High-Throughput Vascular Screening by ARTSENS Pen During a Medical Camp for Early-Stage Detection of Chronic Kidney Disease

Nabeel P M, *Member, IEEE*, Rahul Manoj, Abhidev V V, Jayaraj Joseph, Raj Kiran V, and Mohanasankar Sivaprakasam

***Abstract*— Intervention in the early stages of cardiovascular and kidney diseases is proven to be more effective in preventing disease progression. Large artery stiffness measurement can be a potential early predictor of future risks. The purpose of the study reported in this work was to demonstrate the feasibility of our ARTSENS® Pen device as a high-throughput vascular screening tool for risk assessment. The study was performed during a medical camp conducted for awareness and early-stage detection of kidney diseases. Screening procedures included biosample tests and blood pressure measurements. Alongside, various clinically relevant measures of the arterial stiffness were evaluated using the ARTSENS® Pen, by measuring vessel wall dynamics via our proprietary image-free ultrasound algorithms. Stiffness measurement from the left common carotid artery on 85 participants could be completed within 4 hours, employing two units of ARTSENS® Pen; this also includes time taken for all the procedures enlisted in the study protocol. The associations of carotid stiffness indices with age-, gender-, and risk factor-dependent variations were established.**

***Clinical Relevance*— Demonstrating the feasibility of high-throughput vascular stiffness assessment at the carotid artery, in a resource-constrained setting, using a handheld image-free ultrasound device. It may contribute to the detection of early stages of cardiovascular and chronic kidney diseases.**

I. Introduction

Cardiac and renal failures are the most common clinical complications that shorten life expectancy. Expert groups emphasize the profound need for early detection and treatment of asymptomatic cardiovascular and renal diseases [1], [2]. Non-invasive markers of such disorders and their monitoring techniques need improvement for early-stage detection and efficient monitoring of the response to therapy [3]. Arterial stiffness, which varies with the type and severity of diseases, has been indicated as an early predictor of cardiovascular, renal, and all-cause mortality [4]–[6]. A noninvasive method for assessing large arterial stiffness, which could reliably perform measurements in resource-constrained and high-throughput settings, may contribute to a future screening tool to reduce all-cause morbidity and mortality.

ARTSENS® is a clinically validated image-free ultrasound technique for quick evaluation of arterial wall dynamics [7]. The system uses a single-element ultrasound probe to measure the arterial dimensions with fully automated algorithms, and perform the real-time calculation of various stiffness indices. ARTSENS® Pen is the most evolved form of the developed technology that is extremely compact, portable, plug-and-use type and is optimized to perform quick and fully automated stiffness measurement from the carotid artery. The capability of ARTSENS® Pen to measure carotid stiffness in resource-constrained and high-throughput settings was validated during a recent medical camp. The objectives of the medical camp, methods of vascular stiffness study, and clinical investigations are briefed in the following section. A detailed discussion on the observation and results, with future research directions, are provided in the subsequent sections.

Nabeel P M, Abhidev V V, and Jayaraj Joseph are with the Healthcare Technology Innovation Centre (HTIC), Indian Institute of Technology (IIT) Madras, Chennai, India. Email: nabeel@htic.iitm.ac.in

Rahul Manoj and Raj Kiran V are with the Department of Electrical Engineering, Indian Institute of Technology (IIT) Madras, Chennai, India.

Mohanasankar Sivaprakasam is with the Department of Electrical Engineering and Healthcare Technology Innovation Centre, Indian Institute of Technology Madras, Chennai, India.

II. Materials and Methods

A. Study Population

Carotid stiffness measurement using the ARTSENS® Pen device (Fig. 1 (a)) was part of a recent (August 2019) medical camp organized for early-stage detection of kidney disease, at Karinjapadi, Malappuram, Kerala, India. The study was approved by the local review board and performed in accordance with the tenets of the Helsinki Declaration (as revised in 2013). There were 112 participants in the medical camp. Both male and female subjects of age greater than 18 years were encouraged to participate in the vascular screening session. No benefits were offered to the participants. Once registered for the study (Fig. 1 (b)), they were asked open questions about the lifestyle, family history, and previous events. Post informing the study objectives and protocol, written informed consent was obtained from each participant.

