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Reproducibility of a new method to assess endothelial function by peripheral arterial volume

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Abstract:

Background:

The assessment of endothelial function is crucial in understanding the progression of cardiovascular disease. It is important to have reliable and convenient non-invasive methods for evaluating endothelial function. Peripheral arterial volume (PAV) measurement at the fingertip is a novel approach, but there is limited data on its reproducibility. Hence, this study aims to evaluate the reproducibility of PAV measurement in a clinical setting.

Method:

A total of 152 consecutive patients (average age 55.8±12.3, 83 males) with chest pain were included in the study. PAV tests were conducted on separate days. The amplitude ratio before and after applying pressure, along with the reference ratio, were recorded to calculate PAV. Medical baseline data for these patients were gathered from the hospital's records.

Result:

On test days, the PAV results were 1.15±0.33 and 1.15±0.31 (p=0.99), indicating no significant difference between the two measurements in all subjects. The mean difference was 0.00±0.32, showing no systematic errors, and the intraclass correlation coefficient was 0.66. Furthermore, age, sex, and BMI did not influence the reproducibility of PAV.

Conclusion:

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PAV measurement is not only feasible but also exhibits excellent reproducibility among all the enrolled patients. As a novel fingertip measurement, PAV holds promise for providing a convenient and accurate assessment of endothelial function in adults.

Keywords:

endothelial function, peripheral arterial volume, cardiovascular, reproducibility

Abbreviation

coronary artery disease: CAD

intraclass correlation coefficient: ICC

flow mediated dilation: FMD

periphrial artiral volume: PAV

Introduction:

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Coronary artery disease is associated with several significant risk factors, and endothelial dysfunction is a critical factor in the development of atherosclerosis and cardiovascular events [1]. As non-invasive methods continue to advance, there is a growing need for more convenient and accurate tools to evaluate endothelial function. One commonly used approach to identify patients at risk of cardiovascular issues is flow-mediated dilation (FMD). However, despite its gold standard status in non-invasive testing, FMD has certain limitations when it comes to reproducibility [2].

FMD primarily relies on assessing changes in arterial diameter [3]. The reproducibility of FMD may vary due to differences in detection techniques, measurement locations, and the hardening of arteries, which can impact their ability to dilate. Recent developments in fingertip non-invasive detection techniques have emerged as a promising alternative to overcome the limitations of high-resolution ultrasound assessments of brachial artery flow-mediated dilation. One such technique is peripheral arterial volume (PAV) [4]. *The underlying principle of PAV is similar to that of FMD, but it utilizes a different approach than traditional ultrasound methods to assess vascular endothelial function. PAV employs a photo-plethysmographic fingertip probe to record pulsatile hemoglobin flow, measuring changes in digital arterial volume. This is achieved using light-emitting diodes (940 nm) and a light-sensitive*

sensor to evaluate hemoglobin absorbance, ultimately calculating the PAV value based on the difference in digital artery hemoglobin flow before and after occlusion of an upper limb. Notably, PAV minimizes the impact of local venous dilation, and its fingertip probe can be reused multiple times, enhancing its reproducibility in individuals with coronary heart disease and the general population. Despite the increasing number of recent studies, there remains limited data on the reproducibility of PAV measurements. Therefore, the purpose of this study is to evaluate the reproducibility of PAV in a real clinical setting.

Methods:

Study participants

A total of 152 patients presenting with chest pain and admitted to the hospital were included in this study. Their ages ranged from 31 to 80 years. Exclusion criteria comprised acute coronary syndrome, cardiac insufficiency, persistent atrial fibrillation, severe valvular heart disease, Raynaud's disease, and chronic respiratory, endocrine, and renal conditions, as well as participation in another clinical trial that was not suitable for this study. The study protocol adhered to the ethical principles outlined in the Helsinki Declaration and received approval from the ethical review board of China-Japan Union Hospital of Jilin University.

The study has also been registered with the Chinese Clinical Trial Registry (ChiCTR-DDD-17011214). All patients provided written informed consent.

