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Technical Validation of ARTSENS—An Image Free Device for Evaluation of Vascular Stiffness

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ABSTRACT Vascular stiffness is an indicator of cardiovascular health, with carotid artery stiffness having established correlation to coronary heart disease and utility in cardiovascular diagnosis and screening. State of art equipment for stiffness evaluation are expensive, require expertise to operate and not amenable for field deployment. In this context, we developed ARTerial Stiffness Evaluation for Noninvasive Screening (ARTSENS), a device for image free, noninvasive, automated evaluation of vascular stiffness amenable for field use. ARTSENS has a frugal hardware design, utilizing a single ultrasound transducer to interrogate the carotid artery, integrated with robust algorithms that extract arterial dimensions and compute clinically accepted measures of arterial stiffness. The ability of ARTSENS to measure vascular stiffness *in vivo* was validated by performing measurements on 125 subjects. The accuracy of results was verified with the state-of-the-art ultrasound imaging-based echo-tracking system. The relation between arterial stiffness measurements performed in sitting posture for ARTSENS measurement and sitting/supine postures for imaging system was also investigated to examine feasibility of performing ARTSENS measurements in the sitting posture for field deployment. This paper verified the feasibility of the novel ARTSENS device in performing accurate *in vivo* measurements of arterial stiffness. As a portable device that performs automated measurement of carotid artery stiffness with minimal operator input, ARTSENS has strong potential for use in large-scale screening.

INDEX TERMS Arterial stiffness, ARTSENS, carotid artery, cardiovascular disease, vascular stiffness.

I. INTRODUCTION

Cardiovascular diseases (CVD) is the leading cause of death globally, causing nearly 17.3 million deaths in 2008, with the number expected to increase to 23.3 million by 2030 [1], [2]. According to World Health Organization, over 80% of the world's deaths from CVDs occur in low and middle income countries, as they have less access to effective and equitable healthcare services which respond to their needs, including early detection service [3]. Easy to use diagnostic and screening devices, amenable to field deployment for screening and triaging are important in such scenarios. Arterial stiffness is an independent predictor of cardiovascular morbidity and mortality [4]. Studies have demonstrated significant correlation between cardiovascular disease and carotid artery stiffness values [4]–[10]. Carotid artery stiffness has been demonstrated to have strong association with increased intima-media thickness and even with severity of plaques in aorta [8]. Increased stiffness of artery is thus an early indication of vascular injury. Hence, non-invasive measurements of carotid artery stiffness, that can estimate cardiovascular health, are an attractive option for screening and early detection.

However, state of the art systems for measuring arterial stiffness are highly expensive, and have a laborious operating procedure, and are hence not suited for field applications [9]–[13]. Ultrasound echo tracking systems, such as ALOKA e-Tracking, ARTlab etc., require expert sonologists to examine ultrasound data of the artery to perform stiffness measurements [14]–[16].

There exists an unmet need for a practical, affordable, easy-to-use technology to non-invasively measure arterial stiffness in an automated manner, which could be used by general medical practitioners and health workers. Such a non-expert operable device could overcome the skill

barrier and also reduce the time taken for test, thereby making it suitable for large scale cardiovascular screening in addition to diagnosis. To address this need, we have developed ARTSENS (ARTerial Stiffness Evaluation for Non-invasive Screening), a device that overcomes the limitations of present systems effectively, while performing the measurements with accuracy and precision according to clinically accepted standards [14], [15]. We had previously presented the concept of an image-free system for measurement of arterial stiffness [17]–[21] and also demonstrated the accuracy and repeatability of measurements in controlled laboratory settings [22], [23].

In this paper, we start with a technical overview of ARTSENS device, and its operation, and present a detailed validation of the ability of the device to perform accurate measurements of arterial stiffness in-vivo, in clinical settings. The feasibility of using stiffness measurements performed in sitting posture is also investigated.

From the list of major clinically accepted estimates of arterial stiffness enlisted in Table 1, it is evident that evaluation of the arterial stiffness requires an accurate measurement of arterial distension (ΔD) which is defined as the change in diameter of the artery from its mean position during each pulse, end-diastolic diameter (D_d), systolic diameter ($D_s = D_d + \Delta D$) and the systolic and diastolic blood pressures (P_s and P_d).

TABLE 1. Clinically accepted measures of arterial stiffness.

Measure of Arterial Stiffness	Equation
Pressure strain elasticity, E_p	$E_p = \dfrac{D_d \times \Delta P}{\Delta D}$
Arterial Compliance, AC	$AC = \dfrac{\pi (D_s^2 - D_d^2)}{4 \Delta P}$
Stiffness Index, β	$\beta = \dfrac{\ln\left(P_s/P_d\right)}{(\Delta D/D_d)}$

ARTSENS utilizes a single element ultrasound transducer to interrogate the artery and obtain all relevant arterial dimensional measurements in an automated manner. The principle of image-free measurement and system architecture of ARTSENS is presented in Section II. This section explains the hardware designed to excite the transducer, receive echo signals from the artery and digitize the signals, and also provides a detailed description of algorithms used to extract required parameters from the echo signals. Section III gives the details of validation study of ARTSENS in a clinical setting. The study protocol and methods used for analyses are explained in this section. Section IV presents the results of the study, and illustrates the accuracy of ARTSENS by comparison with state of the art echo tracking system for evaluating carotid artery stiffness. The repeatability of ARTSENS measurements is also analyzed.

II. ARTSENS: SYSTEM ARCHITECTURE

The overall system architecture of the ARTSENS device is illustrated in Fig. 1. A single element ultrasound probe, operated in the pulse echo modality is used to investigate arterial dynamics. This probe, placed on the neck over the carotid artery, sends sharp pulses of high frequency ultrasound into the body that are reflected by the artery walls and other structures in the sound propagation path. These echoes are acquired by the same transducer, amplified and digitized. Intelligent signal processing and automated measurement algorithms automatically identify the arterial wall echoes, track wall motion and measure arterial distension (ΔD) and end-diastolic diameter (D_d) over multiple cycles. These are used to compute various measures of arterial stiffness such as stiffness index (β), pressure strain elasticity(E_p) and arterial compliance (AC).

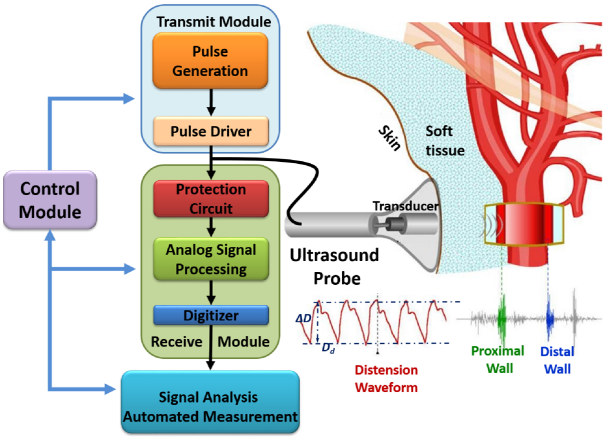

FIGURE 1. System architecture of ARTSENS.