B. Urine and Blood Analysis

On the day of the study, the urine sample was collected for the analysis of sugar level, albumin, and microalbumin using standard reagent strips. From the fasting venous blood sample (Fig. 1 (c)), Urea, creatinine, and sugar level were estimated on an Erba® Chem-7 Biochemistry Analyzer, using standard kits. Subjects were then given a light breakfast and allowed to relax before proceeding with the stiffness measurements.

C. Stiffness Measurement Using ARTSENS® Pen

Initially, the blood pressure was measured from the upper arm with a bladder-type cuff using a clinical-grade oscillometric device, and the systolic (P_S) and diastolic (P_D) pressure values were entered into the GUI of ARTSENS® Pen. Subsequently, the location of the carotid artery was identified by palpation and stiffness measurement was initiated. Single-element ultrasound probe of ARTSENS® Pen was placed over

978-1-7281-1990-8/20/$31.00 ©2020 IEEE

the identified location (Fig. 1 (d)), and it was angulated to capture high-fidelity ultrasound echoes from the measurement site [7]. ARTSENS® Pen's software performs real-time processing of consecutive echo frames and continuously track the echoes corresponding to carotid artery walls [7]. Thus lumen end-diastolic diameter (D_D) and distension (ΔD) were obtained from each cardiac cycle [7]–[9]. When sufficient cycles were captured, the carotid stiffness (as explained below) was calculated, displayed, and recorded. The entire procedure was automated and required no input from the operator. A detailed discussion of ARTSENS® technology, image-free processing and evaluation of arterial dimensions, and measurement algorithm can be found elsewhere [7]–[10].

Various clinically relevant measures of carotid stiffness evaluated using ARTSENS® Pen are given here. We refer to recent reviews for more on the pathophysiology and physical definition of these stiffness indices [5], [6]. Of note, the value of blood mass density (ρ) typically used as 1060 kg/m^3 [11].

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

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

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

$$\text{Systolic pulse wave velocity, } C_S = \sqrt{\frac{P_S\,\beta\,(D_D+\Delta D)}{2\,\rho\,D_D}} \quad (4)$$

Figure 1. (a) ARTSENS® Pen. (b) Registration and data collection. (c) Blood sample collection. (d) Carotid stiffness measurement. (e) Awareness session.

III. Results and Discussion

A. Anthropometry and Baseline Measurements

Descriptive characteristics of the recruited population are summarized in Table I. Of the 112 participants in the medical camp, 85 registered for the vascular screening session. In which, all the measurements were successfully completed on 79 subjects. Among six subjects, whom the measurements were incomplete, two were heavily breathing, an obese short neck subject took more than seven minutes for carotid signal acquisition, and there was data entry error in the remaining three subjects. Overall, 79 subjects (age: 51 ± 12.5 years; 56 males) were included in the analysis reported herein. As per their calculated BMI, 48% of the subjects were normal weight, 5% were underweight, 38% were overweight, and 9% obese subjects. 27% of the subjects had increased blood pressure and 59% were diagnosed with elevated fasting blood sugar. Nearly 50% of them were masked or untreated hypertensive and/or diabetes patients. None of the participants were aware of their renal health, thus volunteered in the medical camp. The camp duration was 5 hours (09:00 AM – 02:00 PM), in which the study was carried out for 4 hours, and a one-hour awareness session (Fig. 1 (e)) to emphasize the importance of vital organ care and routine health checkup.

