: low density lipoprotein, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, PWV: pulse wave velocity

One potential limitation of our study was that the study group consisted of only symptomatic patients who were referred for coronary angiography. Thus, our findings might not be applicable to the general population. However, Nurnberger et al.[28] have found a strong positive correlation between arterial stiffness and CAD in asymptomatic patients who were without a previous history of CAD or atherosclerotic disease. Another limitation was that we assessed arterial stiffness using the PWV measured from a peripheral artery (the carotid-radial artery). The biological and mechanical properties of the central (predominantly elastic) arteries and the peripheral (predominantly muscular) arteries are known to differ in the formation of atherosclerotic lesions and arterial distensibility. However, the functional (flow-mediate vasodilatation) and morphological (intima-media thickness) aspects of the muscular artery status are known to be correlated with clinical CAD.[29][30]

In conclusion, we found that arterial stiffness, as measured by the carotid-radial PWV, had a strong association with the extent of CAD, and this went beyond the effects of the well-known cardiovascular risk factors. Thus, this non-invasive evaluation method may provide results that can be used as a useful marker of coronary atherosclerosis in patients suffering with CAD.

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