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PAPER

Comparison of measurement of the augmentation index from ARTSENS and eTRACKING

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Ashish Kumar Sahani[1,5], **Jayaraj Joseph**[2], **Ravikumar Radhakrishnan**[3], **Mohanasankar Sivaprakasam**[1,2] **and Suresh Seshadri**[4]

[1] Department of Electrical Engineering, Indian Institute of Technology Madras, India
[2] Healthcare Technology Innovation Centre, Indian Institute of Technology Madras, India
[3] Thambiran Heart and Vascular Institute, Chennai, India
[4] MediScan Systems, Chennai, India
[5] Author to whom any correspondence should be addressed.

E-mail: ee10d043@ee.iitm.ac.in

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Abstract

Over past few years our group has been developing a fully automated and low-cost device, ARTSENS (ARTerial Stiffness Evaluation for Non-invasive Screening), to enable non-experts to measure arterial stiffness (AS). It uses a single element ultrasound transducer to obtain A-mode frames from a superficial artery such as the common carotid artery (CCA) and analyzes them to obtain the stiffness parameters of the vessel. We have earlier demonstrated that ARTSENS can accurately measure local arterial stiffness (LAS) and regional arterial stiffness (RAS) by tracing the distension waveforms of the CCA and the femoral artery. In this paper, we show that it is possible to estimate the augmentation index (AIx), a measure of the global arterial mechanics, from the distension waveforms obtained by ARTSENS. AIx measurements from ARTSENS are compared against the state-of-the-art Hitachi-Aloka eTRACKING system for 107 volunteers. Both devices show excellent agreement with a correlation coefficient (r) $= 0.82$ ($p < 0.0001$), which is comparable to similar studies reported in the literature. This development makes ARTSENS a unique device that can measure the three most widely used indices of arterial mechanics—LAS, RAS and the AIx.

1. Introduction

Cardiovascular disease (CVD) causes the highest number of worldwide deaths. In 2008, it caused 17 million deaths, out of which four million occurred at less than 60 years of age, that were largely preventable [1]. Progression of CVD is asymptomatic in nature and the early diagnosis of pathological changes in arterial walls can be the key to the prevention of morbidity and death [1]. The development of atherosclerosis leads to the cumulative stiffening of arterial walls and the evaluation of arterial stiffness (AS) has emerged as an important prognostic marker for estimating risk of future CVD.

Over the years, different indices of AS have been explored by multiple investigators out of which elastic modulus (Ep), pulse wave velocity (PWV) and the augmentation index (AIx) have emerged as the most effective risk predictors. Ep is a measure of local arterial stiffness (LAS). It is generally evaluated for elastic central arteries such as the common carotid artery (CCA) using an ultrasound-based echo-tracking method. PWV is a measure of regional arterial stiffness (RAS). In addition, the AIx is considered as a global surrogate index of arterial mechanics with the influence of arterial function, PWV, wave reflections and heart rate [2].

Unfortunately, most of the technologies to evaluate AS are expensive and require expert handling. 80% of all CVD-related deaths occur in low and middle-income countries [1] where there is a paucity of high-end medical facilities and trained professionals. To cater to this situation, our group has been developing ARTSENS, a new AS measurement device that is fully automated to enable non-expert handling [3]. ARTSENS uses just a single element ultrasound transducer which makes it very low-cost and portable compared to existing ultrasound-based technologies. In a series of earlier publications, we have demonstrated the capability of ARTSENS for the fully automated

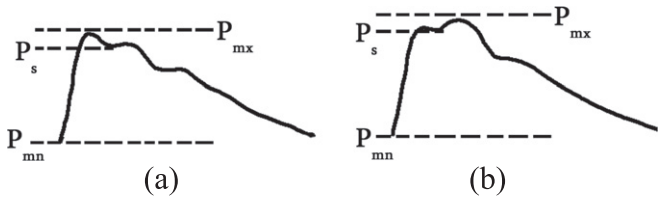

Figure 1. (a) This shows an aortic pressure pulse with a negative AIx; the shoulder occurs after the maximum value. (b) This shows an aortic pressure pulse with a positive AIx; the shoulder occurs before the maximum value. In both cases the absolute value of the AIx is given by equation (1).

