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# A Feasibility Study on the Response of Vascular Impedance to Reactive Hyperemia

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*Abstract*— **Endothelium-dependent vascular reactivity has been recommended as a reliable indicator of vessel health. Ultrasound-based assessment of diameter response to shear stress measured as the proportion of brachial dilatation caused by reactive hyperemia (RH), is the gold standard for evaluating endothelial reactivity. However, the conventional approach does not account for the transient increase in blood flow and subsequent change in the transmural pressure that stimulates the endothelial cells to dilate the artery. In this work, simultaneous measures of blood flow and blood pressure during RH are used to evaluate the response of the brachial artery impedance. Endothelial reactivity is assessed using a three-element impedance blood flow model of the brachial artery. A significant change (> 30%) was observed in the impedance parameters in response to RH. The results were repeatable (ICC > 0.64) over 2 consecutive days for 10 participants. The results demonstrate the applicability of brachial impedance analysis in evaluating endothelial reactivity. This method also directly evaluates endothelial response to shear since the flow velocity and pressure increase precede the diameter change.**

**Keywords: Brachial Impedance, Endothelial Reactivity, Flow-mediated Dilation, Total Arterial Compliance, Vascular stiffness**

## I. INTRODUCTION

Endothelial cells contribute to modulating vascular wall homeostasis. This process is carried out by the production and release of various vasodilators and vasoconstrictor substances [1]. However, the normal functioning of the endothelium can be altered due to various stimuli resulting in endothelium dysfunction. Current evidence suggests that endothelial dysfunction occurs early in the process of atherogenesis and is an independent predictor of future cardiovascular events in patients with atherosclerotic risk factors [2]. Endothelial reactivity (ER) is the endothelial cell response to an input shear stimulus that appears as functional changes in arterial stiffness. The most common method to estimate ER is the ultrasound assessment of brachial diameter normally called the Flow-mediated dilation (FMD) test. In an FMD test, the relative change in the diameter of the brachial artery due to an input shear stress is measured. However, the FMD index fails to include the transient increase in blood flow and the corresponding local perfusion pressure that has resulted in the actual dilation of the artery.

There are numerous studies that investigated the relationship between arterial pressure and flow [3]. Impedance indices are the ratios of the harmonics of pressure to flow. They provide a measure of the opposition to blood flow in a pulsatile system and are a proven indicator of vasculopathy [4]. There exists an association of vascular impedance with age, with arterial stiffness indices [5], and its differentiation among normotensives and hypertensives [6]. The three-element Windkessel (WK) based electrical model is widely used to estimate the arterial impedance indices and has been used as a simple representation of peripheral beds like brachial artery [7].

The response of brachial impedance to reactive hyperemia is a less explored yet potent way of assessing endothelial function, provided that it requires simultaneous pulsatile cycles of both pressure and flow. In this work, we have proposed a method for ER assessment using the response of arterial impedance ($ERA_{IR}$) to RH. We have measured the beat-to-beat blood pressure (BP) and blood flow simultaneously to calculate the functional impedance response to shear. A cuff-based brachial pressure pulse measurement was combined with B-mode ultrasound imaging for brachial artery blood flow. Simultaneous measurements of pressure and flow of the brachial artery during RH were recorded on 10 healthy participants and the data was processed to evaluate the beat-to-beat measurements of brachial impedance matrices. Further, the relative change in brachial impedance indices during hyperemia was estimated using a three-element WK model and the impedance values were used to calculate the proposed $ERA_{IR}$ index. Furthermore, arterial material response represented by the relative change in local pulse wave velocity is also calculated from the estimates of characteristic impedance. $ERA_{IR}$ was then compared against FMD to analyze the differences in measurements due to the influence of pressure and flow measurements possibly due to the influence of pressure and flow.

The details of the measurement principle, measuring system and the conducted study are presented in Section II. A detailed discussion of the results and observations is discussed in Section III, followed by limitations and future scope. The study conclusions are outlined in Section IV.

