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An Image-Free Ultrasound Device for Simultaneous Measurement of Local and Regional Arterial Stiffness Indices

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***Abstract*—The stiffness of large arteries, measured locally from a small segment or regionally over a long trajectory, has a highly clinically relevant role in cardiovascular hemodynamics. A comprehensive measure of vascular stiffness accounting for both the local and regional stiffness indices has strong potential in stratifying risks of future events. Existing technologies are not amenable for such combined measurements, especially with provisions for easy-to-use, minimal operator dependency, portability, and field deployability. In this work, we report a novel device with these features that perform simultaneous measurement of local and regional stiffness indices. The device uses a single-element ultrasound transducer to measure carotid diameter waveforms in an image-free manner. It estimates the carotid local stiffness indices such as stiffness index (β), pressure-strain elastic modulus (E_P), and one-point local pulse wave velocity ($PWV_β$). A bladder-type thigh cuff enabled the synchronized acquisition of femoral pressure pulse wave, and was used to measure the carotid-femoral pulse wave velocity (cfPWV) – the gold-standard regional aortic stiffness index. An in-vivo study on 35 subjects verified the functionality and measurement reliability of the ARTSENS®. The measured beat-by-beat carotid β (range: 2.71 – 11.15), E_P (range: 32.31 – 153.65 kPa), and $PWV_β$ (range: 3.50 – 7.72 m/s) were repeatable with variability < 8.7%. The cfPWV measurements were in agreement with that provided by SphygmoCor device ($R = 0.93$, $p < 0.001$, and mean absolute error = 4.82%). The association between local and regional stiffness indices was further investigated. This study demonstrated a strong potential of using ARTSENS® to easily evaluate local and regional stiffness for screening in clinical and resource-constrained settings.**

Keywords— ARTSENS, arterial stiffness, cfPWV, local, pulse wave velocity, regional, translational studies, ultrasound, vascular

I. Introduction

The highly organized complex structure of the arterial vessel wall is composed of elastic lamellae, collagen fibers, smooth muscle cells, endothelial cells in the intima layer, and other matrix components. Compliance and viscoelastic properties of arteries have a significant role in the 'normal' cardiovascular hemodynamics. The loss of elasticity of artery walls leads to stiffening of the vessels and is one of the major determinants of cardiovascular events and all-cause mortality. Physical estimates of large artery stiffness are highly clinically relevant biomarkers and have independent predictive value for fatal and nonfatal cardiovascular events [1]–[3].

In practice, the important role of arterial stiffness in risk stratification has been demonstrated mostly by means of pulse wave velocity [3], [4]. The current techniques typically measure pulse wave velocity across the carotid-femoral segment, where the pulse is palatable at the skin surface [5], [6]. Carotid-femoral pulse wave velocity (cfPWV) – the regional stiffness index, despite its well-recognized measurement ambiguities [1], is presently considered as the gold-standard estimate of arterial stiffness [2]. Evidence from the randomized and controlled trials on the independent predictive role of cfPWV has indeed established its prominent position in clinical guidelines [2], [7]. In conjunction with the regional stiffness, local stiffness indices could most likely improve cardiovascular risk stratification [1]. Local stiffness indices such as the stiffness index (β), pressure-strain elastic modulus (E_P), and one-point local pulse wave velocity ($PWV_β$) are more closely related to the biomechanical characteristics of the artery [1], [8], [9], and have established correlations with cardiovascular disease events and risk for stroke [1], [2]. The left common carotid artery is an attractive site for local stiffness measurement since it branches directly from the aorta, possesses a central vascular nature, and accessible as superficial for easy measurement. However, since local stiffness indices require dedicated medical imaging systems with a comprehensive analysis package (example: Aloka eTRACKING, Esaote MyLab™), their use is limited to research applications and yet to be incorporated into routine clinical practices.

