

Effect of Fiduciary Point Choice on Pulse Wave Velocity-based Cuffless Pulse Pressure Estimation: Ex-vivo Study

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Abstract— Superiority of central blood pressure (BP) (especially its pulsatile component; pulse pressure (PP)) over that of brachial has been underlined recently through several clinical studies. Local pulse wave velocity (PWV) based cuffless methods using Bramwell-Hill (BH) equation are popularly employed to assess PP. These approaches assume PWV to be constant, whereas, it changes with pressure. Pertaining to this, literature is unclear on which instantaneous local PWV value should be chosen within the cardiac cycle for PP evaluation. Since local PWV can be measured from various fiducial points spread across the blood pulse cycle, it may be relevant to investigate on the choice of particular one(s) for reliable PP calculation. We have conducted an ex-vivo study in this regard employing an excised ovine artery, emulating 21 independent flow conditions by changing the PP and mean arterial pressure (MAP). The measured end-diastolic (ED) PWV was lower than the peak-systolic (PS) PWV by 32%, and in theory they are the extremities of PWV within a cardiac cycle. An underestimation of 26% was observed in the PP evaluated using ED-PWV and overestimation of 30% using PS-PWV. The PWV that is expected to yield an exact PP value corresponded to the instant in the blood pulse cycle where its mean occurred. The ED-PWV underestimated and the PS-PWV over-estimated the expected PWV by 17% and 14%, respectively, which explains the deviations in the estimated PPs. The time instant of the first derivative maximum being closer to that of the cycle's mean makes it a potential choice for measuring PWV for PP estimation.

Keywords— BH-equation, Characteristic-point, Cuffless-BP Incremental-PWV, Incremental-stiffness, and Hyper elasticity.

I. INTRODUCTION

Blood pressure (BP) from brachial artery using cuff-based devices is well established in hypertension and cardiovascular risk management. In the last decade, research on methods and applications of BP measurement is shifting its course to central arteries and cuff-less techniques [1], [2]. While efforts

already exist in measuring cardiac and respiratory markers via wearables [3]–[6], the cuffless approaches for BP allow integrating this vital marker to such systems offering office and ambulatory assessments. Recent literature emphasizes the superior clinical value of the central BP over the conventionally measured brachial. It may be noted that they are not interchangeable, pulse pressure (PP) significantly varies from central to peripheral arteries [7]. These differences in the central-to-peripheral BP were observed to be amplified as a result of various pharmaceutical interventions [7], [8]. Therefore, knowledge of such differential responses is crucial for the development and administration of targeted anti-hypertensive drugs. Central BP further indicates the actual load on the heart and the pressure experienced by the end-organs, as opposed to peripheral arteries [1], [2]. The central PP is also an early indicator for the stiffening process, allowing assessment of early vascular aging [9].

Unlike in the case of a brachial site, employing a cuff is not feasible for central arterial sites. Therefore, several strategies were proposed to scale or calibrate the peripheral BP to estimate the central BP [8], [10]. Such noninvasive methods reportedly masked the clinical superiority of the central BP over the peripheral one [11]. Applanation-Tonometry has been widely practiced where a peripheral pressure waveform is measured using a transcutaneous tonometer, and employing a generalized transfer functions the central BP is evaluated [4]. These methods are vehemently debated concerning their general applicability [12] and are also constrained by practice-related challenges. Operationally, they demand expertise to correctly flatten the artery with appropriate stable hold-down pressure and perform the measurements. The association between the blood pulse propagation speed and PP have led to the introduction of novel techniques that involve the measurement of local pulse wave velocity (PWV) [12], [13].

Bramwell-Hill (BH) equation can be mathematically modified to calculate the central PP using a local PWV measure from central arteries such as carotid [14]. Methods are these are the basis for several cuffless techniques of measuring BP. Such methods' reliability is dependent majorly on the accuracy of the local PWV measured. Even with

This research was partially supported by Science and Engineering Research Board (SERB), Department of Science and Technology (DST) and Indian Institute of Technology (IIT) Madras under Institute of Eminence (IoE) funding from the Ministry of Human Resource Development (MHRD), Government of India.

