Original Article

Additional Value of Brachial-Ankle Pulse Wave Velocity to Single-Photon Emission Computed Tomography in the Diagnosis of Coronary Artery Disease

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Aim: The aim of this study was to investigate whether information on arterial stiffness can improve the value of single-photon emission computed tomography (SPECT) in the detection of obstructive coronary artery disease (CAD).

Methods: A total of 233 patients (age: 62.2 ± 10.8 years, 60.3% males) with detected ischemia on SPECT undergoing invasive coronary angiography (ICA) and brachial-ankle pulse wave velocity (baPWV) measurement within a month was retrospectively reviewed.

Results: Of the 233 patients, 190 (81.5%) had obstructive CAD ($\geq 50\%$ luminal stenosis). The difference in baPWV according to the presence of obstructive CAD was significant in patients in the mild ischemia group [summed stress score (SSS): 4−8] (1,770 ± 364 cm versus 1,490 ± 328 cm, $p < 0.001$) but not in the moderate (SSS: 9−13) or severe (SSS: ≥ 14) ischemia groups ($p > 0.05$ for each). Receiver operating characteristic curve analyses showed that the diagnostic value of baPWV for obstructive CAD was significant only in patients in the mild ischemia group (area under curve: 0.714; $p = 0.001$) but not in the moderate or severe ischemia groups ($p > 0.05$ for each). Adding information on baPWV to SPECT results and clinical parameters significantly increased diagnostic accuracy in the detection of obstructive CAD in patients with mild ischemia (integrated discrimination improvement $p = 0.006$) but not in those with moderate or severe ischemia on SPECT ($p > 0.05$ for each).

Conclusions: The results of this study suggest that baPWV may have additional value to SPECT for the detection of obstructive CAD, especially in patients with mild ischemia on SPECT.

Key words: Arterial stiffness, Coronary artery disease, Pulse wave velocity, Single-photon emission computed tomography

Introduction

Coronary artery disease (CAD) is the most common cause of death worldwide. CAD is highly prevalent, and its social and medical expenses have been steadily rising[1, 2]. Therefore, early detection and intensive management of high-risk patients are important for improving CAD-related poor prognosis. Invasive coronary angiography (ICA) is the gold standard in the diagnosis of CAD; however, it usually carries potential risk and increases the medical costs of patients[3]. In order to overcome these limitations of ICA, various noninvasive tests have been developed to detect CAD and guide ICA. Among them, single-proton emission computed tomography (SPECT), as a conventional method, is one of the most widely used noninvasive imaging tests in clinical settings. SPECT provides not

only diagnostic but also prognostic information in patients with known or suspected CAD[4-10]. It has been reported that diagnostic sensitivity of SPECT for the detection of obstructive CAD (≥50% luminal stenosis) is as high as above 80%, but the specificity of SPECT is as low as about 70%[9]. In addition, a substantial discrepancy between myocardial ischemia and coronary atherosclerosis has been demonstrated, suggesting that SPECT is imperfect as a single test in the detection of CAD[11]. For these reasons, there have been efforts to improve the diagnostic accuracy of SPECT, such as combined[12] or sequential imaging studies[13]. However, the diagnostic yield of ICA is still low, and there is a concern regarding the role of noninvasive tests as gatekeepers of ICA[14].

Arterial stiffness reflects aging, injury, and arteriosclerosis of the arterial walls[15]. Arterial stiffness can be estimated using several tools; among them, pulse wave velocity (PWV) is the most widely applied noninvasive method in the clinical and research fields[16]. There have been several reports showing a significant association between arterial stiffness measured by PWV and CAD[17-20]. It has been suggested that reduced diastolic coronary blood flow and shared common cardiovascular risk factors associated with increased arterial stiffness may be involved in the development and progression of coronary atherosclerosis[20, 21].

Aim

Since both SPECT and PWV are useful in the diagnosis of CAD, it can be speculated that a combination of results from both tests is conceptually attractive in the diagnosis of CAD. We hypothesized that additional information on PWV can improve the diagnostic value of SPECT. Therefore, this study was performed to investigate the incremental diagnostic value of PWV to SPECT in patients undergoing ICA for the evaluation of CAD.

