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# A new peripheral endothelial function measurement improves prediction of symptomatic coronary artery disease

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## Abstract

**Objective:** This study aimed to determine whether a peripheral artery volume (PAV) test can improve the predictive value of the age-adjusted Framingham risk score (AFRS) for coronary artery disease (CAD) in symptomatic patients.

**Methods:** A total of 317 consecutive patients who were referred for coronary angiography were prospectively enrolled. Before cardiac catheterization, a PAV test was performed to measure changes in pulsatile blood flow volume following reactive hyperemia.

**Results:** PAV was significantly lower in patients with CAD than in those without CAD ($1.21 \pm 0.32$ vs. $1.50 \pm 0.45$). Multivariate logistic regression analysis showed that PAV and the AFRS were independent predictors of CAD. Pairwise comparison of receiver operating characteristic curves showed that the predictive power for CAD increased when PAV was incorporated into the AFRS (area under the curve: from 0.76 to 0.80). The net reclassification index was also improved when PAV was added to the AFRS (0.65, 95% confidence interval: 0.44–0.85).

**Conclusions:** Digital endothelial function measurement is an independent predictor of CAD. PAV is potentially useful for identifying patients at high risk for CAD.

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## Background

Coronary artery disease (CAD) is the leading cause of death worldwide. Nearly half of healthy 40-year-old men and one in three healthy 40-year-old women will develop CAD in the future, according to present trends in the USA.[1] Guidelines recommend the age-adjusted Framingham risk score (AFRS) or other similar models for predicting multivariate cardiovascular disease risk.[2] However, although traditional risk factors are important predictors for cardiovascular events, patients with limited or without traditional risk factors can still suffer from a process of initiation and progression of CAD. Therefore, the current risk assessment may not be sufficient.[3] Endothelial dysfunction contributes to each phase of atherosclerosis and has additional predictive value for cardiovascular events. This indicates that assessment of endothelial function might provide additional diagnostic information regarding the presence of CAD beyond risk scores alone.[4]

Measurement of changes in digital pulse volume due to reactive hyperemia is an effective and convenient method of evaluating endothelial function. Moreover, peripheral artery volume (PAV) technology is a newly developed method for quantifying peripheral endothelial function during reactive hyperemia.[5] The basic principle of PAV is the same as that of peripheral arterial tonometry (PAT). PAT technology assesses the arterial pulse wave amplitude of the finger by a pressure sensor, while PAV records pulsatile hemoglobin flow as a surrogate for blood flow volume with a photoplethysmographic finger probe. Only arterial absorbance of hemoglobin from the total signal is extracted because the calculation is made by the change in absorbance over time.[6] Importantly, the effect of local venous distension caused by cuff inflation can be avoided with the PAV test. Therefore, pneumatic finger probes, which are used in the PAT test and are thought to be weak and disposable,[7] are not included in the PAV system. The reusable finger probes in the PAV technique may be helpful for daily use or screening in a large population.

Our previous study showed that peripheral endothelial function as measured by PAV was correlated with cardiovascular risk factors[5] However, the clinical value of PAV and established risk factors in identifying patients with CAD are still unknown. Therefore, we designed this study to investigate the relationship between the AFRS and PAV, and to evaluate the predictive value of PAV for the presence of CAD in patients with chest pain or discomfort.

## Methods

### *Patients and setting*

Consecutive consenting patients with recent chest pain or discomfort who were scheduled to undergo coronary angiography (CAG) were included in the study between May 2017 and November 2017. The principal exclusion criteria were age

<35 or >75 years, acute coronary syndrome, significant valve disease, cardiomyopathy, Raynaud's disease, atrial fibrillation, chronic respiratory disease, kidney disease, and active autoimmune disease. The study was approved by the ethical review board of The Third Hospital of Jilin University (No. 2017040603) and strictly conformed to the ethical guidelines of the Helsinki Declaration. Written informed consent was signed by the patients before enrollment in the study. This prospective, observational, single-center study was registered (April 22, 2017) with the Chinese clinical trial registry (ChiCTR-DDD-17011214).

