Assessment of Endothelial Reactivity using Brachial Pulse Wave Velocity Response to Shear

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***Abstract*— Non-invasive assessment of endothelial reactivity (ER) is done by analyzing the relative change in brachial artery diameter in response to transient forearm ischemia. However, confounding factors such as flow velocity that mediates to dilation of the artery are not considered while calculating the ER index (FMD%). Therefore, we propose a technique for the assessment of ER using the measurement of local pulse wave velocity (PWV) during reactive hyperemia (RH). Continuous diameter and flow velocity were recorded on 10 healthy subjects during baseline, RH and recovery phases and corresponding PWV was calculated using the flow-area (QA) and ln(diameter)-velocity (DU) method. After 54 ± 32s of cuff release, PWV increased to 35.53% and 18.45% compared to baseline, and recovered to 45.6% and 55.62% from RH in 78 ± 16s for both QA and DU methods. The study was repeated for 2 consecutive days. Repeatable diameter and flow measurements were obtained (ICC > 0.6). There existed a significant mean difference in estimation of PWV using QA and DU methods (P < 0.05). The ICC for PWV derived ER was 30% higher than FMD%. Hence, analyzing temporal response of local PWV to ischemia is a reliable technique for assessment of ER. Direct methods for evaluating PWV during the course of the experiment can be a potential and simpler technique for assessment of ER.**

Keywords— Artery diameter, Blood flow velocity, Brachial Artery, Endothelial Reactivity, Flow-Area method, Flow-mediated Dilation, Local pulse wave velocity.

I. INTRODUCTION

Endothelial cells form the luminal surface of blood vessels in the body acting as an anticoagulant barrier between the vessel wall and the blood. The endothelium has a central homeostatic role in the vascular system by the production of vasoactive substances such as nitric oxide responsible for the regulation of vascular tone [1]. Endothelial reactivity (ER) is altered by several cardiovascular risk factors such as tobacco, arterial hypertension, diabetes etc. Endothelial dysfunction is considered to have a critical role in atherogenesis and is hence considered an early marker of vascular events [2].

Non-invasive assessment of ER is widely done using flow-mediation dilation (FMD) where the relative change in brachial diameter following transient ischemia is measured. The measurement involves ~120s of baseline diameter measurement, ~300s of ischemia and ~180s of reactive hyperemia. The relative change in diameter pre and post-ischemia gives the FMD index (FMD%). However, the absolute values obtained vary considerably across studies [3]. This can be attributed to the influence of subject-specific factors such as blood pressure, flow velocity and material properties of the brachial artery. Quantifying these factors as a response to input shear stimulus can be a potential method to improve the reliability of the assessment of ER.

The elasticity of the artery influences the propagation of the pressure wave released by the heart. The velocity of the pulse waves increases with artery stiffness. Changes in material response to shear can be calculated by measuring pulse wave velocity (PWV) which is referred as the gold standard for assessing arterial stiffness [4]. Its inverse relation to distensibility which is in fact influenced by dynamic changes in vascular tone and direct relation to blood flow velocity makes it a potent marker of ER during FMD test. Methods for measuring carotid-radial PWV response to transient ischemia have already been reported as a repeatable method of ER assessment [5]. However, indirect estimation of local PWV using beat-to-beat measurements of brachial diameter and flow velocity waveforms during reactive hyperaemia (RH) is least reported.

In this work, we propose the indirect estimation of local PWV from continuous diameter and flow velocity waveforms recorded during an FMD intervention. The repeatability in measurements of brachial diameter and flow velocity was analysed using inter-day measurements on 10 healthy participants. PWV calculated using 1) Flow-area (QA) method and, 2) ln(diameter)-velocity (DU) method were compared for all participants. ER assessment using the relative change in PWV (ERA_{PWV}) was then compared with conventional FMD% for repeatability.

The subsequent sections describe the methodology, followed by results and observations accompanying insights to future works.

