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High-Framerate A-Mode Ultrasound for Vascular Structural Assessments: *In-Vivo* Validation in a Porcine Model

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***Abstract*— Capturing vascular dynamics using ultrasound at a high framerate provided a unique way to track time-dependent and transient physiologic events non-invasively. In this work, we present an A-model high-framerate (500 frames per second) image-free ultrasound system for monitoring vascular structural and material properties. It was developed based on our clinically validated ARTSENS® technology. Following *in-vitro* verification on arterial flow phantoms, its measurement accuracy and high-framerate data acquisition and processing were verified *in-vivo* on 2 anesthetized *Sus scrofa swine*. Measurements of the carotid artery (the luminal diameter, distension, and wall thickness) obtained using the high-framerate system were comparable to those provided by a clinical-grade reference ultrasound imaging device (absolute error < 4%, < 6.3%, and < 6.6%, respectively). Notably, the morphology of the arterial distension waveforms obtained at high-framerate depicted vital physiological fiduciary points compared to the low-framerate reference waveform. The compression-decompression pattern of the arterial wall was also captured with the high-framerate system, which is challenging with low-framerate ultrasound. Potential applications of these high temporal structural waveforms have also been discussed.**

***Clinical Relevance*—The proposed high-framerate ultrasound system provides a unique way to track transient vascular events, and assess incremental vascular stiffness markers to quantify the age-related impairment in functions of arteries.**

I. Introduction

Ultrasound-based methods have been widely proposed for non-invasive, local assessment of the vascular structural and material properties [1], and are used to quantify the age-related impairment in functions of the large arteries [2]. The structural measurements consist of arterial diameter, luminal distention, wall thickness, wall compression-decompression pattern, and cross-sectional area changes. Evaluation of arterial material properties using the structural parameters with an additional measurement of blood pressure or flow have been extensively studied in the past [3]–[5], but their precise quantification and capturing of time-dependent variations are still lacking. Much previous work measures the material properties, such as the elastic modulus, specific stiffness, arterial distensibility [6], by means of a snapshot of vascular geometry (minima, maxima, and mean values of structural parameters) rather than tracking their transient physiologic events such as the time-dependent alterations in the incremental stiffness [4], [5]. Accumulating evidence now established the independent role of incremental elasticity of large arteries, which calculate the exact behavior of the vascular system itself, for early screening, diagnosis, and management of cardiovascular diseases above and beyond the conventional vascular health markers [4], [5].

Indeed, a high-framerate ultrasound system (a few thousand frames per second) is crucial for the time-shift determination of the vascular structural properties, thereby providing a unique way to monitor incremental material properties. Studies using dedicated high-framerate imaging have shown that the high-resolution arterial distension waveform depicts wall dynamics concerning the structural and functional properties *in-vivo* [7], [8]. However, the conventional ultrasound imaging systems are limited with a few tens of framerate per second due to their limited processing power, line-by-line scanning, image width, and focused beams [9]. Thus, B-mode/M-mode systems are not recommended for observing the transient and incremental vascular material properties. Ultrafast ultrasound imaging is a central research topic in the community. Such techniques rely on a plane wave, or diverging wave transmissions are emerging [9] and have only been commercialized recently. The practical challenges concerning their usability in a resource-constrained setting, cost, and cumbersome have been reviewed elsewhere [4].

We present an A-mode high-framerate ultrasound system for monitoring arterial structural and material properties. It is an image-free technology based on our clinically validated ARTSENS® [10]–[12]. The performance and reliability of the device were verified *in-vitro* using a vascular phantom (beyond this article's scope). Its controlled in-vivo validation on the animal models has been reported in this work. The rationale for performing a study on an anesthetized animal model was the limitation of commercial vascular phantoms in mimicking the true hyperelastic behavior and the incremental elasticity seen in large arteries *in-vivo*. The details of animal preparation, study design, data collection procedure are presented in the following section. The study outcomes and outlook are reported in Section III, followed by conclusions.