measurement of LAS and RAS [3–10]. It has been validated against the state-of-the-art Ep measurement device Hitachi-Aloka eTRACKING [9] and the cfPWV measurement device SphygmoCor [4] where we have demonstrated excellent agreement. The Ep is derived from the distension waveforms obtained from ultrasound echo-tracking in both ARTSENS [3] and eTRACKING [11]. In addition to the Ep, eTRACKING also estimates the AIx by processing the distension waveforms [11]. In this paper, we attempt to estimate the AIx values from the distension waveforms obtained from ARTSENS and compare them with the results obtained from eTRACKING. It has been suggested that a single measure of AS might not be sufficient to characterize the development of CVD and a combination of multiple parameters are needed for a more complete characterization [12]. Currently, there is no device that can give all the three measures of AS. As ARTSENS already measures the Ep [9] and cfPWV [4], an estimate of the AIx would constitute a valuable addition to the overall utility of the system.

2. What is the AIx?

The AIx characterizes the reflected pressure waveforms and is conventionally obtained by analyzing the aortic pressure waveform (APW) [13]. Two typical APWs are shown in figure 1. To determine the AIx, we need to locate the first shoulder of the APW after the systolic rise, where 'shoulder' is defined as the first inflection point after the beginning of the systole. Augmentation pressure is defined as the pressure difference between the shoulder P_s and the maximum value P_{mx} of the APW. The AIx is defined as the ratio of the augmentation pressure to the pulse pressure (figure 1; see also equation (1)). The AIx is negative if P_s occurs after P_{mx} (figure 1(a)); it is negative otherwise (figure 1(b)).

$$|\mathrm{AIx}| = \frac{(P_{mx} - P_s) \times 100}{P_{mx} - P_{mn}}$$

P_{mx} = Maximum systolic pressure,
P_s = Pressure at the shoulder of the pressure pulse and
P_{mn} = Minimum diastolic pressure (1)

3. An overview of the ARTSENS system

ARTSENS uses a single element ultrasound transducer with a center frequency of 5 MHz. The transducer is excited with high voltage pulses at a pulse rate of 50 Hz. After firing each pulse the received echoes are sampled at a rate of 100 mega samples per second for about 52 μs. Thus each frame of data contains about 5200 points and we have about 130 points per mm (assuming velocity of sound as 1540 m s^{-1} in tissues). The frame rate equals the pulse rate. A typical frame of ARTSENS obtained from the CCA can be seen in figure 2.

The transducer has a poor *off*-axis sensitivity and a narrow beam angle (1.3° half-angle) which ensures that significant echoes are received only due to perpendicular reflections from the walls. *Off*-axis reflections have a poor signal quality [14] that is automatically rejected by intelligent wall identification [15] and signal parametrization algorithms [16], reported by us earlier. For details of the hardware implementation of ARTSENS, the reader can refer to our past publications [3, 4, 8, 9].

As ARTSENS is an imageless system, it assists the operator in the placement of the probe and automatically identifies echoes from the arterial walls [5, 7, 15]. Once the wall locations are identified, they are tracked over successive radiofrequency (RF) frames to obtain D (figure 2). Smooth and high resolution distension waveforms can be obtained by tracking the echoes over the RF frame sequences [17]; all distension traces in this paper are unfiltered. Each frame contributes one point to the distension waveform and thus the resolution of D is 50 points per second. All significant components of the power spectrum of a cardiac pulse waveform are contained within 10 Hz [18, 19]. Thus, as per the Nyquist criterion a sampling rate of 50 Hz is more than sufficient for a faithful representation of D. A typical distension waveform obtained from ARTSENS is shown in figure 3.