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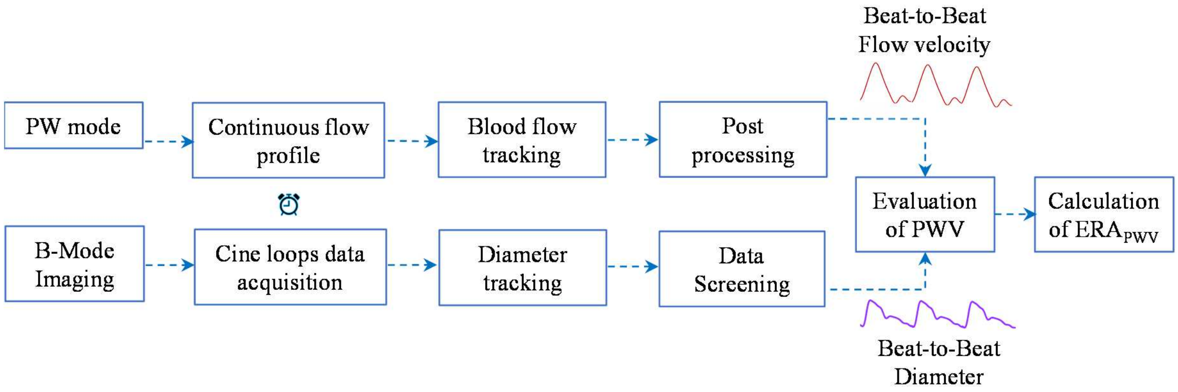


Fig.1. Schematic of the measurement procedure

II. Materials and Methods

A. *Participant Preparation and Measurement procedure*

An in-vivo study was conducted on 10 participants (6 males: 4 females; 24 ± 5y) over two consecutive days (20 measurements). The research was conducted out in a controlled laboratory setting (23 ± 2°C) at the Healthcare Technology Innovation Centre, Indian Institute of Technology Madras, India. Prior to the experiment, participant information such as lifestyle and medical history were obtained. Individuals who were using drugs, had cardiometabolic disorders, smoked, or had a history of tobacco use were excluded from the study. The recommended FMD guidelines were taken into account when examining the study protocol [6]. The study followed the Helsinki Declaration's guidelines (revised in 2013). The study's aims and methodology were described to participants, and informed consent was obtained.

Before the measurement, the participants were encouraged to rest for 10-15min in a supine posture. Oscillometric BP measurements were taken on the brachial artery before the experiment using an automated BP monitor (SunTech®247TM, SunTech Medical, Halma, UK). A trained operator palpates and identifies the location of the artery and orients the ultrasound transducer in the location for quality B-mode images of the brachial artery. Cine loops of B-Mode diameter and PW-Mode flow waveforms were obtained continuously for Baseline (~2min). The bladder cuff placed in the lower arm is then inflated to supra systolic pressure (SBP + 50mmHg) to induce ischemia (~5min). Following the cuff release, the recovery (~3min) measurements during RH was done. Experiment was repeated the next day at the same time to determine repeatability of FMD% versus ERA$_{PWV}$.

B. *Data acquisition and Estimation of PWV*

The algorithm flow for simultaneous acquisition of diameter and flow velocity to estimate ERA$_{PWV}$ is given in Fig. 1. The diameter signals were acquired using an ultrasound transducer (7-15MHz) using B mode scanning and blood flow velocity using PW mode (Sonix Touch+, BK Medicals, US) The data in cine loops was analyzed using a continuous edge-detection and wall-tracking software (FMD Studio, Quipu, Netherlands). The Pressure and flow cycles recorded throughout the experiment were evaluated using a LabVIEW-based platform, and 10 corresponding cycles during baseline, peak (RH), and recovery were used to estimate the relative change in PWV.

Both QA and ln (D)U are single location approaches that rely on simultaneous measurements of velocity (U) and artery diameter (D) to estimate PWV, but the processing methods differ [7]. During the reflection-free period of the cardiac cycle, according to QA method, the PWV in an artery is measured as the ratio of change in blood flow velocity and the change in cross-sectional area of the artery. It is given as:

$$\mathrm{PWV}_{QA} = \frac{\mathrm{dQ}}{\mathrm{dA}} \tag{1}$$

Where Q is the volume flow [8] through the vessel given by,

$$Q = A.U \tag{2}$$

and A is the cross-sectional area of the vessel. Whereas, the variations in flow velocity and diameter is used to calculate PWV in the DU method given by,

$$\mathrm{PWV}_{DU} = \frac{1}{2}\frac{\mathrm{dU}}{\mathrm{d(ln\ D)}} \tag{3}$$

TABLE I. Participant Demography and Parameter description

Parameter	**Value** Mean ± SD
Number of participants	10
Male/Female	6/4
Age(y)	25 ± 4
Height(cm)	174 ± 13
Weight(kg)	73.6 ± 14.3
Heart rate(BPM)	74.2 ± 6.0
Systolic blood pressure(mmHg)	110.64 ± 3.15
Diastolic blood pressure(mmHg)	72.60 ± 6.77
Systolic-extrema diameter(mm)	3.68 ± 0.73
End-diastolic diameter(mm)	3.85 ± 0.43
Flow velocity(cm/s)	75.62 ± 7.31

Where dU is the change in blood velocity and ln(D) is the variation in the natural logarithm of the diameter (D).