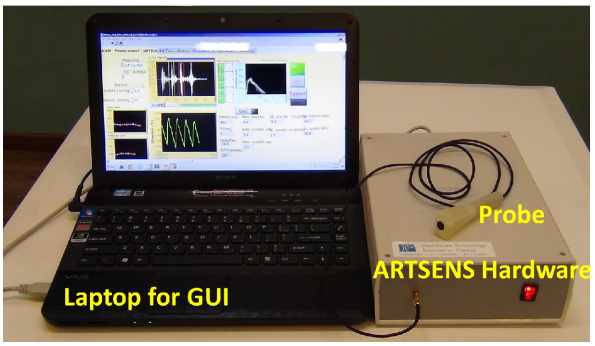

FIGURE 2. ARTSENS desktop prototype.

A desktop prototype of ARTSENS is shown in Fig. 2. The entire measurement is typically completed within a few minutes. The measurement requires no intervention from the operator other than positioning of the probe over the artery as illustrated in Fig. 3.

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FIGURE 3. **ARTSENS used to perform carotid artery stiffness measurement of a volunteer.**

A. HARDWARE

The hardware section of ARTSENS mainly includes three major sections, viz. the pulser and probe unit, analog front end and a high speed digitizer.

The system utilizes a single element 5 MHz ultrasound transducer (10 mm diameter, Hengxuannanshi, China). The ultrasound frequency of 5 MHz was selected based on the conflicting requirements of high resolution while ensuring required depth of penetration which is about 60 mm for measurements on carotid artery considering the attenuation coefficient of soft tissue as 0.7dB/cm/MHz [17]. The transducer's narrow half angle beam width of about 1.3° ensures that strong and distinct echoes will be obtained only when the transducer is kept normal to the artery.

FIGURE 4. **Single element ultrasound probes designed for ARTSENS.**

Custom designed probe housings were developed for the single element transducer, to enable easy operation. A few designs of the single element ultrasound probes are illustrated in Fig. 4. The white probe was used in the current study. The custom analog front end electronics hardware developed for ARTSENS is illustrated in Fig. 5. The board has a low voltage (+/− 15 V, 500 mA) power supply section for the digital logic and analog front end sections, and a high voltage (100 V, 50 mA) section used for ultrasound transducer excitation. Digital pulses generated using a microcontroller are translated to high voltage levels and used to excite the transducer in the pulse echo modality [17]. The reflected echo signals are then passed to an analog signal conditioning section consisting of a high pass filter of cut off frequency 2.56 MHz and a dual stage amplifier with a total gain of 40 dB. A transmit receive switch is used to protect the amplifier section from the high voltage transmit pulses.

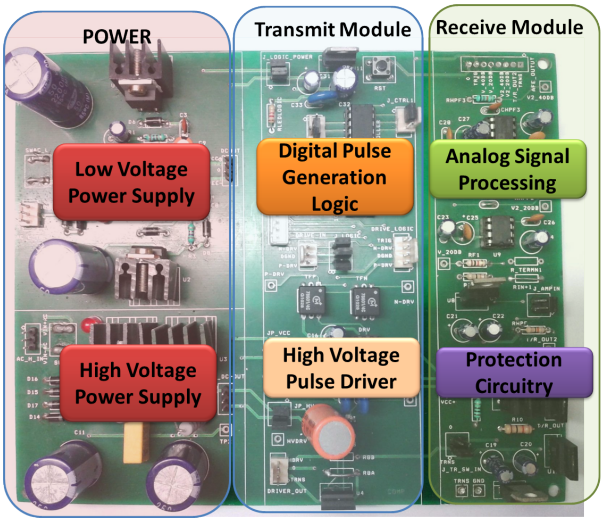

FIGURE 5. **Electronics hardware board used in ARTSENS.**

The conditioned analog signals are digitized at the rate of 100 MS/s using a NI USB 5133 high speed digitizer (National Instruments). The digitized signals, referred to as frames, are then given to subsequent signal processing algorithms for automated measurement.

B. SIGNAL PROCESSING AND MEASUREMENT ALGORITHM

The digitized signals are transferred in real time into a laptop computer and processed using a signal processing virtual instrument, developed in LabVIEW using state machine architecture. The major steps in the automated measurement algorithm are illustrated in Fig. 6.

1) PRE-PROCESSING AND WALL IDENTIFICATION

The raw ultrasound data frames (where each frame is defined as the echo obtained for a transducer excitation pulse) are pre-processed to improve its signal to noise ratio (SNR). The frames are filtered using a 4^{th} order zero phase Butterworth band pass filter with upper cut off frequency of 8 MHz and lower cut off frequency of 1 MHz and then passed through a time gain compensation (TGC) block to compensate for the signal attenuation encountered as it passes through the soft tissue, as seen in Fig. 7. The arterial near (proximal) and far (distal) walls are identified based on the inherent out of phase motion of the wall echoes, as the artery contracts and relaxes

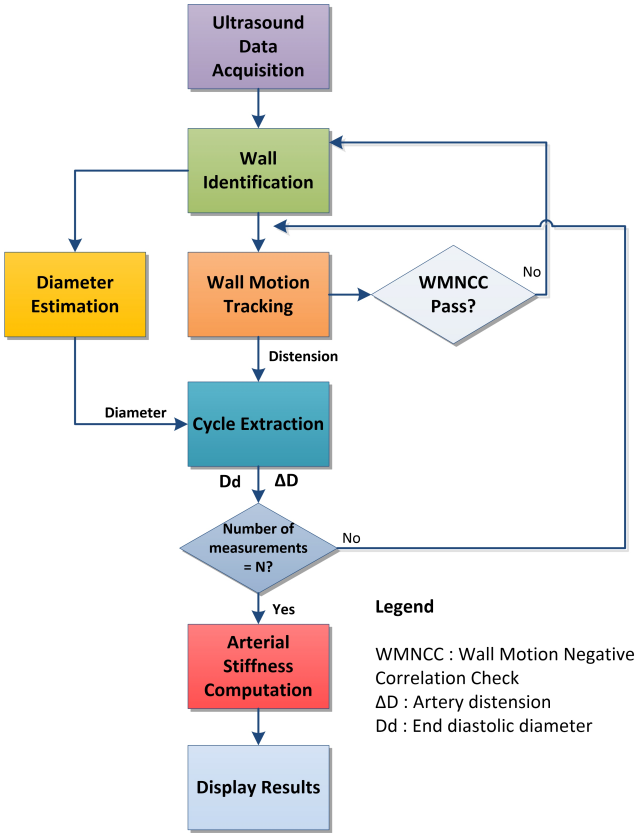

FIGURE 6. **ARTSENS signal processing and automated measurement algorithm flowchart.**