B. Performance of ARTSENS® and Measurement Reliability

Two units of the ARTSENS® Pen device was deployed in the field during the medical camp. The operators had sufficient experience in using the device for vascular screening in field settings. Since all the measurements were performed over the carotid artery, in sitting posture, space requirement in the field was minimal without any special settings. Further, the devices could continuously operate around three hours from the battery power of full-charged host tablet PC; measurements were then continued while recharging the tablet PC from a power source. The field deployability of ARTSENS® Pen, first in hand-held image-free ultrasound device for direct stiffness assessment, established herein. Two units of ARTSENS® Pen performed 85 individual measurements and three repeat attempts within four hours. The average time taken per subject to complete the entire protocol, including anthropometric measurements, blood pressure monitoring, data entry, and stiffness evaluation, was less than five minutes (range: 2.5 – 5 minutes). With this, only six subjects' data were invalid owing to practical

TABLE I. Characteristics of Study Population (N = 79)

Parameter	Mean ± SD	Range
Age (years)	45 ± 10	26 – 75
Gender (male/female)	56/23	-
BMI (kg/m^2)	24.3 ± 4.2	13.3 – 39.4
Serum creatinine (mg/dL)	1.06 ± 0.26	0.6 – 1.6
Fasting blood sugar (mg/dL)	134.5 ± 70.7	70 – 366
Systolic blood pressure (mmHg)	129 ± 23	92 – 220
Diastolic blood pressure (mmHg)	82 ± 16	44 – 165
D_D (mm)	5.93 ± 1.64	2.82 – 9.12
ΔD (mm)	0.34 ± 0.17	0.15 – 1.23
β (–)	8.93 ± 3.73	2.88 – 15.82
E_P (kPa)	125.09 ± 60.32	42.32 – 288.69
C_D (m/s)	6.60 ± 1.58	3.95 – 10.10
C_S (m/s)	8.13 ± 2.11	4.64 – 13.40

limitations as alluded above. The present study indeed demonstrated the performance of ARTSENS® Pen in high-throughput vascular screening in a field setting.

End-diastolic and peak systolic values of carotid luminal diameter measured by ARTSENS® Pen (5.93 ± 1.64 mm and 6.27 ± 1.69 mm, respectively) were comparable to those values reported by independent researchers [12], [13]. The stiffness index β (evaluated using blood pressure and diameter values) accounts for the non-linear pressure-diameter relationship and provides an estimate of the intrinsic material property of the vessel [6]. The E_P provides an estimate accounting stress-strain relationship of the vessel wall as explained in [5]. The absolute values of β (8.93 ± 3.73) and E_P (125.09 ± 60.32 kPa) given by ARTSENS® Pen were comparable to the typical range reported in the literature using medical ultrasound image-based systems [12], [13]. One-point pulse wave velocity corresponding to diastolic pressure, C_D, derived from β, has gained acceptance in recent decades. Compared to the conventional gold-standard pulse wave velocity measured across carotid-femoral artery segment, the pathophysiological implications of the carotid C_D is different as it reflects central vascular stiffness [6]. The absolute value of carotid C_D (in the present study, C_D = 6.60 ± 1.58 m/s) will be typically less than the equivalent carotid-femoral pulse wave velocity. Readers could find a detailed discussion in a recent review article [6]. Pulse wave velocity corresponding to systolic pressure, C_S, is not generally reported in the state-of-the-art vascular stiffness monitoring devices. Only in recent years, the importance of measuring pulse wave velocity at different pressure within a cardiac cycle has gained attention. Especially, C_S and the difference between C_S and C_D (change in pulse wave velocity within a cardiac cycle) have demonstrated clinical significance in advanced cardiovascular monitoring [6]. ARTSNES Pen® reliably measured C_S from all the subjects (range: 8.13 ± 2.11 m/s) and would be used for future applications, which is beyond the scope of current work.

