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Comparison of Approximated and Actual Bramwell-Hill Equation Implementation for Local Pulse Wave Velocity: *Ex-vivo* Study

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***Abstract*— Bramwell-Hill (BH) equation is widely adopted for the evaluation of local pulse wave velocity (PWV), primarily for its theoretical association with the vessel's distensibility. Its implementation, however, requires arterial pressure and diameter waveforms simultaneously from a single site. Owing to the challenges associated with such a noninvasive recording, an approximated BH equation is adopted without requiring the entire pressure waveform but only the diastolic and systolic values. The approximated BH method yields a single value of local PWV as opposed to the actual method that provides instantaneous PWV within a cardiac cycle. This study aims to provide the currently lacking insights into how the approximate versus actual BH implementations compare. The study also addresses the pivotal question of which instantaneous value within the cardiac cycle corresponds to the approximated BH. An *ex-vivo* study was conducted for this purpose, emulating different flow conditions (changing mean and pulse pressures) to vary the local PWV within the range of 4.4 to 8.9 m/s. The results revealed the expected (pressure-dependent) incremental nature of local PWV due to hyper-elastic behavior of the artery, with systolic BH-PWV > diastolic BH-PWV by 13.6%. The approximate BH-PWV was similar to actual BH-PWV obtained from mean pressure level. It further underestimated the systolic, and overestimated the diastolic PWVs by 8.5% and 6.6%, respectively.**

***Clinical Relevance*— When estimated BH-PWV estimates are compared to normal values for patient classification or utilized as a reference standard in validation studies, these findings become extremely important.**

I. Introduction

Pulse wave velocity (PWV) is the speed with which the blood pulse propagates across the vasculature [1]. Its association with the artery's elasticity and blood pressure has led clinicians to adopt its regional measurement (carotid-to-femoral PWV) to tackle vascular aging and hypertension [2]. Recently, its local measurement, that is pertaining to a single point or small segment of the target artery has been gaining attention, given its value above and beyond the regional measure [1]. Particularly, there are have been several clinical applications reported in the literature that utilize and require such localized information on stiffness rather than a global estimate of the vasculature as a whole [1]. Popular local PWV assessment methods are based on transit time, hemodynamic loops, and biomechanical equations [1], [3].

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While transit time methods are the most straightforward of these, local PWV evaluated using Bramwell-Hill (BH) equation has been widely reported in several studies across the literature [1], [4]. Owing to its theoretical relationship to the distensibility of a vessel, it is believed to be an appropriate surrogate of stiffness [1], [4], [5]. An in-silico study suggested that BH method performs best among the several PWV estimation methods that use a pair of non-distinct hemodynamic signals (flow rate, pressure, and diameter) [6]. It is also evident from the sum of the studies that have used BH-based PWV as a reference estimate for comparison [1]. Implementation of BH equation requires vessel's internal pressure and cross-sectional area/diameter measured simultaneously from the same site [4]. It poses an instrumentation challenge while the measurements are to be performed non-invasively [7].

While the measurement of lumen diameter is simpler with established ultrasound technologies, the noninvasive measurement of pressure as a continuous waveform is limited by the available state-of-the-art. Applanation tonometry is a reliable means for measuring pressure waveforms [8], but its accuracy is compromised for arterial sites like carotid where appropriate applanation is not feasible. They require extensive expertise, and also the integration of such modules with the clinically available ultrasound systems may not always be feasible. Hoeks et al. have underlined further considerations pertaining to combining pressure and ultrasound systems [7]. Given such methodological constraints, an approximated version of BH equation is popularly adopted [1], [9]. Few important aspects remain unaddressed in literature, which is crucial when adopting the approximated BH implementation.