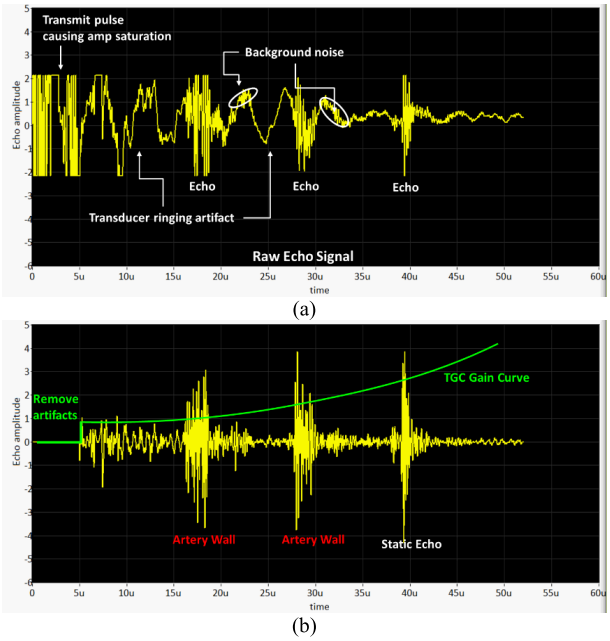

FIGURE 7. **(a) Raw echo signal (frame) received from the artery (b) Signal after pre-processing. Notice significant improvement in SNR, elimination of transducer ringing artefacts and compensation for echo attenuation to improve amplitude of farther echoes.**

during systole and diastole respectively [20]. The phase of wall motion is detected by locating artery wall echo peaks in the first frame, and then using the next few (5 to 10) frames to identify the two consecutive artery wall echoes that move opposite to each other.

2) WALL MOTION TRACKING AND DIAMETER CALCULATION

Once the artery wall locations are identified, the system goes to tracking state where the movements of near wall and far wall echoes are tracked for a few cardiac cycles as they move out of phase w.r.t each other in a quasi-periodic manner. Correlation based algorithm is used to find the shift in the echo location from that of the previous frame. Arterial distension $D(t)$ is calculated from each frame as the sum of relative near and far wall shifts w.r.t. the previous frame. The carotid artery lumen diameter is calculated as the distance between the intima layers on both walls, corresponding to the trailing edge of the near wall echo and leading edge of the far wall echo. A smoothened Hilbert envelope of the region of interest (ROI) is used for lumen diameter calculation [17], [18], [24].

3) WALL MOTION NEGATIVE CORRELATION CHECK (WMNCC)

A wall motion negative correlation check running simultaneously along with tracking ensures that tracking is done on near and far walls without fail [17], [23]. This is ensured by checking that the near and far wall echoes are moving opposite to each other, i.e., the absolute values of the near and far wall motion patterns have a negative correlation. If the condition is not satisfied, the system goes back to wall identification state.

4) CYCLE EXTRACTION AND ARTERIAL STIFFNESS COMPUTATION

The distension and diameter values as obtained from the tracking stage are recorded and stored in a buffer of size B, calculated as the number of points required to store distension of around two cardiac cycles. Once the buffer is filled, the valley locations are found out to obtain distension cycles, from which ΔD is calculated. The diameter values corresponding to these valley points in the distension array are identified as end diastolic diameters D_d [17].

Gaussian error elimination is performed to eliminate any random data which could have been included in the measurement. The arterial stiffness index (β), arterial compliance (AC) and pressure strain elasticity (E_p) are computed using valley to peak distension ΔD and end diastolic diameter D_d , measured by ARTSENS, and systolic and diastolic pressure (P_s and P_d), separately measured and entered by the operator prior to ARTSENS measurement.

C. TECHNOLOGY EVOLUTION OF ARTSENS

A snapshot of the various versions of the ARTSENS device that were developed is illustrated in Fig. 8. A desktop prototype was made initially for early laboratory studies. A tablet version was later developed to make ARTSENS more portable. The hardware for data acquisition and subsequent signal processing modules were embedded

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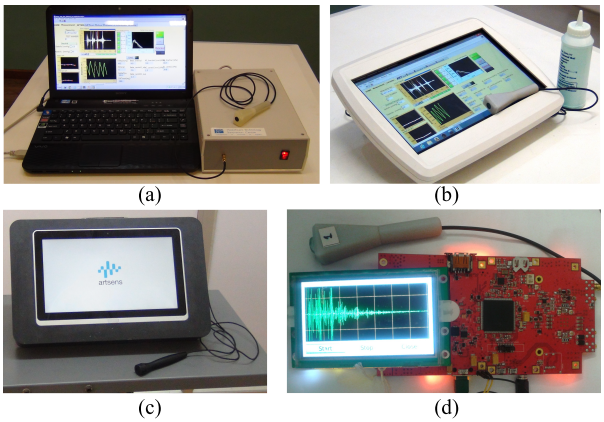


FIGURE 8. Technology evolution of ARTSENS (a) Desktop prototype (b) Tablet version (c) Rugged version for field deployment (d) Handheld version under development.

together in the device, making it easier for the operator to use. Further, a rugged version was designed for use in field settings. This had on-board battery and could also store the subject database. A small, portable handheld version of ARTSENS is also under development.

III. VALIDATION OF ARTSENS

The performance of the signal processing algorithms, the repeatability and reproducibility of the instrument and ARTSENS usability in controlled laboratory settings have already been validated and reported [19]–[22]. Here we present an extensive validation of ARTSENS in clinical setting. The objectives of this study are the following.

(a) To establish feasibility of ARTSENS measurements in clinical setting on large number of subjects
(b) To verify the ability of ARTSENS to provide accurate estimates of stiffness with the subject in sitting posture.
(c) To establish the measurement accuracy of ARTSENS in comparison with state of art image based ultrasound echo tracking system.

The ALOKA α10 Prosound e-Tracking system was taken as the reference equipment for evaluation of carotid artery stiffness [25]–[27].

A. VALIDATION STUDY PROTOCOL

The study was conducted at Thambiran Heart and Vascular Care Institute, Chennai. The procedure of arterial stiffness measurements and the overall study protocol approved by the Institutional Review Board are explained below and are shown in Fig. 9.