## II. MATERIALS AND METHODS

### A. Measurement of brachial blood pressure and flow

The measurement system and schematic of brachial impedance are given in Fig. 1. The continuous pressure measurement is taken using an in-house cuff-based sensing system. The system consists of a 32-bit ARM microcontroller

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(LPC4370FET256, NXP Semiconductors, Netherlands), pressure sensor (Honeywell 24PCCFA6D, US), air pump (12V DC 380mA 500mmHg), solenoid valves, and a bladder cuff (cuff 1) comprise the system. A feedback control is used by the microcontroller to keep the cuff at sub-diastolic pressure. The GPIO lines on the LPC43XX control the driver circuitry that regulates the pump and solenoid valves used to inflate and deflate the brachial cuff. The cuff pressure is monitored by the pressure sensor, and the amplified pressure signals are digitized by the analog-to-digital converter (12-bit ADC) on the LPC4370. The digitized raw pressure data is one-time calibrated to reference Oscillometric pressure (measured using SunTech®247™, SunTech Medical, US).

The continuous flow measurements were performed using longitudinal B-mode scanning of the brachial artery (Sonix Touch+, BK Medicals, US) with a high-resolution ultrasound probe (7-12 MHz) in PW mode. The data in cine loops was analyzed using continuous edge-detection and wall-tracking software (FMD Studio, Quipu, Netherlands). The leakage-compensated pressure signals and plot-digitized flow signals are filtered and time-synchronized based on the recorded start of baseline and further processed for estimation of impedance.

### B. *Determinants of brachial impedance and ERA index*

Using the WK model, the brachial artery segment is modelled as a tube with input resistance r, compliance C and an associated peripheral resistance R(modelling the resistance downstream), analogous to the characteristic resistance Zc, total arterial compliance TAC and total peripheral resistance TPR. The Pressure and flow cycles recorded throughout the experiment were evaluated using a LabVIEW-based platform, and assumed as their electrical alternatives as voltage (v(s)) and current sources (i(s)) in the WK model were used to estimate the arterial impedance parameters as a second-order transfer function in the Laplace domain given by,

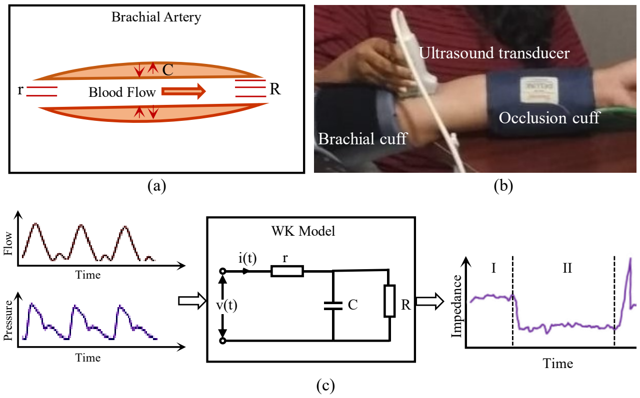
$$\frac{\mathrm{i(s)}}{\mathrm{v(s)}} = \frac{1 + \mathrm{RCs}}{\mathrm{rCs} + (\mathrm{r} + \mathrm{R})} \tag{1}$$

The extrema of impedance parameters during RH ($\mathrm{I_{extrema}}$) and baseline impedance ($\mathrm{I_{baseline}}$) is identified to derive the $\mathrm{ERA_{IR}}$ index given by,

$$ERA_{IR}\,\% = \frac{I_{extrema} - I_{baseline}}{I_{baseline}} \times 100 \tag{2}$$

### C. *Participant Preparation and Measurement procedure*

An in-vivo study was done on 10 volunteers (6 males: 4 females; 24 ± 5y) over two consecutive days (in total 20 measurements) to evaluate the repeatability and reproducibility of measurements. The study was carried out in a controlled laboratory setting (23 ± 2°C) at the Healthcare Technology Innovation Centre, Indian Institute of Technology Madras, India. Prior to the trial, participant information such as lifestyle and medical history was collected. Individuals who had cardiometabolic illnesses, smoked, or had a history of drug or tobacco use were excluded from the study. The recommended FMD guidelines were considered while drafting the study protocol [8], [9]. The guidelines of the Helsinki Declaration (updated in 2013) were followed and approved by the Institutional Ethics Committee, IIT Madras. The objectives and procedures were explained to participants, and informed consent was obtained.