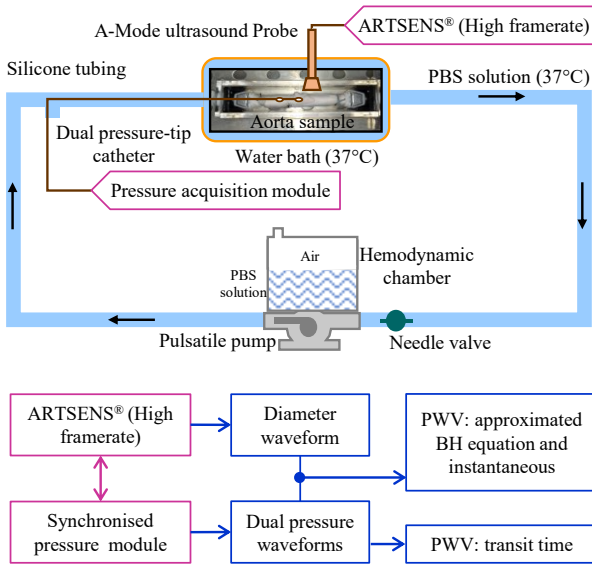


Fig 1. Schematic of the ex-vivo experimental setup and the instrumentation for recording the required high-resolution dual-pressure and diameter signals simultaneously.

employing the robust of techniques and instrumentation for highly accurate local PWV, there is another factor that has to be methodologically considered, which is the hyper-elastic nature of the artery. Due to this property the pulse wave velocity is not constant but changes even within a cardiac cycle due to the diastolic-to-systolic change in pressure. The local PWV significantly increases with an increase in pressure from diastolic minimum to systolic maximum, known as incremental local PWV [14]. Now that the mathematical models derived for the PP estimation assume a constant local PWV, the concern remains which point in the cardiac cycle should be local PWV measured from [14]. The literature is silent on which instantaneous local PWV should be chosen within the cardiac cycle to avoid potential over/underestimation of the PP. Studies using transit time-based methods propose a variety of fiducial points spread across the pulse cycle to evaluate local PWV. Hence, it is relevant to know the role of fiducial point selection in the context of reliable PP estimation using the BH equation.

The presented work addresses this question by conducting an ex-vivo investigation study. The major objectives of the study were to: (i) understand the extremities of the PP deviations that may occur due to fiducial point selection, (ii) demonstrate the association between the deviation of PWV from the expected value and the deviation in PP, and (iii) finally suggest potential fiducial points appropriate for PP evaluation. The experimental methods are presented in section II, followed by results and discussion in section III. The work is concluded by providing the study limitations in section IV.

II. MATERIALS AND METHODS

A. Theoretical Background

For an elastic vessel containing pulsatile flow, the BH equation relates the instantaneous change in pressure P within the vessel to the local PWV [14],

$$PWV_{BH} = \sqrt{\frac{D}{2\rho} \frac{dP}{dD}}. \quad (1)$$

Here ρ is the fluid density, dP is the instantaneous pressure change, dD is the instantaneous diameter change, and D is the

instantaneous diameter of the vessel. This relationship has been used as the basis for cuffless evaluation PP using the PWV. One approach is to re-arrange the (1) and integrate it to obtain a relation that contains PP (ΔP) instead of dP . Another straightforward approach is to approximate the BH equation assuming a linear relationship between the pressure and diameter [14], as shown in (2).

$$PP = (PWV_{BH}^2) \frac{2\rho \Delta D}{D_D}, \quad (2)$$

Here ΔD is the distension and D_D the end-diastolic diameter.