Implementing the actual BH equation using a pressure and diameter waveform results in varying PWV within each cardiac cycle. More specifically, the local PWV increases with an increase in pressure from the end-diastolic to peak-systolic phase within each beat, known as incremental PWV [1], [5], [10], [11]. On the contrary, the approximated BH equation yields a constant value for PWV estimate for the entire cardiac cycle. The question now is which value of the instantaneous PWV obtained using the true BH approach corresponds to the single value obtained using the estimated method. Understanding as such is pivotal while the values from the approximated BH equation are interpreted against nomograms generated from a different method. Also, when the (approx.) BH PWV is used as a reference estimate for validating new techniques, a potential measurement biases could be explained. This study aims to provide insights into the difference between the actual versus approximated implementation of the BH equation. An ex-vivo phantom setup has been developed with an excised ovine aorta sample for the experiments. BH PWVs from the different

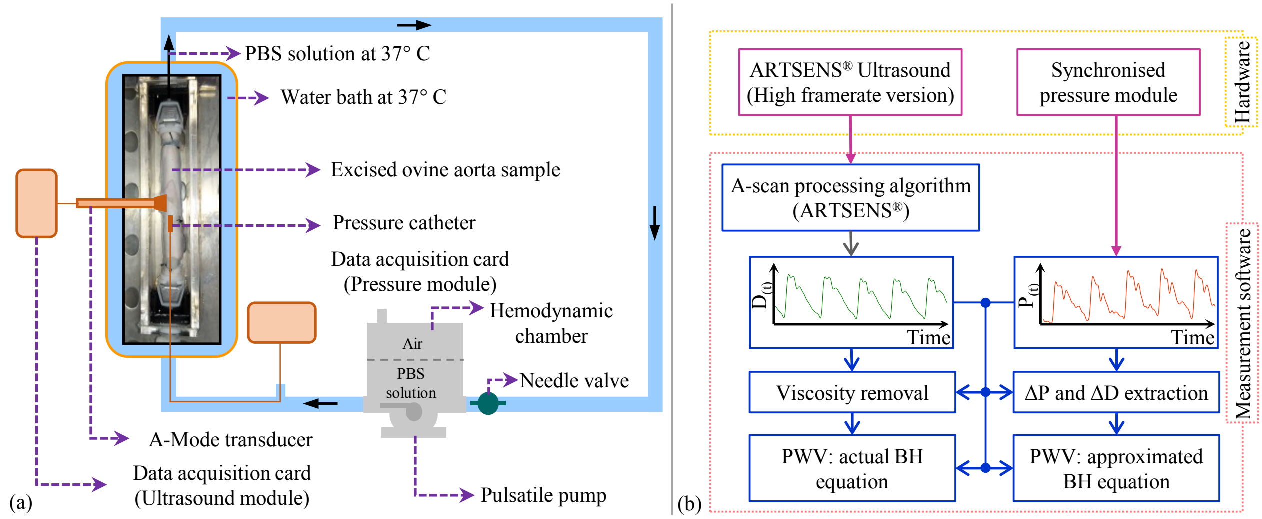

Figure 1. (a) Illustration of the controlled ex-vivo experimental setup for recording the pressure and diameter signals simultaneously. (b) Schematic of the measurement system to yield the actual and approximated BH–local PWVs.

implementations were obtained for different flow conditions and studied, as in section II. The results are presented and discussed in section III and concluded.

II. Materials and Methods

A. BH Equation-Actual Implementation

Bramwell-Hill (BH) equation, as in (1), provides an expression relating the PWV with the distensibility (DC) of an elastic thin-walled vessel,

$$PWV_{BH} = \sqrt{\frac{1}{\rho\, DC}} = \sqrt{\frac{A\, dP}{\rho\, dA}}. \qquad (1)$$

Here ρ is the density of the pulsatile fluid within the vessel, dP is the instantaneous pressure change due to the pulsatile fluid volume change, dA is the instantaneous change in circumference area caused by dP, and A is the instantaneous area of the vessel segment. The same can be expressed in terms of diameter (D) by substituting dA/A as 2dD/D. The BH equation was originally developed for purely elastic vessels, but the presence of viscosity components in the case of arteries makes it challenging to apply the equation directly [1], [12]. Due to the presence of the viscous component, a hysteresis is observed between the pressure and diameter, instead of an exponential curve. Earlier works rely on eliminating this viscous component, before modeling the purely elastic pressure signal [1], [12]. This allows reliable evaluation of dP/dD as the instantaneous slope of modeled P versus D exponential curve for the estimation of PWV. Due to the exponential P-D relationship, the slope dP/dD is not a constant, resulting in an increasing local PWV from the end-diastolic to peak-systolic phase.

