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# Non-Invasive Assessment of Early Atherosclerosis Based on New Arterial Stiffness Indices Measured with an Upper-Arm Oscillometric Device

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The clinical significance of detecting early atherosclerosis is now widely recognized. Measurement methods available at present are usually not suitable for use in primary care where rapid screening for a large population is needed. The Arterial Velocity-pulse Index (AVI) and Arterial Pressure-volume Index (API) are new noninvasive arterial stiffness indices that can be rapidly measured using an oscillometric device. The purpose of this study was to determine whether high AVI and API values are predictive of early atherosclerosis prior to the onset of obstructive coronary artery disease (CAD). A total of 183 patients were enrolled and allocated to the CAD group (n = 109), early atherosclerosis (AS) group (n = 34) or an apparently healthy (non-AS) group (n = 40) based on the results of angiographic examinations. Measurements for arterial blood pressure, AVI, API and brachial-ankle pulse wave velocity (baPWV) were collected. Statistical analyses revealed that AVIs were significantly lower in the non-AS group than in the AS group and the CAD group. The inter-group differences in API were not statistically significant among the 3 patient groups. As a reference, baPWV was found to be statistically higher in the CAD group than in the non-AS group, whereas there was no significant difference between the CAD group and the AS group, or between the AS group and the non-AS group. The AVI and API were both significantly correlated with baPWV. This study demonstrated that AVI was more sensitive than baPWV and API in indicating early atherosclerosis, although elevated AVI and baPWV were both predictive of CAD.

**Keywords:** arterial stiffness index; atherosclerosis; coronary artery disease; noninvasive measurement; oscillometric method
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## Introduction

Over the past decade, ischemic heart disease has held the first place in the list of top 30 causes for years of life lost (YLLs) worldwide (GBD 2015 Mortality and Causes of Death Collaborators 2016). In recent years, increasing emphasis has been placed on detecting early arteriosclerosis because this has been proved to be a predictor for future cardiovascular events (Simon et al. 2006). For the management of patients suspected of having coronary artery disease (CAD), the techniques of coronary angiography, intravascular ultrasound (IVUS), or optical coherence tomography (OCT) remain as "the gold standard" for diagnosis. However, their application in primary prevention of CAD is limited due to their invasive nature and high cost.

It has been well documented that increased arterial stiffness is an independent predictor of adverse cardiovascular outcomes, both in the general population (Mattace-Raso et al. 2006; Willum-Hansen et al. 2006) and in patients with cardiovascular disorders (Blacher et al. 1999; Guerin et al. 2001; Laurent et al. 2001). In the last decade, pulse wave velocity (PWV) has been a widely accepted noninvasive measurement of arterial stiffness (Laurent et al. 2006) and its value in predicting negative cardiovascular events (including both CAD and other cardiovascular diseases) has been extensively demonstrated (Sugawara et al. 2005; Tomiyama et al. 2005; Meguro et al. 2009; Nakamura et al. 2010; Munakata et al. 2012; Vlachopoulos et al. 2012). Nonetheless, the use of PWV measurement remains to be unsuitable for the patient screening or risk stratifica-

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tion in routine clinical practice due to the relatively high cost, requirement of expertise operation and long measurement time. In view of the prevalence of asymptomatic coronary atherosclerosis in the general population, there is an urgent need to develop methods capable of detecting the presence of early atherosclerosis in a rapid and noninvasive way.