A total of 402 patients were initially assessed for the study. Of these, 18 patients with left ventricular dysfunction, 22 with acute coronary syndrome, 4 with significant valvular heart diseases, 10 with chronic pulmonary disease, 6 with chronic kidney disease, and 25 who refused to participate were excluded (Figure 1).

Significant CAD was defined as ≥50% luminal narrowing in one or more major branches as determined by CAG. The CAG result was interpreted by cardiologists who were blinded to the noninvasive study data. The AFRS was calculated by the method described by Wilson et al.[8] and provided the 10-year relative risk of coronary heart disease. The defining risk factors included age, cigarette smoking, systolic blood pressure, diabetes mellitus, total cholesterol levels, and high-density lipoprotein (HDL) cholesterol levels.

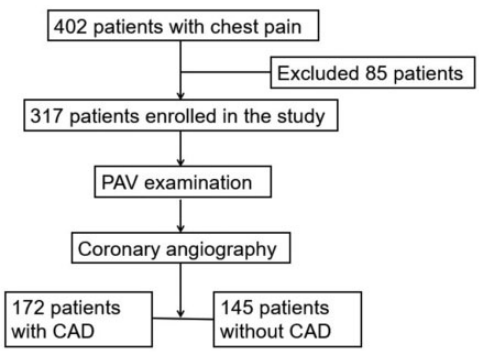


**Figure 1.** Flow chart of selection of patients in the study.

## PAV testing

The PAV test was performed in the early morning before the planned CAG. The patients were instructed to refrain from vasoactive medication, food, caffeine, tea, tobacco, or exercise for at least 12 hours before measurement. The basic principle of PAV is similar to that of PAT. The device for measuring PAV (Saintyear Medical Ltd., Shenzhen, China) consists of two photoplethysmography-based index finger probes. The pulsatile volume changes were assessed by a light-sensitive sensor in conjunction with light-emitting diodes (940 nm).

The PAV method has been described previously.[5] With the patient in the supine position, a blood pressure cuff was placed on the upper arm for undergoing testing of hyperemia, while the contralateral arm served as a control. PAV probes were placed on the index finger of each hand. After a baseline stabilization period of 5 minutes, the cuff was inflated to 50 mmHg above the patient's resting systolic blood pressure for 5 minutes. Following deflation of the cuff, the induced reactive hyperemia was recorded for another 5 minutes. The reactive PAV index was defined as the ratio of the mean pulse wave amplitude (PWA) over a 40-s period beginning after 40 s of reactive hyperemia, divided by the baseline mean PWA over a 40-s period beginning after 40 s of preocclusion baseline. The result of PAV was then calculated by a computer algorithm and automatically normalized to the contralateral arm. To evaluate reproducibility of measurements, a repeated test was performed in 24 patients 2 hours after the initial test.

### *Statistical analysis*

Data are presented as the mean ± standard deviation. The unpaired t-test was used to assess differences between continuous variables. The reproducibility of PAV results was assessed by the intraclass correlation coefficient. The association between PAV and the AFRS was evaluated by least squares linear regression analysis. Univariate logistic regression analysis was performed to assess the associations between cardiovascular risk factors and the presence of CAD. Multivariate logistic regression analysis was used to assess the independent risk predictors for the presence of CAD. Receiver operating characteristic (ROC) curves were generated for the AFRS and PAV to assess their predictive power for CAD, and the areas under curves (AUCs) were compared with a non-parametric approach procedure as described by DeLong et al.[9] Additionally, the net reclassification index (NRI) was used to assess the increased predictive value after adding PAV to the AFRS. All analyses were performed by standard statistical software (SPSS version 17.0, SPSS Inc., Chicago, USA; MedCalc 14.0, MedCalc Software, Mariakerke, Belgium; and R 3.4.4, R Foundation for Statistical Computing, Vienna, Austria). P values $\leq 0.05$ were considered indicative of statistical significance.

## Results

### *Patients' characteristics and reproducibility of test results*

The baseline characteristics of the 317 patients included in the study are shown in Table 1. The mean age was 65 ± 9 years and 228 (71.9%) patients were men. The mean AFRS and PAV were 8.7% ± 4.5% and 1.34 ± 0.41, respectively. A total of 172 (54.3%) patients had CAD on CAG. The patients with CAD had a significantly higher mean AFRS (10.5% ± 4.2% vs 6.5 ± 3.9%) and lower PAV index (1.21 ± 0.32 vs 1.50 ± 0.45) than those without CAD (both P<0.001).