4. Pressure diameter relationship and validity of the measurement

As the AIx is a measure of the reflection of pressure waves, ideally, it should be measured from the pressure

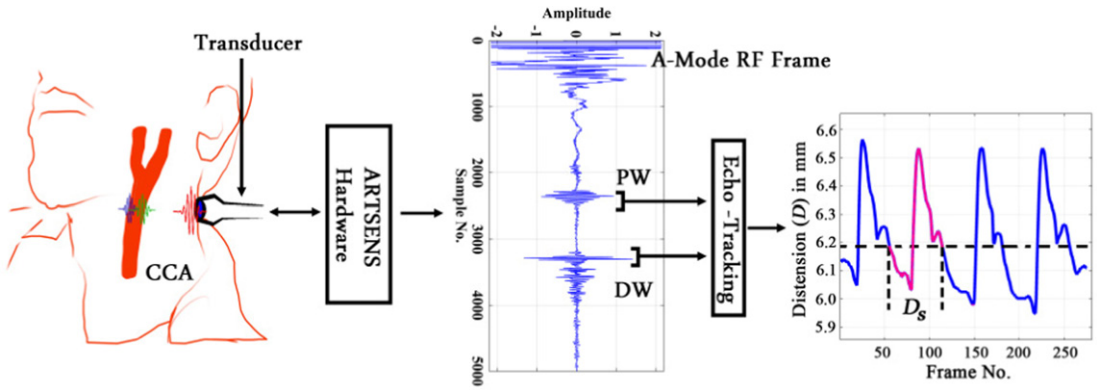

Figure 2. This figure shows the placement of the single element ultrasound probe over the CCA. The ARTSENS hardware excites the transducer with high voltage pulses at regular intervals (≈20 ms). The reflected echoes are digitized to obtain the A-mode frames. One frame is obtained after each pulse. The ARTSENS software assists the operator in the placement of the probe. Once the probe is on the artery, it automatically locates the echoes from the proximal wall (PW) and the distal wall (DW) [7, 15]. The PW and DW are tracked; over successive frames to obtain the distension waveform (D). D is sliced to obtain individual cardiac cycles D_s using one of the methods reported by us earlier [8].

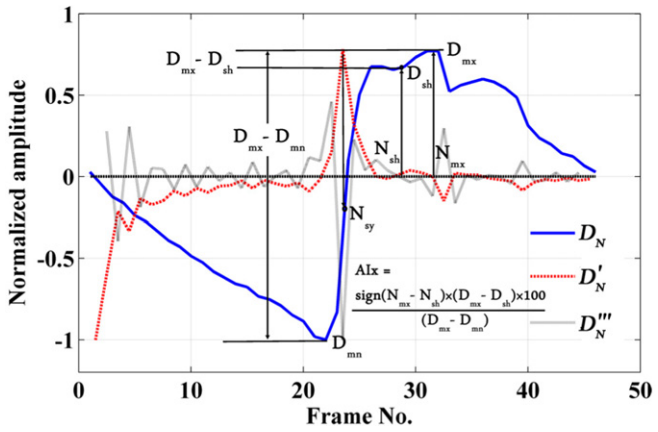

Figure 3. This shows a typical D_N (equation (2)) obtained from the CCA using ARTSENS. D'_N and D'''_N are overlaid. Shoulder point (N_{sh}) is given by the first positive to negative zero crossing of D'''_N after N_{sy}. See equation (3) for definitions of the variables.

waveforms [13, 20]; tomometric systems like SphygmoCor can measure this parameter with an higher accuracy compared to echo-tracking systems like eTRACKING that base their measurement on D. But prior studies have shown that pressure and diameter waveforms from the CCA are highly correlated [21] and distension-based measurements of the AIx can be used as a reasonable estimate of the actual AIx especially at the CCA site [22]. But it is well-known that CCA walls have vasoelastic properties and there is a slight non-linear relationship between its pressure and diameter [23] due to which the diameter-based AIx cannot be considered very accurate. Even then, reasonable estimates of the AIx can be useful in supporting the conclusions derived from the Ep and the PWV and, we believe that this would be a valuable addition to the existing ARTSENS system.