In this context, new methods that permit rapid assessment of arterial stiffness while incurring low cost have been investigated in recent years (Sato et al. 2005; Li et al. 2006; Baulmann et al. 2008). Arterial Velocity-pulse Index (AVI) and Arterial Pressure-volume Index (API) are new arterial stiffness indices measured by a cuff-based oscillometric device (PASESA AVE-1500; Shisei Datum, Tokyo, Japan). The AVI mainly reflects the stiffness of central arteries, while API mainly reflects the stiffness of the brachial artery. These indices were derived by means of quantitatively analyzing the specific characteristics of cuff oscillation waves detected at different cuff-operating pressures (Komine et al. 2012; Liang et al. 2013). So far, studies on AVI and API have been performed mainly in Japan. For example, a population-based study (468 outpatients, 85 hospitalized patients) performed at the University of Kurume demonstrated that AVI correlated strongly with the number of cardiovascular risk factors ($r = 0.62$, $P < 0.01$) in subjects not taking oral medications. Another study from Saitama Medical University (Akiyama et al. 2010) showed that both AVI and API were significantly related to the development of ischemic cardiac disease in patients with type 2 diabetes. Tazawa et al. (2016)found that increased AVI was associated with CAD and reduced exercise capacity in patients with cardiac diseases. A more recent study comprising of 252 participants (149 men and 103 women) revealed that API was independently associated with the Framingham risk score (Sasaki-Nakashima et al. 2017) .

Despite the extensive studies carried out previously, it remains unclear whether AVI and API could predict the risk of subclinical atherosclerosis in patients without significant obstructive lumen changes. Therefore, the main purpose of the present study was to investigate the correlation of AVI and API with the existence of atherosclerosis. In addition, the classical arterial stiffness index baPWV (brachial-ankle pulse wave velocity) was measured as a reference variable.

## Methods

*Patients*

This was a cross-sectional study performed on patients who underwent coronary angiography for the assessment of symptoms indicative of CAD during March, 2016 to October, 2016. The study has been approved by the local institutional review board (Medical Ethics Committee of Shanghai Ninth People's Hospital affiliated to Shanghai Jiaotong University, School of Medicine. Approval number: Hu jiuyuan lunshen [2016] No. 21) and written informed consents were received from all patients. For each patient, the medical records were reviewed to determine the coronary artery status and to collect information on patient profiles, medical history, medication use, and laboratory data. All the enrolled patients were allocated to 3 groups: the CAD group, the early atherosclerosis (AS) group, and the apparently healthy (non-AS) group. Herein, CAD was defined as the presence of a $\geq 50\%$ stenosis in at least 1 major coronary artery determined by coronary angiography or coronary computed tomography examination. Early atherosclerosis was defined as the presence of detectable coronary atherosclerotic plaques but without significant arterial stenosis that would meet the diagnosis criteria of CAD. Similarly, non-AS was defined as the absence of detectable coronary atherosclerotic plaques.

*Measurements of arterial stiffness indices*

To examine the inter-observer variability which might affect our data during the measurements, we performed a preliminary experiment in which 2 observers separately measured the AVI and API in 10 participants. Then a Reliability Analysis was performed and the Intraclass Correlation Coefficient (ICC) for AVI and API were found to be 0.875 (95% CI: 0.578-0.967, type: single absolute agreement) and 0.846 (95% CI: 0.610-0.948, type: single absolute agreement). The AVI and API were measured together with the brachial arterial blood pressures using an oscillometric blood pressure device (PASESA AVE-1500, Shisei Datum, Tokyo, Japan) before coronary angiography. A pattern diagram of the pulsewave for AVI is shown in Fig. 1 (Sueta et al. 2015). The increased AVI indicates the enhancement of reflected waves. The principles and formulas for AVI and API were previously reported by Sueta et al. (2015). The patients were in a supine position during the measurement. The measurement was performed at least twice for each patient at an interval of 2-5 minutes, with the mean of multiple measurements being recorded.

The baPWV was measured using BP-203RPEIII (Omron, Japan) 5 to 10 minutes after the measurement of the AVI and API. The mean value of the left and right baPWVs was calculated and used in the statistical analysis.

*Laboratory examinations*

Laboratory data were obtained from the medical records of all the patients, which included the level of B-type natriuretic peptide (BNP), serum creatinine (SCr), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and estimated glomerular filtration rate (eGFR).

