Aim: Arterial stiffness assessed by brachial-ankle pulse wave velocity (baPWV) is predictive of cardiovascular events. This study was designed to investigate whether baPWV has an additional prognostic value to single-photon emission computed tomography (SPECT) in patients with suspected coronary artery disease (CAD).

Methods: A total of 350 subjects (age, 66.2 ± 10.5 years, 53.4% male) with suspected CAD undergoing myocardial SPECT and baPWV within 30 days were retrospectively analyzed. Cardiovascular events, including cardiovascular death, acute coronary syndrome and ischemic stroke, were assessed. Both fixed and reversible perfusion defects on SPECT were considered abnormal myocardial perfusion imaging (MPI) findings.

Results: During the median follow-up period of 441 days (interquartile range 169–719 days), cardiovascular events occurred in 21 patients (6.0%). In multivariable Cox regression analysis, abnormal MPI (hazard ratio (HR), 2.67; 95% confidence interval (CI), 1.21–10.37; \( p = 0.024 \)) and high baPWV (≥1,790 cm/s) (HR, 2.03; 95% CI, 1.08–6.38; \( p = 0.007 \)) were independent predictors of clinical events even after adjusting for possible confounders. Also, high baPWV had an incremental prognostic value to traditional risk factors and abnormal MPI in predicting cardiovascular events (overall Chi-square, from 24.08 to 27.42; \( p < 0.001 \)). Kaplan–Meier survival curves stratified by baPWV and MPI proved significantly improved prediction of cardiovascular events (log-rank \( p = 0.001 \)).

Conclusions: baPWV has an incremental prognostic value to traditional risk factors and MPI. Therefore, baPWV can be used to identify subjects at higher risk of cardiovascular events in patients undergoing SPECT.

Key words: Arterial stiffness, Prognosis, Pulse wave velocity, Single-photon emission computed tomography

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality worldwide\(^1\). Accordingly, diverse modalities have been developed for patients with suspected or known coronary artery disease (CAD) to diagnose and manage the disease appropriately\(^2\). Among
them, as a conventional method, myocardial single-photon emission computed tomography (SPECT) has been widely used to detect CAD and to guide selective invasive coronary angiography. Importantly, assessment of the viable myocardium using SPECT provides prognostic information in patients who are at risk of having further coronary events. Increased arterial stiffness represents vascular aging and arteriosclerosis, and it is not only directly associated with the presence and severity of CAD but also has incremental prognostic value for poor cardiovascular outcomes. Arterial stiffness can be noninvasively assessed by measuring pulse wave velocity (PWV), which is simple, reproducible, economical, and validated in various populations with certain medical conditions. There have been methodological variabilities in the measurement of PWV, of which brachial-ankle PWV (baPWV) is well correlated with invasive study results of arterial stiffness and risks of further coronary events. Although primary and secondary prevention strategies based on diverse workup tools, including SPECT and baPWV, have improved for decades, the incidence of CAD is still on the rise. At present, a single modality has been shown to have its limitations with respect to diagnostic and prognostic accuracies in spite of technical advances. Hence, multi-disciplinary approach is recently increasing to minimize CAD and to make a better decision.

**Aim**

To date, there has been lack of information on additional benefits of combined information of SPECT and baPWV. Considering the prognostic value of both SPECT and baPWV, we hypothesized that combining information of both tests will become stronger in the prediction of cardiovascular events compared with that of either one. The present study was conducted to investigate whether baPWV has an additional prognostic value to SPECT predicting cardiovascular events in patients with suspected CAD.

**Methods**

**Study Population**

This single center study was performed at Boramae Medical Center (Seoul, Korea). Between June 2009 and December 2012, a total of 442 patients who underwent both SPECT and baPWV within 30 days were retrospectively identified. In this study, all patients who enrolled this study were treated according to the current standard management guidelines, and baPWV measurement was performed at the discretion of the attending physicians. Of these 442 patients, 92 with a history of previous myocardial infarction, coronary revascularization and ischemic stroke, peripheral artery disease with an ankle-brachial index of <0.9, or insufficient clinical information for the analysis were excluded. Finally, 350 patients were analyzed in this study. Patients with diabetes mellitus, hypertension, and dyslipidemia were defined by maintaining their medications and laboratory values. Diabetes mellitus was defined as 1) having a history of diabetes mellitus, 2) taking antidiabetic medication, or 3) having a pretest fasting glucose value of ≥126 mg/dL. Hypertension was defined as 1) having a history of hypertension, 2) taking antihypertensive medication, or 3) having a pretest systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg at rest. Dyslipidemia was defined as 1) having a history of dyslipidemia, 2) taking lipid-lowering medication, or 3) having a pretest total cholesterol level of ≥200 mg/dL or a low-density lipoprotein (LDL) cholesterol of ≥100 mg/dL. Patients with end-stage renal disease (ESRD) were defined as those who had an estimated glomerular filtration rate of <15 mL/min/1.73 m² or those who received renal replacement therapy. Body mass index (BMI) was also calculated as weight (kg) divided by square of height (m²), and BMI ≥25 kg/m² was set as a significant obesity. Blood levels of total cholesterol, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol were obtained after overnight fasting for more than 8 h. The information of patients’ medication was obtained by reviewing their medical records. The Institutional Review Board of Boramae Medical Center (Seoul, Korea) approved this study protocol. Informed consent was waived due to retrospective study design.