1) SUBJECT SELECTION

Male and female subjects, above the age of 18 years, with no documented history of cardiovascular or peripheral vascular disease were included. The subject pool consisted of 125 subjects from 20 to 75 years of age. All subjects were informed of the study objectives, backgrounds and protocol

FIGURE 9. ARTSENS validation study protocol (a) Informed consent (b) Blood pressure (c) Blood sampling (d) Anthropometry (e) ARTSENS measurement (f) ALOKA e-Tracking measurement.

before data collection and informed consents were obtained from them. Each subject was registered to the study with a unique identifier, and the personal details were filled in.

2) BLOOD SAMPLE COLLECTION

Fasting blood samples were collected for biochemistry investigation. Subjects were given a light breakfast and allowed to relax for at least 15 minutes before proceeding with measurements.

3) ANTHROPOMETRIC AND BP MEASUREMENTS

The height of subjects was measured using a tape with resolution 1 mm. Weight was measured using an automatic weighing scale with resolution 0.1 kg. Body composition was measured using an automatic body composition analyzer. Blood pressure at the brachial artery was measured using a sphygmomanometer in both sitting and supine position. The study was performed using brachial pressure measurements, to emulate field conditions.

4) ARTERIAL STIFFNESS MEASUREMENT

The stiffness of the carotid artery of each subject was evaluated both using ARTSENS, and also using an ultrasound echo tracking system (ALOKA α10 Prosound e-Tracking system).

5) MEASUREMENT USING ARTSENS

Subject was seated comfortably and allowed to relax for 5 minutes. The left carotid artery location was identified by palpation and the ultrasound probe was placed nearly 2.5 cm below the carotid bifurcation. The angle of the probe was adjusted to get strong echoes from the near and far wall of the artery. ARTSENS was configured to give the average of five measurement results where each measurement comprised of five continuous cycles of distension. Measurements were taken in sitting postures. Fig. 10 shows a screenshot of ARTSENS Graphical User Interface (GUI) indicating all measurements.

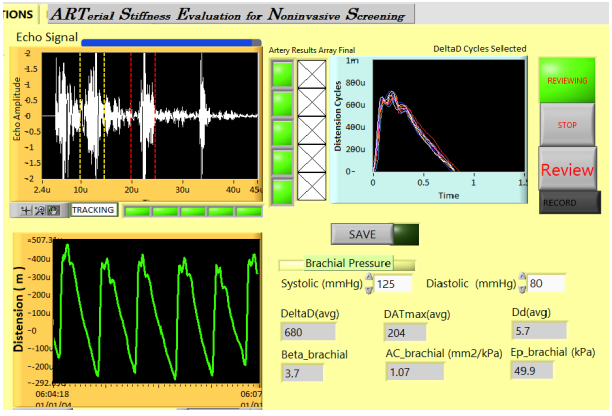


FIGURE 10. Screenshot of ARTSENS GUI indicating measurements.

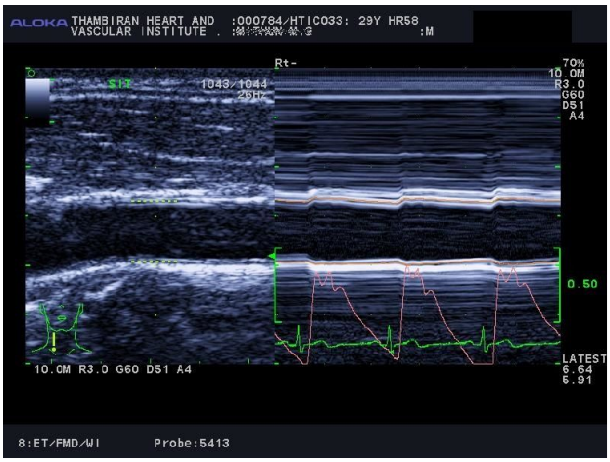
6) MEASUREMENT USING ALOKA E-TRACKING SYSTEM

For measurement using the e-Tracking system, 3-lead Electrocardiogram (ECG) was placed on the subject's body. The carotid vessel was imaged using a 10 MHz linear array probe. The near and far walls of the artery were manually identified on the B-mode image and the wall motion was tracked by the ALOKA α10 Prosound e-Tracking system.

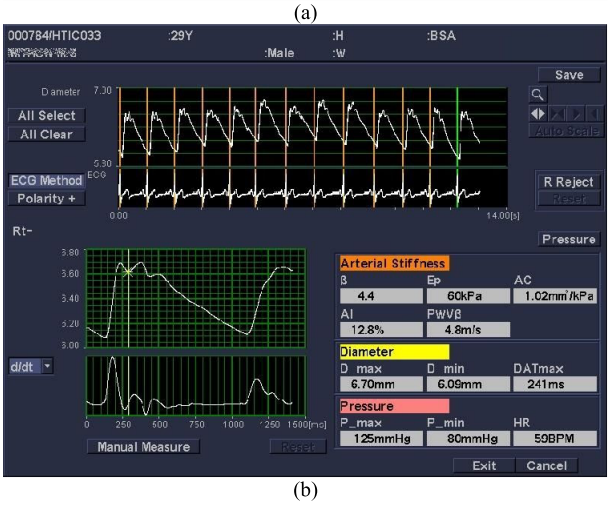
When a steady waveform was obtained for 4-5 cycles, image is frozen to acquire the data which were accumulated over the period to start arterial stiffness analysis. In the analysis window, agreeable waveforms were selected to perform analysis. Measurements were taken in both sitting and supine postures with corresponding systolic and diastolic pressures entered. Fig. 10 shows a screenshot of ALOKA measurement and post analysis screen.

B. STATISTICAL METHODS USED FOR ANALYSIS

The agreement between the arterial stiffness readings given by ARTSENS to those given by the ultrasound imaging system was first investigated by linear regression. Least square regression models, performing linear fit for stiffness estimates from imaging systems and those from ARTSENS were obtained under the assumption that random error is associated with only ARTSENS results and that the results from imaging system are true values without random errors. Further, a Bland Altman analysis was performed to



(a)



(b)

FIGURE 11. Screenshot of ALOKA e-Tracking (a) B-mode indicating cursor locations (b) Post analysis screen.

examine the degree of variation between the two readings. The limits of agreement were defined as $\pm 2SD$ [28]–[30]. Two ARTSENS measurements were performed on a few (n=33) randomly selected subjects. In such cases, the second trial was chosen for regression and Bland Altman analysis. The repeatability of measurements performed by ARTSENS was evaluated by computing coefficient of variability (repeatability) as the ratio of the standard deviation of the differences between the two ARTSENS measurements to the average of the means [31]. A trend analysis was also performed to investigate the ability of ARTSENS to detect age-related changes in arterial stiffness.