Study design:

The study was conducted at the China-Japan Union Hospital of Jilin University Follow-up Center for Cardiology. The PAV technique was employed to assess endothelial function in all patients. While similar in theory to PAT, the PAV technique records hemoglobin flow before and after occlusion of brachial blood flow, as detected by photo-plethysmographic probes. It is based on changes in peripheral arterial volume that are reflected by monitoring pulsatile hemoglobin flow. Prior to the testing days, patients were instructed to abstain from food, cigarettes, coffee, or tea and to rest in a quiet environment for a minimum of 5 minutes. They were also advised to avoid medications that could affect vascular activity, such as nitroglycerin. *Clinical participants with chest pain were selected for the study, while those with acute coronary syndrome, cardiac insufficiency, atrial fibrillation, severe valvular heart disease, Raynaud's disease, and chronic respiratory, endocrine, and kidney diseases were excluded.*

The data collection process involved recording 2-minute baseline amplitude data, inflating the cuff to 180 mmHg, maintaining the occlusion for 3 minutes, and then deflating the cuff. Subsequently,

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2-minute hyperemia reactive data were recorded. The final PAV was calculated by comparing the data before and after pressurization, as well as the baseline amplitude data. To establish the reproducibility of PAV, each patient underwent two measurements under the same conditions on the same day. Medical baseline data for all enrolled patients were obtained from the inpatient system. *The results of the two measurements and patient characteristics, including age, sex, weight, BMI, systolic pressure, and diastolic pressure, were expressed as mean ± standard deviation. Additionally, patients were divided into subgroups based on age (≥60 years), sex, and BMI (≥28 kg/m^2), and differences between these subgroups were analyzed to assess the reproducibility of PAV.*

Evaluation of periphrial artiral volume:

PAV measurements were conducted by a single examiner, with each participant undergoing two assessments by the same examiner. Participants were instructed to lie flat on a bed, place the cuff on their left arm, positioning it 2 cm above the elbow joint, and attach the PAV probes to the fingertips of both index fingers. The PAV device features an optical plethysmograph that detects changes in the quantity of pulsating hemoglobin under uniform pressure applied to the surface of the finger. The PAV measurement process involved inflating the cuff to a pressure 60 mmHg above the systolic pressure, resulting in a 3-minute occlusion of blood flow on the pressurized side. Following the occlusion, the cuff was

rapidly deflated, inducing reactive congestion, and the PAV signal was recorded from both fingertips. An additional 2 minutes of measurement was performed on the non-pressurized fingertip as a control. The PAV value was automatically calculated by the instrument's terminal.

Statistical analysis:

The reproducibility of PAV was assessed in terms of reliability and consistency [5]. *The intraclass correlation coefficient (ICC) was calculated as $SD_b/(SD_b+SD_w)$, where SD_b and SD_w represented the between and within standard deviations of the two measurements, respectively. An ICC value greater than 0.6 was considered indicative of good reliability* [6]. Bland-Altman analysis and the coefficient of variation (CV) were used to evaluate the relationship between the means and differences of the two measurement results. Subsequently, a 95% confidence interval was calculated to assess the consistency of PAV. *The Bland-Altman method illustrated the relationship between differences in PAV1 and PAV2 by plotting the differences of the two repeated measurements against their mean value. To better compare the variability of the two measurements, the CV was calculated as 100 times (standard deviation of the paired differences divided by the overall mean divided by the square root of 2), and expressed as a percentage.*

~~*The results of twice measurements and all of the characteristics with patients:age, sex, weight, BMI, systolic pressure, diastolic pressure were*~~

~~*expressed on mean ± standard deviation,in addition,we divided patients into subgroups using age(60 years),sex,BMI(28kg/m²),*~~ ICC values within each subgroup were compared between the two measurements. Statistical significance was determined using paired t-tests or proliferation and inspection, with p-values less than 0.05 considered significant. All statistical analyses were performed using SPSS 25.