In this work, we have demonstrated the feasibility of a compact, easy-to-use, field-deployable image-free ultrasound device – ARTSENS® to perform simultaneous measurement of local and regional arterial stiffness indices. To our knowledge, this is the first such compact device performing both local and regional stiffness indices as a comprehensive tool for vascular health assessment. An overview of this novel technology is discussed in Section II. We performed an in-vivo study, as detailed in Section III, in order to demonstrate the performance of the ARTSENS® device in simultaneously and continuously measuring local stiffness indices (β, E_P, and PWV_β) and regional stiffness index (cfPWV) in a controlled setting. The observations and results are summarized in Section IV and pinpointing the current limitations and future research directions in the subsequent sections.

II. ARTSENS® for Arterial Stiffness Assessment by Local and Regional Methods

A. Device Hardware and Software Architecture

An advanced version of the ARTSENS® device equipped with oscillometric blood pressure (BP) monitor and pulse wave detection module was developed for simultaneous assessment of local and regional stiffness indices. This compact device (Fig. 1 (a)) can be connected to any laptop computer/tablet and is used to perform signal acquisition, processing, and computations. As depicted in Fig. 1 (b), the analog frontend of the developed device consists of dedicated modules for (1) controlling a single-element broadband ultrasound transducer to acquire arterial luminal diameter waveform; (2) automated measurement of BP and continuous pulse wave acquisition from target arteries. The former module operates the ultrasound transducer (diameter = 5 mm, center-frequency = 5 MHz, spatial half-angle < 1.3°) in pulse-echo mode and captures A-scan frames from the target vessel segment (the common carotid artery in current application). This hardware module was developed employing an ARM Cortex M4 microcontroller (LPC4370FET256, NXP Semiconductor, Netherlands). Its inbuilt high-speed analog-to-digital converter (10 bit, 80 MHz) was used to control the transducer's mode of operation and capture ultrasound echoes. The ultrasound hardware module's power supply unit leverages bus power available at the USB port of host computer/tab and generates desired voltage levels (±5 V, ±40 V, and ±3.3 V) for various sub-units, including ultrasound transducer excitation. A detailed description of the hardware design and configurations can be found elsewhere [10], [11].

The second module is an OEM oscillometric BP monitoring module (Advantage 2.0, SunTech Medical, USA) (Fig. 1 (b)). The BP module was powered using a 9V adapter and communicated from the host computer/tab via USB 3.0. Custom bladder-type pressure cuffs in compliance with medical device recommendations were used for the measurement of brachial BP and to capture continuous femoral pressure pulse waveform in the current application. The output signal from the pressure sensor of the BP module was acquired at a sampling rate of 1 kHz using NI-USB 6009 DAQ card (National Instruments, USA). It was controlled by the measurement software and was operated by synchronizing with ultrasound acquisition module with the help of an initiating trigger signal. Further, the ultrasound module was configured to achieve a frame rate of 100 Hz, with each frame acquired every 10 ms. Therefore, these two modules were started at the same instant, and subsequently, one ultrasound frame was captured for every 10 samples of the pressure signal (which incurs a time of 10 ms). The time synchronization of the diameter (using ultrasound) and pressure (using BP module) signals was achieved in this manner and enabled a negligible time delay or mismatch in acquired signals.

Dedicated software was developed and deployed in the host computer/tab. The software incorporates programs for simultaneous controlling of hardware modules, real-time processing of all the acquired raw signals, intelligent algorithms for obtaining desired physiological measurements, evaluation of the local and regional arterial stiffness indices, and display the results to the user via a custom GUI. National Instruments' LabVIEW platform was utilized for developing such an advanced program.

As illustrated in Fig. 1 (c), the digitized A-scan ultrasound frames (obtained from the neck above the carotid artery, as explained in the following sub-section) are processed in real-

