

# Operator Variabilities in Carotid Pulse Wave Velocity Measured by an Image-free Ultrasound Device

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**Abstract**— Local pulse wave velocity (PWV) has gained much attention in the last decade due to its ability to provide localized stiffness information from a target vessel and cater to several applications beyond regional PWV. Transit time-based methods are the most straightforward, but their reliability is highly dependent on the blood pulse sensing modality. Conventional ultrasound systems directly measure the blood pulse (as diameter or flow velocity); however, they offer limited frame rates resulting in poor resolution signals. Advanced systems supporting high frame rates are expensive, complex, and not amenable to field and resource-constraint settings. We have developed a high frame image-free ultrasound system to address this gap for automated and online measurement of local PWV. In an earlier in-vitro study, we have demonstrated its accuracy. In this work, we aim to investigate its in-vivo reliability. A study on 15 young, healthy subjects was conducted to assess the intra- and inter-operator repeatability of the developed system. The yielded local PWVs from the left carotid artery were within the range of 2.5 to 5.8 m/s. The device provided highly repeatable intra- and inter-operator measurements with ICC of 0.94 and 0.88, respectively. The bias for the intra- and inter-operator trials was statistically negligible ( $p > 0.005$ ). The study demonstrated the potential of the high frame rate device to perform reliable measurements in-vivo.

**Clinical Relevance**— This work aims to provide and validate an easy-to-use, affordable, and fully-automated high frame rate ultrasound technology for the measurement of online local PWV that is currently lacking.

## I. INTRODUCTION

Local pulse wave velocity (PWV) is the measure of blood pulse propagation speed across a smaller segment or at a point of the blood vessel [1]. It has attracted significant interest over the last decade, given its clinical value above and beyond conventionally measured regional PWV. This parameter being a local measure of a specific artery provides insights into local pathologies or vessel degradation. Especially, where the emerging knowledge on arterial stiffening has led clinicians to target central arteries for early cardiovascular risk prediction, local PWV has been investigated with greater magnitude. It has opened several avenues for adopting arterial stiffness measurement such as in-stent restenosis detection, fetal hemodynamics monitoring, cuff-less, central blood pressure assessment, etc. [1], [2]. Recent works further underline the role of local PWV for understanding and quantifying the

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nonlinear elastic nature of the arteries [3]. Such investigations were necessary to assess vascular aging, the degradation of the structure and the function of blood vessels.

Pulse transit time (PTT) based methods are a straightforward way to measure the local PWV, which employs the fundamental distance-time equation [1]. For a given PWV, the PTT reduces with the reduction in the considered pulse propagation distance. This makes PTT measurement challenging over short distances ( $< 10$  mm), where it is typically smaller than 20 ms. The choice of sensors used to measure plays a major role, as such small PTT orders are highly dependent on the captured blood pulse morphology. Optical, force-resistive, magnetic, and accelerometric sensors-based systems are a few examples of affordable means to evaluate local PWV [1], [4]. However, they act as skin surface detectors and are susceptible to morphological alterations due to tissue transfer effects. Imaging, more popularly ultrasound, has been explored as a robust alternative where the accuracy of local PWV measurements is crucial.

Conventionally used ultrasounds in the clinic are image-based that don't support sufficiently high scan rates and yield poor temporally resolved blood pulses. Specialized systems and techniques – M-line with reduced scan lines [5], multiline transmission [6], compounding [7], ECG gated-acquisition [8], etc., though provide high scan rates ( $> 1000$  frames/s), produce offline estimates. They are complex, demand operating-expertise, bulky, and expensive, which makes them non-scalable and not amenable for field or resource constraint settings. Addressing such a need for an easy-to-use, fully automated, and affordable system, we have developed a high-frame-rate version of an image-free ultrasound technology [9] for online measurement of local PWV. We have earlier reported the functionality assessment of its prototype on an in-vitro setup [10]. This work aims to investigate its usability on human subjects by conducting an intra- and inter-operator repeatability study on 15 subjects. The study methods are presented in section II. The results are discussed in section III, followed by the conclusion.