II. Materials and Methods

A. Animal Model, Preparation, and Study Design

The experimental procedure performed in this study was approved by Institutional Animals Ethics Committee (IAEC)

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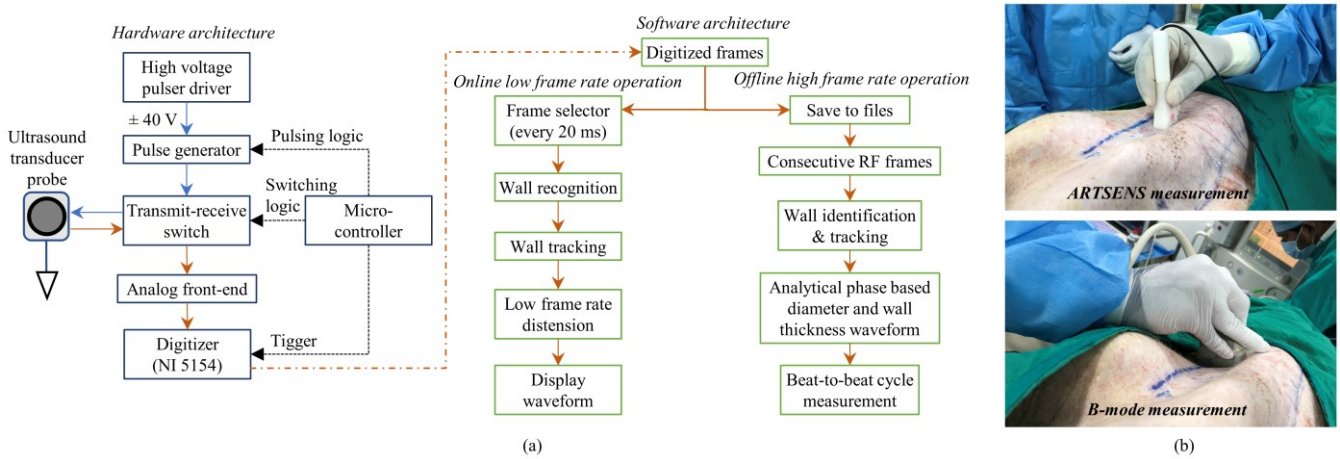

Figure 1. (a) Measurement schematic of the high-frame-rate image-free system. (b) The carotid measurement using the proposed and B-mode systems.

of the Palamur Biosciences Pvt. Ltd. test facility, Telangana, India (PAL/IAEC/2020/5/01/08). Two healthy (nulliparous and non-pregnant) female *Sus scrofa swine* (~ 80 kg) were acquired from Tamil Nadu Veterinary and Animal Sciences University, Madras Veterinary College, Chennai, India. The animals were fed normal diet. On the day of the study, anesthesia was induced with an intravenous injection of Ketamine (dose: 40mg/kg, concentration: 50mg/ml). Animals were intubated and maintained under anesthesia with inhaled isoflurane (1.5 – 2.5%) during the study procedure. Mechanical ventilation was also arranged. The common carotid artery was imaged, and the trajectory was marked over the skin by an experienced sonographer. Following the protocol described below, the measurements using the high-framerate ultrasound system and reference imaging device were performed. Once the study procedure was completed, the animals were allowed for recovery.

B. *High-Framerate A-Mode Ultrasound*

ARTSENS® is an image-free ultrasound technology developed to cater to the need for an affordable, portable, easy-to-use, fully automated means to perform accurate, reliable measurements of arterial stiffness with minimal dependence on the operator. Its established intelligent algorithms enable auto-recognition and discernment of artery walls, and tracking their continuous motion by processing one-dimensional A-mode scans. Given the technology's ability to function with such a drastic reduction in the dimensionality of the scan lines reliably, it was feasible for realizing a fast ultrasound system. The developments in hardware and computing software in regard to enhancing the ability of ARTSENS® are described below.