5. Calculation of the AIx

D is sliced into individual cardiac cycles by using either zero-crossing or ECG-based methods presented by us in our recent publication [8]. A sliced cardiac cycle is denoted by D_s (figure 2). We obtain the normalized diameter D_N using equation (2).

$$D_N = \frac{D_S - \overline{D_s}}{\max(|D_S - \overline{D_s}|)} \tag{2}$$

The key step in the calculation of the AIx is the determination of the first shoulder point of D_N occurring at the sample N_{sh}. N_{sh} is marked by locating the first positive to negative zero crossing of the third derivative of D_N, after the systolic rise [24]. We mark the systolic rise of D_N at N_{sy}, the point of its maximum first derivative. Finally, the AIx is calculated by

equation (3). Figure 3 illustrates a typical D_N obtained from ARTSENS. D'_N, D'''_N and all relevant points required for calculation of the AIx are also shown.

$$\begin{aligned} \mathrm{AIx} &= \frac{(\mathrm{N_{mx}} - \mathrm{N_{sh}}) \times (\mathrm{D_{mx}} - \mathrm{D_{sh}}) \times 100}{|(\mathrm{N_{mx}} - \mathrm{N_{sh}})| \times (\mathrm{D_{mx}} - \mathrm{D_{mn}})} \\ \mathrm{D_{mx}} &= \text{Maximum systolic diameter}, \\ \mathrm{D_{mn}} &= \text{Minimum diastolic diameter}, \\ \mathrm{D_{sh}} &= \text{Pressure at the shoulder of } D_N, \\ \mathrm{N_{mx}} &= \text{Sample no. of } \mathrm{D_{mx}}, \\ \mathrm{N_{sh}} &= \text{Sample no. of } \mathrm{D_{sh}} \end{aligned} \quad (3)$$

The sample corresponding to the shoulder point needs to be identified as accurately as possible. The derivative of discrete data has sample shift issues. For example, if D_N was sampled at t_0, t_1, $t_2, \ldots, t_n$ then D'_N is given by equation (4) which is only known at $\left(\frac{t_0+t_1}{2}\right)$, $\left(\frac{t_1+t_2}{2}\right)$, $\left(\frac{t_2+t_3}{2}\right)$, …, $\left(\frac{t_{n-1}+t_n}{2}\right)$. This means that while the first sample of D_N was at t_0, the first sample of D'_N is at $\left(\frac{t_0+t_1}{2}\right)$.

$$D'_N\left(\frac{t_{n-1}+t_n}{2}\right) = \frac{D_N(t_n) - D_N(t_{n-1})}{(t_n - t_{n-1})} \quad (4)$$

We use spline interpolation to recalculate D'_N at sample times t_0, t_1, $t_2, \ldots, t_n$. A similar process is followed to obtain D'''_N at t_0, t_1, $t_2, \ldots, t_n$. This realigns D_N, D'_N and D'''_N such that they appear to be sampled at the same times. The AIx determination was performed using these realigned waveforms.

During each measurement, spanning over few seconds, we generally obtain a few tens of cardiac cycles. For each cardiac cycle, we get one estimate of the AIx. Motion artefacts can lead to sudden shifts in the distension plots which in turn can lead to erroneous estimates of the AIx. To minimize this effect, the final value of the AIx is taken as the median of estimates from all cardiac cycles.

6. Validation study

We designed a study to validate the accuracy of AIx measurements from ARTSENS. The following subsections give the details of this study.

6.1. Subjects

The study was conducted on datasets obtained from 107 volunteers. Twenty-seven of these volunteers (mean age = 32 ± 5, 14 females) were recruited at MediScan Systems, Chennai and the remaining 80 volunteers (mean age = 34 ± 11, 16 females) were recruited at the Thambiran Heart and Vascular Institute, Chennai. This study was conducted in conformity with the World Medical Association Declaration of Helsinki. Informed consent was obtained from all subjects following an explanation about the operational aspects of ARTSENS and the procedure of the experiment.

