Image-free evaluation of carotid artery stiffness using ARTSENS: A repeatability study

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Abstract— **Evaluation of arterial stiffness is significant in early detection and vascular diagnosis. We have developed and validated an image free system called ARTSENS for evaluation of carotid artery stiffness. In this paper, we present a detailed study on the repeatability of arterial stiffness measurements performed using ARTSENS. The study protocol was designed to emulate typical constraints encountered in field usage of ARTSENS as a screening tool. The intra operator variability (repeatability) of ARTSENS was verified by in-vivo measurements on 18 subjects. Inter operator variability (reproducibility) was also studied. The ability of the instrument to give reliable measurements in both sitting and supine posture of the subject was verified. Further, the variation of arterial stiffness measurements over different times of the day was investigated to verify the ability of the instrument to give a practically usable stable measure of stiffness. The repeatability and reproducibility of ARTSENS measurements was found to be comparable to those provided by state of art image-based systems. Stiffness measurements provided by ARTSENS were found to be stable over a day indicating utility of the instrument in providing a quick and reliable measure of carotid artery stiffness.**

I. Introduction

Evaluation of arterial stiffness has proven utility in vascular diagnosis as an early indicator of vascular damage and risk of coronary heart disease [1]. State of art systems for carotid artery stiffness evaluation require expensive imaging systems and extensive technical expertise to operate, and are not amenable for large scale screening, especially in resource constrained settings in developing countries who suffer from large incidence of cardiovascular disease [2],[3]. We had previously developed and validated the accuracy of an image-free system for automated evaluation of carotid artery stiffness called ARTSENS (ARTerial Stiffness Evaluation for Noninvasive Screening) that provides a quick measure of artery stiffness in an automated manner, without the need of extensive skill from the operator[4],[5].

Repeatability of the stiffness measures provided by ARTSENS is important to ensure its practical utility in vascular screening. In this paper, we present a detailed study on the repeatability and reproducibility of stiffness measurements obtained using ARTSENS. A brief description of ARTSENS and its operation is given in the next section.

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A detailed explanation of the study protocol to evaluate the inter operator and intra operator variability of ARTSENS is provided. The variation of stiffness measurements over a day was also investigated to evaluate the stability of ARTSENS measurements for use as an estimate of vascular health.

II. ARTSENS

The basic principle of image free arterial stiffness measurement used by ARTSENS is illustrated in Figure 1. The system uses a single element ultrasound transducer to investigate the carotid artery and employs intelligent algorithms for signal processing, artery wall detection and motion tracking to automatically provide the stiffness measurement, with no operator input [4][6]. To evaluate stiffness, the operator places a 5 MHz single element ultrasound probe on the neck of the subject over the carotid artery as shown in Figure 2. The transducer sends out a narrow ultrasound beam into the body and captures the echoes reflected by various structures in the sound propagation path.

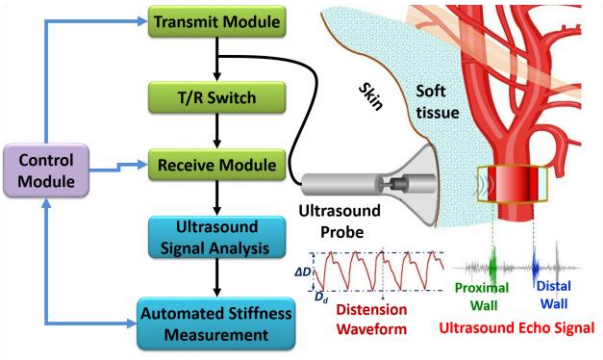

Figure 1. Principle of image free evaluation of arterial stiffness using ARTSENS

Figure 2. Measurement of carotid artery stiffness using ARTSENS

TABLE I. CLINICALLY ACCEPTED MEASURES OF ARTERIAL STIFFNESS[7],[8]

Measure of arterial compliance	Definition
Pressure Strain Elasticity, Ep	$\frac{D_d \times \Delta P}{\Delta D}$
Arterial Compliance, AC	$AC = \frac{\pi[{D_s}^2 - {D_d}^2]}{4\Delta P}$
Stiffness Index, β	$\beta = \frac{\ln\left({}^{P_s}/_{P_d}\right)}{\left({}^{\Delta D}/_{D_d}\right)}$

Intelligent algorithms automatically identify the artery walls, track wall motion and measure the arterial distension (ΔD) and end-diastolic diameter (D_d) over multiple cardiac cycles to evaluate various clinically accepted measures of stiffness [7],[8]. The systolic and diastolic pressure values (P_s and P_d) measured at the brachial artery are used for computing the various stiffness measures listed in Table 1. A detailed description of the hardware modules and explanation of the signal processing and computing modules used in ARTSENS may be found in [4] and [6].