A schematic of the newly developed high-framerate, image-free ultrasound system is depicted in Fig. 1(a). A single element ultrasound transducer is interfaced to the system's hardware that operates it in pulse-echo mode. The high-speed pulser-receiver circuitry controls the transducer's operation mode, during which it excites the transducer to transmit an ultrasound pulse burst and receives from the same transducer the reflected echoes from several tissue structures. The digital logic provided by an embedded microcontroller (LPC4370, NXP Semiconductors, Netherlands) and the necessary pulsing voltage generated by a high-voltage generator aids the pulser-receiver in realizing the pulse-echo mode operation. The pulse repetition frequency is controlled via an embedded controller and is currently configured to 500 Hz. The received A-mode echo frames are digitized by a high-speed digitizer (PXI‑5154, National Instruments, US) at a rate of 200 MHz.

A dedicated LabVIEW (National Instruments, US) based application was developed and deployed on the PXI with a Windows 10 64-bit operating system (Microsoft Corporation, US). The PXI system communicated with the embedded controller for a handshaking trigger signal that notified when the transducer was in the receiving mode to digitize the received analog signals. The digitized frames are stored in local storage as raw files and are post analyzed. In parallel, a frame-decimator selected frames at regular intervals (t = 20 ms) so as to perform online motion tracking of the arterial walls. This provided the real-time distension waveform of the artery with a sampling rate of 50 Hz (this rate depends on the frame-decimator configuration). Automated evaluation of distension waveform from the A-mode frames involved auto-recognition of arterial wall locations and tracking their frame-to-frame shifts; both were performed by the established algorithms of ARTSENS® technology [10]–[12].

C. *Evaluation of Arterial Geometric Parameters*

The stored frames acquired at a high rate were accessed from the files for post-processing. The automated-wall recognition method of ARTSENS® [10]–[12] was used to identify the arterial walls' locations initially. For tracking the motion of wall echoes in subsequent frames, two regions of interest (ROIs) are extracted by gating each frame at the near wall and far wall locations. A cross-correlation-based tracking algorithm was employed to estimate the shift in the echoes within ROIs extracted from successive frames [10]–[12]. However, since frames were acquired at a high framerate, the resolution of tracking should be higher. The echo signals with ROIs were interpolated to 2 GHz for highly resolved shift estimation.

For the estimation of arterial diameter and wall thickness, an analytic phase-based method was employed, which allowed identification of the leading edges of echoes from the media-adventitia interface of the far wall and intima-lumen interfaces of both walls [13]. These interface-of-interest were identified from the extracted ROIs that consisted of the near and far wall echoes of the artery. The diameter was evaluated as the distance between the leading edges of intima-lumen interface

echoes of the near and far walls. Similarly, wall thickness was measured as the distance between the intima-lumen and media-adventitia interface echoes of the far wall. For every frame as the latest locations of arterial walls were evaluated, the center of windows for extracting the ROIs was updated, and with that, the instantaneous diameter and wall thickness were computed. Cycle-to-cycle diameter and wall thickness waveforms were separated for the evaluation of end-diastolic, peak-systolic, and mean measures.

D. In-vivo Data Acquisition and Measurements

The measurement by the proposed and the B-mode system on the carotid artery is shown in Fig. 1(b). The data acquisition was first performed by the high-framerate ultrasound A-mode device (employing the post-processing software alluded above for geometric parameter evaluation). Further, a reference B-mode imaging device (DP-50, Mindray Medical International Limited, China) was used for the measurement of geometric parameters. For this, the B-mode imaging probe was placed approximately at the same location from where the proposed systems' measurements were recorded. Once the desired quality of ultrasound image exhibiting longitudinal scan of the artery with the double-line pattern was observed, continuous video-graphic cine-loops were recorded for ~20-30 seconds. Multiple video-graphic clips were obtained as the imaging system lacked a real-time display of the distension waveform as the feedback for valid wall-motion dynamics. This helped to ensure that sufficiently reliable reference measurements were performed during the study, despite some of the video recordings being deemed unfit by the post-analysis tool and rejected. The recorded B-mode clips were then analyzed offline using a commercial image processing tool (Carotid Studio, Quipu, Netherlands). The software yielded waveforms for the arterial diameter and provided average estimates (over multiple cycles) of the mean intima-media thickness (IMT_M), end-diastolic diameter (D_D), and peak distension (ΔD).

