Demonstration of Pressure-Dependent Inter and Intra-Cycle Variations in Local Pulse Wave Velocity Using Excised Bovine Carotid Artery

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***Abstract*— Pulse wave velocity (PWV) is a function of the artery's material property, and its incremental nature in elastic modulus led to the concept of incremental PWV. Recent advancements in technology paved the way for reliable measurement of the variation in PWV within a cardiac cycle. This change in PWV has shown its potential as a biomarker for advanced cardiovascular diagnostics, screening, and has recently started using as a vascular screening tool and medical device development. In this work, we have demonstrated the concept of inter and intra-cycle variations of PWV with pressure using an excised bovine carotid artery. Results demonstrated that local PWV measured at the foot of the waveform followed the same trend as of the pressure. As the pressure level was increased to 68% across the cycles, resulting PWV increased up to 81%. An exponential PWV-Pressure relationship was obtained, in agreement with the widely used models. The incremental nature of PWV was recorded in a reflection-free region of the pressure pulse wave. This was further demonstrated in continuous pulse cycles with varying pressure ranges, by comparing the PWV values at two fiduciary points selected in the upstroke of the pressure wave. On average, a 48.11% increase in PWV was observed for 31.04% increase in pressure between the selected fiducial points within a pulse cycle. The article concludes, highlighting the clinical significance of incremental PWV.**

***Clinical Relevance*— This experimental study supplements the evidence for the incremental nature of PWV within a cardiac cycle, which has the potential for being a biomarker for advanced cardiovascular screening and diagnostics.**

I. Introduction

Pulse wave velocity (PWV) measured between carotid and femoral artery is a known biomarker for arterial stiffness, and is now part of reference guidelines for arterial stiffness measurement [1]. The measure of PWV from a small segment of the artery, called local PWV is gaining acceptance as a better biomarker for local stiffness measurement and early prediction of cardiovascular risks [2]. Recently, due to the technological advancements, it is now practically feasible to measure PWV from various fiducial points within a cycle. This has been observed by a few reaserchers that the value of PWV is different across the cardiac cycle, and is refered to as incremental PWV. The incremental nature of PWV is attributed to the hyperelastic structure of the arterial walls, reported in the literature as incremental elastic modulus[3], [4]. Incremental PWV is a potential index for cardiovascular diagnostics and screening, as established by the studies [5]–[8]. This concept is also explored in the advancement of medical instrumentation in developing calibration-free cuffless blood pressure measurement devices [9].

Local PWV measurement methods vary from, multi-site measurement of physiological signals to single-site acquisition of multiple signals from an arterial segment, of which transit time-based methods are the simplest and straightforward method to evaluate PWV [2]. They employ simultaneous recording of a waveform pair, separated by a small distance and analyze the transit time between the two waveforms (called as Pulse Transit Time (PTT)) to calculate PWV based on well known distance-speed relation. The PTT measurement using invasive techniques that capture the hemodynamic signals are considered to be the gold-standard estimate [10]. Despite the invasive procedures, usage of dual pressure catheters to perform direct measurmenets of pulse waveform, makes it the ideal method to characterize local PTT/PWV and considered as the gold standard approch.

In this work, we demonstrate the concept of incremental PWV within a cardiac cycle using invasive measurement techniques on a bovine carotid artery in a controlled environment, replicating hemostasis conditions to a large extent. The subsequent sections highlight the experimental materials, methods and instrumentation used to create the pulsatile flow through the excised artery followed by a detailed discussion of the inter and intra-cycle variations of PWV with the distending pressure. A sub-section on the clinical importance of the incremental PWV towards medical diagnostics, screening and advancement in instrumentation is also reported.

II. Materials and Methods

A. Experiment Setup

The bovine carotid artery was harvested with a length of 7 cm along with the surrounding tissue. It was preserved in phosphate buffer solution (PBS, pH:7.4, temperature:4°C).