*Statistical analysis*

All statistical data are presented for each patient cohort in the form of either mean ± standard deviation or percentage. Comparison of variables among the 3 patient groups was carried out using a one-way ANOVA (a post-hoc test of Tukey HSD or Dunnett-T3 was selected in the light of the variance homogeneity or non-homogeneity). The Chi-square test was adopted when percentage values were compared. The correlations among AVI, API, baPWV, and other variables were quantified by correlation coefficients. We used the Pearson or Spearman correlation analysis method depending on the results of the normality test for variables. For variables exhibiting an extremely large inter-patient variation (i.e., BNP), log transformation was applied prior to correlation analysis to obtain a normal data distribution. Moreover, stepwise regression analysis was conducted to determine the predictive factors of arterial stiffness indices. All probability values were calculated from a two-tailed test, with statistical significance being inferred at $P < 0.05$.

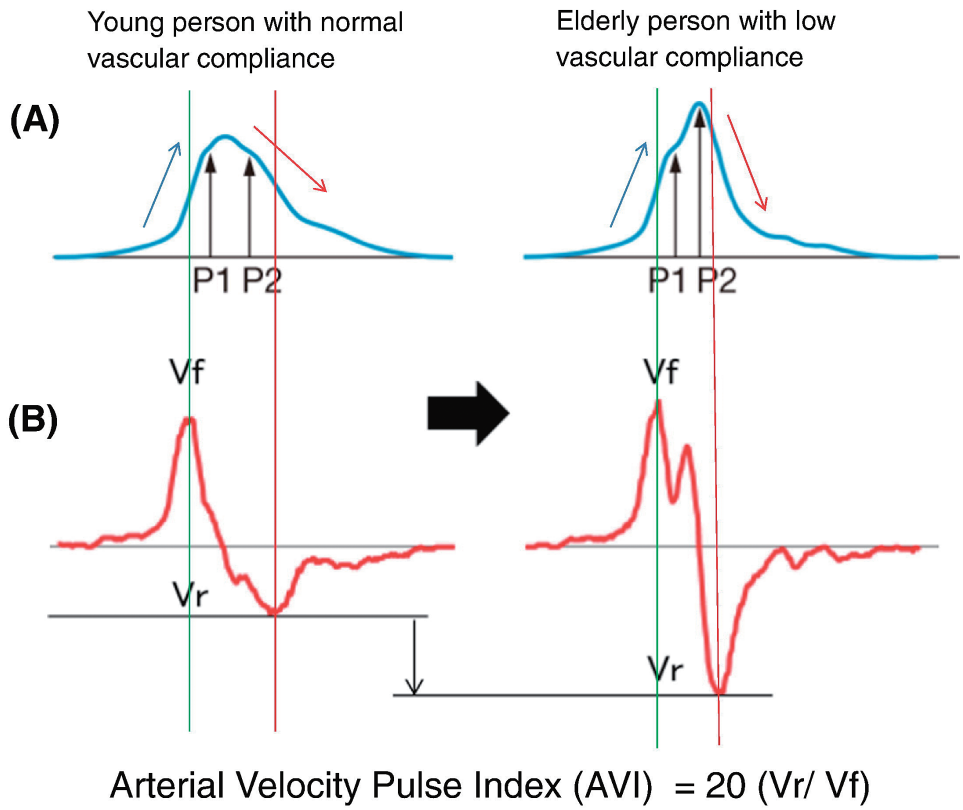


Fig. 1. Pulsewave pattern diagrams of AVI.
The diagrams were adapted from Sueta et al. (2015) Int. J. Cardiol, 189, 244-246 with permission of Elsevier. Pulsewave (A) and differentiated waveform between pulsewave and time (B) in a young person with normal-vascular compliance and an elderly person with low-vascular compliance, respectively. P1 indicates an incident wave while P2 indicates a reflected wave. Vf: the first peak of differentiated waveform between pulse wave and time which is not influenced by the reflected wave, Vr: the bottom of the trough of differentiated waveform between pulse wave and time which mainly reflect the steepness of the pressure decline after the second peak. Therefore, the ratio |Vr|/|Vf| indicates the tendency toward an increase in aortic stiffness.