IV. RESULTS AND DISCUSSION

A. IN-VIVO MEASUREMENT CAPABILITY

A total of 125 subjects were included in the study. ARTSENS was used to measure the carotid artery stiffness of all these subjects. Typical time taken for a measurement was less than 5 minutes. There was no subject on whom measurement could not be performed. This demonstrated the ability of ARTSENS to perform in-vivo measurements of arterial stiffness. In very

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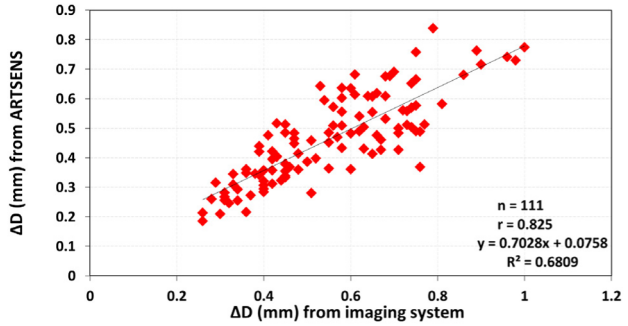

FIGURE 12. Comparison of arterial distension (ΔD) measurements from ARTSENS with those obtained from imaging system in sitting posture.

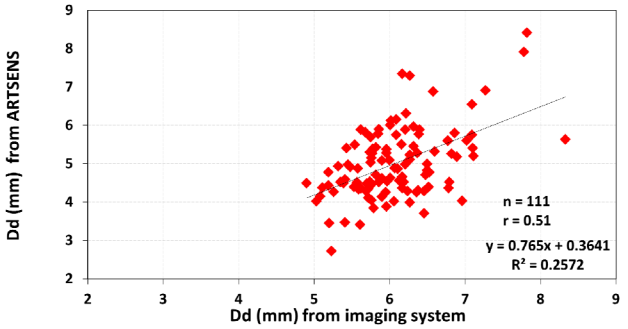

FIGURE 13. Comparison of end-diastolic diameter (D_d) measurements from ARTSENS with those obtained from imaging system in sitting posture.

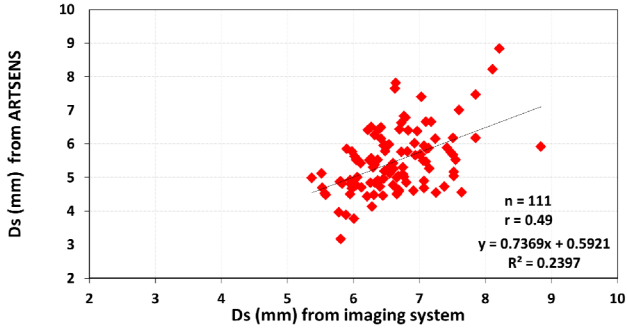

FIGURE 14. Comparison of systolic diameter (D_s) measurements from ARTSENS with those obtained from imaging system in sitting posture.

few cases, the measurement took more time, as it was difficult to position the probe at the correct location to get stable distension waveforms. It was also difficult to perform measurements using the imaging system in those cases.

B. DATA SELECTION AND OUTLIER ELIMINATION

Of the total 125 subjects, a few subjects on whom it was difficult to perform the measurements on the exact same locations due to change in posture or probe dimensions illustrated less repeatability in measurements. Such suspected cases of measurement error, in which there was significant variation in the stiffness values recorded by the two instruments (ARTSENS and ALOKA e-Tracking) were eliminated as outliers [28]. After eliminating a few suspected cases of data entry error and cases with missing data, a total of 111 subjects were selected for analysis. This represented 88 % of the total data set.

TABLE 2. Linear regression analysis of arterial stiffness measurements by ARTSENS with those given by imaging system in sitting posture.

Parameter		Imaging system in sitting Posture			
	r	R^2	Slope		Intercept
			Coeff.	p value	
Δ_D	0.82	0.68	0.703	<0.001	0.076
D_d	0.51	0.26	0.765	<0.001	0.364
D_s	0.49	0.24	0.737	<0.001	0.592
β	0.91	0.83	0.991	<0.001	-0.009
E_p	0.94	0.89	1.035	<0.001	-2.699
AC	0.77	0.59	0.579	<0.001	0.112

TABLE 3. Linear regression analysis of arterial stiffness measurements by ARTSENS with those given by imaging system in supine posture.

Parameter		Imaging system in supine posture			
	r	R^2	Slope		Intercept
			Coeff.	p value	
Δ_D	0.81	0.65	0.641	<0.001	0.102
D_d	0.48	0.23	0.753	<0.001	0.347
D_s	0.46	0.22	0.703	<0.001	0.724
β	0.81	0.66	0.845	<0.001	0.592
E_p	0.89	0.79	0.938	<0.001	3.402
AC	0.67	0.45	0.411	<0.001	0.253

C. STATISTICAL ANALYSIS OF MEASUREMENT ACCURACY

1) LINEAR REGRESSION ANALYSIS

A summary of the linear regression analysis is provided in Table 2 and Table 3. All the ARTSENS measurement results, viz. ΔD, D_d, D_s, β, AC and E_p were found to have a strong positive correlation with the corresponding values obtained from the imaging system, measured in sitting posture, as indicated in Table 2. Arterial distension measured using ARTSENS was found to have a correlation coefficient (r) of 0.82 with the value given by the imaging system. The correlation of both end-diastolic diameter and systolic diameter were observed to be 0.5. This slightly lower values of correlation coefficient are expected in direct comparison of dimensional measurements, as these measurements were performed sequentially, using two different instruments and hence perfect matching of the site of measurement is not possible due to practical limitation of positioning the larger imaging probe on the exact same location as that of the smaller ARTSENS probe. Moreover, physiological variations in arterial distension with time, associated with slight changes in the instantaneous blood pressure values, also affect this result.

However, the material property of the vessel wall is not expected to show such significant variations, especially under controlled settings as was achieved in the study. This is also illustrated by the high correlation coefficient value of 0.9 of the β stiffness index value measured by ARTSENS with respect to that given by the imaging system, as shown in Fig. 15. The pressure strain elastic modulus (E_p) measured by ARTSENS also shows strong correlation with those obtained using the imaging system, with a correlation coefficient of 0.94. The correlation of arterial compliance (AC), was lower (0.77), owing to its direct dependence on dimensional parameters.

Strong correlation was observed even when the ARTSENS stiffness estimates measured on subjects in sitting posture were compared with those made using the imaging system on subjects in supine posture. It may be observed from Table 3, that the arterial stiffness estimates (both β and E_p) measured by ARTSENS showed strong correlation, with r values of 0.81 and 0.89 respectively. The r values of arterial distension and end-diastolic diameter were 0.81 and 0.48 respectively. It may be remembered that there is a difference in the arterial pressures, both systolic and diastolic, when the subject moves from sitting to supine posture, and this will cause corresponding differences in the arterial distension and end-diastolic diameter values.

However, the strong observed correlation of arterial stiffness estimates validates the use of ARTSENS to evaluate stiffness in the sitting posture. This is relevant, as a supine measurement may not be often possible in field settings, when ARTSENS is deployed for screening.