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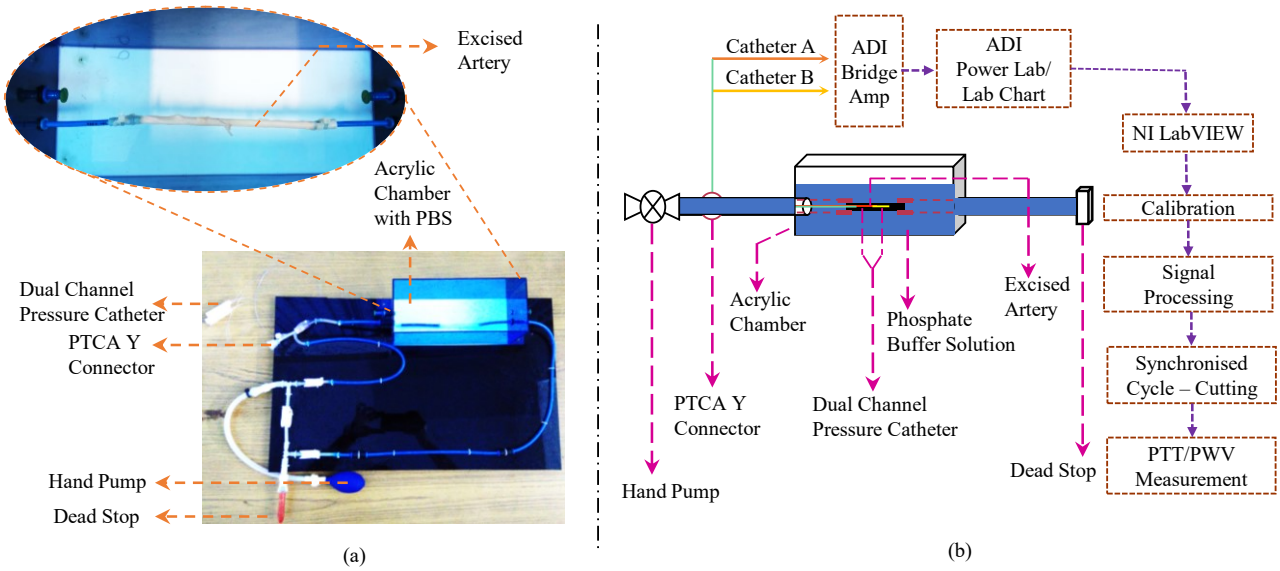

Fig.1. (a) Experiment setup with excised artery (b) Schematic representation of the experiment setup with instrumentation and software architecture

Once the artery was cleaned from the surrounding connecting tissues, it was confirmed, the artery had no leaks through vasa vasorum, by flushing in PBS through one end of the arterial segment. Any such potentially leaking vasa vasorum were sutured before connecting the artery to the experimental setup. The average internal diameter of the excised artery was 3 mm, with an average thickness of 0.5 mm. The excised arterial segment was attached to the hardware setup via custom connecting tubes. Two high fidelity Micro-Tip© pressure catheters (SPR-882 – 2F, Sensitivity: 5µV/V/mmHg) by Miller Instruments, USA were attached together, with a tip-to-tip distance of 3 cm as the proximal – distal sensor separation distance. The catheters were inserted into the experimental hardware setup through PTCA Y connector (hemostasis valve) and both the tips were positioned in the middle of the arterial segment. The catheters were calibrated against mercury manometer for ranges of pressure from 0 mmHg to 300 mmHg. The arterial segment with the connectors was immersed in an acrylic chamber filled with PBS at 4°C. The artery was kept at a depth of 10 cm of the liquid column. Pressure pulsations using PBS as the blood-mimicking liquid was manually created using a hand pump connected to one end of the setup, as shown in Fig.1(a).