The local PWV evaluated in this manner requires a recording of arterial pressure and diameter waveform, ideally from a single measurement site. There are several methodological challenges to performing simultaneous recording of pressure and diameter. Ultrasound is employed to measure the diameter waveforms and conventional systems do not have provision for integrating a synchronous pressure acquisition module. Additionally, B-mode probes are wide dimensioned, and when a pressure transducer is secured alongside, it results in further pseudo hysteresis [7]. Several works, therefore, have adopted local PWV evaluated from an approximated form of BH equation in their studies [1].

B. BH Equation-Approximated Implementation

Instead of the pressure signal, it is more convenient to measure just the systolic and diastolic pressure values, as can be obtained from automated brachial BP monitors, for instance. This instrumentation advantage has been exploited for the evaluation of the local PWV using an approximated form of BH equation, given in (2). Such a method is based on replacing dP with the pulse pressure ΔP (= SBP–DBP), dD with the maximum distension ΔD (difference of peak systolic and end-diastolic diameters), and finally, D with the end-diastolic diameter D_D, resulting in the expression

$$PWV_{BH\_apx} = \sqrt{\frac{D_D\, \Delta P}{2\rho\, \Delta D}}. \qquad (2)$$

Contrary to the actual method, the approximated method yields a single value of PWV. For comparing both the methods, it is required to extract a single value from the instantaneous values of local PWV provided by the actual method for each cardiac cycle.

C. Ex-vivo Setup for Pressure and Diameter Recording

An ex-vivo phantom setup was arranged, as shown in Fig. 1(a) to perform controlled experiments for investigating the differences between the actual and approximated BH PWVs. The artery was prepared initially for the ex-vivo setup. A 100 mm length of the ovine aorta and surrounding tissue were harvested and preserved in phosphate buffer solution (PBS, pH:7.4, temperature:37°C). The artery was cleaned by removing all the surrounding muscle and fatty tissues. The artery had a few vasa vasorum identified by flushing in PBS solution. The identified leak sites were sutured, and the arterial segment was made leak-proof. The manually measured diameter of the artery was ~10 mm, and the length was ~100 mm. The artery segment was immersed in a small acrylic chamber filled with PBS. The chamber was kept inside a water bath maintained at 37 °C. The arterial segment was stretched for a pre-tension, and connected to the experimental setup via silicone tubing as demonstrated in the Fig. 1(a). A syringe-based pulsatile pump (PD-1100, BDC lab, United States) was

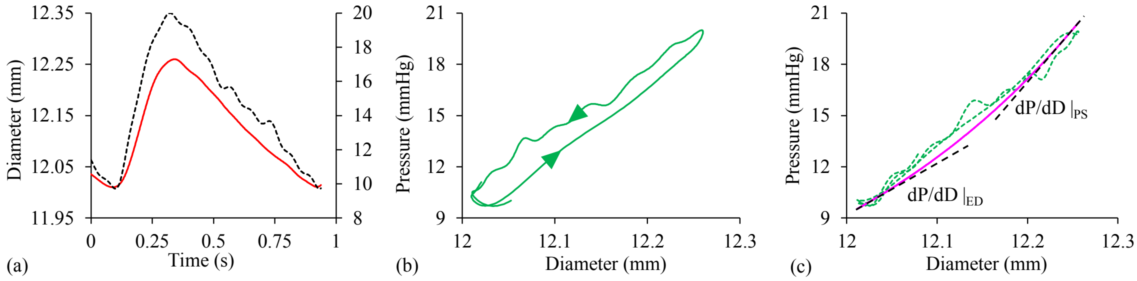

Figure 2. (a) A cycle of simultaneously measured catheter pressure (dotted line) and diameter (solid line), (b) the hysteresis P-D loop, (c) hysteresis compensated, and modeled P-D curve representing an exponential relationship, and changing slope from end diastolic (ED) to peak systole (PS).

used to generate continuous pressure cycles for various flow and pressure conditions (flowrate: 1 to 2 L/min, Pulse Pressure: 6 to 28 mmHg, MAP: 21 to 124 mmHg). The pump ensured a continuous and circulatory flow of PBS with a temperature maintained at 37 °C.