Results:

Patient characteristics：

Table 1. Baseline Patient Characteristics

Variable	n =152
Age (year)	55.8±12.3
Male sex (%)	83(55)
Height (cm)	164.7±7.2
Weight (kg)	67.9±12.7
Body mass index (kg/m^2)	25.0±4.7
Systolic blood pressure (mm Hg)	117.5±19.4
Diastolic blood pressure (mm Hg)	79.2±17.5
Heart rate (beats per minute)	73.4±11.3

Values are presented as mean ± SD or number (%)

A total of 152 patients (55% male) were included in this study. Table 1 presents the demographic information of the participants, which includes age, sex, height, weight, BMI, systolic blood pressure, diastolic blood

pressure, and heart rate. The mean age was 55.8 years, with mean±standard deviation values for height and weight of 164.7±7.2 and 67.9±12.7, respectively. The mean±standard deviation values for systolic and diastolic blood pressure were 117.5±19.4 and 79.2±17.5, respectively. BMI and heart rate were calculated to be 25.0±4.7 and 73.4±11.3, respectively.

Relationship between PAV1 and PAV2

To evaluate the reproducibility of PAV, several factors that could be influenced by endothelial function, such as age, BMI, and sex, were considered as patient characteristics. Based on these characteristics, patients were divided into three subgroups, and the results of the two PAV tests were compared within each subgroup.

The data in Table 2 indicated that there were no significant differences between the results among the subgroups. In the male group, the first and second PAV test results were 1.11±0.27 and 1.16±0.30, respectively ($p=0.09$). For females, the corresponding results were 1.21±0.38 and 1.15±0.34 ($p=0.19$).

Table 2. Differences in the Two Repeated PAV Exams Using Patient Characteristics

	n	PAV –Exam 1	PAV –Exam 2	Mean of differences	P	ICC
Total	152	1.15±0.33	1.15±0.31	0.00±0.32	0.99	0.66
Sex-Male	83	1.11±0.27	1.16±0.30	-0.03±0.27	0.09	0.72
Sex-Female	69	1.21±0.38	1.15±0.34	0.06±0.38	0.19	0.63
Age＜60 years	85	1.22±0.37	1.18±0.36	0.04±0.37	0.33	0.64
Age≥60 years	67	1.07±0.25	1.12±0.24	-0.05±0.24	0.09	0.70
BMI＜28kg/m2	117	1.15±0.34	1.15±0.31	0.00±0.35	0.98	0.60
BMI≥28kg/m2	35	1.16±0.32	1.16±0.33	0.00±0.24	0.98	0.84

Values are presented as mean ± SD or number (%). BMI: body mass index, PAV: peripheral artery volume, ICC: intraclass correlation coefficient, CV: coefficients of variation.

Factors associated with PAV:

Patients were categorized into three subgroups based on sex, age, and BMI. To evaluate the reliability of PAV measurements, within the sex subgroup, an ICC of 0.72 was observed for males, while females

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exhibited an ICC of 0.63. Among subgroups divided by age, an ICC of 0.64 was recorded for those aged less than 60 years, and for those aged 60 years or older, the ICC was calculated as 0.70. Similar ICC values were noted within the BMI subgroup. When the BMI was below 28 kg/m^2, the ICC was 0.60, whereas it was 0.84 for a BMI of 28 kg/m^2 or higher.

Analyzing ICCs in each subgroup revealed no significant differences, indicating that there was no apparent correlation with sex, age, or BMI between the two PAV measurements in this clinical study.

In the sex subgroup, the coefficient of variation was 23.58% for males and 26.10% for females. For the age subgroup, the coefficient of variation was 25.88% for those younger than 60 years and 20.56% for those aged 60 years or older. In the BMI subgroup, the coefficient of variation was 27.31% for those with a BMI below 28 kg/m^2 and 23.60% for those with a BMI equal to or greater than 28 kg/m^2.