III. REPEATABILITY STUDY PROTOCOL

The procedure of arterial stiffness measurements as well as the overall study protocol is explained in this section.

A. Subject Selection

Measurements were performed on a pool of 18 healthy subjects. Both male and female subjects, with no documented history of cardio vascular health problems were included in the study. The subject pool included subjects from age of 22 to 47 years. The average age was 25.5 years.

B. Anthropometric measurements

The height of subjects were measured with a tape with resolution 1 mm. Weight was measured using an automatic weighing scale with resolution 0.5 kg. The distance from the brachial artery (h_{bc}) to the carotid artery was measured with a tape of resolution 1 mm.

C. Blood pressure measurements

The blood pressure was measured using *Trust Check HL888HC* automatic blood pressure monitor with a resolution of 1 mmHg. Measurements were performed on the brachial artery using a cuff. Blood pressure was recorded in both sitting and supine posture.

D. Arterial stiffness measurement

Arterial stiffness measurements were performed at the carotid artery using ARTSENS. Subject identification number, name, anthropometric data and blood pressure were entered into the ARTSENS device. Then stiffness measurements were performed using the ultrasound probe. The approximate location of the left common carotid artery was identified by palpation. Probe was positioned on the lower neck over the common carotid artery, at a location nearly 2 cm below the carotid bulb identified by palpation. The probe angulation was adjusted till the ARTSENS device could visualize and automatically identify echoes from the proximal and distal walls. The probe was held in the same position while the system performed wall tracking and distension cycle measurements. No operator input was given to the ARTSENS device at this time. For each trial, a maximum of 10 cardiac cycles were recorded and averaged to get the stiffness values.

E. Measurement protocol for repeatability study

Measurements were performed on subjects at various times during the day to emulate typical use of ARTSENS in a screening scenario. Subjects were allowed to rest for only less than 5 minutes before measurements were initiated. This was intentionally done to include the effect of possible physiological variations that may occur practically, on the measurements taken during this study as well. Thus, the protocol ensured that the results of the study would be representative of the typical performance expected from ARTSENS under practical, field conditions.

After taking anthropometric measurements and blood pressure readings in supine posture, stiffness was evaluated by two operators with the subject in supine posture. Each operator measured stiffness two times. Carotid blood pressure was estimated by normalizing the measured arterial distension waveform based on the assumption that the diastolic pressure and mean arterial pressure remains unchanged across the arterial tree [9]. Further, the subject was moved into sitting posture. Blood pressure in sitting posture was recorded and entered into the system. Arterial stiffness was evaluated by the same two operators in sitting posture as well. Brachial pressure was directly used to compute stiffness in sitting posture.

IV. RESULTS AND DISCUSSION

A. Repeatability and reproducibility of ARTSENS measurements

The variation of stiffness readings obtained from the two operators, on different subjects in supine and sitting posture are illustrated in Figure 3 and Figure 4 respectively. Few subjects in which ARTSENS was unable to identify the wall echoes properly were eliminated as outliers from analysis. Data from 14 subjects in sitting posture and 17 subjects in supine posture was analyzed. Readings taken by two operators OP1 and OP2 in two trials A and B are indicated as OP1A, OP1B, OP2A and OP2B. It may be seen that the readings obtained from the two trials A and B performed by each operator are close, indicating reasonable repeatability of measurements. Further, there is significant agreement between the readings taken by the two operators in majority of the readings, especially in sitting posture.

A quantitative analysis of the repeatability and reproducibility of ARTSENS was performed using Bland Altman analysis following recommendations of the British Standards Institution [10]. The coefficient of variation for repeatability and reproducibility studies were computed using eq.1.

$$\text{Coefficient of Repeatability/ Reproducibility} = \frac{n\,\sigma}{\sum_1^n D_i} \quad (1)$$

where n is the total number of subjects, σ is the standard deviation and D_i is the difference between readings of the i^{th} measurement.