## II. MATERIALS AND METHODS

### A. Participants and Measurement Protocol

The study was conducted as part of validating the functionality of a high-frame image-free ultrasound device developed for the measurement of local PWV. In brief, the operator (intra and inter) variabilities in the local PWV furnished by the device were evaluated on 15 young, healthy participants (Male:Female = 9:6). Their lifestyle and medical history were collected using a questionnaire prior to excluding any participant with a habit of smoking, alcohol consumption, substance abuse and any cardiovascular risk symptoms. The study was conducted in the premises of our research and

development laboratory – Healthcare Technology Innovation Centre (HTIC), Chennai, India. The employees of the Centre were recruited opportunistically without any compensation. The study protocols were verified by the internal review committee of HTIC, and the procedures adhered to the principles stated in the Declaration of Helsinki, 1975. Every participant provided informed consent in writing.

Two operators (A and B) experienced on the image-free ultrasound technology (more than a year) performed all the measurements during the study, as shown in Fig 1(a). The study was conducted in a temperature-controlled room (20 to 24 °C) and quiet environment. Three measurements were performed on each participant having an intervening gap of 15 mins, with two from both operators and the third by operator A. The order was randomized, and the operators were blinded to each other’s measurements. Each participant was appointed with a slot. They were instructed to refrain from any caffeinated beverages, strenuous exercise, and drugs affecting vascular function prior to 8 hours of the appointment or within the trials. Further, they were suggested to have a cup of water to be adequately hydrated during the study. Study was conducted between 9 AM to 12 PM prior to lunch.

### B. Physical Assessments

The subjects were also familiarized with the assessment room prior to the study. Height, weight and body mass index measurements were collected using a stadiometer and electronic scale (WB-800H, Tanita India Pvt. Ltd, India). These measurements were entered into the device’s software along with the subject’s correspondence. The subject was then allowed to relax for 10 minutes in supine posture. The resting heart rate, brachial systolic and diastolic blood pressures (SBP and DBP) were measured from the left arm with an automated oscillometric device (HEM-8712, Omron Healthcare, Japan).

### C. High-frame-rate Image-free Ultrasound Recording

The pilot in-vitro accuracy verification of this high-frame-rate image-free ultrasound device was reported in our earlier

study [10]. The same prototype (Fig. 1(b) and (d)) was employed to measure online local pulse wave velocity in-vivo during this study. A two-element ultrasound probe was interfaced with the device via RF connectors which were operated in the pulse-echo mode for acquiring A-mode signals from a pair of proximally spaced sites (35 mm) on the carotid artery. The transducers were narrow beam type with diameter = 5 mm, and operating frequency = 10 MHz. The hardware constituted a pulser-receiver arrangement for exciting the transducers with high voltage pulses, switching their modes, and capturing the echoes scattered from various tissue boundaries. The scans were configured for a depth of ~40 mm and rate of 500 frames/s, which are software-programmable. The received echo signals are filtered (high pass with cutoff = 250 Hz), amplified (gain = 160), and digitized with a high-speed scope (NI-5154, National Instruments, United States) at a rate of 100 MHz, resulting in frame size of 5000 samples. The equivalent distance between the two samples was 7.6 μm.

The operator first identified to approximate the carotid artery site during the measurements by palpating. The probe was positioned at the region where strong pulses were felt (Fig. 1(c)). The device’s software interface provided a live animated display of the frames from the two measurement sites. In addition, it also displayed the continuous distension waveform resulting by processing the frames, beat-to-beat local PWV, and scores to represent the quality of the arterial wall echoes. These feedback elements assisted the operator in performing high-quality recordings and allowed prompt correction of the probe’s position/angulation, otherwise.