Methods

Study Population

This single-center study was performed at Boramae Medical Center (Seoul, Korea). Between January 2010 and December 2015, a total of 274 patients with ischemia detected on SPECT who underwent ICA within two weeks were retrospectively reviewed. Brachial-ankle pulse wave velocity (baPWV) was measured within 30 days of SPECT and/or ICA in all study patients. Forty one patients with the following conditions were excluded: (1) prior history of myocardial infarction and coronary revascularization with percutaneous coronary intervention (PCI) or coronary

bypass surgery ($n = 26$), (2) ankle-brachial index < 0.9 or > 1.4 ($n = 4$), (3) non-sinus rhythm ($n = 6$), and (4) numerous missing variables ($n = 5$). Finally, 233 patients were analyzed in this study. This study complies with the Declaration of Helsinki, and the Institutional Review Board (IRB) of Boramae Medical Center approved this study protocol. Written informed consent was waived by the IRB due to the retrospective study design and routine nature of the information collected.

Data Collection

Body mass index (BMI) was calculated by dividing weight in kilograms by height squared in meters. Information on cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidemia, and smoking status was obtained. Hypertension was defined as either repeated measurements of blood pressure ≥140/90 mmHg or currently using antihypertensive medications. Diabetes mellitus was defined as fasting serum glucose level ≥126 mg/dL at least twice, hemoglobin A1c (HbA1c) ≥6.5%, or currently using antihyperglycemic medications. Dyslipidemia was defined as either a history of dyslipidemia or currently using antidyslipidemic medications. Smoking was defined as a history of cigarette smoking during the past 12 months. The pretest probability of CAD was defined based on the patient's age, sex, and chest pain nature[22] and classified as low ($< 10\%$), intermediate ($10\% - 90\%$), or high ($> 90\%$). Venous blood samples were acquired in the morning after more than eight hours of fasting. Blood levels of hemoglobin, creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, C-reactive protein, and HbA1c were measured. Estimated glomerular filtration rate (eGFR) was calculated using the following formula: $175 \times$ serum creatinine$^{-1.154} \times$ age$^{-0.203}$ ($\times 0.742$ if a woman).

SPECT Protocol

The SPECT protocol has previously been described and published elsewhere[13, 23]. Myocardial perfusion SPECT was performed with a one-day protocol using dual isotopes of ^{201}TI and ^{99m}Tc-sestamibi. First, rest SPECT images were acquired five minutes after the intravenous administration of ^{201}Tl chloride (111 MBq). For the pharmacological stress test, adenosine was continuously injected at a rate of 0.14 mg/kg/min for six minutes. Three minutes after adenosine infusion, ^{99m}Tc-sestamibi (555 MBq) was injected without the interruption of continued adenosine infusion, and then stress SPECT images were obtained four hours after ^{99m}Tc-sestamibi injection. SPECT images were acquired using a dual-headed camera (Infinia, Hawkeye 4, Gen-

Table 1. Clinical characteristics of the study subjects

Characteristic	Total ($n=233$)	CAD ($-$) ($n=43$)	CAD ($+$) ($n=190$)	p value
Age, years	67.3 ± 10.8	63.8 ± 11.9	68.0 ± 10.5	0.020
Male, n (%)	140 (60.1)	17.0 (39.5)	123 (64.7)	0.002
Body mass index (kg/m^2)	24.5 ± 4.1	24.9 ± 4.9	24.4 ± 3.9	0.435
Risk factors, n (%)				
Hypertension	148 (63.5)	22 (51.2)	126 (66.3)	0.062
Diabetes mellitus	91 (39.1)	8 (18.6)	83 (43.7)	0.002
Dyslipidemia	75 (32.2)	9 (20.9)	66 (34.7)	0.080
Smoking	53 (22.7)	5 (11.6)	48 (25.3)	0.054
Pretest probability, n (%)				
Low ($<10\%$)	10 (4.3)	3 (7.0)	7 (3.7)	
Intermediate ($10\%-89\%$)	195 (83.7)	37 (86.0)	158 (83.2)	0.362
High ($>90\%$)	28 (12.0)	3 (7.0)	25 (13.2)	
Laboratory findings				
Hemoglobin, g/dl	13.5 ± 7.3	13.1 ± 1.6	13.6 ± 8.0	0.670
Estimated GFR, mL/min/1.73 m^2	74.7 ± 26.1	78.0 ± 26.1	73.9 ± 26.1	0.361
Total cholesterol, mg/dl	158 ± 46	163 ± 39	157 ± 47	0.446
LDL cholesterol, mg/dl	99.0 ± 50.6	97.1 ± 34.9	99.5 ± 53.6	0.786
HDL cholesterol, mg/dl	42.7 ± 12.3	47.3 ± 13.7	41.6 ± 11.8	0.008
Triglyceride, mg/dl	131 ± 86	108 ± 58	136 ± 90	0.014
C-reactive protein, mg/dl	0.73 ± 1.89	0.49 ± 1.34	0.78 ± 1.99	0.377
HbA1c, %	6.87 ± 1.72	6.26 ± 0.99	7.0 ± 1.81	0.007