III. Results and Discussion

A. Reliability of High-Framerate A-Mode Acquisition

The proposed system recorded high-fidelity A-mode frames (SNR > 20 dB) with well-defined near- and far-wall echoes. At the configured rate of 500 Hz pulse repetition rate, no frame drop was observed. The display of the raw A-mode frames, echo-gating, quality indicators for the walls, and low-resolution distension waveform as real-time feedback enabled high-quality data acquisition. The temporal resolution of the distension waveform displayed in real-time was 20 ms (50 Hz framerate), and computation time for assessing each distension point was ~6 ms which was way smaller. By processing the frames (acquired at a high rate), the desired waveforms and phase-annotated values of diameter and wall thickness were evaluated. Similarly, the B-mode video clips were successfully processed to obtain the desired geometric measures. The frame rates achieved with B-mode were approximately 25 Hz. On each animal model, five recordings of B-mode imaging were processed. (Of the total ten, three recordings were poorer for performing reliable image processing. Therefore, those were subject to rejection, which is a common challenge with imaging systems devoid of real-time measurement feedback.) In contrast, the online feedback allowed real-time adjustment of the probe's angulation and positioning for the proposed system, allowing high-fidelity signal acquisition.

TABLE I. Comparison of Geometrical Measures

Measurement on Animal-1				
	High frame-rate ARTSENS®	***B-mode***	***Difference***	***Absolute % Error***
D_D (mm)	5.60	5.81	0.21	3.55
ΔD (mm)	0.44	0.45	0.01	2.66
IMT_M (mm)	0.58	0.54	-0.04	6.62
Measurement on Animal-2				
D_D (mm)	5.93	5.97	0.04	0.64
ΔD (mm)	0.11	0.10	-0.01	6.25
IMT_M (mm)	0.46	0.44	-0.02	4.76

B. Reliability of Arterial Geometric Measurements

Comparison between respective geometric measurements performed by the proposed high-frame image-free system and the B-mode imaging systems are shown in Table I. An absolute percentage difference smaller than 7% was observed, demonstrating the reliability of measurements performed on the anesthetized porcine models. Like other commercially available tools, the B-mode image processing tool provided only a mean measure of the arterial wall thickness. In addition to the mean value, the proposed system gives the phase annotated wall thickness values, i.e., corresponding to the end-diastole and peak-systole. Even better, it provides wall thickness waveforms. A sample of wall thickness waveforms obtained from the two animals is shown in Fig. 2(a). The clinical relevance of the substantial change in wall thickness within a cardiac cycle is being understood only in recent years. Studies have reported its association with age, low-density lipoprotein cholesterol, pulse pressure, and cardiovascular risk factors [14], [15]. Since arteries are hyper-elastic in nature, the interaction between the wall layers contributes to the viscous properties. Assessment of intra-cardiac cycle changes in wall thickness allows measurement of such non-linear dynamic of arteries. For instance, a recent study introduces a method to measure the longitudinal elongation of arteries, emphasizing its need to evaluate volumetric compliance [16].

C. High-Resolution In-Vivo Pulse Waveforms

In Fig. 2 (b)-(c), a sample of diameter waveform obtained by the high-frame-rate image-free system is compared against that obtained from the low-framerate B-mode imaging system. As may be observed, there are several pulse-contour features evident in the high-resolution pulse waveform, otherwise lost in the low-resolution ones. The continuous data points in the high-framerate waveforms capture instantaneous variations in accordance with the arterial hemodynamics. The assessment strategies for arterial-wall material properties are evolving even to measure the gradient of local stiffness between different target arteries or the variations incurred within each cardiac cycle. Several studies in this regard have emphasized the imperative need for advanced fast imaging systems [10]–[12] for the measurement of local pulse-wave velocity and its gradient [4], incremental arterial elasticity [4], and cuffless central blood pressure [17]. The system presented in this work offered an advantage of online assessment of arterial wall distension, feedback much needed for reliable data acquisition.