**Table 1.** Baseline patients' characteristics and univariate logistic regression analysis for the presence of CAD.

| Characteristic | Value | OR | 95%·CI | P |
|---|---|---|---|---|
| Age (years) | 65±9 | 0.89 | 0.84–0.95 | <0.001 |
| Male sex | 228 (71.9) | 3.71 | 2.71–6.10 | <0.001 |
| Body·mass·index·(kg/m$^2$) | 24.9±·3.7 | 1.01 | 0.96–1.01 | 0.66 |
| Hypertension | 166 (52) | 0.441 | 0.17–1.15 | 0.09 |
| Family history·of CAD | 94 (30) | 1.70 | 0.75–3.88 | 0.20 |
| Current·smoking | 146 (46) | 0.57 | 0.24–1.35 | 0.20 |
| Diabetes mellitus | 75 (24) | 1.30 | 0.43–3.92 | 0.63 |
| Hypercholesterolemia | 88 (28) | 0.17 | 0.05–0.57 | 0.004 |
| Systolic·blood pressure·(mmHg) | 142±27 | 1.04 | 1.02–1.07 | 0.001 |
| Total cholesterol·(mmol/L) | 4.5±1.1 | 0.78 | 0.46–1.33 | 0.36 |
| HDL cholesterol (mmol/L) | 1.1±0.5 | 5.64 | 1.93–16.5 | 0.002 |
| AFRS·(%) | 8.7±4.5 | 1.94 | 1.53–2.48 | <0.001 |
| PAV·index | 1.34±·0.41 | 0.07 | 0.02–0.22 | <0.001 |

Values are presented as mean ± standard deviation or number (%). CAD: coronary artery disease, HDL: high-density lipoprotein, LDL: low-density lipoprotein, AFRS: age-adjusted Framingham risk score, PAV: peripheral artery volume, OR: odds ratio, and CI: confidence interval.

Twenty-four patients completed the repeated PAV test for reproducibility. There was no significant difference between the results of the two tests ($1.23 \pm 0.28$ vs. $1.24 \pm 0.30$, $P = 0.80$), and the intraclass correlation coefficient was 0.76.

### *Relationship between PAV and cardiovascular risk factors*

The PAV index was significantly lower in patients with hypertension ($1.23 \pm 0.35$ vs $1.43 \pm 0.44$, $P<0.001$), hypercholesterolemia ($1.22 \pm 0.37$ vs $1.39 \pm 0.42$ $P = 0.003$), diabetes mellitus ($1.25 \pm 0.37$ vs $1.37 \pm 0.42$ $P = 0.02$), current smoking ($1.27 \pm 0.40$ vs $1.40 \pm 0.41$ $P = 0.006$), or a family history of CAD ($1.25 \pm 0.31$ vs $1.38 \pm 0.44$ $P = 0.008$) than in those without such cardiovascular risk factors. Least squares linear regression analysis showed a significant inverse correlation between PAV and the AFRS ($r = -0.19$, $P = 0.001$; Figure 2).

### *Factors associated with CAD*

In univariate logistic regression analysis, older age, male sex, hypercholesterolemia, higher systolic blood pressure, lower HDL cholesterol levels, a higher AFRS, and a lower PAV index were significantly associated with the presence of CAD (all $P<0.01$; Table 1). Multivariate logistic regression analysis showed that the AFRS and PAV index were independent predictors for the presence of CAD (both $P<0.001$; Table 2).

**Table 2.** Multivariate logistic regression analysis for the presence of coronary artery disease.

| | OR | 95% CI | P |
|---|---|---|---|
| AFRS (%) | 1.28 | 1.19–1.38 | <0.001 |
| PAV index | 0.16 | 0.08–0.35 | <0.001 |

AFRS: age-adjusted Framingham risk score, PAV: peripheral artery volume, OR: odds ratio, and CI: confidence interval.