### D. Local PWV Evaluation

The received echo frames are processed to obtain distension waveforms using cross-correlation-based wall-recognition and tracking algorithms, as is previously described in detail [11]–[13]. However, performing these operations in real-time for all the 500 frames each second has a computational limitation, especially because the system doesn’t involve graphic processors or field-programmable

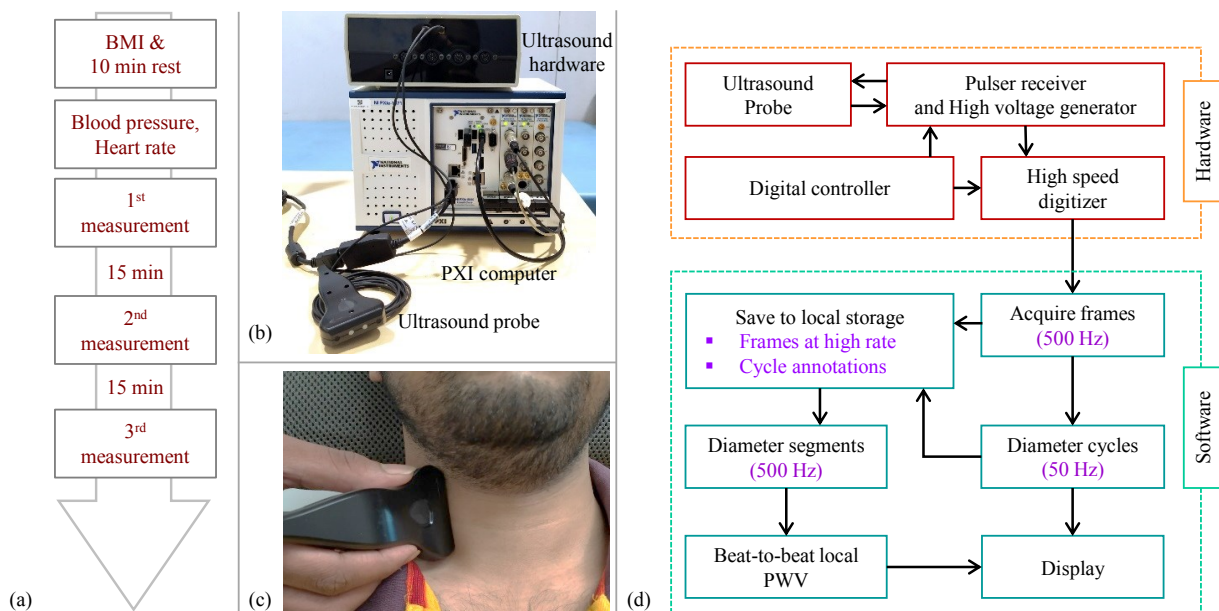


Figure 1. (a) Outline of the study protocol for both the intra- and inter-operator trials. (b) Illustration of the measurement device and (c) Placement of the measurement probe on carotid artery of the subject. (d) The schematic of the measurement device showing the hardware and software components

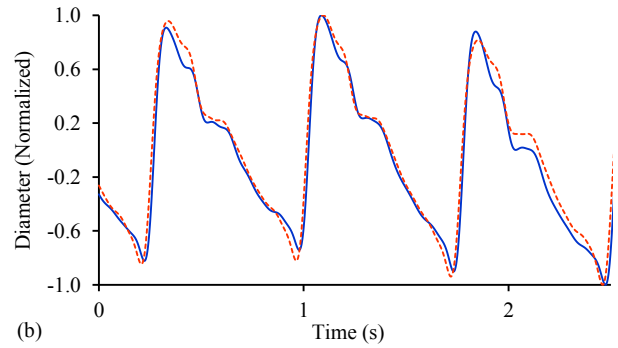
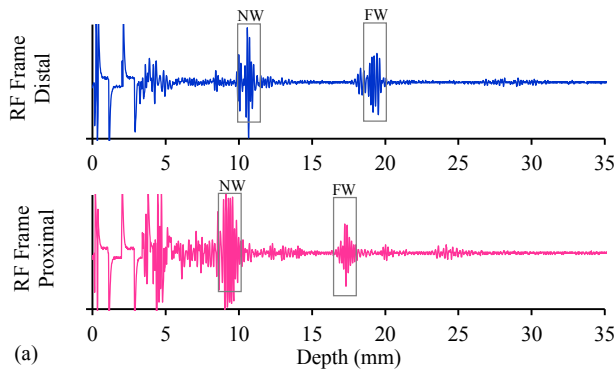