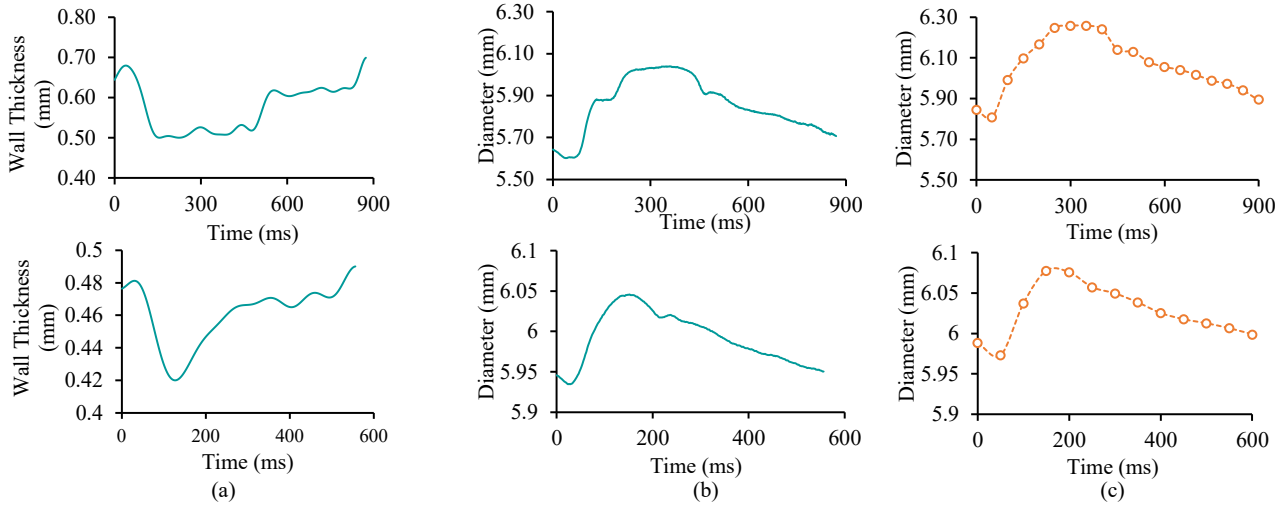

Figure 2. (a) Wall thickness waveforms measured by the proposed high frame system. (b) Diameter waveform obtained from the high frame-rate system. (c) Diameter obtained from B-mode ultrasound system. (Illustrations in the top and bottom correspond to the Animal-1 and Animal-2, respectively)

D. Limitations and Future Scope

A limitation of the study is that it was performed on a small sample size. However, note that it was a preliminary study to demonstrate the feasibility of performing high-resolution measurements of instantaneous diameter and wall thickness *in-vivo*. This study was the first stepping stone to the other interventional understanding of the clinical role of non-linear material properties of arteries and their potential applications. Further studies are also in progress to examine and quantify the sufficient framerate and influence of framerate in capturing transient physiologic events and incremental vascular stiffness markers from the elastic and muscular arteries.

IV. Conclusion

A novel A-mode, high-framerate ultrasound system based on image-free technology has been presented. The device's performance, accuracy, and high-fidelity vascular structural waveform acquisition were validated *in-vivo* on two porcine models. Besides comparable measurements of arterial lumen diameter, distension, and wall thickness against conventional imaging, the device's high temporal waveforms yielded vital morphological features from the arterial distension and wall compression-decompression pattern. Contrary to the B-mode or M-mode imaging systems and recent ultrafast ultrasound imaging devices, the proposed A-model system is affordable, portable, and suitable for early vascular screening in clinical, out-of-hospital, and resource-constrained settings. Extensive verification and validation of the developed high-framerate ultrasound system on suitable animal models over a wide range of physiological conditions are in progress. Results of these studies will be reported in our future scientific articles.

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