The coefficient of repeatability (variation) computed as the ratio of the standard deviation of differences between two measurements taken by an operator to the average of the means of each pair, was used to evaluate intra-operator variability. The coefficient of reproducibility (variation), computed as the ratio of the standard deviation of the differences between pairs of measurements obtained by different operators, to the average of the means of each pair of readings, was used to evaluate the inter operator variability of measurements [10]. Repeatability and reproducibility of various stiffness measurements in both sitting and supine postures were evaluated. *Beta* and E_p were found to be most repeatable.

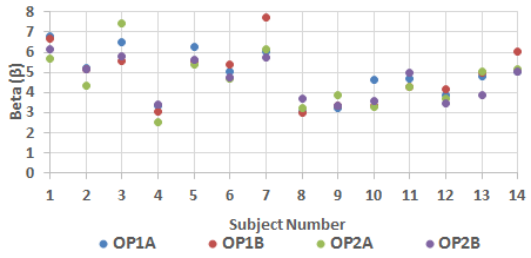

Figure 3. Variation of stiffness index, *Beta*,measured in two trials in sitting posture by two operators on all subjects

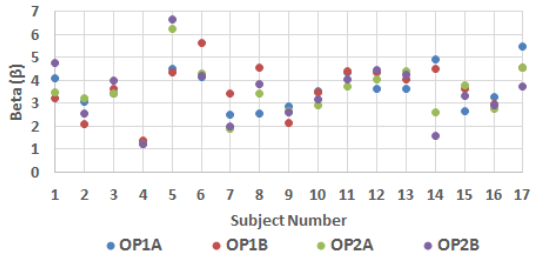

Figure 4. Variation of stiffness index,*Beta*, measured in two trials in supine posture by two operators

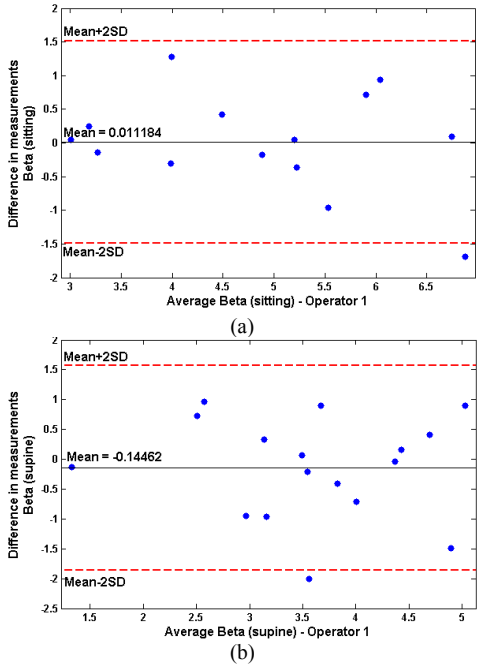

Figure 5. Repeatability of stiffness index, Beta, measured by Operator 1in (a) sitting and, (b) supine posture

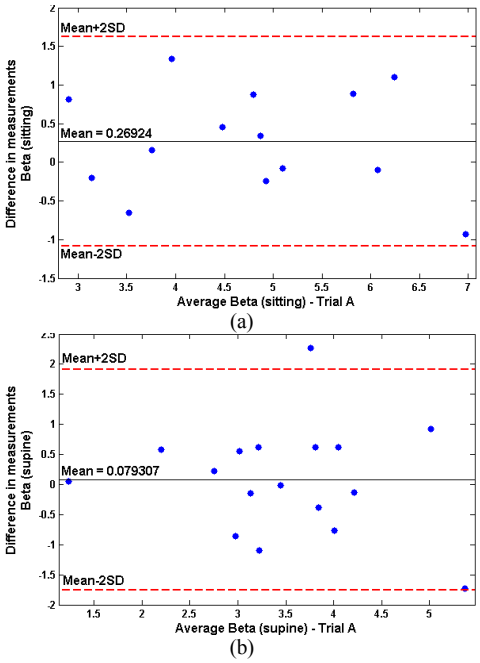

Figure 6. Reproducibility of stiffness index, Beta, in Trial A in (a) sitting and (b) supine posture