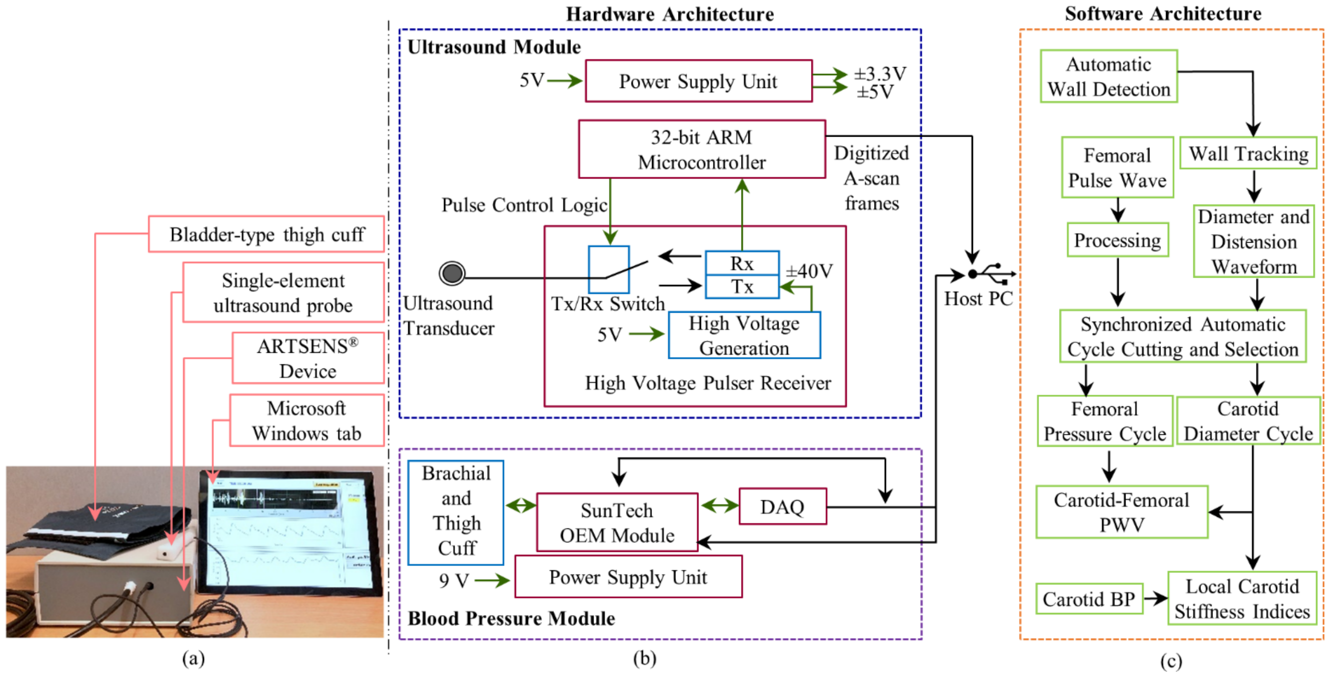


Fig. 1. (a) ARTSENS® interfaced to a tablet computer, developed single-element ultrasound probe (for local stiffness evaluation) and thigh cuff (for regional stiffness evaluation) are shown. (b) Hardware architecture of ARTSENS® (c) Software architecture of ARTSENS®.

time. Such a frame from the target arterial site encompasses echoes arising from specular reflections from various structures such as arteries, veins, moving tissue, etcetera. The developed 'wall-detection' algorithm initially identifies two echoes corresponding to the arterial near and far walls in an automated manner [10]. It operates on the fundamental fact that near and far walls always possess an out-of-phase motion as blood pulse propagates. The identifies wall echoes are then continuously tracked (via 'wall-track' algorithm [11]), and their frame-to-frame shifts are estimated by employing a cross-correlation technique. The correlation coefficient between the shifts of near and far walls are periodically evaluated to ensure that the right set of echoes are always tracked; a negative value is expected during a valid tracking (refer to the 'wall motion negative correlation check' algorithm [11]). During the tracking phase, the continuous distension of the arterial lumen (referred to as the distension waveform) is obtained from the measured frame-to-frame shift of near and far walls. This distension waveform resembles instantaneous variations of the target artery diameter as a function of time [12]). The change in distention within a cardiac cycle is equal to the difference between the end-diastolic and peak systolic diameter (D_D and D_S), denoted as ΔD. Further, the absolute value of lumen diameter is evaluated continuously by extracting a region from the A-scan frame that encompasses both the near and far wall echoes [11].

