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Measurement of Local Pulse Wave Velocity: Agreement Among Various Methodologies

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***Abstract*— The local pulse wave velocity (PWV) is the velocity with which the arterial pulse wave travels from the left ventricle to the vascular bed. Local PWV is clinically significant as a prognostic indicator of vascular damage. The measurement of local PWV involves several direct and indirect methods. However, there are limited studies that compare agreement among different methodologies. In this work, we investigated the agreement among several methods of measurement of PWV, such as the haemodynamic loop-based, Bramwell-Hill, transit-time-based and computational models of PWV. A small cohort of 35 participants (21 male/14 female) aged between 21 and 51 years was recruited on voluntary consent. The measurement setup included duplex mode recording of carotid diameter and flow velocity waveforms from an ultrasound machine and simultaneous acquisition of dual-diameter waveforms and tonometry waveforms using an in-house developed bi-modal arterial probe. The carotid pressure waveform, flow velocity and dual diameter waveforms for evaluating the various methods of PWV measurement were obtained from the data processing. The group average value of PWV were obtained between 3.07±1.17 m/s to 5.02±1.00 m/s for various methods. The lowest and the highest group average PWV was reported using the haemodynamics-loop-based methods. There exists a strong and statistically significant correlation among PWV obtained using Bramwell-Hill equations and computational models ($r > 0.91$, $p < 0.001$), whereas a moderate and statistically significant correlation was observed between Bramwell-Hill and transit-time-based methods ($r = 0.67$, $p < 0.001$). The correlation was poor between Bramwell-Hill and loop-based methods ($r \sim 0.2$, $p < 0.001$). The study confirms the variations in the measurements in PWV using different methods and suggests their interchangeable usage is not advised.**

Keywords— local PWV, pulse transit time, loop-based methods, Bramwell-Hill PWV, carotid artery

I. INTRODUCTION

The carotid-femoral pulse wave velocity (PWV) is the current clinical standard for assessing the magnitude of large artery stiffening [1]. Owing to recent developments in sensing technologies, the measurement of PWV from a shorter segment (local PWV) is gaining acceptance in the research and clinical community because of its superior features over conventional regional PWV. The measurement errors associated with the blood propagation distance, modifications in the morphology of waveforms from the two measurement sites and the effect of arterial reflections are minimal in local PWV compared to regional PWV [2]. Therefore, local PWV provides the true stiffness of a localised artery over an average estimate given by regional measurements. Local PWV is clinically significant and is a prognostic indicator of vascular damage, coronary heart disease and stroke [3], [4]. The measurement of local PWV at the carotid artery provides information on the vascular pathologies of the central circulatory system [5], [6].

There exist several direct (two-site technique) and indirect methods (single-site techniques) for estimating and/or measuring local PWV, classified as loop-based [7]–[10], transit-time based [11], impedance-based [12], theoretical [13] and computational-based [14] methods. The prominent factor impeding the accuracy of local PWV measurement among all the methods is the influence of arterial wave reflections [14]–[17] in the systolic phase of the cardiac cycle. Wave reflections of the pressure waveforms typically occur in the early and late systolic half and corrupt the identification of the systolic foot, resulting in biased estimates of local PWV [15]. The PWV estimated from loop-based methods (PWV_{PU}, PWV_{QA}, $PWV_{ln(D)U}$, PWV_{D2P}) [7]–[10], impedance analysis (PWV_{Zc}) [12], Bramwell-Hill relationship (PWV_{BH}) [13] and computational ($PWV_{\Sigma PU}$) [14] comes under indirect single site techniques. This single-site technique was introduced with the intention of measuring PWV with minimal effect of reflection. The method involves the acquisition of haemodynamic signals such as Blood Pressure (BP), Diameter (D) and flow velocity (U) or flow rate (Q) from the same arterial site. A description of these techniques is tabulated in TABLE I. The PWV estimated from loop-based methods, fundamentally derived from water-hammer theory, requires the identification of a linear region in the hemodynamic loop devoid of reflection (typical in the early upstroke of the pulse). The $PWV_{\Sigma PU}$ is developed based on the minimisation of the net wave energies over a cardiac cycle and doesn't involve any loop construction. The PWV_{BH} is the theoretical reference of PWV, obtained from the modifications of Moens-Korteweg 1D wave propagation theory in elastic tubes. A more direct measurement of PWV is achieved using the simultaneous acquisition of two pulse signals separated by a small distance