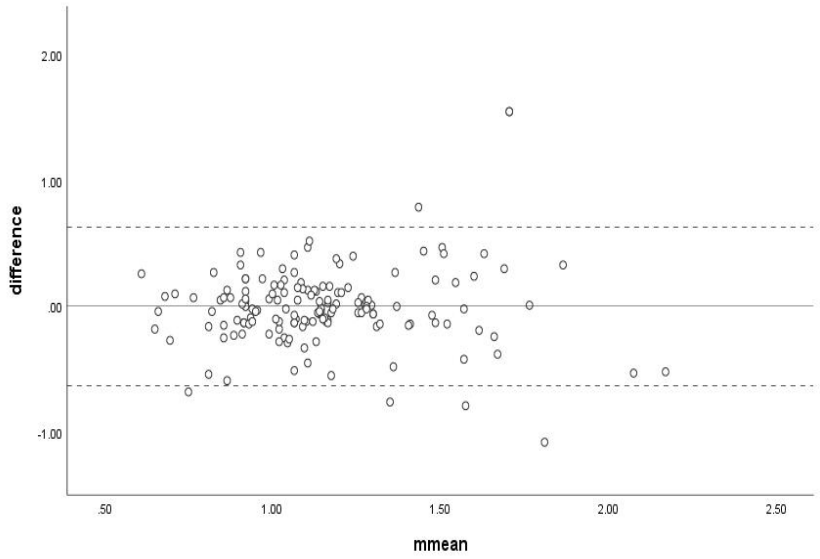

Figure 1: Bland-Altman Plot: The mean of two repeated PAV measurements is displayed on

the abscissa axis, while the difference between the two measurements is depicted on the vertical axis. Additionally, the graph allows for the calculation of a 95% confidence interval.

Reproducibility of PAV：

To assess the presence of systematic errors, measurement errors, and the trend of reproducibility between the two measurements, we generated a Bland-Altman plot, as illustrated in Figure 1. In this plot, only four data points are dispersed outside the interval, while the majority of the data falls within the interval. The analysis of all the data we have calculated indicates that PAV measurements exhibit good reliability in this clinical study.

Discussion:

Numerous studies have recently shown that non-invasive measurements of endothelial function, such as Peripheral Arterial Volume (PAV), can predict cardiovascular events. *PAV, a novel technique employing photoplethysmography, shares similarities with Flow-Mediated Dilation (FMD). It is automatic, operator-independent, and mitigates subjective errors. Unlike the intricate FMD, PAV offers a more convenient non-invasive method for assessing fingertip endothelial function. However, the reproducibility of PAV, being a novel technique, has not been extensively studied. Prior research [7] identified a linear correlation between PAV and FMD in patients with chest pain. It also linked PAV with high-risk factors for coronary heart disease (CAD), such as diabetes,*

hypertension, hyperlipidemia, or a family history of CAD. Another study [4] demonstrated that combining age-adjusted Framingham risk scores (AFRS) with PAV effectively enhances CAD prediction.

Our study confirmed the reproducibility of PAV in assessing endothelial function in adults during this clinical investigation (ICC = 0.76, CV = 24.49%). This result is especially notable when compared to recent results for PAT in adults (ICC = 0.61, CV = 18.0%) and the ICC range of FMD (0.54 to 0.92) across different groups of people. The differences in ICC and CV between various detection techniques are not substantial. *Furthermore, we found that PAV exhibits no significant correlation with age, sex, or BMI in the adult population.* This suggests that PAV, as a novel technique for evaluating fingertip endothelial function, possesses reliable reproducibility. Previous studies have established that sex, BMI, and age can impair endothelial function, but they do not significantly impact PAV.

Endothelial dysfunction is not only an independent predictor of cardiovascular disease prognosis but also plays a crucial role in the progression of coronary atherosclerosis. Methods for assessing endothelial function are rapidly evolving, with increasing interest in non-invasive vascular endothelial function detection due to its convenient operation and good reproducibility. Consequently, evaluating the reproducibility of non-invasive methods holds significance.

FMD, regarded as the "gold standard" for non-invasive assessment of endothelial function [10], has versatile applications. However, it primarily reflects the endothelial function of larger vessels and is only responsive to conventional risk factors. Its primary drawback lies in its limited repeatability, which can be attributed to operator-dependent factors, leading to potential errors during the measurement process [11]. Recently, not only has fingertip non-invasive detection emerged as an innovative method for assessing endothelial function, but it has also demonstrated significant potential for predicting cardiovascular events [4].

With the emergence of innovative fingertip detection technology as a representative method, it offers advantages such as the ability to exclude distal venous dilation caused by occlusion and the capability for repeated probe usage [7]. As mentioned in previous studies, PAV not only serves to predict coronary heart disease [7] but also assess its reliability within a similar population. In this study, a sample of endothelial function data was collected from 152 healthy adults to evaluate the reproducibility of PAV. The results of this investigation demonstrated that the reproducibility of PAV was superior. The reproducibility of PAV can be influenced by various factors, including subjects and environmental conditions. To minimize systematic errors, we implemented a rigorous experimental protocol and subsequently calculated PAV values twice using precise instruments, with the primary aim of assessing the

repeatability of PAV in clinical applications among healthy individuals.