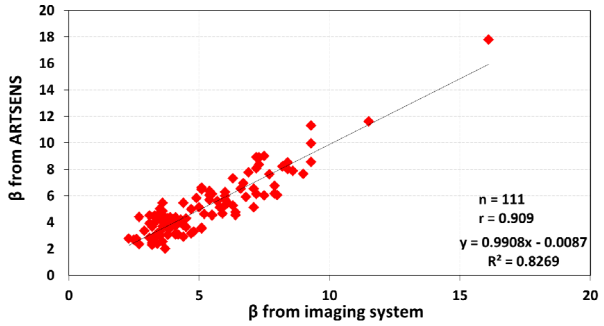

FIGURE 15. Comparison of stiffness index (β) measurements from ARTSENS with those obtained from imaging system in sitting posture.

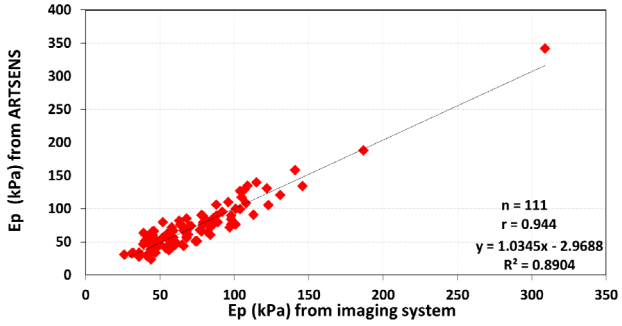

FIGURE 16. Comparison of pressure strain elastic modulus (E_P) measurements from ARTSENS with those obtained from imaging system in sitting posture.

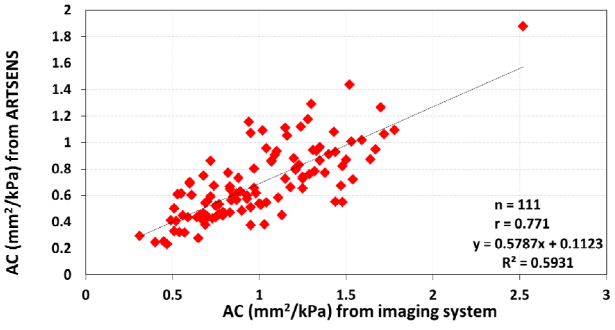

FIGURE 17. Comparison of arterial compliance (AC) measurements from ARTSENS with those obtained from imaging system in sitting posture.

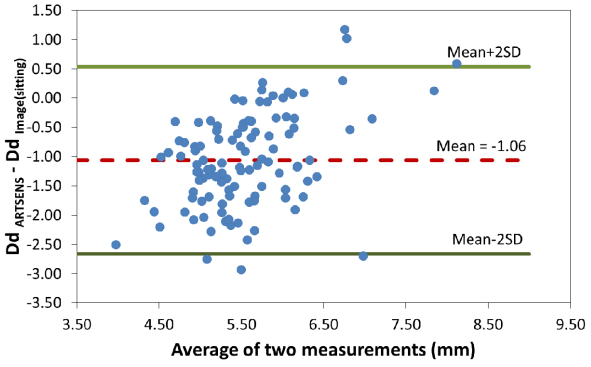

FIGURE 18. Bland Altman plot of end diastolic diameter (D_d) measured from ARTSENS ($Dd_{ARTSENS}$) and imaging system in sitting posture ($Dd_{Image(sit)}$).

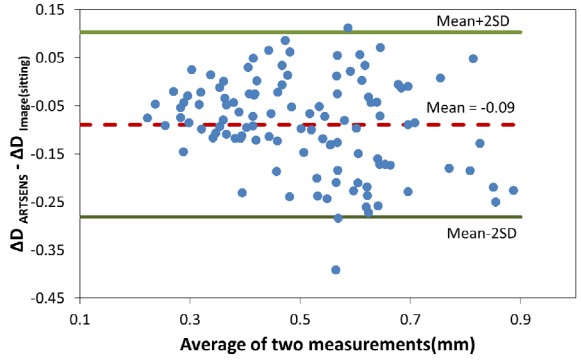

FIGURE 19. Bland Altman plot of arterial distension (ΔD) measured from ARTSENS ($\Delta D_{ARTSENS}$) and imaging system in sitting posture ($\Delta D_{Image(sit)}$).

2) BLAND ALTMAN ANALYSIS

To evaluate the degree of agreement between stiffness measurements provided by ARTSENS and the imaging system, Bland-Altman plots with limits of agreement defined as $\pm 2SD$ [24]–[26], were created for all the directly measured parameters and the stiffness estimates. This is illustrated in Fig. 18 to Fig. 22. The corresponding histograms showing the distribution of differences are shown in Fig. 23 - Fig. 25.

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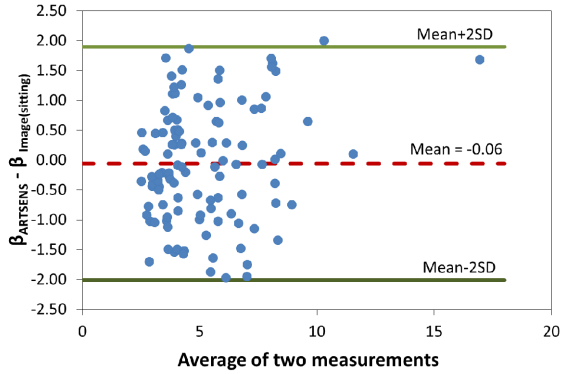

FIGURE 20. Bland Altman plot of arterial stiffness index (β) measured from ARTSENS ($\beta_{ARTSENS}$) and imaging system in sitting posture ($\beta_{Image(sit)}$).

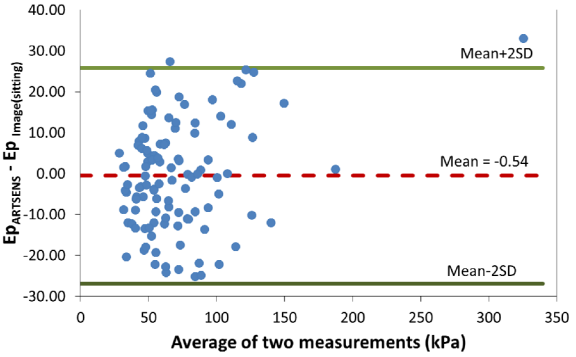

FIGURE 21. Bland Altman plot of pressure strain elastic modulus (E_p) measured from ARTSENS ($Ep_{ARTSENS}$) and imaging system in sitting posture ($Ep_{Image(sit)}$).