CAD, coronary artery disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

eral Electric Co., USA), employing 64 projections over 180° (from right anterior oblique 45° to left posterior oblique 45°), low-energy high-resolution collimator, and step/shoot acquisition at 3° intervals and for 25 seconds per step. For dual isotopes, images were obtained with a 20% window centered over both 70 and 167 keV photopeaks for ^{201}Tl chloride and a 20% window centered over the 140 keV photopeak for 99 mTc-sestamibi. SPECT images were reconstructed by the filtered back projection method using a Butterworth filter (cut-off frequency 0.49, order 5) and iterative reconstruction, and the reconstructed images were transferred to a designated workstation (Xeleris, General Electric Co., USA) for interpretation. The SPECT study was repeated when its image quality was suboptimal after scrutinization of the reconstructed images. SPECT images were interpreted by well-trained nuclear medicine physicians who were blinded to clinical information in accordance with the recommendation of the American Society of Nuclear Cardiology. Summed stress scores (SSS) were calculated to quantify myocardial ischemia by adding the scores of 17 myocardial segments[24]. Mild ischemia was defined as SSS $4-8$, moderate ischemia as SSS $9-13$, and severe ischemia as SSS ≥ 14. Visual assessment of perfusion defect was performed using a 5-point scoring system, and perfusion defect was classified as small ($<10\%$ of myocardium), medium ($10\%-20\%$ of myocardium), and large ($\geq 20\%$ of myocardium)[25].

ICA

Techniques of the ICA and PCI procedures were based on the current guideline's recommendations[3]. PCI decision was made by the interventional cardiologist performing ICA according to ICA results. Obstructive CAD was defined as $\geq 50\%$ luminal stenosis of one or more major epicardial coronary arteries in ICA.

Measurement of baPWV

Patients were examined in the supine position after five minutes of rest. baPWV was measured using a volume-plethysmographic apparatus (VP-1000; Colin Co. Ltd., Komaki, Japan) in accordance with the manufacturer's recommendations[23, 26]. Cuffs were wrapped on both upper arms and ankles. The baPWV values were calculated by measuring the time for the pulse wave to travel between the brachial and posterior tibial arteries. Caffeine consumption or cigarette smoking were not allowed before the examination. To measure blood pressure and semiconductor pulse wave, the measurement cuffs were placed around bilateral antecubital areas and ankles. Pulse volume waveform, pho-
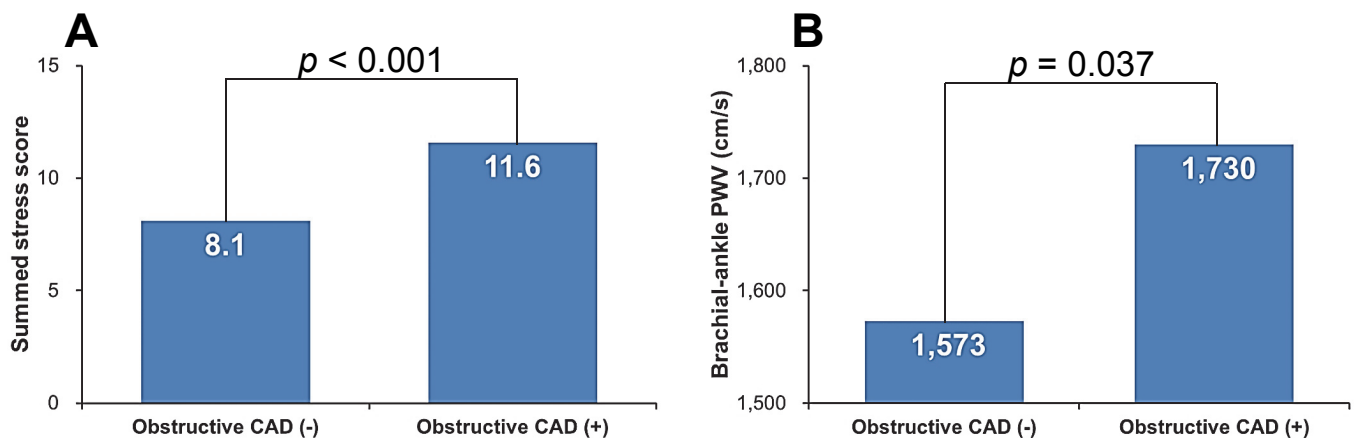
Fig. 1. Values of SSS (A) and brachial-ankle PWV (B) according to the presence of obstructive CAD