The schematic of the measurement system is shown in Fig. 1(b). A high-fidelity Micro-Tip® pressure catheter (SPR-882 – 2F, Sensitivity: 5μV/V/mmHg, Miller Instruments, USA) was inserted via a PTCA Y connector (hemostasis valve) and guided by ultrasound imaging to the center of the arterial segment. The catheter was calibrated from 0 to 300 mmHg against a standard pressure gauge prior to the experiment. The pressure signal was amplified and digitized at 500 Hz sampling rate using NI-6218 data acquisition card (National Instruments, United States). This acquisition hardware was synchronized with a high frame rate version of image-free ultrasound device, ARTSENS [13], [14]. A-mode frames of 40 mm depth were acquired at the rate of 500 frames per second using a 10 MHz and 5 mm single element focused ultrasound transducer. The echo signals were acquired at a sampling rate of 200 MHz employing a NI-5124 scope card (National Instruments, United States), providing a diameter tracking resolution of ~4 μm. Diameter waveform was evaluated using our established automated algorithms [15], [16], and with it, the acquired pressure waveform was employed for assessing the BH PWVs.

D. *Statistical Analysis*

The group average values are reported as mean ± standard deviation (SD). For this study, three independent values of PWV corresponding to end-diastolic, peak-systolic, and mean arterial pressures (PWV_D, PWV_S, and PWV_M) were extracted for comparison with PWV_{BH_apx}. To illustrate the differences or similarities between the PWVs box-and-whisker plots are constructed representing the median and interquartile ranges. The coefficient of variation (CoV, expressed in %) quantified the beat-to-beat repeatability.

III. Results and Discussion

A. *Quality of the Diameter and Pressure Recordings*

High-quality A-mode frames, having a signal-to-noise ratio of 26 ± 2 dB, were recorded during the experiment for all the flow conditions. The obtained pressure and diameter waveforms had a high temporal resolution of 2 ms. Such high resolutions are important to tackle with jitter noise and include essential high-frequency components of the blood pulse [7]. The several methodological concerns alluded have been considered for measurement arrangement. The catheter tip and ultrasound transducer were aligned, avoiding any extra time delay component due to pulse propagation. Also, when noninvasive pressure module is used, the transmural pressure pulse may suffer alterations due to the tissue transfer function, to which the current experimental setup is not prone. Finally, the inter-channel delay between the ultrasound and pressure module was in sub-microseconds (< 1 μs), not significantly contributing to the delay between them.

This ensured reliable acquisition by accounting for the sources of the errors listed in literature, thereby allowing reliable implementation of the BH methods. Fig. 2 illustrates a sample of diameter and pressure cycle, the P-D loop before and after compensating for viscosity and the modelled P-D curve. After eliminating the possible sources of erroneous lags between the pressure and diameter, the lag that's still observed between them (4 ± 2 ms) results from the viscous pressure component, causing the hysteresis, as observed in Fig. 2(b). These lags are directly corrected, or the viscous component is assessed with models such Kelvin-Voigt to remove the hysteresis [1], [12] before modeling the P-D relationship curve, as in Fig 2(c).

The pressure and diameter cycles for the individual flow configurations were repeatable with 0.2 to 1.5 % CoV. The end-diastolic diameters and distension achieved during the study varied between 11.75 to 16.77 mm and 0.18 to 0.79 mm, respectively. Similarly, the mean arterial and pulse pressures varied from 21 to 124.4 mmHg and 5.9 to 28.4 mmHg, respectively. The local PWV varied between 4.4 to 8.9 m/s.