Figure 2. (a) Illustration of A-mode frames from distal (in blue) and proximal (in pink) measurement sites, with strong near and far wall (NW and FW) echoes, and (b) the corresponding obtained diameter waveform pair (normalized in amplitude).

gate arrays. Therefore, a selective segment processing scheme was developed where the frames were processed at lower rates (50 equispaced frames per second) to display the distension waveforms as feedback and annotate in each distension cycle the details on the segment that is to be processed at the higher rate. The frames incoming at higher rates are stored to a file and retrieved for the annotated segment. The annotated segment comprises only a fifth of the total distension cycles' frames, reducing the computation load. Processing the subset of frames yields the high-resolution distension segment pair from which local PWVs were evaluated for the individual beats. The high-resolution distension segment pair was resampled to 10 kHz using a cubic spline interpolation scheme to achieve higher temporal resolution. The PTT was evaluated from the foot (second derivative maximum) of the cycle segments, and PWV was assessed as (35mm/PTT(in ms)). Once local PWV is evaluated for a sufficient number of high-fidelity distension cycles, the final estimate is obtained by averaging 5-10 closer measurements.

### E. Statistics

Population characteristics and measured parameters are expressed as mean  $\pm$  standard deviation (SD). The measurement groups were compared using regression and Bland-Altman analysis. Paired t-test was used to assess whether the difference among the group means was significant. Operator repeatability were quantified using the intraclass correlation coefficient (ICC). The beat-to-beat variability was presented using the coefficient of variation (CoV), calculated as the ratio of SD to mean of measurements from 15 cardiac cycles. The signal-to-noise ratio (SNR) of the frames were evaluated as the amplitude ratio of the smallest of the two wall echoes with respect to the noise present in the frame portions devoid of any echoes.

## III. RESULTS AND DISCUSSION

Table I presents the descriptive characteristics of the population. Four of the total participants were hypertensive. The measured carotid local PWVs were within the range of 2.5 to 5.8 m/s. This is concurrent with the ranges reported in the literature [1] for carotid arteries' PWV.

### A. Quality of the Ultrasound Recordings

The A-mode frames recorded from all the subjects were of sufficiently high fidelity, exhibiting an SNR greater than 20 dB. In our earlier phantom study, the SNR observed was more than 30 dB [10]. However, the SNR observed in the case of in-

vivo subjects is expected to be lesser than that of in-vitro due to the heterogenous nature of the tissue, as is also observed in this study. Frames with the achieved SNR provided distension cycle with adequate high quality. The CoV of the cycles was within 0.5 to 1.2%, where the required 10 best cycles were achieved within a recording of 15-20 beats for the entire population during operator 'A' trials and within 35-50 beats for operator 'B'. This may be attributed to the experience of operator A in holding the probe stable for the measurement course. All the measurements were successful by both the operators, and none of the data was excluded from the analysis. A sample of A-mode ultrasound frames and the resulting distension waveforms (normalized in amplitude) are illustrated in Fig. 2, demonstrating the recording quality.

### B. Reliability of the Local PWV Measurements

The PTT measurements were in the range of 6 to 14 ms ( $8.8 \pm 1.9$  ms). High-resolution waveforms allowed the measurement of PTTs with a resolution of 0.1 ms. The minimum theoretical PTT that could be measured was 2 ms, owing to a frame rate of 500 Hz. The measured PTTs were sufficiently higher in amplitude. The local PWV was repeatable across multiple beats, manifesting a CoV smaller than 5%. The regression plots that compare intra- and inter-operator variabilities are illustrated in Figures 3(a) and (b). It may be observed that the measurements showed a strong and significant correlation for both cases, the ones performed by operator 'A' over two trials and likewise by both the operators ( $r > 0.89$ ,  $p < 0.05$ ). The ICC for the intra- and inter-operator measurements was 0.94 and 0.88, respectively. The Bland-Altman plots depicting the differences between these corresponding measurements are illustrated in fig. 3(c) and (d).