The pressure pulse wave (obtained from the femoral artery, as explained in the following sub-section) is processed in parallel while extracting the distension waveform. Since the frequency of blood pulse signals ranges from 0.7 to 3 Hz [13], the waveform from the pressure sensor was initially filtered using a 2nd order zero phase-shift Butterworth low-pass filter with a cutoff frequency of 10 Hz (allowing the fundamental and at least two harmonic components while eliminating the out-of-band noise). The use of the zero phase-shift filters helped to overcome the potential time lag or phase difference between the raw and filtered pressure waveforms. It was then used for cfPWV measurement, as explained below.

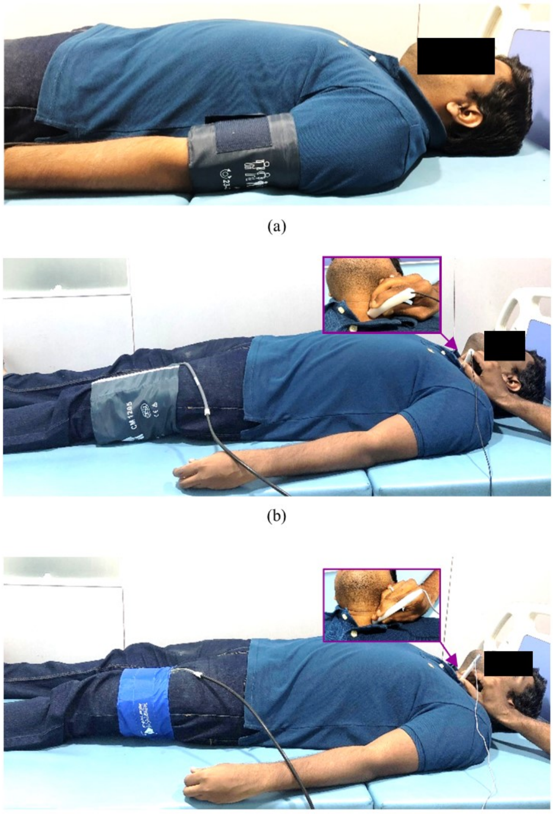
B. *Method for Local Stiffness Evaluation*

Once sufficient recordings are obtained for predefined cardiac cycles (say ten cycles), a custom cycle cutting algorithm extracts individual cycles of arterial diameter and distention from the waveform train. End-diastolic diameter D_D and arterial distension ΔD values are obtained for each cardiac cycle. Systolic and diastolic BP values measured from the brachial artery is then systematically scaled to the carotid artery (where arterial diameter measurements are performed) with the help of established techniques [14]. Systolic and diastolic pressure values at the carotid site (denoted as P_S and P_D respectively) are then used to evaluate the local stiffness indices (that is, the stiffness indices of the carotid artery) such as stiffness index β, pressure-strain elastic modulus E_P, and one-point local pulse wave velocity (PWV_β) [1], as given below. Here, ρ is the blood mass density whose value is typically considered as a constant equal to 1060 kg/m^3 [15].

$$\text{Stiffness index, } \beta = \frac{\ln\left({P_S}/{P_D}\right)}{\left({\Delta D}/{D_D}\right)} \quad (1)$$

$$\text{Pressure} - \text{strain elastic modulus, } E_P = \frac{(P_S - P_D)}{{\Delta D}/{D_D}} \quad (2)$$

$$\text{Local pulse wave velocity, } PWV_\beta = \sqrt{\frac{P_D \beta}{2\rho}} \quad (3)$$



(a)

(b)

(c)

Fig. 2. In-vivo study protocol: (a) Brachial blood pressure measurement using ARTSENS®. (b) Simultaneous measurement of local and regional stiffness (β, E_P, PWV_β, and cfPWV) using ARTSENS®. (c) Reference cfPWV measurement using SphygmoCor.

C. *Method for Regional Stiffness Evaluation*

Once the carotid distension and femoral pulse waveforms are processed, respective cycle pairs corresponding to each heartbeat are collated with their absolute timestamp. For matching the carotid distension and femoral pulse waves' temporal resolution, the former was upsampled (to 1 kHz) using a cubic spline interpolation technique. The resolution-matched cycles were used to evaluate the regional carotid-femoral pulse transit time (cfPTT) in a beat-by-beat manner. The cfPTT is obtained by identifying a fiduciary point in the carotid and femoral cycles via the 'second derivative method' [1]. The time delay between the fiduciary points of carotid and femoral cycles is recorded as the cfPTT – the expected time delay required by the arterial pulse to propagate across carotid and femoral arteries. This transit time is then used in the distance-time equation to obtain beat-by-beat cfPWV; that is by, dividing the physical length of the carotid-femoral segment [16] with the cfPTT and expressed in units of m/s.