CAD, coronary artery disease.

nogram, blood pressure, and heart rate were recorded simultaneously. The average value of the left and right baPWV values was used in the analysis. All values were measured by the same experienced operator who was blinded to the patients' information. The coefficient of variance for inter-observer reliability of baPWV was 5.1% in our laboratory[23].

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are expressed as percentages. Univariate comparisons between patients with and without CAD were made using Student's t-test for continuous variables and the chi-square test for dichotomous variables. Trend of the incidence of obstructive CAD according to the severity of ischemia on SPECT was estimated by the linear-by-linear chi-square test. Receiver operating characteristic (ROC) curve analyses were used to evaluate the additional value of baPWV to SPECT. The integrated discrimination improvement index (IDI) was used to compare areas under curve of ROC[27]. A p value of < 0.05 was considered statistically significant. All analyses were two-sided. All data were analyzed using SPSS for Windows 18.0 (IBM, Armonk, NY, USA). R version 3.2.1 (http://www.r-projec-t.org) was used to calculate IDI.

Results

Clinical Characteristics of the Study Patients

The clinical characteristics of the study subjects are shown in **Table 1**. For the study patients ($n = 233$), the mean age was 67.3 ± 10.8 years, and there were 140 male patients (60.1%). Most patients ($n = 190$, 81.5%) had obstructive CAD in ICA. Patients with

CAD were older (68.0 ± 10.5 years versus 63.8 ± 11.9 years, $p = 0.020$) and predominantly male (64.7% versus 39.5%, $p = 0.002$) compared with those without CAD. There was no difference in BMI according to the presence of obstructive CAD ($p = 0.435$). All traditional risk factors including hypertension, diabetes mellitus, dyslipidemia, and smoking tended to be more prevalent in patients with CAD than in those without ($p < 0.10$); however, only diabetes mellitus showed a significant difference between these two groups (18.6% versus 43.7%, $p = 0.002$). Most study patients (83.7%) had intermediate pretest probability, which was not significantly different between patients with and without CAD ($p = 0.362$). In the laboratory test results, the HDL cholesterol level was lower and the triglyceride and HbA1c levels were higher in patients with CAD compared with those without CAD ($p < 0.05$ for each).

SSS values of SPECT (11.6 ± 6.5 versus 8.1 ± 4.3, $p < 0.001$) and baPWV values ($1,730 \pm 461$ cm/s versus $1,573 \pm 361$ cm/s, $p = 0.037$) were significantly higher in patients with CAD than in those without (**Fig. 1**).

The Association between the SPECT Results and the Incidence of Obstructive CAD

About half of the patients ($n = 111$, 47.6%) had mild ischemia, 55 patients (23.7%) had moderate ischemia, and 67 patients (28.7%) had severe ischemia on SPECT. The incidence of obstructive CAD increased proportionally according to ischemia severity on SPECT (73.9% in the mild ischemia group, 83.6% in the moderate ischemia group, and 92.6% in the severe ischemia group; p for trend = 0.002) (**Fig. 2**).