The catheters were interfaced to ADInstrument's Quad Bridge Amp and PowerLab 4/35 hardware units. These hardware units were controlled using ADInstrument's Lab Chart software. The software facilities runtime visualization and saving of the captured pressure waveforms. The amplified pressure waveforms from Bridge Amp were sampled at 1 kHz and saved appropriately. The proximal and distal pressure waveforms obtained were later processed offline using National Instrument's LabVIEW for pressure and PTT/PWV measurements.

B. Signal Processing and Acquisition

All the programming logic and digital signal processing were implemented in the LabVIEW environment. The developed software, control configurations and synchronized acquisition of the desired signals. The architecture is illustrated in Fig.1(b). The pressure signals sampled at 1kHz were filtered using a 2nd order lowpass filter of 14 Hz cut-off frequency. The usage of zero phase filters ensured no additional lags in the waveforms. The pressure waveforms, after scaled by the calibration curve, were up-sampled to 10 kHz with spline interpolation to obtain a temporal resolution of 0.1 ms. A cycle cutting algorithm was run to select individual cycles from both the waveforms. These cycles were then normalized between –1 and +1, before analyzing PTT at various fiducial points of the pressure waveform.

C. Experiment Procedure

The hand pump was used to generate continuous cycles of pulsatile pressure ranging from 10 mmHg at minima (P_L– corresponding to diastolic or foot of the waveform) to 120 mmHg at maxima (P_P – corresponding to systolic or peak). Care was taken during the manual pumping to avoid turbulence to the liquid as it will distort the pressure recording. Sufficient number of cycles were continuously recorded at different pulse pressure and pulse rates. P_L was systematically increased from 10 mmHg to 40 mmHg and then decreased back to 10 mmHg with enough cycles at each pressure levels. Since the pumping was completely manual, monitoring of the pressure waveforms on the software, provided real-time feedback to adjust the force applied for better control. Offline signal processing was then conducted as explained in the sub-section above.

III. Results and Discussions

A. Reliability of Signals and PTT/PWV Measurements

A quasi-periodic pressure waveform resembling the transmural pressure was generated at varying pressure levels from P_L = 10 mmHg to P_P = 120 mmHg. These pressure cycles were reliably recorded using the dual-channel catheter sensors with an SNR of 20dB. A sample of the proximal and distal waveform, after processing, cycle cutting, and normalizing (between -1 and +1) is shown in Fig.2(a). The transit time shift at the foot of the waveform for cycles with P_L of 13.0.1±1.77