## Results

*Baseline characteristics of all subjects*

A total of 183 patients were enrolled in this study, and their baseline characteristics are summarized in Table 1: 109 patients in the CAD group, 34 patients in the AS group, and 40 patients in the non-AS group. The mean age of patients did not differ significantly among the three groups (68.0 ± 10.5 years vs. 63.8 ± 8.5 years vs. 65.8 ± 13.7 years, P = 0.127).

*Differences of arterial stiffness indices among patient groups*

The results from ANOVA indicated that the AVI was significantly different among the 3 patient groups (P < 0.001). Results of multiple comparison showed that the mean values of AVI in the CAD group and the AS group were both significantly higher than that in the non-AS group (25.6 ± 6.7 vs. 19.6 ± 4.4, P < 0.001, 27.0 ± 8.4 vs. 19.6 ± 4.4, P < 0.001, respectively) (shown in Fig. 2A). However, no statistically significant difference in AVI was observed between the CAD group and the AS group (25.6 ± 6.7 vs. 27.0 ± 8.4, P = 0.750).

The results from ANOVA for baPWV revealed significant differences among the 3 patient groups (P = 0.001). The mean baPWV in the CAD group was significantly higher than that in the non-AS group (16.9 ± 3.4 vs. 14.6 ± 2.8, P < 0.001) (shown in Fig. 2B). However, no significant difference between the CAD and AS groups (16.9 ± 3.4 vs. 16.1 ± 2.9, P = 0.426) or between the AS and non-AS groups (16.1 ± 2.9 vs. 14.6 ± 2.8, P = 0.113) was found.

When the measured API values were compared among the 3 patient groups, no statistically significant difference was identified (28.0 ± 6.2 vs. 27.1 ± 7.2 vs. 25.4 ± 5.1, P = 0.071) (shown in Fig. 2C).

With regard to the interrelationships among the arterial stiffness indices, AVI and API were both correlated with baPWV (see Fig. 3).

*Results of correlation analysis and regression analysis*

Correlation analyses were performed with the data obtained from all the patients. Table 2 shows the calculated correlation coefficients between the arterial stiffness indices (i.e., AVI, API, baPWV) and other variables (Pearson's cor-

Table 1. Baseline characteristics of all patients.

| | CAD group (n=109) | AS group (n=34) | non-CAS group (n=40) | P value |
|---|---|---|---|---|
| **Demographic data** | | | | |
| Age (years) | 68.0±10.5 | 63.8±8.5 | 65.8±13.7 | 0.127 |
| Sex (m/f %) | 64.2/35.8 | 41.2/58.8 | 37.5/62.5 | 0.004** |
| BMI (kg/m²) | 25.5±3.2 | 25.2±3.3 | 23.5±3.5 | 0.007** |
| SBP (mmHg) | 127.9±16.9 | 127.3±21.5 | 120.0±16.4 | 0.054 |
| PP (mmHg) | 55.4±14.7 | 56.4±18.4 | 53.0±15.2 | 0.613 |
| MAP (mmHg) | 91.0±12.7 | 89.7±11.8 | 84.7±9.3 | 0.018* |
| **Laboratory data** | | | | |
| eGFR (ml/min/1.73m$^2$) | 73.4±28.0 | 80.4±22.3 | 72.3±23.1 | 0.373 |
| BNP (pg/ml)† | 1.8±0.5 | 1.7±0.5 | 1.8±0.4 | 0.326 |
| CHOL (mmol/l) | 4.2±1.1 | 4.5±0.9 | 4.0±0.9 | 0.095 |
| TG (mmol/l) | 1.8±1.1 | 1.9±1.0 | 1.4±1.1 | 0.147 |
| LDL-C (mmol/l) | 2.6±0.9 | 2.9±0.7 | 2.5±0.8 | 0.175 |
| HDL-C (mmol/l) | 0.9±0.3 | 1.0±0.3 | 1.1±0.3 | 0.062 |
| **Comorbidity** | | | | |
| Hypertension (%) | 74.3 | 67.6 | 52.5 | 0.04* |
| Diabetes (%) | 32.1 | 26.5 | 25.0 | 0.001** |
| Stroke history (%) | 22.0 | 14.7 | 17.5 | 0.598 |
| **Medication** | | | | |
| Antihypertensive drugs (%) | 75.2 | 58.8 | 37.5 | <0.001*** |
| ACEI/ARB (%) | 61.5 | 47.1 | 32.5 | 0.006** |
| Ca antagonist (%) | 33.9 | 23.5 | 15.0 | 0.060 |
| Diuretics (%) | 13.8 | 17.6 | 10.0 | 0.633 |
| Beta blockers (%) | 56.9 | 41.1 | 45.0 | 0.184 |
| Anti-diabetic drugs (%) | 17.4 | 5.9 | 0.0 | 0.001** |
| Lipid-lowering drugs (%) | 96.3 | 85.3 | 17.5 | <0.001*** |