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TABLE I TECHNIQUES FOR PWV MEASUREMENT

METHOD	EXPRESSION	EVALUATION TECHNIQUE
Bramwell-Hill	$PWV_{BH} = \sqrt{\frac{D_D}{2\rho}\frac{\Delta P}{\Delta D}}$	Distensibility is calculated from pulse pressure (ΔP), distention (ΔD) and end-diastolic diameter (D_D). PWV is evaluated from distensibility.
PU Loop	$PWV_{PU} = \frac{1}{\rho}\frac{dP}{dU}$	Slope of the linear region of the loop in the early systole is constructed from Pressure (P) and Flow Velocity (U).
QA Loop	$PWV_{QA} = \frac{dQ}{dA}$	Slope of the linear region of the loop in the early systole is constructed from Area (A) and Flow Rate (Q).
ln(D)U Loop	$PWV_{\ln(D)U} = \frac{1}{\rho}\frac{dU_{\pm}}{\ln(D)_{\pm}}$	Slope of the linear region of the loop in the early systole is constructed from Flow Velocity (U) and natural logarithm of Diameter (ln(D)).
D^2P Loop	$PWV_{D2P} = D_M\sqrt{\frac{1}{\rho}\frac{\Delta P}{\Delta D^2}}$	Slope of the linear region of the loop in the early systole is constructed from Pressure (P) and square of Diameter (D^2). D_M is the mean diameter.
Σ^2PU	$PWV_{BH} = \frac{1}{\rho}\sqrt{\frac{\sum dp^2}{\sum dU^2}}$	Summation of incremental changes of Pressure (P) and Flow Velocity (U) over one cardiac cycle is used for the calculation of PWV.
Impedance Analysis	$PWV_{Zc} = A\frac{Z_C}{\rho}$	Characteristic Impedance (Z_C) is estimated as the magnitude average of Input Impedance from 4^{th} to 10^{th} harmonics. A is the lumen cross sectional area at diastole.
Transit-Time	$PWV_{TT} = \frac{Length}{PTT}$	Temporal delay (PTT) is calculated from simultaneously acquired Diameter pulses, separated by a distance of 35 mm.

from the carotid artery. The PWV is calculated from the time delay between the signals (pulse transit time, PTT) and the known distance between the pulse signals. This approach is referred to as the transit-time method (PWV_{TT}).

In this work, we investigate the agreement between all the above-mentioned methods of measuring/estimating PWV. For this, a small cohort of 35 participants was recruited, and measurements were performed to record BP, D and U or Q from the carotid artery for implementing the single-site techniques and dual diameter signals from a physical separation of 35 mm for transit-time method. In the subsequent sections, details of the measurement methodologies, data acquisition, and processing are provided, followed by the comparative analysis, observations, and future research directions.

II. MATERIALS AND METHODS

A. Measurement Methodologies of PWV

The methodologies for the measurement of local PWV are broadly classified into Single Site Techniques, which include Bramwell-Hill method, Impedance Analysis method, Hemodynamic loop methods, computational methods and multi-site techniques such as transit-time method. The description for each method is referred to the TABLE I.

B. In-vivo Study Population & Measurement Protocol

The study cohort consists of 35 participants (21 males, 14 Females) in the age group of 21 to 51 years. The study was conducted as part of a vascular screening camp organised at at Healthcare Technology Innovation Centre (HTIC), Indian Institute of Technology Madras, Chennai, India. The study protocol and data collection were in adherence to the principles laid in the declaration of Helsinki, 1975, as revised in 2013 by the World Medical Association for conducting a study involving human participants. The study protocol was implemented upon review by Institute Ethics Committee. The participants were informed of the study protocol and measurement procedure and written informed consent was collected on their voluntary participation.

The participants were allowed to be in a resting supine position for 10 minutes before the measurement. A trained operator initially performs the brachial SBP and DBP measurement on the left arm of the participant using an oscillometric BP device. This is followed by orienting a linear ultrasound probe over the carotid artery along the longitudinal axis. The ultrasound measurement records diameter and flow velocity waveforms at the carotid artery. This is followed by measurement using a bi-modal arterial probe [18] that measures dual-diameter waveforms separated by 35 mm and a tonometry waveform from the carotid artery. All the measurements were performed in a sequential manner. Before the end of the study, brachial SBP and DBP were obtained again from the same participant, and an average of initial and final BP recordings were used for further analysis. A detailed description of the individual measurement setup is elaborated in the subsequent section and refer to fig.1.