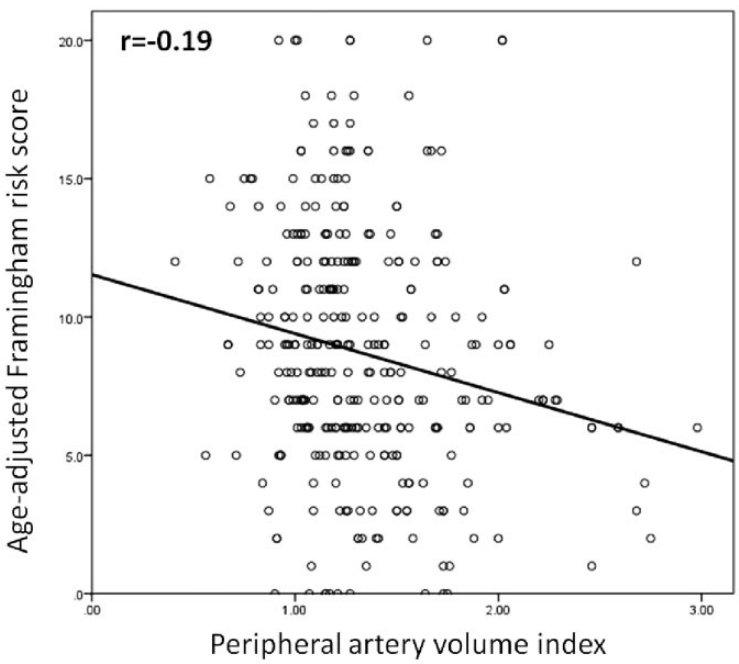


**Figure 2.** Interrelationship between peripheral artery volume and the age-adjusted Framingham risk score.

### *Prediction of CAD*

The AUCs for the AFRS and PAV were 0.76 (95% CI 0.71–0.81, P = 0.02) and 0.70 (95% CI 0.65–0.75, P = 0.03), respectively, for predicting CAD (Figure 3). The cut-off value of PAV was 1.31 (sensitivity, 76.2%; specificity, 62.8%). Pairwise comparison showed that the AUC of the AFRS was significantly higher than that of PAV (Z = 1.54, P = 0.04). The combined parameters of the AFRS plus PAV were used to evaluate the incremental effect of adding PAV for predicting CAD. The AUC of the AFRS plus PAV was 0.80 (95% CI 0.75–0.84, P = 0.02; Figure 3). Pairwise comparison of the ROC curves showed that the AUC of the AFRS plus PAV was significantly higher than that of the AFRS (Z = 2.13, P = 0.03). The NRI was also significant with addition of PAV to the AFRS (0.65, 95% CI: 0.44–0.85, P<0.001).

## Discussion

We performed this study to assess the feasibility of measuring peripheral endothelial function by the new PAV test to predict the presence of CAD in patients with chest pain or discomfort. Our study showed that the PAV index was lower in patients with CAD than in those without CAD. Although the AFRS was a better predictor of the presence of CAD than PAV, the predictive power of a combination of these parameters (AFRS plus PAV) was better than that of either the AFRS or PAV alone. These findings suggest that peripheral endothelial function as assessed by PAV has clinical value for discriminating patients with CAD.

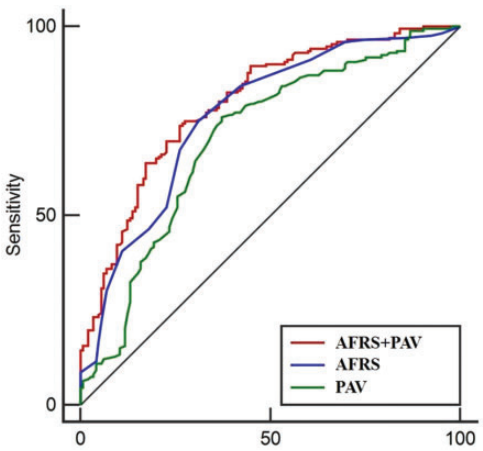


**Figure 3.** Receiver operating characteristic curves of PAV, the AFRS, and the AFRS plus PAV for prediction of coronary heart disease. AFRS: age-adjusted Framingham risk score, PAV: peripheral artery volume.