TABLE II. REPEATABILITY AND REPRODUCIBILITY OF STIFFNESS MEASUREMENTS PERFORMED WITH ARTSENS

Stiffness measure	**Coefficient of repeatability (%)**		**Coefficient of reproducibility (%)**	
	Operator 1	Operator 2	Trial A	Trial B
Beta (sitting)	15	16	**14**	16
Beta (supine)	24	16	26	33
E_p (sitting)	**13**	16	**14**	15
E_p (supine)	25	17	24	29

Bland Altman plots illustrating the repeatability of stiffness measurements in both sitting and supine posture are given in Figure 6. It may be observed that all readings, except one in supine posture, fall within the limits of ±2 SD of the mean value. The mean of differences is close to zero in all cases, indicating the ability of ARTSENS to perform repeatable measurements in both sitting and supine posture. A similar result was obtained for elastic modulus, E_p as well.

Measurements performed in sitting posture were found to be more repeatable than those in supine posture. The coefficient of repeatability was found to be 13% for E_p measurements performed by operator 1 and 16% for operator 2. The repeatability of stiffness index, Beta, was 15% and 16% respectively for the two operators. These are comparable to previously reported results on carotid stiffness measurements performed using ultrasound imaging systems as well [11]-[14] and indicate that ARTSENS can provide repeatable measurements of stiffness even in sitting posture.

The reproducibility of ARTSENS readings may be understood from the inter-observer variations indicated in Figure 8. The coefficient of reproducibility, nearly 14%, was found to be comparable for both *Beta* and E_p in sitting posture. However, measurements in supine posture were less reproducible.

The relatively low repeatability and reproducibility of supine measurements is attributed to the skill of the operators both of who reported measurements in sitting posture to be more easy and comfortable. Improved repeatability in sitting posture further strengthens the case for potential use of ARTSENS in screening scenario where measurements will have to be performed quickly and often with the subject seated on a chair. A summary of the coefficients of repeatability and reproducibility of stiffness readings made using ARTSENS is given in Table II.

B. Stability of ARTSENS readings

To verify the stability of stiffness measurements provided by ARTSENS, a study was conducted to investigate the variations in stiffness readings performed at different times of the day. Carotid stiffness of one subject was measured at 5 times during the day, twice in the forenoon and thrice in the afternoon. All measurements were performed with the established protocol described in Section III.D. Average of all measurements performed in a day is taken and used for analysis.

The variations in stiffness indices across the 5 days are compared in Table III. It may be observed that the values of stiffness remain more or less similar, from day to day, and the coefficient of variation is only 10 %, indicating good repeatability of measurements. To investigate the variation of measurements within a day, measurements taken at the same time were averaged across multiple days and compared. This is shown in Table IV. It may be seen that the arterial stiffness indices are very much repeatable with coefficient of variation less than 10 %. A one way ANOVA study was also conducted to verify that no statistically significant changes in arterial stiffness were observed within a day, and also across days during this study ($p>0.05$). This study indicates that ARTSENS can provide a repeatable and reliable measure of arterial stiffness that is repeatable across different times of the day, and also across multiple days.

TABLE III. REPEATABILITY OF ARTSENS MEASUREMENTS TAKEN ON DIFFERENT DAYS (MEAN ± STANDARD ERROR OF MEAN)

	Day1	Day2	Day3	Day4	Day5	Coefficient of Variation (%)
Beta	4.7 ±0.2	5.1 ±0.1	5.3 ±0.2	5.4 ±0.1	5.3 ±0.4	**10.0** ±2.3
Ep	63.1 ±3.9	67.3 ±1.5	70.2 ±3.3	69.5 ±1.7	67.0 ±5.5	10.6 ±2.5
AC	0.7 ±0.1	0.6 ±0.03	0.5 ±0.01	0.6 ±0.03	0.6 ±0.03	11.8 ±2

TABLE IV. REPEATABILITY OF ARTSENS MEASUREMENTS TAKEN AT DIFFERENT TIMES OF THE DAY (MEAN ± STANDARD ERROR OF MEAN)

	10.45 AM	12.45 PM	2.45 PM	4.45 PM	6.45 PM	Coefficient of Variation (%)
Beta	5.8 ±0.2	4.6 ±0.2	5.2 ±0.2	5.4 ±0.3	5.1 ±0.1	**9** ±1.1
Ep	74.0± 2.3	59.7 ±3.5	67.4 ±2.8	70.7 ±3.2	69.0 ±1.8	9 ±1.2
AC	0.53± 0.01	0.63 ±0.02	0.64 ±0.05	0.59 ±0.03	0.57 ±0.02	10.2 ±1.9

This illustrates that ARTSENS readings may be used a representative measure of the arterial stiffness of an individual.