In both approaches to evaluate the PP, the local PWV is treated to be constant for the entire cardiac cycle. However, the hyper-elastic nature of the artery suggests that the wall stiffness is a function of the pressure. Therefore, the PWV, a surrogate of stiffness, increases with pressure within a beat. The instantaneous local PWV is related to the pressure as [14],

$$PWV_{INS}(P) = \sqrt{\frac{P}{z\rho} \left(\beta + \ln \left(\frac{P}{P_D} \right) \right)}. \quad (3)$$

In the expression, P_D is the diastolic pressure, and β is the specific stiffness of the artery. This implies that the PWV across the different fiducial points within the cycle differ in magnitude as the pressure distends from diastolic minimum to systolic maximum. The direct estimation of PWV involves measurement of pulse transit time (PTT) from a particular fiducial point,

$$PWV_{TT} = \frac{\text{Pulse propagation distance}}{PTT}. \quad (4)$$

In this case, the accuracy of the PP depends on the selection of fiducial point that yields PWV_{TT} closer to PWV_{BH} in (2).

B. Ex-vivo Setup for Experimentation

An ex-vivo phantom, as shown in Fig. 1, was set up to perform controlled experiments for investigating the role of fiducial point selection on the reliability of the PP estimated using the BH equation. An ovine aorta (length = ~ 100 mm) was harvested along with the surrounding tissue, cleaned, and sutured for leaks. The leak-proof artery was connected to the experimental setup with a pretension. The artery thus formed the part of a silicon tubing loop through which a syringe-based pump (PD-1100, BDC lab, United States) circulated a pulsatile flow. The pump was attached to a hemodynamic chamber and resistance valve, and together they controlled the flow conditions inducing different mean and pulse pressures. The artery was secured in an acrylic container filled with phosphate buffer solution (PBS; pH:7.4). The container resided inside a water bath that controlled the temperature of the solution, keeping it at 37 °C. The pump arrangement as well consisted of a temperature controlling unit to maintain the circulating fluid at 37 °C. The diameter of the artery was recorded using a single-element ultrasound transducer and high-frame-rate A-mode system (500 fps) [15], [16]. The invasive pressure pulse wave was measured at two proximal spaced sites using a dual-pressure tip catheter (SPR-751 – 5F, Sensor spacing = 30 mm, Bandwidth: 2 kHz, Miller Instruments, USA) at 20 kS/s. The diameter and catheter pressure signals were used to evaluate the PWV_{BH} and PWV_{INS} . On the other hand, the dual catheter pressure waveforms were used to evaluate the PWV_{TT} . The diameter

and pressure waveform acquisition were simultaneously acquired.

C. Specific Study Objectives and Analysis

The primary purpose of the study was to investigate the role of fiducial point choice for the PWV-based cuffless estimation of the pulse pressure. For this, the study analysis was divided into three parts addressing specific objectives as listed below.

(i) To quantify the magnitude of the deviation in the estimated pulse pressures as a result of fiducial point choice.

As the local PWV is expected to be minimum at the foot that is end-diastole (ED) and maximum at peak systole (PS), the PP was evaluated from the local PWVs (estimated using (4)) at these fiducial points. A comparison of these PPs (from ED-PWV and PS-PWV) with respect to actual PP invasively measured would quantify the deviation extremities.

(ii) To demonstrate the relation between the deviation in local PWV and that of the estimated PP.

Substituting the actual PPs (invasively measured) into (2), the expected PWV was evaluated (approx. BH-PWV). This was compared against ED-PWV and PS-PWV to indicate the influence of the PWV's deviation from the expected value on the deviation in PP. Likewise, as the local PWV exhibits an incremental relationship with respect to the pressure (refer (3)), the instant within the pressure cycle was identified to which the approx. BH-PWV corresponded.

(iii) To identify and recommend appropriate fiducial points for the PWV to obtain reliable PPs.