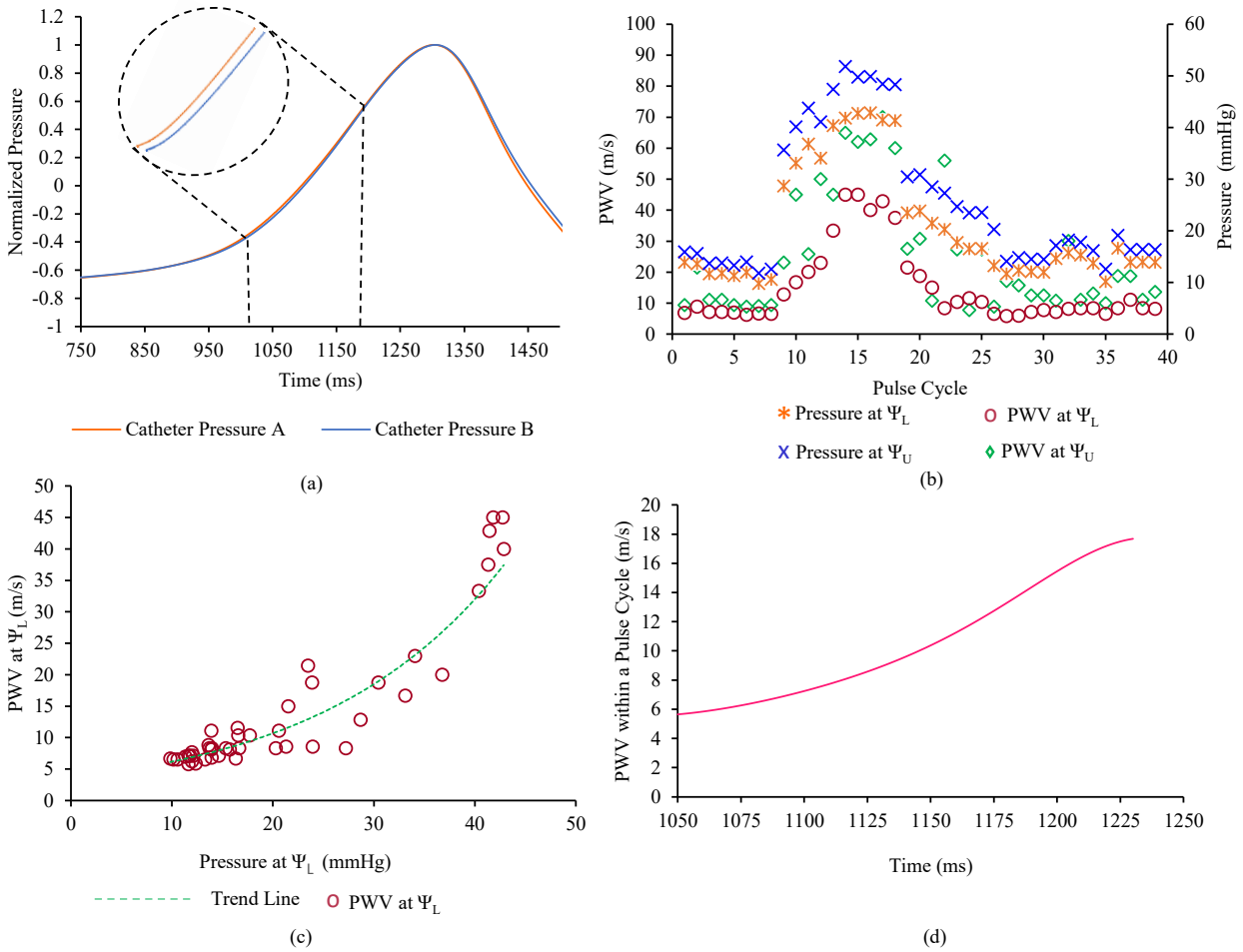

Fig.2. (a) PTT for a section of the pulse wave. (b) Intra-cycle variation and Inter-cycle variation of PWV with pressure, (c) Exponential trends in inter-cycle variation of PWV with pressure, (c) Incremental PWV for a reflection -free region of a pulse cycle.

mmHg, was observed to be 4.10±0.60 ms. For P_L with pulse-to-pulse variation 13.61%, the pulse-to-pulse variation in PTT was found to be 14.77%, illustrating the reliability of measurement system.

B. *Intra-cycle Variation in PWV with Pressure*

As P_L was increased in gradual steps from 13.0.1±1.77 mmHg to 41.76±0.93 mmHg and then decreased back to 13.01±1.77 mmHg over a sufficient number of pulse cycles, it was observed the PWV at the foot of the waveform, follows the same trend of pressure variation, illustrated in Fig.2(b). As the P_L level was increased to 68%, resulting PWV increased up to 81%. The intra-cycle variability in PWV was observed to follow an exponential trend with P_L, as shown in Fig.2(c). The general from of PWV-Pressure relation obtained is shown in (1) and agrees with the widely used PWV-pressure empirical model [11],

$$PWV = Ae^{B(P)} + C \quad (1)$$

where A, B and C are constants that depend of the material property, transit time, pressure and lumen diameter. Note that in 1930s, J. Murray [12] demonstrated the variation in PWV with varying diastolic pressure across cardiac cycles. This was further reported in [13]–[15], by drug induced pressure changes and ex-vivo artery studies. Recently, this concept was explored for cuffless blood pressure measurement by measuring regional [16] and/or local PWV [17] with subject specific or one-time calibration for the constants.