**The baPWV Measurement**

After a patient was placed in the supine position for 5 or more min, blood pressure and baPWV were automatically generated using a noninvasive automated waveform analyzer (VP-1000; Colin Co. Ltd., Komaki, Japan), as described previously. Briefly, baPWV was measured in patients’ bilateral upper and lower extremities using a plethysmographic sensor, which simultaneously recorded blood pressure, an electrocardiogram, and heart sounds in accordance with the manufacturer’s recommendations. Also, baPWV (cm/s) was calculated as the length between arterial sites divided by time interval and was measured in both brachial and posterior tibial arteries. The higher value between left and right baPWV measurements was chosen for further analysis. All measurements were made by the
same experienced operator blinded to the clinical information. The intra-observer coefficient of variation was about 5.1%, as similar to other studies\textsuperscript{22, 23)}, and the inter-observer coefficient of variation could not be calculated as there was only one examiner in this study. Patients were allowed to take their regular medications during examination.

### SPECT Protocol

SPECT was performed using a dual-headed camera (Infinia Hawkeye 4, General Electric Co., USA) equipped with a low-energy high-resolution collimator. Rest images were obtained 5 min after an intravenous injection of thallium-201\textsuperscript{(201T)}-chloride(111 MBq), and stress images were acquired 3 h after an intravenous injection of technetium-99 m\textsuperscript{99 mTc}-MIBI(925 MBq)\textsuperscript{24). For pharmacological stress, adenosine (0.14 mg/kg/min) was continuously infused for 6 min, and \textsuperscript{99 mTc}-MIBI was injected at 3 min after a starting injection of adenosine. SPECT scanning was performed using a step-and-shoot method with 3° interval, 25 s for each step, and acquired images were reconstructed by the filtered back projection method using a Butterworth filter (cut-off frequency 0.49, order 5) and iterative reconstruction methods. SPECT images were interpreted by well-trained nuclear physicians who were blinded to the clinical information in accordance with the recommendations of the American Society of Nuclear Cardiology\textsuperscript{25). Patients were categorized as presence and absence of perfusion defect, which was assessed on the stress image (segmental tracer activity \(\geq 75\%\) of maximum), and both fixed and reversible perfusion defects on SPECT were considered as abnormal myocardial perfusion imaging (MPI) findings.

### Clinical Events

Follow-up information was obtained from hospi-
Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD), whereas categorical variables are presented as absolute values and their proportions. Differences between continuous variables are compared by the student’s t test for independent samples, and differences between categorical variables are compared by the χ² test or Fisher’s exact test, as appropriate. The optimal cut-off value of baPWV for the prediction of clinical events was obtained using receiver operating characteristic (ROC) curve analysis. Kaplan–Meier survival curves were used to estimate the risk of cardiovascular events according to myocardial SPECT findings and baPWV measurements during the follow-up period. Differences between time-to-event curves were compared with the log-rank test. Two steps of multivariable analyses were conducted. Initially, the Cox proportional hazard regression model with a forward selection method was used to assess the risk of a

Clinical events, including cardiovascular death, nonfatal acute coronary syndrome (ACS), and nonfatal ischemic stroke, during the follow-up period were evaluated. ACS included acute myocardial infarction (AMI) and unstable angina, which were confirmed by cardiologists with objective evidences. Ischemic stroke was diagnosed by typical neurological signs and symptoms that were assessed by neurologists and findings of noninvasive brain imaging studies, such as brain computed tomography and/or magnetic resonance imaging (MRI). Ischemic stroke occurring within 24 h after coronary catheterization (n=1) was excluded from analysis because it may have resulted from the procedure itself. Cardiovascular death was defined as the death after ACS/stroke or sudden cardiac death.