V. CONCLUSION

An image-free system for evaluation of arterial stiffness was presented. The repeatability of stiffness measurements given by ARTSENS was thoroughly evaluated by in-vivo studies. The intra-operator repeatability and inter-operator reproducibility was found to be reasonable with coefficient of variation less than 16 % for measurements performed in sitting posture. The repeatability and reproducibility of ARTSENS was comparable to that of ultrasound image based systems reported in literature. The repeatability of ARTSENS measurements performed over multiple days was also found to be good with coefficient of variation of nearly 10 %. The study demonstrated that ARTSENS can provide reliable estimates of arterial stiffness in a reliable and automated manner, with no operator input. ARTSENS could be used to obtain a quick and reliable estimate of carotid artery stiffness and has potential for use in screening and diagnosis.

REFERENCES

[1] J.M. Dijk, A. Algra, Y.v. Graaf, D.E. Grobbee and M.L. Bots, "Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease: The SMART study," *Eur Heart J*, vol. 26, pp. 1213-1220, April, 2005

[2] S. Carerj *et. al.*, "Normal vascular aging evaluated by a new tool: e-tracking," *Eur J of Echocardiogr.*, vol. 7, no. suppl 1, pp. S49–S49, 2006.

[3] M.-J. Jurasic, S. Josef-Golubic, R. Sarac, A. Lovrencic-Huzjan, and V. Demarin, "Beta stiffness - setting age standards," *Acta Clin Croat*, vol. 48, pp. 253–258, 2009.

[4] J. Joseph and V. Jayashankar,"A virtual instrument for automated measurement of arterial compliance," *ASME J Med Dev*, vol. 4, no. 4, art.045004, 2010.

[5] J. Joseph, E.A. Thomas and M. Sivaprakasam, "ARTSENS- An image free system for noninvasive evaluation of arterial compliance," in *Proc. of 35th Annual International Conference of the IEEE EMBS*, 2013, pp. 4054 – 4057.

[6] A.K. Sahani, J. Joseph and M. Sivaprakasam, "Automated system for imageless evaluation of arterial compliance," in *Proc. 34th Annual International Conference of the IEEE EMBS*, 2012, pp. 227-231

[7] S. Laurent *et. al.*, "Expert consensus document on arterial stiffness : methodological issues and clinical applications," *Eur Heart J*, vol. 27, pp. 2588–2605, 2006.

[8] James J Oliver and David J Webb, "Non invasive assessment of arterial stiffness and risk of atherosclerotic events," *Arterioscler. Thromb. Vasc. Biol.*, vol. 23, pp. 554–566, 2003.

[9] M. E. Safar, A. Protogerou, and J. Blacher, "Central blood pressure under angiotensin and calcium channel blockade," *Hypertension*, vol. 54, no. 4, pp. 704–706, Oct. 2009.

[10] British Standards Institution, "Accuracy (trueness and precision) of measurement methods and results: basic methods for the determination of repeatability and reproducibility of a standard measurement method." 1994; HMO London. BS ISO 5725 part 2.

[11] B. McGrath, "Non-invasive measurements of arterial structure and function: repeatability, interrelationships and trial sample size," *Clinical Science*, vol. 95, pp. 669–679, 1998.

[12] Gamble G, J Zorn, Sanders G, S McMahon, and N Sharpe, "Estimation of arterial stiffness, compliance, and distensibility from M-mode ultrasound measurements of the common carotid artery," *Stroke*, vol. 25, pp. 11–16, 1994.

[13] K. Niki, *et. al.*, "A new non-invasive measurement system for wave intensity: evaluation of carotid arterial wave intensity and reproducibility," *Heart Vessels*, vol. 17, no. 1, pp. 12–21, Nov. 2002.

[14] E. C. Godia *et. al.*, "Carotid artery distensibility A reliability study," *J Ultrasound Med*, vol. 26, pp. 1157 – 1165, 2007.