III. In-vivo Study Materials and Methods

A. *Study Objectives*

- To demonstrate the functionality of ARTSENS® with an integrated BP monitoring system as a full-fledged tool for vascular health assessment
- To establish the usability of ARTSENS® for real-time, simultaneous assessment of local and regional arterial stiffness indices
- To investigate the association between local carotid stiffness and carotid-femoral regional PWV

B. Study Population

The performance of the developed device under baseline conditions is validated by conducting an in-vivo study on a cohort of 35 subjects. The study population recruited included healthy adults without documented history of atherosclerosis and cardiovascular diseases. This study was carried out in compliance with the Helsinki Declaration of 1975, as revised in 2000. All the procedures were performed in accordance with the guidelines of the review committee of the Healthcare Technology Innovation Centre (HTIC), IIT Madras. All subjects were informed of the study objectives and protocol and gave their informed consent before the trials. All the measurements were performed in a temperature (~ 23°C) controlled room by a single operator.

C. Simultaneous Measurement of Stiffness Indices

The subject was adopted a supine posture and allowed to relax for a few minutes to achieve baseline physiological condition. Initially, an upper arm cuff was attached to the subject (Fig. 2 (a)). Brachial BP was then measured using ARTSENS®'s BP module, and the values were updated in the graphical user interface. After removing the upper arm cuff, a thigh cuff was wrapped, as shown in Fig. 2(b), to access the femoral artery. The distance between suprasternal notch to carotid and that to femoral artery were measured with measuring tape with 1 mm resolution and fed to the software. Of note, regional pulse propagation distance was evaluated, as explained in [16]. Subsequently, local stiffness (β, E_P, and $PWV_β$) measurement on the left common carotid artery and regional stiffness (cfPWV) measurement across the carotid-femoral segment were initiated (Fig. 2 (b)). The carotid artery location was identified by palpation to place the ultrasound probe, and it was rightly angulated to capture strong echoes from the near and far wall of the artery. During this procedure, the thigh cuff was inflated and held at a pressure level close to the measured mean arterial pressure, and the femoral pulse waves were continuously recorded. When both the carotid and femoral signals were captured for a sufficient number of cardiac cycles, the measured local and regional stiffness indices were displayed on the screen and saved for future reference, along with all the raw waveforms.

It may be noted that the measurement feasibility, accuracy, inter- and intra-operator repeatability of regional stiffness measurement using ARTSENS® have been extensively validated and can be found elsewhere [10], [11], [17]. Therefore, this article has no intention to report such a basic comparison with a reference imaging ultrasound device. However, this is the first time we are reporting regional stiffness (cfPWV) measurement using ARTSENS® along with the local indices. As such, the accuracy and reliability of the cfPWV measurement were compared against the reference SphygmoCor XCEL (AtCor Medicals, Australia). The reference cfPWV measurement was started by performing carotid-femoral distance measurement, as explained above. Pressure pulse waves from the carotid using SphygmoCor's tonometer and femoral pulse wave using its thigh cuff, with the subject in the supine position. Once the waveforms are captured, the system analyzes them, computes the cfPWV, and displays them on-screen, which was used for further analyses.

IV. Results and Discussion

A. In-vivo Measurement Capacity

The present study was performed on a total of 35 subjects with age ranges from 21 – 40 years (mean age = 28.5 ± 5 years), and BMI ranges from 18.6 – 34.2 kg/m^2 (mean BMI = 24.6 ± 3.8 kg/m^2). This pool of subjects includes normotensives and suspected cases of high BP. The measured brachial BP was in the range of 101 – 154 mmHg for systolic BP and 58 – 98 mmHg for diastolic BP. As expected by theory [14], the brachial BP values, when converted to carotid BP, diastolic values were comparable, and an average reduction of 18.5 mmHg was observed in the systolic BP. Carotid and the femoral signals were taken on all the recruited subjects without fail, demonstrating the ability of ARTSENS® to perform reliable measurements. A discussion of various measurement aspects is summarized in the following sections.