C. *Age-Related Trends of Vascular Stiffness*

The age range was 25 – 75 years in the study population, it was categorized into five different quartiles of increasing age to investigate the ability of ARTSENS® Pen in detecting the age-related trends in arterial stiffness. In each age quartile, the mean and standard deviation of subjects' β, E_P, C_D, and C_S were calculated. As depicted in Fig. 2 (a) – (d), a significant trend of increased arterial stiffness with age could be observed in all the measured stiffness indices. A closer look at variation across the age categories gives an insight that the values of β and E_P (vessel wall material properties) exhibited more evident age-associated increase (R^2 of trend line ≈ 0.97). Besides the overall trend (R^2 of trend line ≈ 0.93), a significant difference was not observed among 3rd, 4th, and 5th quartiles for the C_D and C_S (pressure-dependent pulse wave velocity parameters) in the current population. The factors that contribute to the overall increase in vascular stiffness related to chronological aging, such as stiffer collagen, loss of longitudinal elasticity, cross-linking of elastin and collagen, increase in smooth muscle cell stiffness, medial arterial calcification, etcetera [14] affect the organized structure of the vessel wall. This may be directly reflected as an increase in the values of β and E_P, as also seen in the current study.

The study population was further divided into four groups across gender in accordance with the age median (50 years): male/female subjects < 50 years and those ≥ 50 years. Besides the discussed age-related difference in stiffness indices among the younger and older population (Fig. 2 (e) – (h)), the gender difference in the carotid stiffness measures was statistically significant ($p < 0.01$). As depicted in Fig. 2 (e) – (h), all the measured stiffness indices were significantly higher in female