SBP, brachial systolic blood pressure; DBP, branchial diastolic blood pressure; MAP, mean blood pressure; PP, brachial pulse pressure; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; CHOL, cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACEI, angiotensin converting enzyme inhibitor. ARB, angiotensin receptor blocker.
Data are presented as mean ± SD (standard deviation), median (interquartile range), or percentage.
The antihypertensive drugs contain all of ACEI / ARB, Ca antagonists, diuretics, and beta blockers. *P < 0.05. **P < 0.01, ***P < 0.001, †log transformed.

relation analysis was performed for the log transferred BNP, while Spearman's correlation analysis was used for other variables). The values of AVI, API, and baPWV all correlated positively with age, brachial systolic blood pressure (SBP), and pulse pressure (PP). Strong correlations were observed especially between API and PP, and between API and SBP. The AVI and baPWV were inversely related to eGFR.

Stepwise regression analysis was carried out to identify the associated factors of AVI and baPWV which have been found to differ significantly between the CAD group and the non-AS group. The results showed that BNP was the primary independent factor of AVI, followed by baPWV and pulse pressure, and that AVI was the primary independent factor of baPWV, followed by pulse pressure and eGFR (see Table 3).

## Discussion

Previous studies have demonstrated that the AVI is associated with the number of cardiovascular risk factors, the Framingham risk score (Sasaki-Nakashima et al. 2017) and CAD (Tazawa et al. 2016). The predictive value of AVI in ischemic cardiac disease has also been confirmed in patients with type 2 diabetes mellitus. However, the relationship between AVI and early atherosclerosis remains to be determined, which is a key issue when discussing the

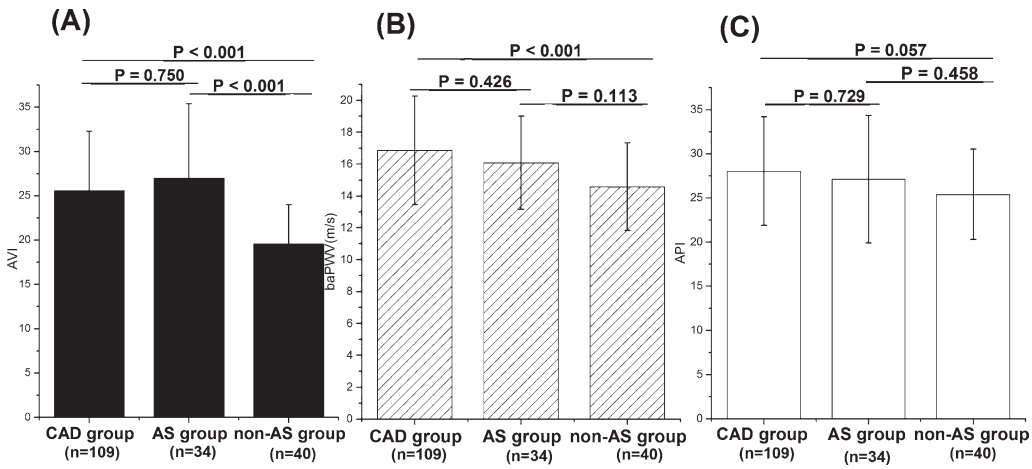


Fig. 2. Differences in AVI, baPWV, and API among CAD, AS, and non-AS groups.
Compared were the values of AVI (A), baPWV (B), and API (C) among the CAD group, the AS group, and the non-AS group. The AVI values were significantly lower in the non-AS group than in the AS group and the CAD group. BaPWV values were higher in the CAD group than the non-AS group, whereas there was no significant difference between the CAD group and the AS group, or between the AS group and the non-AS group. The inter-group differences in API values were not statistically significant among the three patient groups.