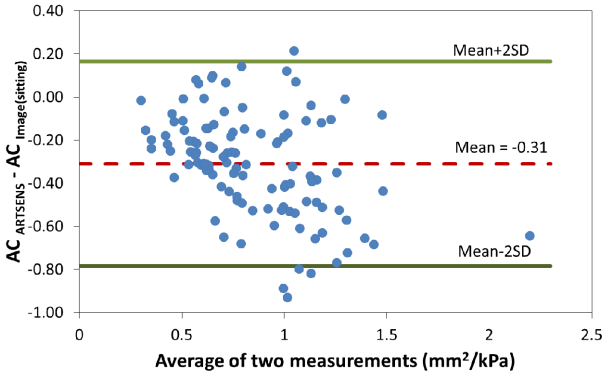

FIGURE 22. Bland Altman plot of arterial compliance (*AC*) measured from ARTSENS ($AC_{ARTSENS}$) and imaging system in sitting posture ($AC_{Image(sit)}$).

It may be observed that there is a high degree of agreement between ARTSENS readings and stiffness values provided by the imaging system. The mean of differences, known as the bias, for directly measured artery dimensional parameters is slightly higher than those reported in literature using image based systems [32], owing to reasons explained earlier in Section IV.C1. The bias is close to zero for the arterial stiffness results β and E_p, showing that ARTSENS is not

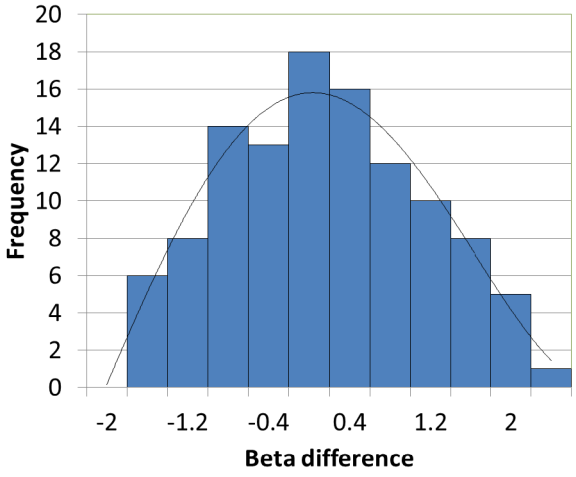

FIGURE 23. Distribution of the differences between Beta measurements given by ARTSENS and imaging system in sitting posture.

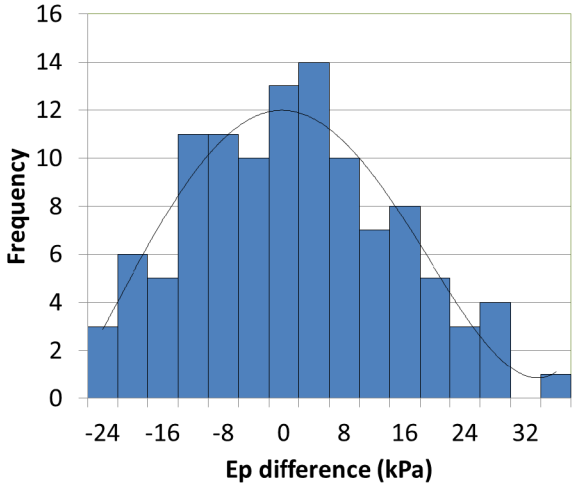

FIGURE 24. Distribution of the differences between E_p measurements given by ARTSENS and imaging system in sitting posture.

expected to underestimate or overestimate the stiffness values. It can be also be inferred from the plots that the bias and the limits of agreement are very low when compared to the absolute values of the parameters measured. The variability in measurements exhibits even distribution in all plots, irrespective of the magnitude of the value measured.

Table 4 summarizes the results obtained from Bland-Altman analysis. It may be noted that the analysis also takes into account the minor differences introduced owing to minor changes in probe location and subject physiology as the measurements are performed sequentially.

Mean difference between the β measurements given by imaging system and ARTSENS was found to be 0.06 ± 1.04, indicating no bias in measurement. Bland Altman plot indicates the difference to be randomly distributed, with 99% of the measurements within $\pm$2SD as shown in Fig. 20. As per the calculated limits of agreement, the difference between the stiffness index measurements, β is less than 2, which

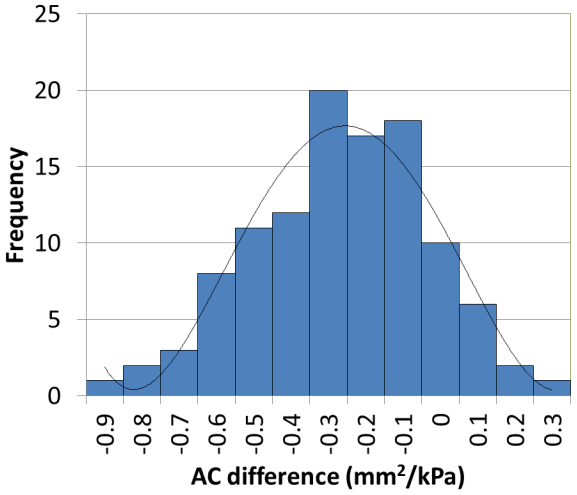

FIGURE 25. Distribution of the differences between *AC* measurements given by ARTSENS and imaging system in sitting posture.

TABLE 4. Results of Bland Altman analysis of arterial stiffness measurements by ARTSENS with those given by imaging system in sitting posture.

Parameter measured	Mean (Bias)	Standard Deviation
ΔD (mm)	-0.09	0.096
D_d (mm)	-1.06	0.800
β	-0.06	0.976
E_p (kPa)	-0.54	13.180
AC (mm^2/kPa)	-0.31	0.237

is within clinically acceptable limits of variation expected in stiffness [15] for estimation of local arterial stiffness for screening [33]. The noticeable bias in the lumen diameter measurement may be attributed to the fact that the automated algorithm in ARTSENS measures the inner lumen diameter, whereas it is normally difficult to locate lumen interface on ultrasound imaging system and hence the measurement by imaging system is expected to overestimate the diameter [34].

It may be observed that AC measured by ARTSENS express slightly higher bias and limits of agreement when compared to the absolute value of measurement. Also, as already mentioned, the correlation of AC between the two methods was slightly lower when compared to other stiffness readings. Hence it may be concluded that AC is not the best measure of arterial stiffness provided by ARTSENS. The stiffness index, β, and the elastic modulus E_p, are the best estimates of stiffness provided by ARTSENS.