B. *BH Methods Comparison Results*

The overall CoV of PWV_S, PWV_M, PWV_D, and PWV_{BH_apx} ranged from 0.28 to 2.02%, which is lowest for PWV_S (1.43 ± 4.60 %) and highest for, PWV_D (1.45 ± 4.36 %). These PWV measurements are compared in Fig. 3(a), showing the box-and-whisker plot. PWV_S was systematically greater than PWV_D for all the beats and flow conditions, as expected physiologically due to hyper-elasticity of the artery. Typical silicone-based artery-mimicking models are not hyper-elastic in nature, and they have a linear stress-strain relationship as opposed to actual arteries. Therefore, contrary to the study results, such mimicking models are expected to provide similar PWV_S and PWV_D as the slopes dP/dD wouldn't differ, rather are constant.

The PWV_{BH_apx} was significantly ($p < 0.05$) smaller than PWV_S, larger ($p < 0.05$) than PWV_D and closer to PWV_M. The PWV_{BH_apx} strongly correlated to PWV_M ($r^2 = 0.99$, $p < 0.001$), as shown in Fig. 3(b). The bias between PWV_S versus PWV_D was 0.78 m/s (13.63%), PWV_S versus PWV_M was 0.37 m/s (6.54%), PWV_M versus PWV_D was 0.40 m/s (7.73%), and

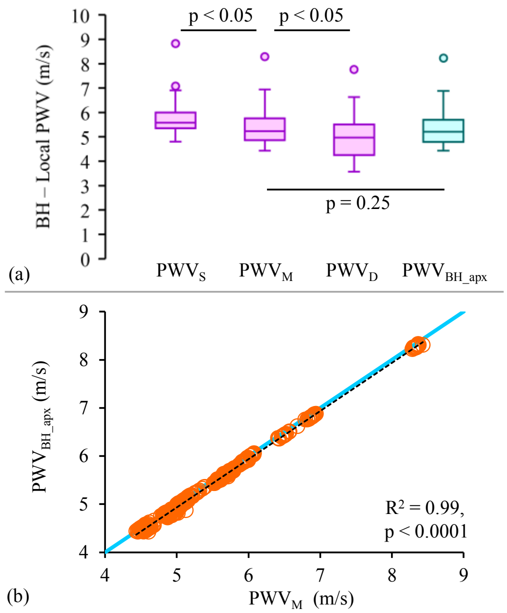

Figure 3. (a) Box-and-whisker plots to illustrate the differences between the various BH – Local PWVs measured (PWV_S, PWV_M, PWV_D, and PWV_{BH_apx}). (b) Regression plot between PWV_M and PWV_{BH_apx}.

PWV_M versus PWV_{BH_apx} was 0.06 m/s (1.19%). These inferences have got several application-level implications. When PWV evaluated using approximated BH method is used as a reference method to validate other methods, care has to be taken on interpreting the bias obtained. For instance, when transit time-based local PWV is evaluated from systolic foot, it will underestimate the PWV_{BH_apx}. The reason is MAP is closer to the first-derivative maximum of the blood pulse, and PWV_{BH_apx} being closer to the PWV_M is expected to be greater than the foot-PWV.

Another important aspect of this study result concerns interpreting reference ranges for local PWV measurements. Since, the PWV_{BH_apx} may not always be interchangeable with local PWV estimated from other methods or not similar to PWV estimated from other phases of the blood pulse (far from the mean level), the look-up reference data has to be carefully considered for avoiding any misclassifications. In the literature, the approximated BH equation forms the basis for cuffless evaluation of pulse-pressure, where the local PWV is measured and substituted in the expression [1], [17]. Pertinent to this, substituting the right estimate of local PWV taken from the appropriate instance of the cardiac cycle, is crucial for avoiding potential under/over-estimation in the pulse pressure.

IV. Conclusion

The ex-vivo study compared the actual versus approximated BH PWVs over a range of 4.4 to 8.9 m/s. The results revealed that the actual BH method produces instantaneous values of local PWV within a cardiac cycle. The approximated BH method yields a single PWV value equivalent to the actual one obtained for the mean pressure level. Further, it was evidenced that the approximated BH method's PWV underestimates the systolic and overestimates the diastolic level PWVs. Therefore, such an aspect must be noted with caution when using them for validation studies or interpreting them against normal reference values generated from different population studies.

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