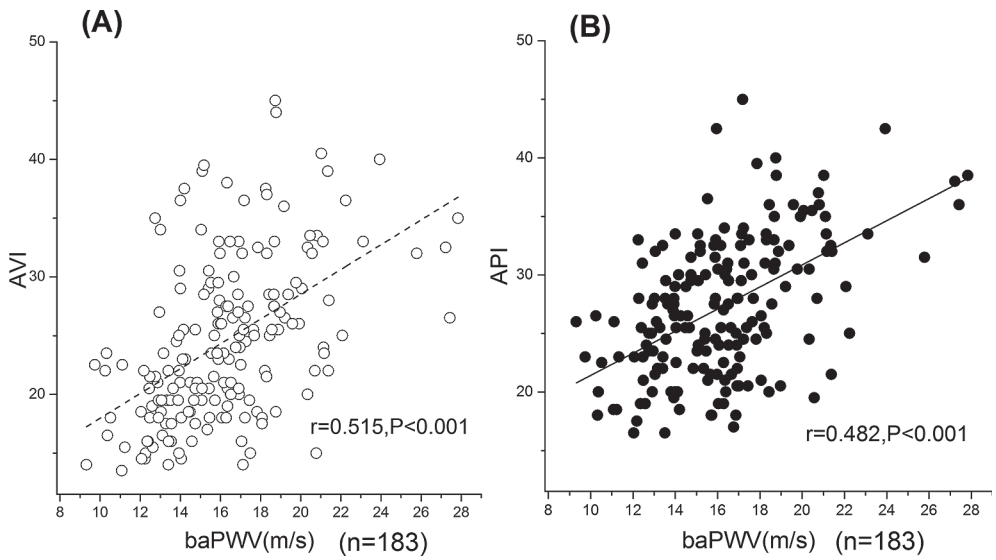


Fig. 3. Correlation between AVI or API and baPWV.
A. Correlation between AVI and baPWV. B. Correlation between API and baPWV.
The AVI and API were both significantly correlated with baPWV in a total of 183 patients.

value of AVI in preventive medicine. Our results for patients with CAD were basically consistent with those reported in previous studies. A new finding was that AVI values were significantly higher not only in the CAD group but also in the AS group in comparison with those in the non-AS group. This implies that increased AVI may be indicative of early atherosclerosis or CAD. It was interesting to find that baPWV, as a standard measure of arterial stiffness, could not predict the presence of early atherosclerosis, although its predictive value in CAD was confirmed in our study.

With regard to API, there have been some reports of the association of API with cardiovascular disease or Framingham risk score. In our study, however, no statistically significant difference was observed among the 3 patient groups. A potential explanation for this discrepancy is that the small patient sample of our study may have increased the uncertainty of the statistical analysis of the relationship between API and early atherosclerosis. Another explanation is that the patient cohort investigated and the criteria of patient grouping differed between our study and other studies. Our study focused on hospitalized patients with symptoms indicative of AS, while previous studies involved outpatients regardless of the presence or absence of indications of AS. Recalling the mechanisms underlying the measurement of AVI and API, these 2 indi-

Table 2. Correlations among arterial stiffness indices (AVI, API and baPWV) and other variables.

| | AVI† | | API† | | baPWV† | |
|---|---|---|---|---|---|---|
| | r | P value | r | P value | r | P value |
| Age (years) | 0.326 | <0.001*** | 0.236 | 0.001 | 0.228 | 0.002** |
| BMI (kg/m²) | NS | NS | 0.151 | 0.041 | NS | NS |
| PP (mmHg) | 0.432 | <0.001*** | 0.711 | <0.001 | 0.436 | <0.001*** |
| SBP (mmHg) | 0.428 | <0.001*** | 0.735 | <0.001 | 0.465 | <0.001*** |
| BNP (pg/ml)† | 0.23142 | 0.003 ** | NS | NS | NS | NS |
| eGFR (ml/min/1.73m$^2$) | −0.228 | 0.003 ** | NS | NS | −0.303 | <0.001** |

SBP, brachial systolic blood pressure; DBP, branchial diastolic blood pressure; MAP, mean blood pressure; PP, brachial pulse pressure; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate. **P <0.01, ***P<0.001. †log transformed.