Fig. 1. Event free survival rates according to SPECT result.

SPECT, single-photon emission computed tomography; MPI, myocardial perfusion imaging.
tes mellitus, dyslipidemia, and ESRD were 65.7%, 46.6%, 56.6%, and 7.1%, respectively. Coronary angiography (CAG) was performed in two thirds of patients to evaluate CAD. Percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery progressed in 106 (30.3%) and 14 (4.0%) patients on the basis of CAG results. Two hundred and twenty patients (62.9%) took an antiplatelet agent, and over a half of patients (54.6%) were prescribed statins. The proportion of patients taking renin-angiotensin system (RAS) blocker, beta blocker, calcium channel blocker, and nitrate were 45.7%, 37.1%, 31.1%, and 18.3%, respectively.

Comparison between Patients with and without Clinical Events
During the median follow-up period of 441 days (interquartile range, 169–719 days), clinical events, including cardiovascular death (n=4), nonfatal ACS given variable as expressed with a hazard ratio (HR) and corresponding 95% confidence interval (CI) after adjusting for potential confounders. Secondly, the added value of baPWV to clinical and SPECT findings predicting cardiovascular events were analyzed using global Chi-square scores. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS 22.0 statistical package (IBM Co., Armonk, NY, USA).

Results
Baseline Characteristics of Study Patients
The baseline characteristics of study patients are shown in Table 1. The mean age of the patients was 66.2±10.5 years, and approximately 75% of patients were over 65 years of age. About half of patients (53.4%) were male, and 21.7% were current smokers. The proportion of patients with hypertension, diabetes mellitus, dyslipidemia, and ESRD were 65.7%, 46.6%, 56.6%, and 7.1%, respectively. Coronary angiography (CAG) was performed in two thirds of patients to evaluate CAD. Percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery progressed in 106 (30.3%) and 14 (4.0%) patients on the basis of CAG results. Two hundred and twenty patients (62.9%) took an antiplatelet agent, and over a half of patients (54.6%) were prescribed statins. The proportion of patients taking renin-angiotensin system (RAS) blocker, beta blocker, calcium channel blocker, and nitrate were 45.7%, 37.1%, 31.1%, and 18.3%, respectively.
Kaplan–Meier curves showed that the occurrence of clinical events was significantly higher in patients with perfusion defect than that in patients without perfusion defect (8.2% vs. 2.3%; log-rank test, \( p = 0.026 \)) (Fig. 1). baPWV was significantly higher in patients with events than that in patients without events (1,930 ± 674 cm/s vs. 1,760 ± 546 cm/s; \( p = 0.018 \)). In addition, a baPWV of 1,790 cm/s was obtained as the best cut-off value in predicting cardiovascular events using ROC curve analysis (area under curve, 0.63; 95% CI, 0.51–0.75; \( p = 0.047 \); sensitivity 62.0% and specificity 62.3%). When patients were classified into 2 groups according to the cut-off value of baPWV, the cumulative event rate was significantly higher in

\( (n = 10) \), and nonfatal ischemic stroke \( (n = 7) \), occurred in 21 patients (6.0%). Comparisons of characteristics between patients with and without clinical events are also shown in Table 1. Patients with cardiovascular events were older, less obese, more frequently had ESRD, and received more statin therapy than those without events \( (p < 0.05 \) for each).

**Clinical Events According to SPECT, baPWV, and Their Combined Results**

Among the patients with abnormal MPI in SPECT \( (n = 220) \), invasive CAG was performed in 193 patients (87.7%). Among them, 92 (41.8%) and 13 (5.9%) patients underwent PCI and CABG, respectively. Kaplan–Meier curves showed that the occurrence of clinical events was significantly higher in patients with perfusion defect than that in patients without perfusion defect (8.2% vs. 2.3%; log-rank test, \( p = 0.026 \)) (Fig. 1). baPWV was significantly higher in patients with events than that in patients without events (1,930 ± 674 cm/s vs. 1,760 ± 546 cm/s; \( p = 0.018 \)). In addition, a baPWV of 1,790 cm/s was obtained as the best cut-off value in predicting cardiovascular events using ROC curve analysis (area under curve, 0.63; 95% CI, 0.51–0.75; \( p = 0.047 \); sensitivity 62.0% and specificity 62.3%). When patients were classified into 2 groups according to the cut-off value of baPWV, the cumulative event rate was significantly higher in