C. Data Acquisition

The measurement setup consists of brachial SBP and DBP, carotid tonometry, Duplex mode imaging (B-Mode imagining, doppler flow velocity) and dual channel A-Mode ultrasound measurements at the carotid artery. The brachial SBP and DBP were measured using an automated cuff-based oscillometric BP device on the left hand of the participants. The carotid tonometry was acquired using a high-fidelity tonometer (SPT – 301, Millar Instruments, USA), part of the bi-modal arterial probe [18]. The pulse signals from the tonometer were amplified using a single-Bridge Amp (AD

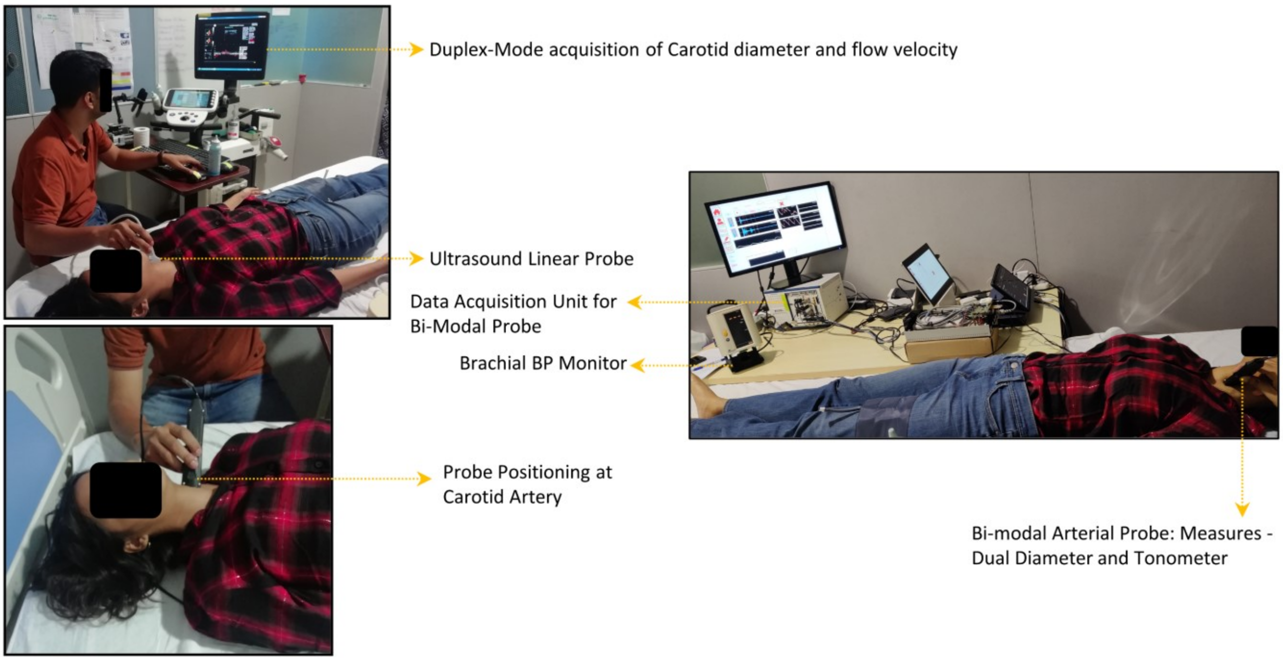


Fig.1. Measurement Setup illustrating the different types of measurements performed.

Instruments, Australia). The amplified signals were processed in the AD Instrument's Power-Lab Hardware, which can be connected to a computer via USB 2.0. The acquired signals in Power Lab were accessed in real-time, processed, and saved for further analysis using Lab Chart 8.0 (AD Instruments) software. The bi-modal probe also acquires simultaneous diameter waveforms separated by a physical distance of 35 mm. The details of the bi-modal probe hardware and software architecture can be refed elsewhere [18].