(a) (b) (c)

Fig 1. The measurement system showing (a) brachial artery impedance, (b) device setup and, (c) the WK as a transfer function model

Participants were instructed to relax in a supine position for 10-15 minutes before the study. Before the experiment, an automated BP monitor was used to obtain Oscillometric BP measurements on the brachial artery. A trained operator palpates and detects the brachial artery before orienting the ultrasound transducer. Baseline (2 min) cine loops of B-Mode diameter and PW-Mode flow waveforms were acquired continuously. The bladder cuff is then wrapped around the lower arm and inflated to supra-systolic pressure (SBP + 50mmHg) for 5 minutes to induce ischemia. Following cuff removal, recovery (3 min) RH measurements were taken. The data were analyzed in LabVIEW to get estimates of $\mathrm{ERA_{IR}}$%. The experiment was repeated at the same time the next day to test the repeatability of FMD% vs $\mathrm{ERA_{IR}}$%.

### D. *Statistical Analysis*

Continuous data are represented as a range and/or mean ± standard deviations. Data repeatability was evaluated using the intraclass correlation coefficient (ICC) and coefficient of variability (CoV) over 10 cardiac cycles. A value of ICC greater than 0.6 and with a CoV less than 20% is considered as highly reproducible. The agreement between FMD% and $\mathrm{ERA_{IR}}$% was tested using linear regression analysis and represented using Pearson's correlation coefficient (R), with a value of p less than 0.05 considered statistically significant. The before and after graph was used for a time-series representation of impedance extrema in response to shear stress.

## III. RESULTS AND DISCUSSION

The subjects' baseline demographics, are detailed in TABLE I.

### A. *Sensitivity of impedance measurements*

Continuous cycles of brachial pressure and flow velocity were measured with SNR > 20 dB. The mean arterial pressure and flow velocity during baseline for 10 cardiac cycles in 10 individual participants is 85.53 ± 3.23 mmHg and 75.62 ± 6.31 $\mathrm{cms^{-1}}$ respectively. The values are in line with earlier reported studies [10]. Fig. 2 shows the measured simultaneous pressure and flow for one participant. Fig. 3 depicts the response of mean arterial pressure (MAP) and flow velocity during baseline, ischemia, extrema during RH and recovery phases of measurements. The mean flow velocity in baseline, which reduces to 8.94% during ischemia, peaks to 28.70% during RH

TABLE I. SUBJECT DEMOGRAPHY AND PARAMETER DESCRIPTION

| Parameter | Range (Mean ± SD) |
|---|---|
| Number of participants | 10 |
| Male/Female | 6/4 |
| Age(y) | 25 ± 4 |
| Height(cm) | 174 ± 13 |
| Weight(kg) | 73.6 ± 14.3 |
| Heart rate (BPM) | 74.2 ± 6.0 |
| Systolic blood pressure(mmHg) | 110.64 ± 3.15 |
| Diastolic blood pressure(mmHg) | 72.60 ± 6.77 |
| Systolic-extrema diameter(mm) | 3.68 ± 0.73 |
| End-diastolic diameter(mm) | 3.85 ± 0.43 |
| Flow velocity(cms$^{-1}$) | 75.62 ± 7.31 |

and reduces to 20.01% during recovery. Whereas the mean pressure observed during baseline increased by 3.99% during ischemia, reduced by 4.94% during RH and increased by 3.01% during recovery. Both flow velocity and pressure recover to the baseline measures. Though the relative pressure difference is not as evident as flow, a flow-induced fall in pressure during RH exists as hypothesized in literatures [11]. There exist a significant correlation between FMD% and ERA$_{IR}$% (R=0.71, $p < 0.05$). Inter-day ICCs and CoV for diameter and flow and estimated impedance parameters are given in TABLE 2. The observed CoV and ICC for all participants show good repeatability (CoV < 13% and ICC > 0.65). Fig. 4 gives the time-series plots of (a) Zc, (b) TPR and (c) TAC for RH intervention for a single participant.