Table 1. Anthropometric and BP statistics for all subjects.

	Weight (kg)	Height (cm)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Mean	68.5	165.2	121.5	78.4
SD	13.9	9.8	12.8	10.0

6.2. Devices and protocols

First of all, anthropometric data was recorded for all volunteers. After allowing the patient to relax for 10 min, their blood pressure (BP) was measured using a standard sphygmomanometer. The mean and standard deviation of the anthropometric values and the BP are tabulated in table 1. Then the AIx of the CCA was measured by a trained radiologist using the Hitachi-Aloka eTRACKING System for each volunteer. Immediately after this, the AIx was measured using ARTSENS by the same operator. All measurements were entered into a spreadsheet for further analysis.

6.3. Results

We compiled the AIx calculated by ARTSENS and eTRACKING for all volunteers and subsequently performed a regression analysis (figure 4(a)) and a Bland–Altman analysis [28](figure 4(b)). The AIx from ARTSENS is denoted by $\mathrm{AIx_A}$ and the one from eTRACKING is denoted by $\mathrm{AIX_e}$. From regression analysis, we found the best linear model to predict $\mathrm{AIx_e}$ from $\mathrm{AIX_A}$ as $\mathrm{AIx_e} = 0.95 \times \mathrm{AIx_A} - 1.13$ which is very close to the ideal relationship $\mathrm{AIx_e} = \mathrm{AIx_A}$. The Pearson's correlation coefficient (r) is 0.82 with a p-value of less than 0.0001 which means $\mathrm{AIx_A}$and $\mathrm{AIx_e}$ are strongly positively correlated. The mean bias between $\mathrm{AIx_e}$and $\mathrm{AIx_A}$ is −1.5 with 95% confidence intervals between −3.0605 to 0.0398. The paired t-test gives a p-value of 0.06 which means that the difference between $\mathrm{AIx_e}$ and $\mathrm{AIx_a}$ is statistically insignificant. The Bland–Altman plot shows that the 95% limits of agreement (LoA) are between 14.3% and −17.4%. Table 2 gives a summary of prior comparison studies between different devices measuring the AIx. Clearly, the correlation, mean bias and 95% LoA obtained for ARTSENS are comparable to the results of comparison studies reported in literature, by other authors.

7. Limitations of the current study

The diameter-based AIx is an indirect estimate of the AIx. As the AIx is a measure of the augmentation pressure, a validation study against pressure-based AIx measurements would have been a stronger marker of accuracy. The data for this study was collected as a part of the LAS validation of ARTSENS against eTRACKING [9, 29]. As the LAS measurement does not need CCA pressure waveforms, they were not recorded during this study. There is the scope of further