Changes in baPWV Values According to the Degree of Ischemia on SPECT

In the mild ischemia group, the baPWV values
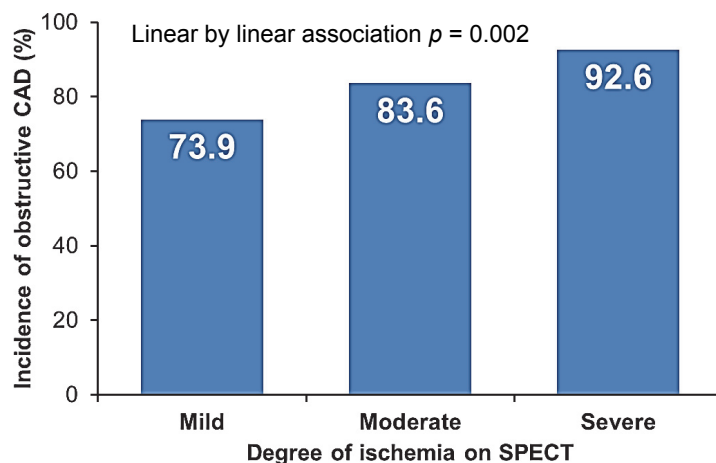
Fig. 2. Incidence of obstructive CAD according to the degree of ischemia on SPECT

CAD, coronary artery disease; SPECT, single-photon emission computed tomography.

were significantly higher in patients with CAD than in those without (1,770 ± 364 cm versus 1,490 ± 328 cm, $p < 0.001$). However, there were no significant differences in the baPWV values between patients with and without CAD in the moderate or severe ischemia groups ($p > 0.05$ for each) (**Fig. 3**).

**Incremental Prognostic Value of baPWV Predicting Obstructive CAD**

ROC curve analyses showed that the diagnostic value of baPWV for obstructive CAD was significant only in the mild ischemia group (cut-off value: 1,494 cm/s; sensitivity: 81.7%; specificity: 58.6%; area under curve: 0.714; $p = 0.001$) but not in the moderate or severe ischemia groups ($p > 0.05$ for each) (**Table 2**). Adding information on baPWV to SPECT results and clinical parameters significantly increased diagnostic accuracy for the detection of obstructive CAD in patients with mild ischemia (IDI $p = 0.006$) (**Fig. 4**) but not in those with moderate or severe ischemia on SPECT. When we used the data on visual assessment of perfusion defect instead of SSS, ROC curve analysis showed that diagnostic value of baPWV predicting obstructive CAD was significant only in patients with small perfusion defect (area under curve: 0.830; $p = 0.001$) but not in those with medium or large perfusion defects ($p > 0.05$ for each) on SPECT (**Table 3**).

Discussion

The main finding of our study was that baPWV had incremental value to SPECT for the diagnosis of CAD in patients with a mild degree of myocardial ischemia but not in those with moderate or severe ischemia on SPECT. Our patients with mild ischemia on SPECT showed the followings: (1) the baPWV values were significantly higher in patients with angiographic obstructive CAD than in those without, (2) prediction of CAD by baPWV was evident in ROC curve analysis, and (3) baPWV provided additional diagnostic information to clinical parameters and SPECT results for the detection of obstructive CAD. However, these diagnostic values of baPWV were not observed in patients with moderate or severe ischemia on SPECT. This is the first study to provide evidence that baPWV is useful for detecting CAD, especially in patients with mild ischemia on SPECT.