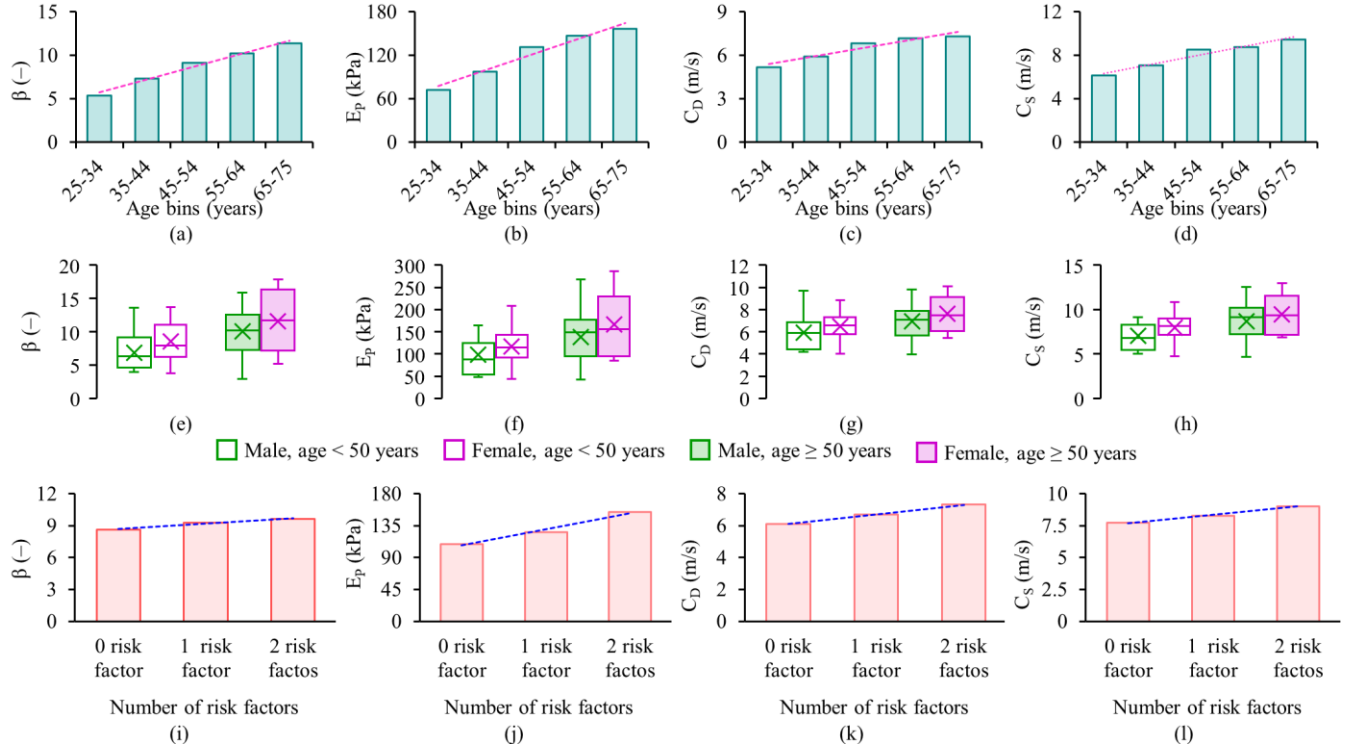

Figure 2. Summary of results obtained uisng ARTSENS® Pen: Age related trends in carotid (a) β, (b) E_P, (c) C_D, and (d) C_S. Gender-specific difference in younger and older population in carotid (e) β, (f) E_P, (g) C_D, and (h) C_S. Variation in carotid (i) β, (j) E_P, (k) C_D, and (l) C_S among 0 to 2 risk categories.

subjects in both groups. These results are in compliance with the evidence support gender difference in the time course of aging-related vascular stiffness [15]. Medical conditions more common in females, gender-specific mechanisms, or female-specific pathologies cause increased vascular stiffness and related morbidity/mortality almost twofold higher in women when compared to men [15]. This increases disproportionately in postmenopausal women as expounded in a recent review article [15]. Indeed, ARTSENS® Pen could potentially use as a tool to monitor the effectiveness of gender-specific therapies to lessen cardiovascular risk.

D. Vascular Stiffness in the Presence of Risk Factors

To investigate the potential utility of the ARTSENS® Pen in vascular screening applications, for various disease and risk stratification, the changes in measured carotid stiffness indices in the presence of different risk factors were evaluated. During the analysis, following risk factors were considered: (1) high serum creatinine level (> 1.2 mg/dL); (2) elevated fasting blood sugar (> 100 mg/dL); and (3) hypertension based on increased systolic/diastolic blood pressure (>130/80 mmHg). Based on the clustering of these risk factors, the subject pool was classified into '0, 1, or 2 risk factors'. In which, 23% of subjects had no risks, 42% had at least one risk factor, and 35% were suspected with two risk factors. There were no subjects with all three risk factors.

As depicted in Fig 2. (i) – (l), a statistically significant increasing trend of arterial stiffness was observed in subjects with more number of risk factors. The pulse wave velocity parameters C_D and C_S were more associated with the clustering of risk factors (R^2 of trend line > 0.99), followed by E_P and β (R^2 of trend line ≈ 0.98 and 0.97, respectively). Thus, it was found that ARTSENS® Pen could detect the variations in carotid stiffness associated with the presence of multiple risk factors. In the current population, the most prevailing clustering of risk factor was hypertension and diabetes (22%), followed by diabetes and low creatinine clearance level (14%). Subjects identified with higher risk factors were directed for a detailed check-up from the medical camp. They were also requested to perform regular follow-up investigation of the arterial stiffness during treatment or disease management.

E. Study Limitations and Future Research Direction

The major limitation concerns the cross-sectional design of the current study. It was performed during a one-day medical camp, which limits the follow-up investigation. Owing to the practical constraints, not all essential cardiovascular and renal biomarkers were included for screening and analysis. Since the medical camp was conducted for early-stage disease detection, patients undergoing treatment did not participate. As such, the pathophysiological diversity of data and range of vascular stiffness indices (and the corresponding reference biomarkers) were bounded up to the early stage of suspected diseases. To overcome these limitations, in the future, multi-centric studies will be executed over a wide range of pathophysiological conditions. Such studies would help developing nomograms for carotid stiffness indices, and may give new insight into the detectable classical but complicated relationship between arterial stiffness, renal, and cardiovascular conditions.