Many studies have shown that impaired endothelial function initiates progression of atherogenesis and that endothelial dysfunction is a powerful independent predictor of future cardiovascular events in individuals with heart disease.[10,11] In the current clinical setting, measurement of endothelial function is often used daily or in large patient populations, and thus should be noninvasive and easy to perform.[12] In recent years, several noninvasive methods have been developed based on the same principle of reactive hyperemia.[13–16] The PAT technique is an automatic and operator-independent method, and this technique has gained increasing attention.[17,18] Assessment of the peripheral vasodilator response is a promising method of evaluating peripheral endothelial function. The PAV technique is a newly developed method based on the same principle and is also user-friendly, automatic, and operator independent; additionally, the contralateral arm serves as an internal control.[5] Unlike PAT, PAV uses a photoplethysmography-based index finger probe to measure changes in digital arterial volume accompanied by pulse waves. Because blood volume in the veins and arteriovenous anastomoses is relatively constant, the change in arterial absorbance of hemoglobin can be extracted from the total signal. Therefore, PAV is likely to be a proxy only for arterial distensibility of the vascular digital district.

Similar to the PAT test,[19,20] PAV measurement had an acceptable reproducibility (intraclass correlation coefficient = 0.76) in the current study.

The Framingham Heart Study showed that brachial and digital measurement of vascular function had differing relationships with cardiovascular risk factors and might reflect distinct aspects of endothelial function.[17,21] Similar to PAT reported in this previous study, peripheral endothelial function measured by PAV was also associated with hypertension, smoking, diabetes, hypercholesterolemia, and a family history of CAD in our study. Furthermore, PAV was reduced in patients with established CAD, which is consistent with our previous study.[5] As a conventional predictor of the risk of CAD, the AFRS shows a strong positive correlation with the prevalence of significant CAD.[22] In the present study, we adopted the AFRS as the baseline model to assess the probability of CAD before CAG. A significant inverse correlation was identified between PAV and the AFRS. However, the r value was 0.19, which is considerably lower than that reported between flow-mediated dilation (FMD) and the AFRS ($r = -0.43$).[23] This discrepancy between findings is most likely because PAV and FMD reflect distinct information on vascular function.

In this study, multivariate logistic regression analysis showed that PAV and the AFRS were independent predictors of CAD, which is consistent with previous studies on FMD and PAT.[23–25] This result suggested that peripheral endothelial function as measured by PAV could be a predictor of CAD in patients with chest pain. In ROC curve analysis, the AFRS was more powerful than PAV in detecting the presence of CAD, which indicated the importance of conventional risk factors for CAD in the clinical setting. However, adding PAV to the AFRS significantly improved the predictive power and risk stratification, as shown by comparison of the ROCs and the NRI. This finding suggests that PAV has additional predictive value for CAD in symptomatic patients. PAT was also reported to improve risk stratification when added to traditional risk factors, while FMD did not show a similar benefit.[23,24,26] Therefore, peripheral endothelial function measured on the finger might provide additional information for measurement on the brachial artery.

There are some limitations to this study. First, medication may affect endothelial function. However, the patients were instructed to refrain from vasoactive medication, food, or exercise for at least 12 hours before the study. Second, the AFRS is a well-established tool for predicting 10-year cardiovascular risk, but it was not designed for predicting the presence of CAD. Third, although our study was prospectively designed and blinded to the physician interpreting the CAG results, selection bias might have affected the study because all patients who were enrolled were clinically suspected to have CAD. We do not recommend using PAV to predict the severity of coronary artery disease. Assessing the severity of coronary stenosis should be cautiously performed by coronary computed tomography angiography or CAG.

## Conclusion

This prospective study shows that, in symptomatic patients referred for CAG, peripheral endothelial function as assessed by the new PAV test is an independent predictor of CAD beyond traditional risk factors. PAV shows improved predictive power in the AUC and NRI when added to the AFRS. Therefore, the PAV test as a simple, rapid, and accurate bedside method is potentially useful for identifying patients at high risk for CAD.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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