The ERA_{PWV} index was calculated as the related change from baseline to peak PWV during RH given by,

$$ERA_{PWV} = \frac{PWV_p - PWV_b}{PWV_b}.100 \qquad (4)$$

where PWV_p represents the average PWV of 10 cycles of diameter and flow during RH and PWV_b is the average value of PWV for 10 baseline cycles.

C. *Statistical Analysis*

Continuous values are presented as a range and/or mean ± standard deviations. The repeatability of measurements was calculated using Intraclass correlation coefficient (ICC) and coefficient of variability (CoV) for 10 cardiac cycle in individual participants. A value of ICC greater than 0.6 and CoV < 20% is considered as highly repeatable. To compare PWV estimations between two methods, the Bland Altman approach was used. The agreement between estimated PWV using two methods was investigated via linear regression analysis and expressed using Pearson's correlation coefficient (R), a value of $p < 0.05$ was considered statistically significant.

III. RESULTS AND DISCUSSION

TABLE I details the participants' baseline demographics. All parameters are within the normal range.

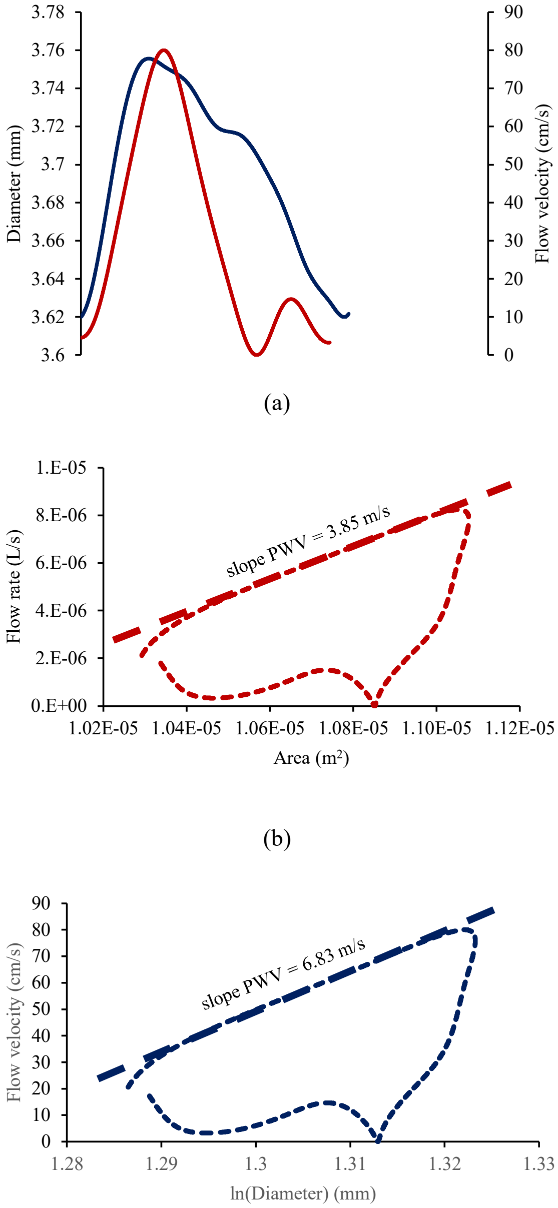
A. *Reliability and Repeatability of Diameter and Flow velocity measurements*

Beat-to-beat cycles of brachial diameter and flow velocity was measured with SNR > 20dB. The mean end-diastolic diameter and flow velocity during baseline for 10 cardiac cycles in 10 individual participants is 3.85 ± 0.43mm and 75.62 ± 7.31cms^{-1} respectively. The values are in line with earlier reported studies [9]. Fig. 2 (a) shows the measured simultaneous diameter and flow waveform for one cardiac cycle (~0.8s).

Inter-day ICCs for diameter and flow are given in Table 2, together with their corresponding CoV. The observed CoV and ICC in beat-to-beat measurements of diameter and flow for all participants show good repeatability (CoV < 12% and ICC > 0.6). There was a significant agreement (P < 0.001) between the inter-day measurements. Hence, the acquired diameter and flow waveforms are reliable and can be used for calculation of material responses during RH.