B. Reliability of Continuous Signal Acquisition from Carotid and Femoral Arteries

The ARTSENS® device with an integrated BP module, developed to evaluate local and regional stiffness indices, has demonstrated the expected functionality. The device performed non-invasive BP measurements for reference and as required for local stiffness measurement. The use of an optimized custom single-element ultrasound probe enables reliable capturing of A-mode echoes with a signal-to-noise ratio (SNR) ~ 20 dB from the carotid artery. As depicted in the sample of the acquired echo (Fig. 3 (a)), both the near and far wall echoes were clearly defined. The developed algorithms efficiently tracked the artery walls and recorded the carotid diameter waveform and could also capture the femoral pulse waveform in a synchronized with the carotid diameter wave over continuous cardiac cycles.

A sample of simultaneously recorded carotid and femoral waveforms from a particular subject is illustrated in Fig. 3 (b). The time delay between carotid and femoral pulse waves are evident from the shown figure, and they were distinguishable. Similar quality signals were recorded from all the required subjects under both the baseline and induced changes in BP

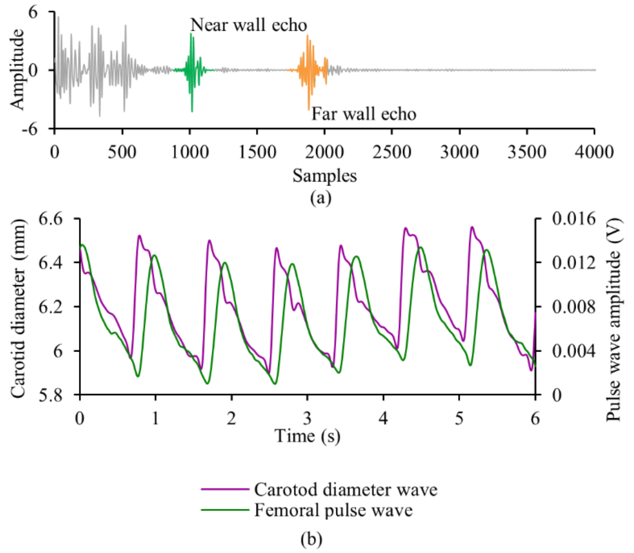


Fig. 3. (a) A sample of A-mode ultrasound echo from the carotid artery provided by ARTSENS®, in which vessels' both near and far walls are clearly defined. (b) Simultaneously acquired carotid diameter waveform and femoral pulse waveforms, used for local and regional stiffness measurement by ARTSENS®.