The commonly employed fiducial point locations from the anacrotic phase were identified and compared with the instant within the pressure cycle that corresponded to the approx. BH-PWV. The fiducial points include the second derivative maximum (SDMax: representing the systolic foot), first derivative maximum (FDMax: representing the systolic rise), and second derivative minima (SDMin: point close to the systolic peak) [14]. The analysis would reveal the proximity of the various fiducial points' locations to the point where the expected PWV corresponds to. To maintain uniformity across the various flow conditions, the time-instants for the fiducial points were subtracted with the time-instants of the ED minima for the cycles. Further, the relative time instants were represented as the fraction of cycle's width (expressed in %).

D. Statistics

The group average values are reported as Mean(standard deviation) (SD). Clustered column charts were presented to illustrate and compare the mean values for various categories. The error bars in these charts represent the SD. To illustrate the differences or similarities between the fiducial point locations, box-and-whisker plots are constructed representing the median and interquartile ranges. The coefficient of variation (CoV, expressed in %) was used to quantify the beat-to-beat repeatability. It was calculated as the ratio of SD to mean of beat-to-beat measurements for 15 pulse cycles. The similarity or difference between the groups were tested for statistical significance employing t-test paired two sample for means, with significance level as 0.05.

III. RESULTS AND DISCUSSIONS

A. Ultrasound and Pressure Catheter Recordings

A total of 21 flow conditions were emulated by varying the PP (mean = 12(4.1) mmHg, 7 to 26 mmHg) and MAP (mean = 60(25.2) mmHg, 24 to 124 mmHg), as measured from pressure catheter signals. The dual-pressure catheter waveforms had a temporal resolution of 0.05 ms, offering reliable means to measure the pulse transit time (as required in (4)). The measured PTTs were within the range of 3.4 to 8.5 ms, which were sufficiently larger than the temporal resolution of catheter waveforms. The recorded A-mode signals were of high-fidelity, with signal-to-noise-ratio greater than 27 dB. High-resolution diameter waveforms were yielded from these frames (amplitude resolution = 10 μ m and temporal resolution = 2 ms). As a result of the changing flow conditions, end-diastolic diameter and the peak distension varied from 10 to 17 mm and 0.18 to 0.79 mm, respectively. Beat-to-beat variability of the pressure and diameter measurements were within 0.02 to 4.96%. In this manner, the high-quality recordings ensured reliable raw recordings for the further analysis