TABLE I. CHARECTERISTICS OF STUDY POPULATION

Parameters	Value Mean $\pm$ SD (Min - Max)
Participants (N)	15
Male/Female (N)	9/6
Age (Years)	25.3 $\pm$ 3.9 (20 - 34)
Body mass index (kg/m <sup>2</sup> )	23.3 $\pm$ 3.0 (19 - 30)
Heartrate (BPM)	73.6 $\pm$ 7.8 (56 - 90)
Brachial SBP (mmHg)	119 $\pm$ 11 (98 - 136)
Brachial DBP (mmHg)	74 $\pm$ 7 (62 - 92)
Local PWV (m/s)	3.99 $\pm$ 0.89 (2.5 - 5.8)

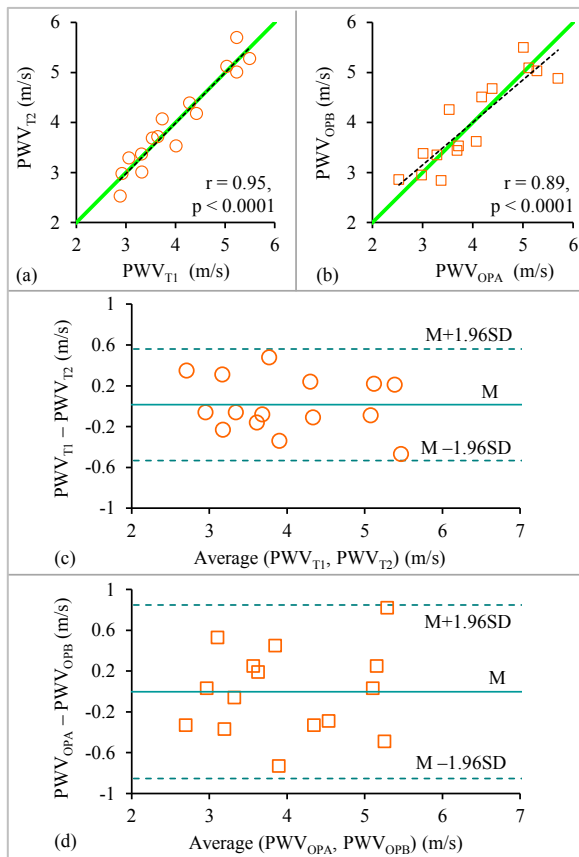


Fig 3. (a) and (b) Illustrate the regression plots comparing the two trials during the intra- and inter-operator study, respectively. (c) and (d) are the corresponding Bland-Altman plots

The bias for the intra-operator measurements was 0.010 m/s and for inter-operator was -0.003 m/s, the former smaller in magnitude than the latter. These biases were statistically insignificant ( $p > 0.05$ ) and concur with that reported in the literature. The local PWV was repeatable for both cases with a confidence interval of  $\pm 0.56$  m/s for intra-operator and  $\pm 0.84$  m/s for inter-operator measurements. These results demonstrate the device's ability to yield repeatable and reproducible local PWV measurements.

#### IV. CONCLUSION

We have presented an image-free ultrasound device that performs high rate A-mode scanning (500 Hz) from two channels and evaluates local PWV online. Given that the device's ability to perform accurate measurements was tested via in-vitro experiments earlier, in this work, its reliability to perform in-vivo measurements was shown by reporting its intra- and inter-operator performance. An excellent  $ICC > 0.88$  and insignificant biases in measurements demonstrated the device's repeatability and reproducibility. Studies on anesthetized animal models with drug interventions are in progress to fully establish the device's clinical usability. Such studies would allow investigation of the device's potential to capture early vascular aging syndrome and decipher the clinical value of local PWV over regional PWV.

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