3) REPEATABILITY OF ARTSENS MEASUREMENTS

Two ARTSENS measurements were performed on a few randomly selected subjects (n=33). The repeatability and reproducibility of ARTSENS in a controlled environment has already been reported [23]. The repeatability of the arterial stiffness index value (β), pressure strain elasticity (E_p), arterial compliance (AC), distension (ΔD) and

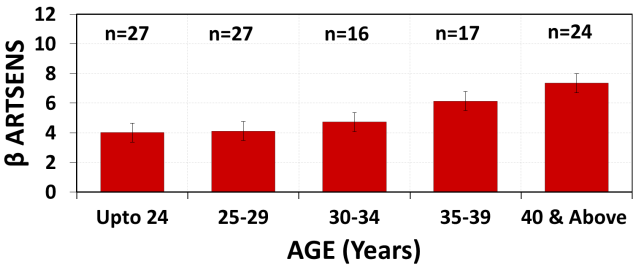

FIGURE 26. Age related increase in stiffness index (β), measured using ARTSENS.

end diastolic diameter (D_d) were analysed to investigate the performance of the device in field.

The coefficient of variability (repeatability) computed as the ratio of the standard deviation of the differences between the two ARTSENS measurements to the average of the means was calculated from the data. The calculated coefficients of variability shown in Table 5 are comparable to the previously reported results on carotid stiffness measurements performed using ARTSENS and other ultrasound imaging systems [11], [14], [15], [23], [35]. This indicates the ability of the instrument to give precise measurements of stiffness irrespective of the field conditions.

TABLE 5. Coefficients of repeatability for ARTSENS measurements.

Parameter measured	Coefficient of repeatability (variability) in %
ΔD (mm)	8.45
D_d (mm)	10.52
β	15.31
E_p (kPa)	13.99
AC (mm^2/kPa)	16.59

D. AGE RELATED CHANGES IN ARTERIAL STIFFNESS

To investigate the ability of ARTSENS to detect subtle changes in arterial stiffness, the data was analyzed to examine if ARTSENS could pick up trends in arterial stiffness associated with age. To eliminate the influence of other factors that may affect stiffness, subjects under medication were eliminated from this analysis. No subjects recruited in the study had any history of cardiovascular disease. A total of 102 subjects were included in this age-trend analysis.

To study the trend in variation of each parameter with age, the mean and standard deviation of stiffness index (β), pressure strain elastic modulus (E_p) and arterial compliance (AC) in sitting posture were calculated for different age bins. As the age of the subjects recruited for the study was slightly skewed towards the younger age group, a classification based on age quartiles will not properly reflect the age related changes in arterial stiffness. Hence age bins selected for analysis were chosen to ensure nearly uniform distribution of the overall subject pool among the various age bins.

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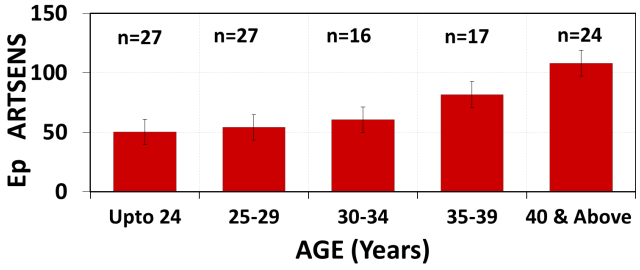

FIGURE 27. Age related increase in pressure strain elastic modules (E_p) measured using ARTSENS.

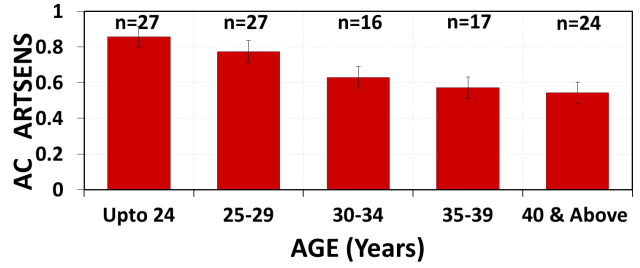

FIGURE 28. Age related decrease in arterial compliance (*AC*) measured using ARTSENS.

The results are illustrated in Fig. 26 to Fig. 28. A strong positive trend between arterial stiffness measures and age could be inferred from these plots. This illustrates the ability of ARTSENS to detect subtle changes in arterial stiffness that occurs due to ageing, thereby indicating potential use in vascular screening and diagnosis.

E. ADVANTAGES OF ARTSENS OVER IMAGE-BASED SYSTEMS

Unlike the commercially available image-based systems, ARTSENS has completely automated measurement and is the only image free system available for direct measurement of arterial dimensions to evaluate stiffness. Because of its image free technology, an expert ultrasonographer is not required for performing the measurement. The time taken for measurement (typically 5 minutes) is much less than that required for image-based systems, and the measurement procedure is simple and less laborious. The portable nature of the instrument and the ability of the intelligent algorithms to quickly perform the measurement without any operator input make it very amenable for field deployment.

F. LIMITATIONS OF ARTSENS

ARTSENS measurements could not be performed on few volunteers, where the artery was very superficial due to which the near wall could not be identified clearly. The use of a silicone delay block can help in such cases. The hardware of the device is being improved to reduce the apparent blind spot close to the probe surface, by increasing the transducer damping. In all subjects whose data were eliminated as outliers in this study, the quality of the echo signal was found to be very low, as the artery walls could not be distinguished clearly. The enforcement of a stricter protocol of probe positioning and angulation to ensure high quality echo signals during measurement will eliminate such cases. An automated signal quality evaluation algorithm is being developed to avoid this in screening scenarios.

V. CONCLUSION

A novel image free instrument for non-invasive evaluation of arterial stiffness, called ARTSENS was presented. ARTSENS uses a single element ultrasound probe, and is an affordable, compact, user friendly device for measurement of arterial stiffness. The hardware and software architecture of the system was explained. The ability of ARTSENS to easily perform in-vivo measurement of carotid artery stiffness was verified by the study conducted on 125 subjects. The accuracy of the measurements provided by ARTSENS was verified by comparing with a reference, state of art ultrasound imaging system. The stiffness estimates provided by ARTSENS strongly correlated with those obtained using the imaging system. Bland Altman analysis demonstrated significant degree of agreement between ARTSENS measurements and imaging system measurements. The results show that ARTSENS is at par with state of art technology for measurement of arterial stiffness. Measurements of β stiffness index, considered to be better estimate, as it characterizes stiffness independent on distending pressure, was found to be repeatable and accurate in ARTSENS. ARTSENS device demonstrated enough sensitivity to detect age related trends in arterial stiffness, thereby indicating potential for use in large scale screening studies. ARTSENS allows quick and easy measurement of arterial stiffness even in sitting posture, and its automated measurement algorithms allow it to be used by any operator with minimal training. ARTSENS can thus be deployed in primary or secondary care facilities, and even in field scenarios, thereby making vascular stiffness measurements feasible in large scale epidemiological studies as well as for early detection and screening. The relative significance of various measures of stiffness, and normative values in Indian population would be explored in future epidemiological studies using ARTSENS.

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