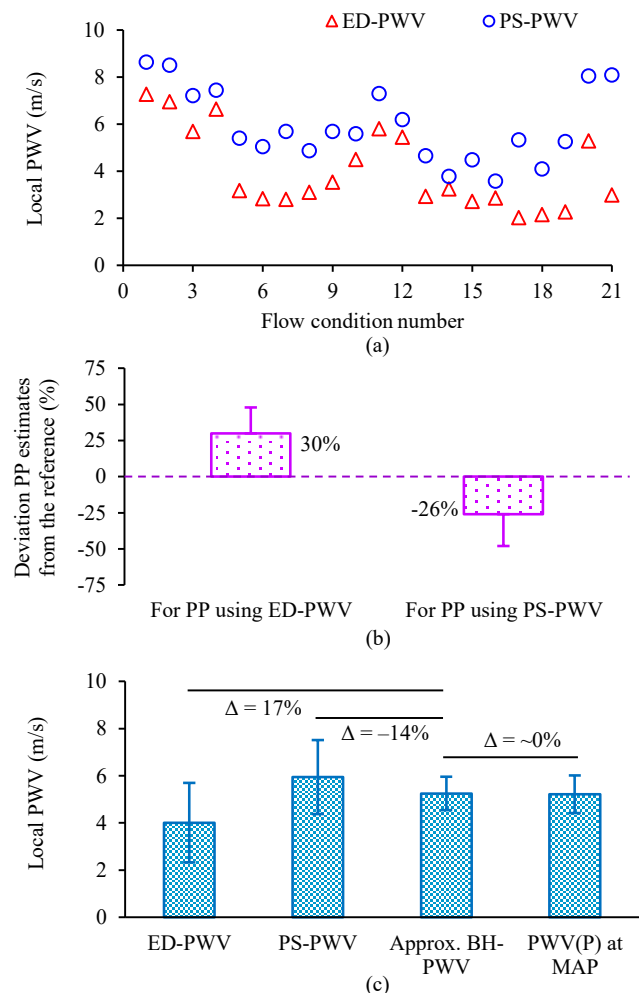


Fig 2. (a) Illustration of transit time-based local PWVs corresponding to the end-diastole (ED) and peak-systole (PS), measured for all the flow conditions. (b) The deviations in PP estimates from the actual measured ones, where the estimation used the independent ED-PWV and PS-PWV. (c) Comparison of the ED-PWV and PS-PWV with the expected PWV. Also, the instantaneous PWV estimated from mean pressure level is compared.

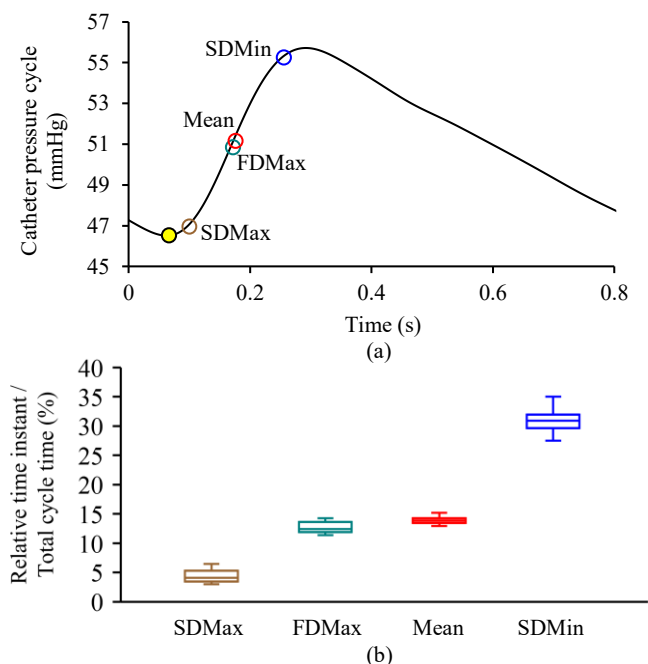


Fig 3. (a) A sample of measured pressure cycle, on which the conventionally reported fiducial points are marked. The first marker (along the time-axis) is the end-diastolic minimum of the cycle. (b) Comparison various fiducial point time instances relative to end-diastolic minimum (expressed as % of cycle width).

B. Extremities of the PP Deviation

The local PWV measured for the fiducial points ED and PS using (4), for all the flow conditions, are shown in Fig. 2(a). The mean ED-PWV was 4.01(1.68) m/s, and likewise, PS-PWV was 5.94(1.57) m/s. As may be observed from Fig. 2(a) that the PS-PWV being taken from the systolic-peak, the highest-pressure level within a cardiac cycle, is systematically higher than ED-PWV that is obtained from the lowest-pressure level within the cardiac cycle. These represent the extremities of the PWV variations within the cardiac cycle [14], and so does the deviations in PP evaluated from these. In Fig. 2(b), the deviations in the PP (respectively calculated from ED-PWV and PS-PWV) from the actual measured PP is illustrated. It was observed that the PP using ES-PWV overestimated the actual PP and the one from PS-PWV underestimated it. This underlines the need for cautious selection of the appropriate fiducial point, which otherwise may potentially incur deviations as large as 25%.

C. Association of PWV Deviation with PP Deviation

As a closer analysis, the ED-PWV and PS-PWV are compared to the expected PWV (i.e. the approx. BH-PWVs that yield the exact PPs), in Fig. 2(c). The ED-PWV underestimates the approx. BH-PWV by 17%, whereas, the PS-PWV overestimated it by 14%, which was statistically significant ($p < 0.05$). This deviation in the PWV explains the deviations in the PP as observed in Fig. 2(c). This also suggests that the PWV that is expected to yield reliable PP estimates corresponds to fiducial point neither located close to ED nor PS.