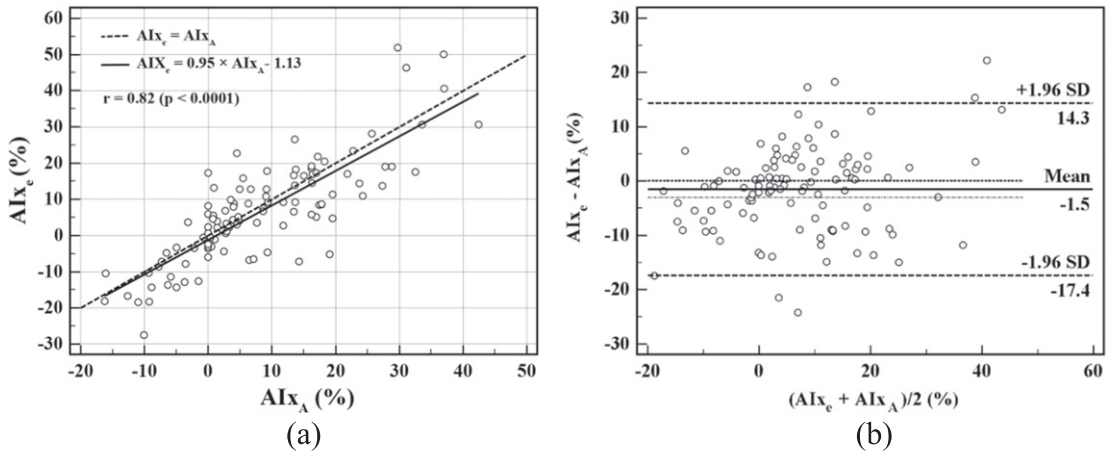

Figure 4. (a) Linear regression shows that AIx_e is strongly positively correlated with AIx_A ($r = 0.82$, $P < 0.0001$). The regression line ($AIx_e = 0.95 \times AIx_A - 1.13$) is very close to the line of equality ($AIx_e = AIx_A$). (b) The Bland–Altman plot shows a very small mean bias of −1.5 (95% confidence interval is between −3.0605 to 0.039 86, shown as dotted lines around the mean bias). The 95% LoA is comparable to those reported in the literature.

Table 2. A summary of previous studies comparing different devices to measure the AIx.

Comparison study	Reference	No. of subjects	r	MB (%)	SD (%)
Omron HEM-9000AI and SphygmoCor[a]	[25]	303	0.85($p < 0.001$)	≈1	≈8
eTRACKING and SphygmoCor	[22]	47	0.82($p < 0.0001$)	3	13.7
Vasotens and SphygmoCor	[26]	160	0.74	0.75	≈10
ARCSolver and SphygmoCor	[27]	302	Not mentioned	1.2	7.9
ARTSENS and eTRACKING	This paper	107	0.82 ($p < 0.0001$)	1.5	8.1

[a] Compares measurements of the peripheral AIx.

MB: mean bias; SD: standard deviation and 95% LoA are given by MB ± 1.96 × SD.

consolidating the results by validating the device against the AIx obtained from pressure waveforms recorded using applanation tonometry or invasive catheters.

The measurement of AIx explained in this paper assumes a linear relationship between the pressure and distension of the CCA which might not hold true for highly calcified arteries and high hypertension cases where it might be inaccurate to assume the CCA pressure–distension relationship is linear. As such, AIx measurements from ARTSENS should only be considered as estimates of its real value; and they might not be considered independently as a measure of AS. However, we believe that in conjunction with the Ep and PWV obtained from the device this would provide valuable insights on AS.

Although a majority of subjects are male (72%), this is not expected to have a serious effect on the results of the comparison study. As the study was mainly on young normotensive subjects, we cannot draw strong conclusions regarding the applicability of these results on a hypertensive or elderly population. Jiang *et al* [22] had shown that measurements of the AIx based on the distension of the CCA are reasonably accurate for asymptomatic cases but, no such study exists for pathological cases. Further clinical studies would be required to validate the accuracy of this measurement in patients with developed vascular morbidities.

8. Conclusion

ARTSENS is being developed as a fully automated and low-cost system for the measurement of AS. In our earlier work, we have demonstrated the capability of ARTSENS to perform the accurate measurement of LAS and RAS. It has been suggested in previous literature that multiple indices of AS would give a more comprehensive picture of the development of CVD. Along this line, we attempted to estimate the AIx by performing pulse wave analysis on distension waveforms recorded using ARTSENS. To validate this measurement, we performed a study on over 107 volunteers where AIx readings from ARTSENS were compared against the state-of-the-art Hitachi-Aloka eTRACKING System. Both devices showed excellent agreement with a correlation value of 0.82 ($p < 0.0001$). The correlation, mean bias and standard deviation of our results are in a similar range to

other comparison studies reported in the literature. This development enables us to obtain both the AIx and LAS from a single measurement at the CCA. ARTSENS can now measure the three major indices of arterial mechanics—LAS, RAS and the AIx and is currently the only device that can do so.

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