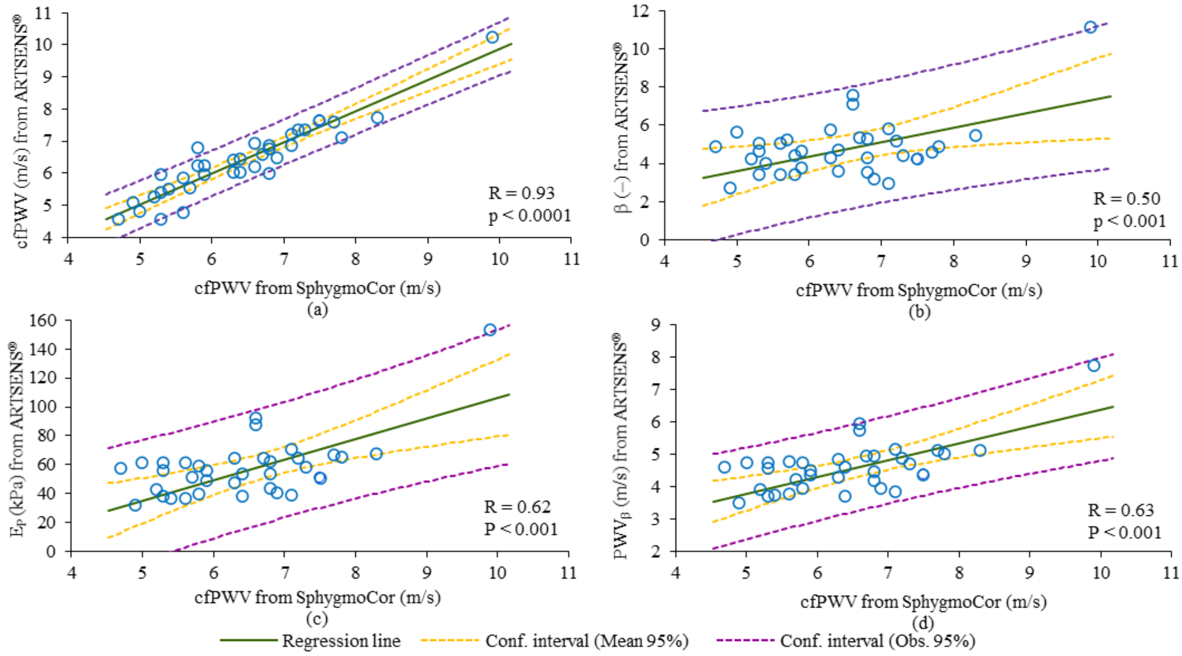


Fig. 4. Linear regression plots illustrating correlation between cfPWV (SphygmoCor) and (a) cfPWV, (b) β, (c) E_P, and (d) PWV_β measured using ARTSENS®.

conditions. The SNR of the femoral pulse wave was ~ 25 dB with a peak-to-peak amplitude of 8 -15 mV. It was also observed that to achieve the most reliable femoral pulse waves, the thigh cuff was required to inflate at a pressure level close to the mean arterial pressure. Since the device performing BP measuring from each subject in the supine posture, the system automatically inflates the thigh cuff at a pressure level equal to (or close to) the mean arterial pressure. The quality of acquired carotid and femoral waveforms and diameter values were sufficient for reliable calculation of all the desired local and regional stiffness indices.

C. Analysis of Local and Regional Stiffness Measurements

High-fidelity echoes from the carotid site allowed reliable measurement of lumen diameter and distension for continuous cardiac cycles. The ΔD and D_D values were repeatable with a coefficient of variation (CoV) 3.3% and 4.8%, respectively, for the recruited population. The group average of the measured ΔD and D_D were 0.57 ± 0.22 mm and 6.11 ± 0.55 mm, respectively. These measures were in agreement with the previously reported carotid diameter obtained via medical imaging systems [18], [19]. These results have demonstrated that the ARTSENS® is capable of performing lumen diameter from the carotid artery in a fully automated manner.

The measured carotid diameter waveform and the carotid pressure values were used to evaluate local stiffness indices (β, E_P, and PWV_β) in a beat-by-beat manner, and their average values were used for analyses. The average CoV for β, E_P, and PWV_β was less than 8.7% for the entire recruited population. High CoV, close to 10%, was typically observed in subjects with weak pulsation and/or high breathing rate. The range of measured β, E_P, and PWV_β were 2.71 – 11.15 (4.80 ± 1.53), 32.31 – 153.65 kPa (57.75 ± 21.58 kPa), and 3.50 – 7.72 m/s (4.60 ± 0.78 m/s), respectively. The measured local stiffness parameters were in agreement with the previously reported studies [18]–[20]. These studies were performed in clinical settings. ARTSENS®, in contrast to such imaging devices, provides field-amenability and computational advantage allowing real-time and operator-independent measurement.

While the values of β and E_P are more associated with the material property of the target arterial site, the PWV_β is a comprehensive index accounting for both the material property and the transmural pressure level at the time of measurement. As reported in a recent review article [1], non-invasive assessment of local PWV (such as PWV_β) is essential for advanced vascular screening and target specific disease assessment. The PWV_β has found a variety of applications [1], which are indeed impractical with the regional PWV (cfPWV) [1]. Similarly, the application of PWV_β, β, and E_P have now extended to the cuffless evaluation of arterial pressure [21], [22]. In sum, local stiffness indices obtained from the ARTSENS® have incremental value and potential use above and beyond the quantification of vascular stiffness in managing artery-specific vascular diseases.