D. Potential Choice of Fiducial Point

A fiducial point that is proximal to center for anacrotic phase is expected to provide minimal deviations during PP estimation. To investigate this hypothesis the instantaneous incremental PWV was evaluated for the anacrotic phase using (3), to which the approx. BH-PWV was compared. This

revealed that approx. BH-PWV concurred with the instantaneous PWV at MAP level, 5.24(0.71) m/s versus 5.22(0.80) m/s as shown in Fig. 2(c). The results reveal that a fiducial point in the vicinity of the mean level of the blood pulse cycle is a potential choice as opposed to the ED or PS. The popular fiducial points enlisted in the earlier section SDMax, FDMax, and SDMin are illustrated on a pulse cycle along with the location of the pulse's mean. Intersecting tangent method yields another fiducial point for identifying the systolic foot that is similar to SDMax.

It can be evidenced that the FDMax is closer to the mean of the cycle, in Fig. 3(a). This is also evident from the Fig. 3(b), that for all the flow conditions the relative position of FDMax from foot is closest to that of mean. Therefore, FDMax or the mean of the cycle are potential choices from which local PWV can be measured for reliable PP estimation. Earlier works adopting the equivalent fiducial points have reported appreciable performance figures concerning the PP evaluation [12]–[14]. However, jitter and early-systolic arterial wave reflections are an important methodological concerns when choosing such fiducial point from center of the anacrotic phase [14]. High resolution systems assist in tackling the jitter, though the majority frequency content of blood pulse signal is limited to 20 Hz, a sampling rate in the orders > 200 Hz are required. Now concerning the early systolic wave-reflections, appropriate wave separation technique may be employed to minimize the effect of reflections, as in our earlier work [15].

IV. LIMITATIONS OF STUDY

The phantom setup being not an extensive mimic of the in-vivo circulatory system, the dicrotic notch (a potential fiducial point) [14] couldn't be emulated and included in the analysis. Likewise, the intersecting tangent being similar to SDMax [14], has also not been included in the analysis. There are indirect methods to estimate the PWV, such as lnDU, QA, and D^2U , that require a flow velocity/rate waveform [14] that wasn't measured during this study. So, efforts are in progress to compare the PPs evaluated from such PWV estimates with those based on transit time.

V. CONCLUSION

The ex-vivo study demonstrated the importance of fiducial point selection for PWV measurement in the context of PP estimation using BH equation. The results revealed a significant difference in PWV measured from ED and PS. The ED-PWV and PS-PWV respectively underestimated and overestimated the expected PWV that yields accurate PP. This explained the deviation of PP estimated using the ED-PWV and PS-PWV from the reference. The expected PWV corresponded to the instantaneous PWV obtained from mean of the pulse cycle. A comparison showed that FDMax is the closest fiducial point to the cycle's mean in anacrotic phase. So, this makes it a potential option for the PP evaluation, as also observed in earlier works.

VI. REFERENCES

- [1] A. Kollias, S. Lagou, M. E. Zeniodi, N. Boubouchairopoulou, and G. S. Stergiou, "Association of central versus brachial blood pressure with target-organ damage: systematic review and meta-analysis," *Hypertension*, vol. 67, no. 1, pp. 183–190, 2016, doi: 10.1161/HYPERTENSIONAHA.115.06066.
- [2] J. E. Sharman and S. Laurent, "Central blood pressure in the management of hypertension: soon reaching the goal?," *J. Hum. Hypertens.*, vol. 27, no. 7, pp. 405–411, 2013, doi: 10.1038/jhh.2013.23.