Traditionally, stress tests, including the exercise treadmill test and SPECT, have played a main role in the noninvasive assessment of CAD. However, the diagnostic value of these tests for coronary obstruction is still modest[28], and there is a concern regarding their roles as gatekeepers for invasive cardiac catheterization[14]. With technical advances, emerging coronary computed tomographic angiography (CCTA) has shown reliable accuracy in the diagnosis of obstructive CAD, with particularly high negative predictive value for excluding obstructive CAD[29, 30]. However, the use of CCTA is limited by relatively higher false positive rates and lack of information on myocardial ischemia[31]. In this context, combined information from two different noninvasive imaging tests has been used to make up for the shortcomings of each other and improve diagnostic accuracy. In particular, many reports have shown the improved diagnostic accuracy of integrated anatomical and functional imaging
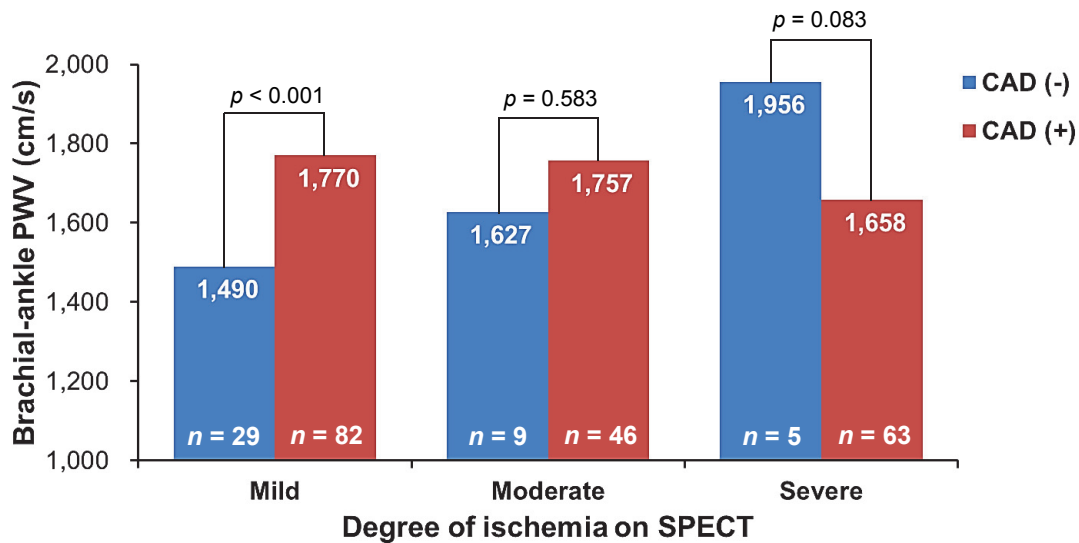
Fig. 3. Values of brachial-ankle PWV according to groups based on the degree of ischemia on SPECT
PWV, pulse wave velocity; SPECT, single-photon emission computed tomography.

Table 2. ROC curve analyses showing value of baPWV predicting obstructive CAD

| SSS value	Area under curve	95% confidence interval	*p*
4−8 (mild ischemia)	0.714	0.60−0.82	0.001
9−13 (moderate ischemia)	0.510	0.33−0.68	0.927
≥14 (severe ischemia)	0.302	0−0.61	0.142

ROC, receiver operating characteristic; baPWV, brachial-ankle pulse wave velocity; CAD, coronary artery disease; SSS, summed stress score.

results for obstructive CAD compared with that of either result of a single test[12, 32]. Although combined imaging seemed promising, medical costs and radiation hazards hinder their wide use in clinical practice[32]. New modalities that can give complementary information and improve diagnostic power for CAD are needed. baPWV is noninvasive and a very simple measuring method, and it can be useful for mass screening[33]. In addition, there have been numerous data about the reliability and utility of baPWV in clinical practice[20, 26, 34-36]. In this context, our study results are valuable and deserve attention because we first showed the incremental diagnostic value of baPWV for obstructive CAD, especially in patients with mild ischemia on SPECT. Of course, we do not think that baPWV can replace the role played by noninvasive tests; however, baPWV can help determine whether patients should undergo invasive testing, especially when combined with other tests.

Our study demonstrated that additional diagnostic value of baPWV to SPECT was found only in patients with mild ischemia but not in those with moderate or severe ischemia on SPECT. The underlying pathophysiology explaining why baPWV has value only in mild ischemia cases is unknown. However, a hypothesis can be suggested. Patients with moderate or severe ischemia on SPECT have a higher likelihood of having obstructive CAD, as shown in our results (83.6% in moderate ischemia and 92.6% in severe ischemia on SPECT), and thus, there may be very little space for diagnostic value to be improved by baPWV. However, the diagnostic accuracy of SPECT was relatively low (73.9% of patients had obstructive CAD), and baPWV could increase the diagnostic value of SPECT in the mild ischemia group. The result of the present study is in line with that of a previous study showing the usefulness of additional information of CCTA in those with mild ischemia but not with moderate or severe ischemia on SPECT[13].