B. *Correlation of PWV estimation using QA and DU methods*

The slope of the QA and DU loops in Fig. 2 (b and c) gives the corresponding PWV (part of loop corresponding to early systole). The mean PWV estimated using QA and DU methods during baseline was 3.85 ± 1.23ms^{-1} and 6.87 ± 1.97ms^{-1}. There was a 35.96% increase in mean PWV_{QA} from baseline to RH and 17.54% increase in PWV_{DU} (Fig. 4). The increase in PWV during RH can be attributed to its direct correlation to blood flow velocity which increases 17.19% from baseline to RH as against to a 9.47% increase in diameter (Fig. 3). It can also be attributed as the influence of factors like blood pressure which varies between participants [10]. Following RH, there was a 48.28% decrease in PWV_{QA} and 44.60% decrease in PWV_{DU} during recovery (within 90 seconds). This is an interesting observation which requires extending the recovery period of the test in future to study the effect of recovery PWV in ER.



(a)

(b)

(c)

Fig.2. (a) Measured diameter and flow waveform for 1 cardiac cycle during baseline, (b) QA loop and, (c) DU loop

TABLE II. COV AND ICC OF THE INTER-DAY MEASUREMENTS

Parameter	CoV (%)	ICC
End-diastolic diameter	11.36	0.61
Blood flow velocity	9.66	0.68
PWV_{QA}	13.41	0.54
PWV_{DU}	12.76	0.60

Table. 2 shows the ICC and CoV values of PWV_{QA} and PWV_{DU} for two consecutive days in 10 participants. The observed ICC and CoV values gave good repeatability (CoV < 14% and ICC > 0.5) owing to the potential of PWV as a reliable and repeatable marker of ERA. The scatter plot in Fig. 5 (a) shows the comparison of beat-to-beat PWV during baseline , RH and recovery phases for QA and DU methods. The linear regression analysis comparing PWV_{QA} and PWV_{DU} gave a statistically strong correlation ($r = 0.89$, $P < 0.05$). The Bland-Altman analysis reveals the level of agreement between both PWV estimations where the mean bias was $2.55 ms^{-1}$. The measurements agree within a 95% confidence interval of $\pm 1.96 ms^{-1}$.

C. *Repeatability of ERA_{PWV}*

The mean value of ERA_{PWV} using QA and DU methods were 14.7 ± 4.5% and 22.6 ± 2.7% respectively and their corresponding mean FMD% was 16.23 ± 3.4%. It can be observed from Table. 3 that as compared to the moderate repeatability of FMD% measured over two consecutive days for 10 participants, the ICC and CoV values of ERA gave better repeatability (CoV < 16% and ICC > 0.65). Measurement reproducibility over time was found to be more sensitive to intraindividual variation in pressure. Therefore, simultaneous measurement of pressure alongside diameter is required to eliminate individual differences during assessment of ERA. Further, indirect measurement of PWV can be influenced by measurement errors in diameter and flow. Also, PWV is largely dependent on pressure, Hence, efforts need to be done for directly estimating PWV during RH [11] using simultaneous and continuous measurements of pressure, diameter and flow. Cuff-based designs and methods in this line for direct estimation of PWV can reduce CoV in measurements to a large extend.

There are a plethora of devices that measure PWV but the reliability of the same in the context of its response to RH can yield varying results. This depends on the technique used for measurement like a piezoelectric transducer or by Oscillometric measurement, the sites of measurement yielding to a regional or a local estimate of PWV. Hence, the repeatability of PWV estimates using different techniques are not interchangeable. Pulse wave velocity deceleration to RH was suggested as an alternative to FMD% elsewhere but the repeatability and reliability of the same has conflicting results. To the best of our knowledge, indirect estimation of PWV using ultrasound technique from a single location and its response to RH is a first of its kind method and the observed PWV response to shear has a potential to be a reliable marker for ERA.