- [3] A. S. Anusha *et al.*, "Electrodermal Activity Based Pre-surgery Stress Detection Using a Wrist Wearable," *IEEE J. Biomed. Heal. Informatics*, vol. 24, no. 1, pp. 92–100, Jan. 2020, doi: 10.1109/JBHI.2019.2893222.
- [4] S. P. Preejith, A. Jeelani, P. Maniyar, J. Joseph, and M. Sivaprakasam, "Accelerometer based system for continuous respiratory rate monitoring," *2017 IEEE Int. Symp. Med. Meas. Appl. MeMeA 2017 - Proc.*, pp. 171–176, Jul. 2017, doi: 10.1109/MEMEA.2017.7985870.
- [5] S. P. Preejith, A. Alex, J. Joseph, and M. Sivaprakasam, "Design, development and clinical validation of a wrist-based optical heart rate monitor," *2016 IEEE Int. Symp. Med. Meas. Appl. MeMeA 2016 - Proc.*, Aug. 2016, doi: 10.1109/MEMEA.2016.7533786.
- [6] S. Vijayarangan, R. Vignesh, B. Murugesan, P. Sp, J. Joseph, and M. Sivaprakasam, "RPnet: A Deep Learning approach for robust R Peak detection in noisy ECG," *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS*, vol. 2020-July, pp. 345–348, Jul. 2020, doi: 10.1109/EMBC44109.2020.9176084.
- [7] A. P. Avolio *et al.*, "Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data," *Hypertension*, vol. 54, no. 2, pp. 375–383, 2009, doi: 10.1161/HYPERTENSIONAHA.109.134379.
- [8] H. M. Cheng *et al.*, "Central blood pressure for the management of hypertension: Is it a practical clinical tool in current practice?," *J. Clin. Hypertens.*, vol. 22, no. 3, pp. 391–406, 2020, doi: 10.1111/jch.13758.
- [9] P. Verdecchia, F. Angeli, and S. Taddei, "At the beginning of stiffening: Endothelial dysfunction meets 'pulsology,'" *Hypertension*, vol. 48, no. 4, pp. 541–542, 2006, doi: 10.1161/01.HYP.0000239236.12524.d3.
- [10] C. M. McEniery, J. R. Cockcroft, M. J. Roman, S. S. Franklin, and I. B. Wilkinson, "Central blood pressure: current evidence and clinical importance," *Eur. Heart J.*, vol. 35, no. 26, pp. 1719–1725, 2014, doi: 10.1093/eurheartj/ehs565.
- [11] T. J. Niiranen, B. Kalesan, N. M. Hamburg, E. J. Benjamin, G. F. Mitchell, and R. S. Vasan, "Relative contributions of arterial stiffness and hypertension to cardiovascular disease: the Framingham heart study," *J. Am. Heart Assoc.*, vol. 5, no. 11, pp. 1–9, 2016, doi: 10.1161/JAHA.116.004271.
- [12] J. Vappou, J. Luo, K. Okajima, M. Di Tullio, and E. E. Konofagou, "Non-invasive measurement of local pulse pressure by pulse wave-based ultrasound manometry (PWUM)," *Physiol. Meas.*, vol. 32, no. 10, pp. 1653–1662, 2011, doi: 10.1088/0967-3334/32/10/012.
- [13] J. Joseph, P. M. Nabeel, M. I. Shah, and M. Sivaprakasam, "Arterial compliance probe for cuffless evaluation of carotid pulse pressure," *PLoS One*, vol. 13, no. 8, pp. 1–19, 2018, doi: 10.1371/journal.pone.0202480.
- [14] P. M. Nabeel, K. V Raj, J. Joseph, V. V. Abhidev, and M. Sivaprakasam, "Local pulse wave velocity: theory, methods, advancements, and clinical applications," *IEEE Rev. Biomed. Eng.*, vol. 13, pp. 74–112, 2020, doi: 10.1109/RBME.2019.2931587.
- [15] K. V Raj, P. M. Nabeel, D. Chandran, M. Sivaprakasam, and J. Joseph, "High-frame-rate A-mode ultrasound for calibration-free cuffless carotid pressure: feasibility study using lower body negative pressure intervention," *Blood Press.*, vol. 31, no. 1, pp. 1–11, 2022, doi: 10.1080/08037051.2021.2022453.
- [16] 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. 41002, 2015, doi: 10.1115/1.4030873.