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patients with a baPWV of ≥1,790 cm/s (n = 213, 60.9%) than in patients with a baPWV of <1,790 cm/s (n = 137, 39.1%) (9.5% vs. 3.8%; log-rank test, p = 0.012) (Fig. 2). To assess the value of combined information of baPWV and MPI findings, patients were stratified into 4 groups as follows: 1) patients with normal MPI and a baPWV of <1,790 cm/s (n = 71, 20.3%), 2) those with normal MPI and a baPWV of ≥1,790 cm/s (n = 59, 16.9%), 3) those with abnormal MPI and a baPWV of <1,790 cm/s (n = 140, 40.0%), and 4) those with abnormal MPI and a baPWV of ≥1,790 cm/s (n = 80, 22.9%). Kaplan–Meier curves showed that the event rate was significantly different between the 4 groups (0.0% vs. 5.1% vs. 13.8%; log-rank test, p = 0.001) (Fig. 3). During the follow-up period, no clinical event occurred in patients with normal MPI and a baPWV of <1,790 cm/s.

### Independent Predictors for Clinical Events

In order to evaluate independent predictors for clinical events, multivariable Cox regression analysis was performed. Age ≥65 years (HR, 4.37; 95% CI, 1.32–14.51; p = 0.016), ESRD (HR, 4.86; 95% CI, 1.42–16.65; p = 0.012), statin therapy (HR, 4.13; 95% CI, 1.07–15.91; p = 0.040), abnormal MPI (HR, 2.67; 95% CI, 1.21–10.37; p = 0.024), and a baPWV of ≥1,790 cm/s (HR, 2.03; 95% CI, 1.08–6.38; p = 0.007) were independently associated with an increased risk of cardiovascular events (Table 2).

### The Incremental Prognostic Value of baPWV

Abnormal MPI findings had an incremental prognostic value to traditional risk factors in the prediction of clinical events (global Chi-square score, from 17.85 to 24.08; p < 0.001). Furthermore, a baPWV of ≥1,790 cm/s had an incremental prognostic value to combined information of traditional risk factors and abnormal MPI findings (global Chi-square, from 24.08 to 27.42; p < 0.001) (Fig. 4). This incremental prognostic value of baPWV was indirectly revealed by comparing event-free survival rates between group 3 and 4 in Kaplan–Meier survival curve (the annual rate of clinical events, 2.3% vs. 3.7%; log-rank test, p = 0.008) (Fig. 3).

### Discussion

The present study demonstrated that increased arterial stiffness evaluated by baPWV was independently associated with a higher risk for cardiovascular events. More important, baPWV provided an additional prognostic value over conventional risk factors and perfusion defect on SPECT toward the prediction of future clinical events in patients with suspected CAD. To the best of our knowledge, this is the first report showing clinical implications of the integrated approach of PWV and SPECT for the risk stratification of CAD.

### Prognostic Power of baPWV

The prevention and treatment of cardiovascular disease have focused on risk factors known to be detrimental to arterial integrity. Arterial damage by atherosclerosis or aging process can be assessed by measuring arterial stiffness. Previous studies have described the value of PWV predicting future cardiovascular events in various medical conditions, such as hypertension, diabetes mellitus, stroke, and renal insufficiency. However, clinical use of baPWV in patients with suspected or known CAD has been reported in only a few clinical studies. In our study, we showed that high baPWV increased the risk of future cardiovascular events in patients with suspected CAD. This is in line with results shown in other high-risk groups of previous studies. Increased arterial stiffness induces vascular structural changes, which derives an increase in the velocity of pressure wave as it travels down the aorta. As arteries stiffen, the reflected flow coming back from the periphery reaches the heart at systole instead of diastole and augments the afterload. These serial changes consequently result in reductions in coronary filling and then in further myocardial ischemia. In addition, arterial stiffening is related with a widened pulse pressure, which can progress to systolic hypertension, a well-known cardiovascular risk