Table 3. Stepwise regression of AVI & baPWV and associated variables.

| | Independent variables | β | t | P value |
|---|---|---|---|---|
| AVI[1] | PP | 0.160 | 4.772 | <0.001 |
| | baPWV | 0.721 | 4.824 | <0.001 |
| | BNP† | 1.866 | 1.985 | 0.049 |
| baPWV[2] | AVI | 0.172 | 5.211 | <0.001 |
| | PP | 0.039 | 2.576 | 0.011 |
| | eGFR | −0.020 | −3.174 | 0.002 |

[1]Adjusted R-squared value = 0.339, P < 0.001; [2]Adjusted R-squared value = 0.295, P < 0.001. †log transformed.

ces reflect the regional arterial stiffness of the central aorta and the local arterial stiffness of the peripheral artery, respectively. Central aortic stiffness is generally considered to be more valuable than peripheral arterial stiffness in predicting primary coronary events (Boutouyrie et al. 2002; Mattace-Raso et al. 2006). In particular, API seemed more sensitive to the level of blood pressure which was indicated by the strong positive correlation between API and PP, and between API and SBP. For the patients enrolled in the present study, ACEI/ARB and/or calcium antagonists were routinely prescribed to treat hypertension during hospitalization. Therefore, the decrease in API secondary to a decrease in blood pressure as a consequence of anti-hypertensive treatment may have compromised the analysis on the association between API and CAD.

Used as a reference index, our results showed that baPWV was similar to AVI in predicting the risk of CAD. However, baPWV failed to predict early atherosclerosis. A potential explanation for this phenomenon is that baPWV, by its measurement principle, reflects the regionally averaged stiffness of arteries located between the brachial and ankle arteries, which compromises its sensitivity in capturing the changes in central arterial stiffness (Vlachopoulos et al. 2015).

Any noninvasively determined arterial stiffness index would be potentially influenced by multiple bio-factors due to the high nonlinearity of systemic hemodynamics (Liang et al. 2013). Correlation analysis and stepwise regression analysis revealed that AVI was positively related to age, PP, SBP and BNP. Advanced age, increased PP and SBP are well documented risk factors for cardiovascular events (Darne et al. 1989; Tokitsu et al. 2015), while increased BNP level is a strong predictor of cardiac dysfunction (Goetze et al. 2003; McLean et al. 2003). In this sense, AVI may be an integrated embodiment of several indicators of cardiovascular disorders.

The study is subject to several limitations. Firstly, this is a single center observational study enrolling a relatively small population with symptoms indicative of AS, which may partly account for the discrepant findings for API. The prognostic value of AVI and API for cardiovascular diseases remains to be confirmed in a larger population with a long-term follow up. Secondly, most patients involved in our study took a variety of cardiovascular medications, such as anti-diabetic, lipid-lowering, and anti-hypertensive medications. It is unclear how such medications would affect the biomechanical properties of the cardiovascular system and the readings of arterial stiffness measurement. To clarify the issue, well-devised longitudinal clinical trials would be required.

In summary, we have provided the first evidence of the predictive value of the new arterial stiffness index AVI for early atherosclerosis. Fully automatic and rapid measurement may enhance the practical value of adopting the indices in primary care prevention to identify subjects at high risk of atherosclerosis through large population screening. However, further studies are awaited to extensively validate the clinical utility of the indices in larger patient cohorts.

## Acknowledgments

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## Conflict of Interest

The authors declare no conflict of interest.

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