IV. CONCLUSION

To our knowledge, this study is the first to demonstrate the feasibility of high-throughput stiffness assessment from the carotid artery in a field setting using an image-free ultrasound device. Along with the arterial lumen dimensions, stiffness indices accounting vessel wall material property and pressure-dependent pulse wave velocity were reliably measured within five minutes. Their association with age, gender, and risk factor were analyses and reported. The current results and observations confirm ARTSENS® Pen as a useful tool for high-throughput vascular screening and analysis of metabolic factors affecting arterial stiffness.

ACKNOWLEDGMENT

There was no funding source for this study. The authors acknowledge the efforts of Helping Hands Charitable Trust, Calicut, Kerala, India for organizing a cost-free medical camp for awareness and early detection of kidney disease. Authors also acknowledge the efforts of the Chentharakam Charitable Society, Karinjapadi, Malappuram, Kerala, India in arranging the study premises and supporting data collection.

REFERENCES

[1] O. J. Wouters *et al.*, "Early chronic kidney disease: diagnosis, management and models of care," *Nat. Rev. Nephrol.*, vol. 11, no. 8, pp. 491–502, 2015.

[2] S. S. Chugh, "Early identification of risk factors for sudden cardiac death," *Nat. Rev. Cardiol.*, vol. 7, no. 6, pp. 318–326, 2010.

[3] Daniel Duprez, "Early detection of cardiovascular disease-the future of cardiology?," *ESC Counc. Cardiol. Pract.*, vol. 4, no. 19, pp. 1–4, 2006.

[4] M. E. Safar, G. M. London, and G. E. Plante, "Arterial stiffness and kidney function," *Hypertension*, vol. 43, pp. 163–168, 2004.

[5] A. Avolio, "Arterial stiffness," *Pulse*, vol. 1, no. 1, pp. 14–28, 2013.

[6] P. M. Nabeel, V. K. Raj, J. Joseph, V. V Abhidev, and M. Sivaprakasam, "Local pulse wave velocity: theory, methods, advancements, and clinical applications," *IEEE Rev. Biomed. Eng.*, 2019.

[7] J. Joseph *et al.* "Technical validation of ARTSENS-an image free device for evaluation of vascular stiffness," *IEEE J. Transl. Eng. Heal. Med.*, vol. 3, p. 1900213, 2015.

[8] A. K. Sahani, J. Joseph, R. Radhakrishnan, and M. Sivaprakasam, "Automatic measurement of end-diastolic arterial lumen diameter in ARTSENS," *J. Med. Device.*, vol. 9, no. 4, p. 041002, 2015.

[9] A. K. Sahani, J. Joseph, and M. Sivaprakasam, "Evaluation of the algorithm for automatic identification of the common carotid artery in ARTSENS," *Physiol. Meas.*, vol. 35, no. 7, pp. 1299–1317, 2014.

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

[11] J. Joseph, P. M. Nabeel, and M. Sivaprakasam, "Cuffless evaluation of pulse pressure with arterial compliance probe," *PLoS One*, vol. 13, no. 8, p. e0202480, 2018.

[12] O. Vriz *et al.*, "Comparison of sequentially measured Aloka echo-tracking one-point pulse wave velocity with SphygmoCor carotid–femoral pulse wave velocity," *SAGE Open Med.*, vol. 1, p. 2050312113507563, 2013.

[13] E. C. Godia *et al.*, "Carotid artery distensibility: a reliability study," *J. Ultrasound Med.*, vol. 26, no. 9, pp. 1157–1165, 2007.

[14] P. Segers, E. R. Rietzschel, and J. A. Chirinos, "Brief review on how to measure arterial stiffness in humans," *Arterioscler. , Thromb. , Vasc. Biol.*, pp. 1–10, 2020.

[15] J. J. DuPont *et al.*, "Sex differences in mechanisms of arterial stiffness," *Br. J. Pharmacol.*, vol. 176, no. 21, pp. 4208–4225, 2019.