Diagnosis of CAD is important for risk stratification and proper management. Although ICA is the gold standard for the detection of coronary stenosis,
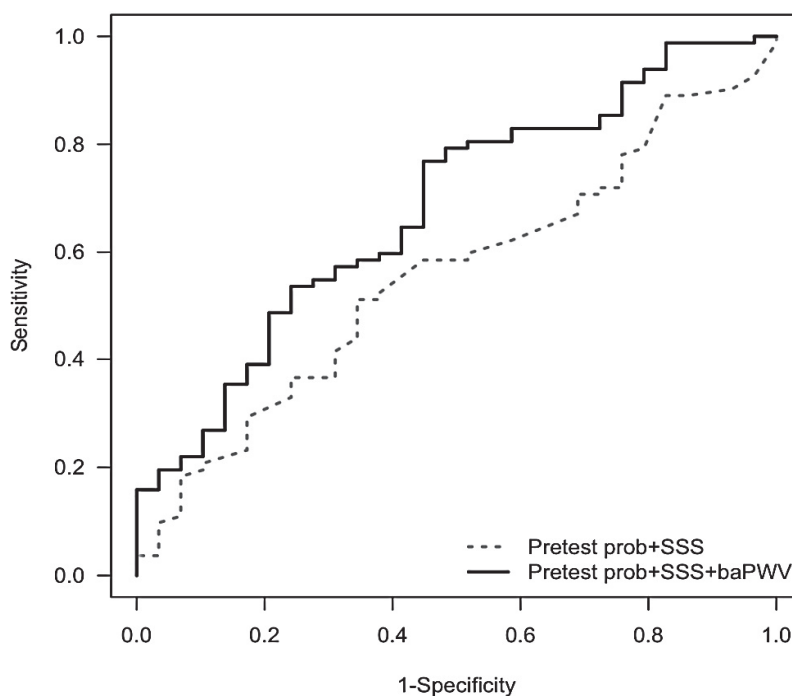
Fig. 4. ROC curve analysis showing additional value of baPWV to SSS in the diagnosis of obstructive CAD

prob, probability; SSS, summed stress score; baPWV, brachial-ankle pulse wave velocity.

Table 3. ROC curve analyses showing value of baPWV predicting obstructive CAD

Visual assessment of perfusion defect on SPECT	Area under curve	95% confidence interval	p
Small	0.830	0.68−0.97	0.001
Medium	0.448	0.30−0.59	0.534
Large	0.696	0.48−0.91	0.087

ROC, receiver operating characteristic; baPWV, brachial-ankle pulse wave velocity; CAD, coronary artery disease; SPECT, single-photon emission computed tomography.

its invasive nature and cost limit routine use in clinical practice. Several noninvasive tools have been developed and widely used in clinical fields; however, they have shown limited diagnostic value as a single test[14]. Recent studies have shown an independent association between baPWV and CAD, suggesting that baPWV can be applied in CAD diagnosis[34, 36]. The results of the present study demonstrated that baPWV improved the diagnostic value of SPECT, especially in patients with mild ischemia on SPECT. In practice, it is more difficult for physicians to decide whether they should perform ICA in patients with mild ischemia as compared with those with moderate or severe ischemia on SPECT. Therefore, such patients more frequently need further diagnostic tests. Based on its noninvasiveness,

simplicity, and reliability[32], baPWV is useful in the diagnosis of CAD in patients with mild ischemia on SPECT. ICA can be considered in patients with high baPWV even though they have mild degree ischemia on SPECT. However, other tests or medical follow-up, rather than directly performing ICA, can be other options in patients with low baPWV and mild ischemia on SPECT.

Contrary to our expectation, mean value of baPWV was numerically higher in patients without CAD than those with CAD in patients with severe ischemia on SPECT (**Fig. 3**). Although underlying pathophysiology was not revealed in our study, there may be a possibility that coronary microvascular dysfunction existed in patients without CAD but with

severe ischemia on SPECT[37]. This can partially explain the increased baPWV in patients with severe ischemia in spite of the absence of obstructive CAD. Further researches are warranted to prove our hypothesis.

Besides its retrospective study design, our study has several limitations. Firstly, our cross-sectional analysis did not confirm a causal relationship between arterial stiffness and CAD. Secondly, there was a time delay among the three tests, including baPWV, SPECT, and ICA. Thirdly, this study did not include patients who did not receive ICA, even though they had ischemia on SPECT; thus, there is a possibility of selection bias. Fourthly, some parameters did not reach statistical significance due to the relatively small number of study subjects. Lastly, this study did not provide information on the extent/severity of CAD or the location of the culprit lesion in ICA.

In conclusion, baPWV may provide additional value to SPECT for the detection of obstructive CAD, especially in patients with mild ischemia on SPECT. As a simple measurement, baPWV can be useful for CAD diagnosis. Further studies with a larger sample size are needed to confirm our findings.

Acknowledgments

Conflict of Interest

The authors declare that there is no conflict of interest associated with this manuscript.

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