The B-Mode ultrasound imaging of the carotid artery in longitudinal view along with the pulsed wave doppler velocity waveforms was obtained using the duplex mode in Sonix Touch+ ultrasound system (BK Medicals, UK). The gain, focus, and depth were adjusted in a manner to obtain clear and sharp vessel walls of the carotid artery. The thresholding gates for doppler flow were adjusted to get repeatable flow velocity waveforms, with clear distinction of peak magnitude. The duplex mode measurements are saved as a video file in .avi format for further processing.

D. Data Processing

The diameter waveform data extraction from the video file was performed using an edge detection-based image processing software (Cardiovascular Suite, Quipu). Upon loading the file and calibrating the pixel units to mm, the region of interest was defined where the carotid artery walls were well defined. The software, in an automated manner, assigns markers onto the walls and tracks the wall motion frame to frame to arrive at the diameter waveform. The final output was in .csv format. For extracting the flow velocity waveform, an online tool for plot digitising was utilised. The extracted output was in .csv format.

The amplified tonometry signals saved using the Lab Chart software were available in .csv format and were loaded into a LabVIEW-based program loaded along with the diameter and flow waveform for data processing. All three waveforms were processed with a zero-phase Butterworth filter (order:2, cut-off frequency: 15 Hz). Since the sampling rates for all the waveforms were not the same, software up sampling to 1000 Hz was performed to bring the waveforms to the same time axis. Individual cycles (from 1st end-diastolic foot to 2nd end-diastolic foot) were extracted based on a cycle cutting algorithm, and all three cycles were aligned with respect to their dicrotic notch [19]. For the transit time method, the simultaneously recorded pulse echo waveforms from the bi-modal probe were processed into diameter waveforms, and the temporal delay between the foot of the waveforms was calculated for PTT [18].

TABLE II PARTICIPANTS INFORMATION

Total participants	35
Male	21
Female	14
Age (Years)	21 – 51
Systolic blood pressure (mmHg)	95 – 147
Diastolic blood pressure (mmHg)	55 – 96
PWV_{BH} (m/s)	3.00 – 7.76
PWV_{TT} (m/s)	3.20 – 7.94
PWV_{PU} (m/s)	2.30 – 8.46
PWV_{QA} (m/s)	1.21 – 5.46
$PWV_{ln(D)U}$ (m/s)	2.13 – 8.03
$PWV_{\Sigma PU}$ (m/s)	3.37 – 8.39
PWV_{D2P} (m/s)	3.62 – 7.68

Haemodynamic loops were constructed according to each method – PU, QA, D^2P and ln(D)U as described in TABLE I. A linear region in the upstroke of the haemodynamic loop was identified to calculate the slope of the curve and PWV. The BH equation method and computational method were implemented based on the respective expressions as in TABLE I.

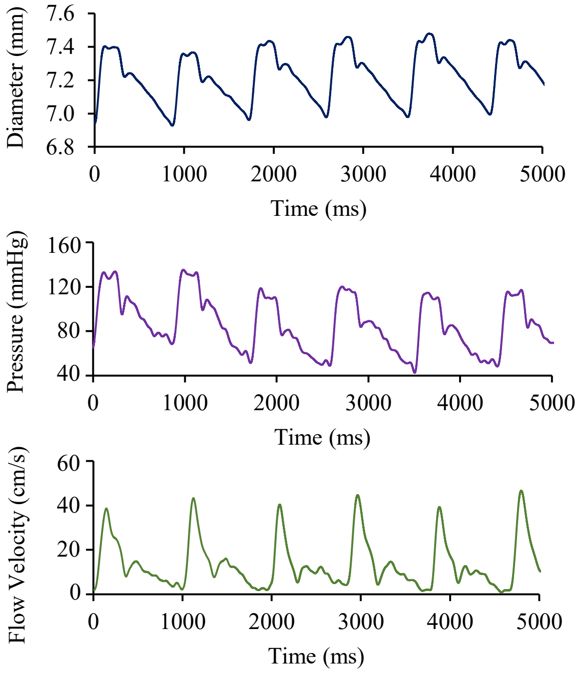


Fig.2. Sample waveforms of diameter, pressure, and flow velocity

E. *Statistical Analysis*

The average values of measured and calculated variables are reported in the article as mean ± standard deviation. The beat-to-beat repeatability was expressed as the coefficient of variation (CoV). The CoV was calculated as the ratio of standard deviation to mean, described in terms of percentage. The deviation of mean differences between variables was compared using a paired t-test and illustrated using box-whisker plots. The level of significance of $\alpha = 0.05$ was used for all tests. A p-value < 0.05 confirmed a statistical significance to reject the associated null hypothesis.