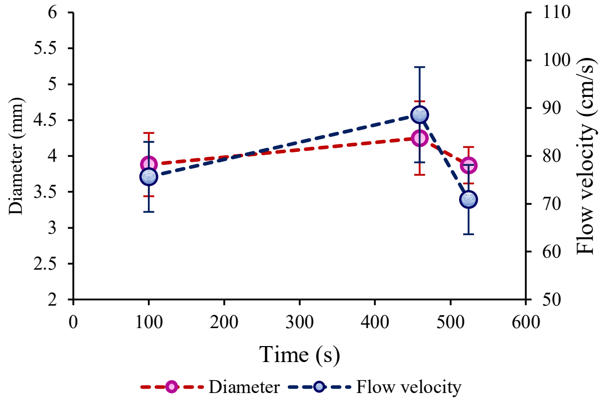


Fig.3. Mean diameter and flow velocity during baseline, RH and recovery

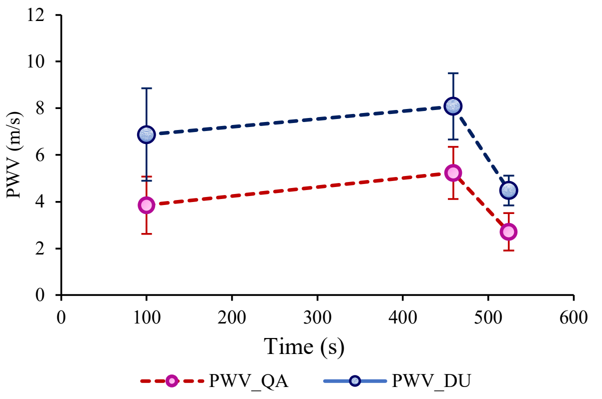
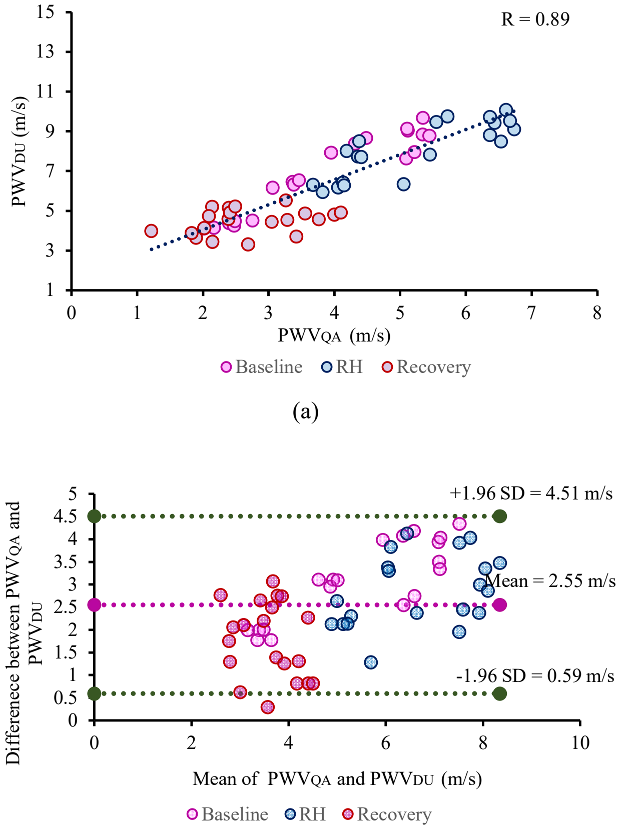


Fig.4. Mean PWV_{QA} and PWV_{DU} during baseline, RH and recovery.



(a)

(b)

Fig.5. Comparison of PWV_{QA} and PWV_{DU} using (a) Regression and (b) Bland-Altman plot

TABLE III. CoV AND ICC OF THE INTER-DAY ER ASSESSMENT

Parameter	CoV (%)	ICC
FMD%	17.43	0.54
$ERA_{PWV}(QA)$	15.67	0.69
$ERA_{PWV}(DU)$	15.23	0.71

IV. LIMITATIONS AND FUTURE SCOPE

Endothelial function studies based on ultrasound image analysis are known to be highly variable, with coefficients of variation of up to 40% [12]. Thus, there is a need for image-free ultrasound devices for PWV assessment during RH [13], [14]. Multimodal image-free methods for simultaneous pressure [15], diameter [16], and stiffness estimations [17] can enhance measurements even further to satisfy clinical requirements. This can be further combined with automated continuous measurements of heart rate [18], respiratory rate [19] etc. The study constraints, particularly the use of small sample space for analysis of repeatability needs to be considered while all the measurements were done in controlled environment. Thus, the reported observations are reliable and needs extension to a large sample space. This study is an indirect method for calculation of PWV where the diameter and flow signals are measured in real-time and processed offline to estimate local PWV response to shear stress. To improve the reliability of measurement and to reduce the post-analysis time, a direct approach for real-time measurement of PWV is required. This can also mitigate the methodological concerns during PWV estimation using pulse transit time method [20].

V. CONCLUSION

In this work, we have proposed indirect measurement of local PWV during RH by using continuous beat-to-beat measurements of brachial artery diameter and blood flow. ERA_{PWV} was estimated for 10 healthy participants for 2 consecutive days using QA and DU methods and was compared with conventional FMD%. Repeatable measurements of diameter and flow velocity was ensured and the corresponding ERA_{PWV} gave high repeatability as compared to FMD%. Hence, this method have a potential to be a reliable technique for assessment of ER. Development of direct methods for estimation of PWV during RH is underway.

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