High-fidelity carotid diameter and femoral pulse waves enabled beat-by-beat evaluation of cfPTT from all the recruited subjects. It was then used for the calculation of cfPWV, the regional stiffness index, as explained previously. The range of cfPWV measure from the recited population was 4.7 – 9.9 m/s (mean cfPWV = 6.35 ± 1.11 m/s). It was comparable to the reference cfPWV. It may also note that the absolute values of cfPWV were significantly higher than the corresponding local estimate PWV_β; it complies with the expected physiology [1]. Beat-by-beat cfPWV measurements were found to repeatable with CoVs less than 13%. Because the reference SphygmoCor device does not provide beat-by-beat cfPWV measurements, the average value of cfPWV obtained from the ARTSENS® over 20-25 cardiac cycles was used for direct comparison. As depicted in Fig. 4(a), cfPWV measured using ARTSENS® correlated significantly (Person's correlation coefficient $R = 0.93$, $p < 0.001$) with the reference cfPWV obtained from SphygmoCor. The mean absolute error observed in cfPWV measurement between ARTSENS® and SphygmoCor was 4.82%, demonstrating the functionality and measurement accuracy. The current results demonstrate an accuracy on a par with and better than existing cfPWV devices such as Complior, Arteriograph, and Vicorder, that were compared against SphygmoCor [23], [24].

It may be noted that the characteristic features of carotid stiffness indices and cfPWV are not directly comparable as they are measured along different vessel trajectories [1]. In the present study, the associations between the reference cfPWV from SphygmoCor and ARTSENS® measured β, E_P, and PWV_β are exhibited in Fig. 4 (b) – (c). Among these local stiffness indices, PWV_β was found to correlated better with cfPWV ($R = 0.63$, $p < 0.0001$). A similar association was reported in an earlier study using an ultrasound imaging system [20]. While carotid stiffness indices depict the local estimates of a small arterial segment, the cfPWV reflects an average estimate of regional stiffness of a long heterogeneous section. However, the combined use of local and regional stiffness, as a comprehensive indicator of the vascular system, would help for efficient screening/diagnosis. Simultaneously measured local and regional stiffness indices would further help to monitor the effect of medication or disease prognosis overall the arterial system and/or on any target arterial site such a central or peripheral segment. In this regard, the developed ARTSENS® device is the first of its kind, providing such a comprehensive stiffness assessment that has a potential utility in routine clinical practice. More importantly, it is a compact, easier-to-use, and portable device with automated algorithms for vascular stiffness evaluation in the field and resource-constrained settings with minimal operator expertise.

D. Limitations of Present Study and Future Works

Since the present study was performed to demonstrate the functionality of ARTSENS®, it was performed on a small cohort, which is a primary limitation. An extensive study on a large heterogeneous population with a diverse age group will be conducted at different centers. Another limitation concerns the ratio of male-to-female participants; about 75% of the participants were male. Since the study was performed in our research lab premises, accessing the femoral artery for the pulse wave acquisition was a practical hindrance owing to privacy issues and the reluctance among female volunteers to participate. This consideration is particularly relevant in the social context of Asian countries [16]. The upcoming studies will be performed in a clinical setting to ensure maximum participation from both male and female subjects.

V. Conclusion

We reported the utility of a novel image-free ultrasound device, ARTSENS®, for automated evaluation of local carotid stiffness and regional cfPWV. Unique instrumentation was designed and developed for this purpose, which enables simultaneous capturing of high-fidelity diameter and pressure waveform from the target arterial sites. cfPWV measured using ARTSENS® was comparable to that provided by the reference device. A statistically significant association was observed between the local and regional stiffness. However, they may not be interchangeably used for vascular risk stratification or diagnosis. The present study demonstrates the utility of ARTSENS® in measuring both the local and regional stiffness indices, which otherwise is measurable only by using two different devices. The results demonstrate the potential utility of ARTSENS® as a more practical, easy-to-use device for a comprehensive evaluation of vascular stiffness.

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