III. Results and Discussion

A. *Participants Demography*

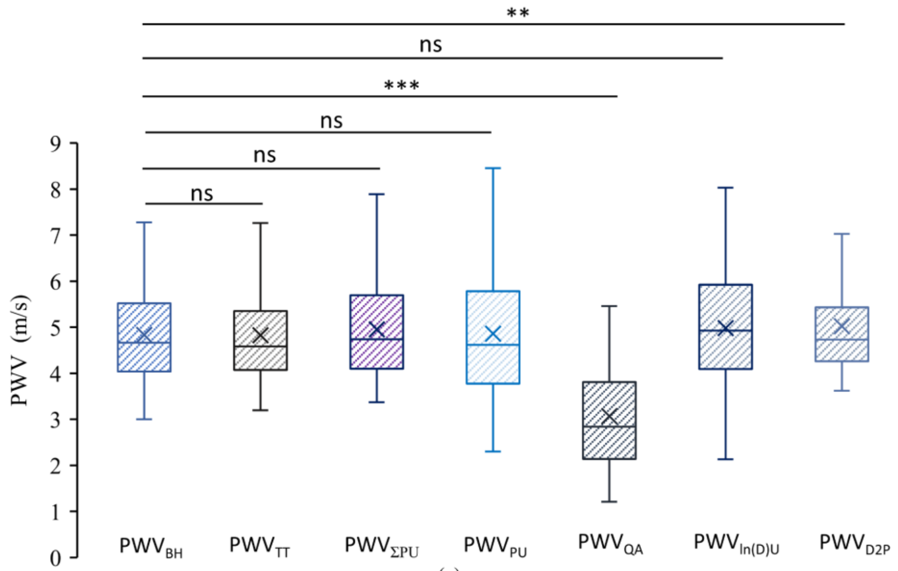
The participants (n =35) were within the age group of 21 to 51 years, with 21 males and 14 females. The SBP varied from 95 mmHg to 145 mmHg and DBP varied from 55 mmHg to 96 mmHg. The descriptive statistics of the participants information is depicted in TABLE II. The participants were having normal range BMI and did not have any history of diabetes or cardiovascular diseases. Out of 35 subjects, 3 participants had a habit of smoking. The entire measurement protocol was completed in 5-10 min, per subject.

B. *Reliability of Signals*

Fig. 2 illustrates the sample waveforms obtained after processing. The calibrated pressure waveforms from carotid tonometry and the digitized diameter and flow velocity waveforms from the duplex mode video frames were continuous and quasi-periodic in nature. The SNR on average for all the signals were > 20 dB, ensuring high signal quality. The video frames from the ultrasound duplex mode were acquired with the highest resolution and 70 Hz of frame rate, and the pressure waveforms with 500 Hz sampling rate. The average D_D for the population was 5.06±0.12 mm with a beat-to-beat CoV per subject < 5%. The average ΔD was 0.60±0.03 mm. The mean peak velocity for the study population was 52 cm/s. The beat-to-beat CoV for the flow peak for intra-participant was < 7%.

C. *Agreement Among PWV Measurement Methods*

The group average value of PWV for PWV_{BH} , PWV_{TT}, $PWV_{\Sigma PU}$, PWV_{PU}, PWV_{QA}, $PWV_{ln(D)U}$ and PWV_{D2P} are 4.84±1.04 m/s, 4.83±1.11 m/s, 4.95±1.04 m/s, 4.86±1.54 m/s, 3.07±1.17 m/s, 4.98±1.40 m/s, 5.02±1.00 m/s respectively. The range of the values is listed in the TABLE II. Fig.3(a) depicts the box-whisker plot, with the results from ANOVA on the statistical significance of the deviation of mean from the PWV_{BH}. Among all the methods, PWV_{QA} was observed to be underestimating the PWV in comparison to PWV_{BH} by 58% (a change of 1.8 m/s). The mean values of PWV from all the other methods were comparable (p > 0.05) except for



(a)