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**Table 2. Independent predictors of clinical events**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age ≥65 years</td>
<td>4.37 (1.32–14.51)</td>
<td>0.016</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.52 (0.94–2.51)</td>
<td>0.536</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.76 (0.54–5.75)</td>
<td>0.346</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.26 (0.48–3.28)</td>
<td>0.642</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.45 (0.53–4.02)</td>
<td>0.471</td>
</tr>
<tr>
<td>ESRD</td>
<td>4.86 (1.42–16.65)</td>
<td>0.012</td>
</tr>
<tr>
<td>PCI</td>
<td>0.88 (0.33–2.41)</td>
<td>0.810</td>
</tr>
<tr>
<td>CABG</td>
<td>0.87 (0.10–7.72)</td>
<td>0.901</td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>0.95 (0.27–3.39)</td>
<td>0.938</td>
</tr>
<tr>
<td>Statin</td>
<td>4.13 (1.07–15.91)</td>
<td>0.040</td>
</tr>
<tr>
<td>Abnormal MPI</td>
<td>2.67 (1.21–10.37)</td>
<td>0.024</td>
</tr>
<tr>
<td>baPWV ≥1,790 cm/s</td>
<td>2.03 (1.08–6.38)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; baPWV, brachial-ankle pulse wave velocity; MPI, myocardial perfusion imaging. Other abbreviations are same as Table 1.
factor. On the basis of this hemodynamic background, our results led to a proper conclusion that baPWV can be useful as a prognostic marker of CAD that clinicians can use to obtain the additional information in patients with known or suspected CAD.

Combined Information of Noninvasive Modalities for Better Risk Stratification

In the past few decades, noninvasive cardiac imaging modalities have been considerably developed, which have played a significant role in risk stratification and CAD prevention/management. Despite this progress, CAD remains highly prevalent and represents a healthcare burden in modern societies, which is derived from a potential limitation of evaluating CAD by a single noninvasive imaging. Therefore, numerous attempts to integrate diverse noninvasive modalities have been made. Schepis et al. proved that the addition of coronary calcium score improved the sensitivity of SPECT from 76% to 86% for the detection of CAD, and Kim et al. showed that the sequential use of SPECT and coronary computed tomographic angiography (CCTA) had an incremental prognostic value to the respective modalities alone. In addition, Di Carli and Hachamovitch demonstrated that an integrated approach with cardiac positron emission tomography (PET) and CCTA overcame the discrepancy between anatomical and physiological measurements of stenosis severity. Recently, in 20 patients with AMI, hybrid cardiac PET-MRI provided not only high-quality cardiac images but also quantitative information on the metabolic process, which improved risk stratification. However, current combined imaging systems have several practical constraints. There are quite a few barriers to perform these tests due to ambiguous indications and high cost. Furthermore, they result in more exposure to radiation, which could be hazardous. In this context, we suggest baPWV as a new noninvasive modality to overcome these limitations. The measurement of baPWV is noninvasive and easy to perform. It does not provide further exposure of radiation. Furthermore, the value of baPWV has been validated in numerous previous clinical studies and meta-analysis. Notably, given that combined information from baPWV and SPECT had an incremental prognostic value as shown in our study,
adding information of baPWV to that of SPECT may be effective in the evaluation and management of CAD. In addition, on the basis of our results, if a patient shows both a normal MPI and low baPWV, it may be relatively much safe from further cardiovascular events. This is potentially applicable to clinical practice by providing meticulous monitoring and aggressive management to patients at higher risk.

Study Limitations

Besides the retrospective study design, this study has several limitations that should be considered. First, we enrolled patients with known or suspected CAD; thus, generalization of our results to other population is difficult. Accordingly, to extend the applied population, further studies are required. More important, a potential novel finding of our study, the incremental prognostic value of baPWV to myocardial SPECT in patients with known or suspected CAD, should be confirmed by larger validated studies including more participants from a range of hospitals and regions. Second, although we reviewed patients’ oral medications, it is somewhat incomplete due to outside prescription and lack of information in drug switch. However, the bias may be minimized by relatively long follow-up period and collecting data at the closest timing from both exams. Third, baPWV was known to be influenced by other cardiovascular conditions, such as peripheral artery disease, severe LV dysfunction, concomitant aortic disease, or high blood pressure, during the exam. Although we excluded patients having influence factors as much as possible, some study population (44/350, 12.6%) had never performed echocardiography during the follow-up period; therefore, we could not be completely free from clinical impact of possible confounders. Lastly, because baPWV measurements were determined mainly by attending physicians, there was a possibility of a selection bias in this study.

Conclusions

The results of this study suggest that baPWV may be valuable estimating the risk of cardiovascular events in patients with suspected or known CAD. More important, baPWV has an incremental prognostic value to SPECT in predicting cardiovascular events. As a simple and noninvasive method, baPWV can be used to identify subjects at higher risk in patients performing SPECT for the evaluation of CAD. Further studies with prospective design are needed to confirm our findings.

Acknowledgements

None.

Disclosure

None.

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