C. *Inter-cycle Variation in PWV with Pressure*

Another important observation in the current study was variation in PWV throughout a pulse cycle. For the sample proximal and distal cycle, a reflection-free region of the systolic phase was observed to have an incremental trend in PWV, as shown in Fig.2(d). It was further validated by measuring PWV from two fiducial points (a lower and upper point, where reflection is minimal) were performed for a set of 50 continuous cycles with varying pressures as shown in Fig.2(b). Clearly, as the pressure increased from the P_L to P_P in the up-stroke phase, corresponding PWV also increased from the lower fiducial point (Ψ_L – corresponding to the foot of the waveform) to upper fiducial point (Ψ_U – corresponding to first derivative maxima of the waveform), illustrated in Fig.2(b), confirming the incremental trend in PWV. On an average, a 48.11% increase in PWV was observed for 31.04% increase in pressure between the selected fiducial point pair within a cycle.

These results are in agreement with the incremental nature of elasticity [3], [4] observed within a cardiac cycle of central arteries. This is associated with the non-linear mechanical property of the arterial walls, due to the structural nature of elastin and collagen fibers. The PWV being a function of

material property [11], this incremental nature is expected in PWV as well, which is demonstrated as an inter-cycle variation in PWV in the present study. These results establish the concept of incremental nature of PWV within a cardiac cycle. Note that the PWV from a single point (typically taken from the foot of waveform) is generally used for all physiological analysis. However, in recent years, the importance of measuring PWV at different pressure levels was reported by independent research [5]–[8] as explained in the next paragraph, highlighting the clinical significance of incremental PWV.

In [5], a study conducted during cardiac catheterization to demonstrate pressure dependency on arterial stiffness and pressure-area relationship, the reported local PWV values for systolic was significantly greater than diastolic measurement. Another study for screening vascular Ehlers-Danlos syndrome (eVDS) [7] reported significant correlation and steady increment with the difference in carotid local PWV at systole and diastole (gradient of incremental PWV) with age and eVDS condition. In [6], pressure dependency of local PWV within the cardiac cycle at population level screening provide evidence for association of left ventricular mass index (LVMI) with incremental local PWV at the carotid artery. This association between LVMI and incremental local PWV is a marker for cardiac risk and load induced myocardial hypertrophy. In [8], the feasibility of incremental local PWV and intima-media thickness at the carotid artery for future cardiovascular risk prediction is reported. As expected, the incremental local PWV in hypertensive subjects were found to be higher than those of normotensive. Recently, from a potential medical instrumentation point of view, a method and system for calibration-free cuffless evaluation of central pressure based on the theory of incremental PWV were developed [9] and demonstrated the feasibility.

D. Limitations and Future Works

As only a small length of the artery was used and all other parts of the experiment hardware being rigid structures, results in severe reflection of the pulse wave, as such only a small region in the systolic phase was preserved unaffected for analysing the variation of PWV. The higher values of PWV, as reposted in this work, might due to the rigid tubing in the hardware setup, and these values may not be directly used to compare with any in-vivo measurement data. Further works using more optimized experiment setup is in progress to resemble the physiological conditions. Such future study also includes drug/chemically induced changes in the artery wall to investigate the effect of material property on incremental PWV varying with the transmural pressure.

IV. Conclusion

In this work, we have demonstrated the minimally investigated phenomenon of incremental PWV using a gold standard technique. Being a direct measurement technique, devoid of any surrounding tissue influence, the dual-channel pressure measurement provided evidence for the intra and inter-cycle variation in PWV with pressure. The widely agreed exponential trend in PWV-pressure was successfully demonstrated here using an excised artery. Continuous variation in PWV within in a cardiac cycle, as the pressure changes from minima to maxima was also demonstrated. The potential application of such incremental PWV should be explored further and incorporated into routine clinical diagnostics and screening.

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