Comparison with PWV_{BH}	Correlation (r-value) (p<0.001)
PWV_{TT}	0.67
$PWV_{\Sigma PU}$	0.97
PWV_{PU}	0.23
PWV_{QA}	0.68
$PWV_{ln(D)U}$	0.22
PWV_{D2P}	0.96

(b)

Fig.3(a). Comparison of PWV among all the methods. (*** p < 0.001, ** p < 0.01, ns: not significant) (b) Correlation between all the methods and PWV_{BH}

PWV_{QA} and PWV_{D2P}. PWV_{PU} showed the largest deviation between the smallest and the largest value of PWV measured (2.3 m/s to 8.46 m/s). The ranges of PWV were comparable among PWV_{BH}, PWV_{TT}, $PWV_{\Sigma PU}$, and PWV_{D2P}. There exists a strong and statistically significant correlation among PWV_{BH} and $PWV_{\Sigma PU}$ ($r = 0.97$, $p < 0.001$) and among PWV_{BH} and PWV_{D2P} ($r = 0.96$, $p < 0.001$). A moderate and statistically significant correlation was observed between PWV_{BH} and PWV_{TT} ($r = 0.67$, $p < 0.001$) and between PWV_{BH} and PWV_{QA} ($r = 0.68$, $p < 0.001$). The correlation was poor among PWV_{PU}, PWV_{InDU}, with PWV_{BH} ($r \sim 0.2$, $p < 0.001$).

There are limited studies that compare the agreement among different methodologies of PWV measurement [20], [21]. In [19], the PWV_{PU} tends to overestimate $PWV_{BH,}$ and the PWV_{QA} tends to underestimate PWV_{BH} for the carotid artery. The PWV_{BH} is the theoretically derived value of PWV from the principles of fluid dynamics as applied to a pulsatile flow in an elastic tube. Therefore, since there exists no absolute reference for the measurement of PWV, the PWV_{BH} is taken as a reference PWV to compare all other measurements of PWV. In the current study, the underestimation of PWV_{QA} was evident, whereas the overestimation of PWV_{PU} was not prominent for the group average values. In general, a higher range of values was obtained for PWV_{PU}, in comparison with PWV_{BH}; having this higher spread of values might have caused mean values to be similar. The poor correlation of PWV_{PU} with PWV_{BH} was also in coherence with the previous studies [19].

The loop-based methods for estimating local PWV are adaptations of water-hammer theory and, by definition, require reflection-free regions. It's a frequent assumption that the early systole is a period where the effects of wave reflections are minimal, and these methods are safely applied. Unfortunately, all these methods have proven to be influenced by an error in wave reflection. The effect of reflection on multi-model signals is not alike. The effects may be observed to be of an opposing nature for both pressure and flow. These effects also depend on the measurement site as well. Further, the single-site measurement methods only provide a single estimate of PWV, whereas it is known that PWV is of incremental nature within a cardiac cycle due to the non-linear load sharing between elastin and collagen fibres with pressure. Attempts to correct the errors due to reflection have been undertaken without real, applicable success. A detailed analysis on the methodological constraints on PWV is discussed elsewhere [22].

The applications that utilises measurement of local PWV is not limited to arterial stiffness estimation, but extends to wearable ambulatory patch probes for blood pressure measurement [5], [23]. Combining the local PWV measurement with arterial distension [24], heart rate variability [25] and stress detection [26] would provide more insights on cardiovascular risk stratification strategies for large scale population studies.

IV. Conclusion

In this work, we have investigated the agreement among various methodologies for the measurement of local PWV. The study was conducted on a small cohort of 35 participants aged from 21 to 51 years. Sequential measurements were performed using the duplex mode of an ultrasound system for diameter and flow velocity waveforms followed by simultaneous acquisition of dual-diameter waveforms and skin surface force using the tonometer part of an in-house developed bi-modal arterial probe. A significant difference in the mean value of the calculated PWVs from various methods with respect to PWV_{BH} was observed for PWV_{QA} and PWV_{D2P}. The PWV_{QA} underestimated PWV_{BH} by 58% (a change of 1.8 m/s). In this study, the underestimation of PWV_{QA} was evident, whereas the overestimation of PWV_{PU} was not prominent. The study confirms the variations in the measurements in PWV using different methods and suggests their interchangeable usage is not advised.

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