All tests were conducted in a consistent environment to evaluate the effects of age, BMI, and gender on PAV reproducibility simultaneously. Analyzing the degree of dispersion in this study, the Bland-Altman plot we generated illustrated the good consistency of PAV. In comparison to past data on Peripheral Arterial Tonometry (PAT) reproducibility, the Bland-Altman plot showed that PAT results consistently demonstrated good consistency across different experiments, including variations in sex, age, and BMI, among others. In our subgroup analyses regarding PAV reproducibility, we observed that the coefficient of variation was lower in males than in females within the sex subgroup, which aligns with guidelines indicating that sex is a risk factor for coronary heart disease. Within the age subgroup, the coefficient of variation was higher in individuals younger than 60 years, suggesting a decline in endothelial function with advancing age. When the BMI was greater than or equal to 28 kg/m^2, the data exhibited a relatively lower coefficient of variation, indicating that obesity also contributes to changes in arterial blood flow, further affecting endothelial function.

Despite being considered the gold standard for non-invasive testing technology, FMD has a notable drawback due to its subjective measurement. According to FMD guidelines, a mean difference of 20% to 30% is deemed acceptable [5], while the data from our study regarding

PAV showed a 24.49% difference. Studies have verified that the ICC for PAT in adults was 0.61 [12], and the ICC of PAV falls within the range of FMD [13]. Since the ICC reflects the consistency of two measurements, the ICC of PAV demonstrates similar good reproducibility in this clinical study among adults, owing to its inherent advantages. Grounded in PAT theory [15,16], PAV remains a reliable fingertip technique for evaluating endothelial function in the adult population. Although there is a scarcity of studies on PAV repeatability, several theories support its application. Firstly, non-invasive fingertip techniques, besides assessing endothelial function in coronary heart disease, can also evaluate endothelial function in healthy adult populations. This not only advances the development of non-invasive fingertip detection for endothelial function [16] but also facilitates screening for coronary heart disease patients and timely prediction and evaluation of coronary heart disease [17]. Secondly, when considering risk factors for coronary heart disease, test samples divided into different subgroups, mainly based on age, sex, or BMI, showed no significant differences in PAV reproducibility. In contrast, the repeatability of PAT can be applied not only to detect endothelial function in coronary heart disease patients but also in patients with heart failure and hypertension, as previous studies have indicated [18]. More research is required to evaluate the repeatability of PAV.

As a novel non-invasive fingertip measurement for predicting CAD, its

primary application pertains to coronary artery disease patients. Additionally, the age range of all patients included in this study was from 31 to 80 years, and the sample sizes were relatively small. Consequently, the reproducibility of PAV measurements was relatively limited. To assess endothelial function in the broader population conveniently, it is essential to expand the characteristics of the population requiring testing.

Although there is limited existing data on the reproducibility and reliability of PAV measurements, evidence suggests that PAV can predict the development of cardiovascular disease and improve prognosis in clinical applications. PAV holds promise as a fingertip technique for assessing endothelial function and evaluating the risk factors for multiple coronary diseases in asymptomatic or subclinical populations.

Conclusion:

The current data demonstrates that PAV is a promising method for evaluating endothelial function in a clinical setting, supported by its good reproducibility. Comparatively, PAV appears to be a more practical option for assessing endothelial function when compared to classical non-invasive detection techniques.

Fundings and Ethics approval:

This study received funding from the Excellent Youth Foundation of Science and Technology of Jilin Province (No. 20180520054JH) and the "13th Five-Year" Science Project of Jilin Province Education Department (No. JJKH20190062KJ). The funding organizations did not influence the study's design, data collection, analysis, interpretation, or manuscript preparation. The study obtained ethical approval from the China-Japan Union Hospital of Jilin University's ethical review board and was registered with the Chinese clinical trial registry on September 17, 2017. Written informed consent was obtained from all patients before their enrollment in the study. Technical support was provided by Shenzhen Shengye Medical Technology Co., Ltd.

Availability of data and materials：

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

Competing interests：

The authors declare no conflicts of interest.

Consent for publication：

Not applicable.

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