### B. *Zc response to shear stimulus*

The mean Zc estimated using the electrical impedance model during baseline is 3.01 ± 0.32 mmHg.s.cm$^{-3}$. There is only a moderate change in Zc from baseline to ischemia and an increase of 25.12% during RH followed by a 13.25% decrease during recovery (Fig. 4(d)). Even though we found Zc response following the flow trend, the relative change is not as evident which can be due to the influence of changes in wall stiffness and/or diameter [12].

### C. *TPR response to shear stimulus*

The mean TPR during baseline is 63.16 ± 3.23 mmHg.s.cm$^{-3}$. There was 21.34% increase in mean TPR during ischemia and a 37.25% decrease during peak (Fig. 4(e)), possibly due to the transient increase in flow and corresponding decrease in pressure [13]. Following RH, there was a 11.87% increase in TPR during recovery which can be attributed to the structural and functional changes in the resistance artery during RH [14].

### D. *TAC response to shear stimulus*

The mean TAC for all participants during baseline is 0.0093 ± 0.0022 mmHg$^{-1}$s$^{2}$. There was a 90.91% increase in mean TAC from baseline to ischemia and 14.2% increase during RH. TAC reduces to 41.67% during recovery (Fig. 4(f)). The compliance increase during the buffering state and its peaking during RH is as expected as compliance is inverse to arterial stiffness and follows its relation to diameter [15].

### E. *Repeatability of ERA$_{IR}$*

The mean value of ERA$_{IR}$ using Zc, TPR and TAC were 89.70 ± 5.3%, 23.86 ± 3.9% and 158.06 ± 7.6% respectively and their corresponding mean FMD% was 16.23 ± 3.4%. It can be observed from the TABLE. 3 that as compared to the moderate repeatability of FMD% measured over two consecutive days for 10 participants, the ICC and CoV values of ERA gave better repeatability (CoV < 16% and ICC > 0.65). This validates the applicability of the proposed method of ERA over FMD having a poor repeatability.

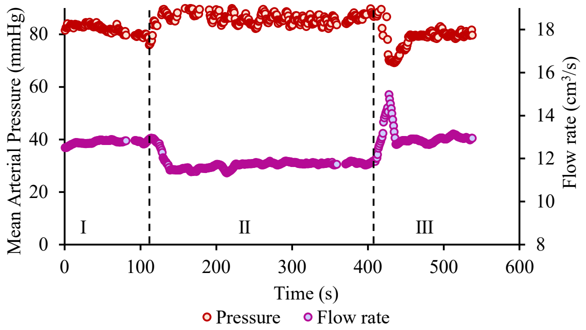


Fig 2. A sample of simultaneously recorded brachial pressure and flow during RH intervention illustrating baseline (I), intervention (II) and recovery (III)

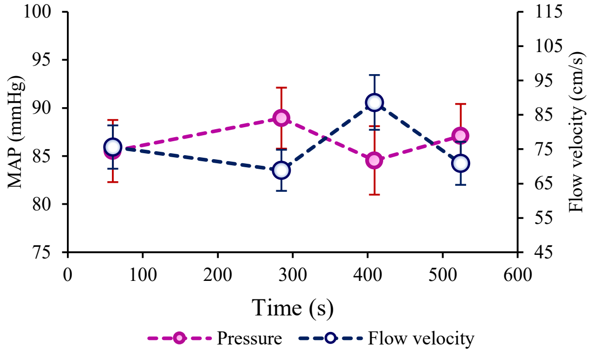


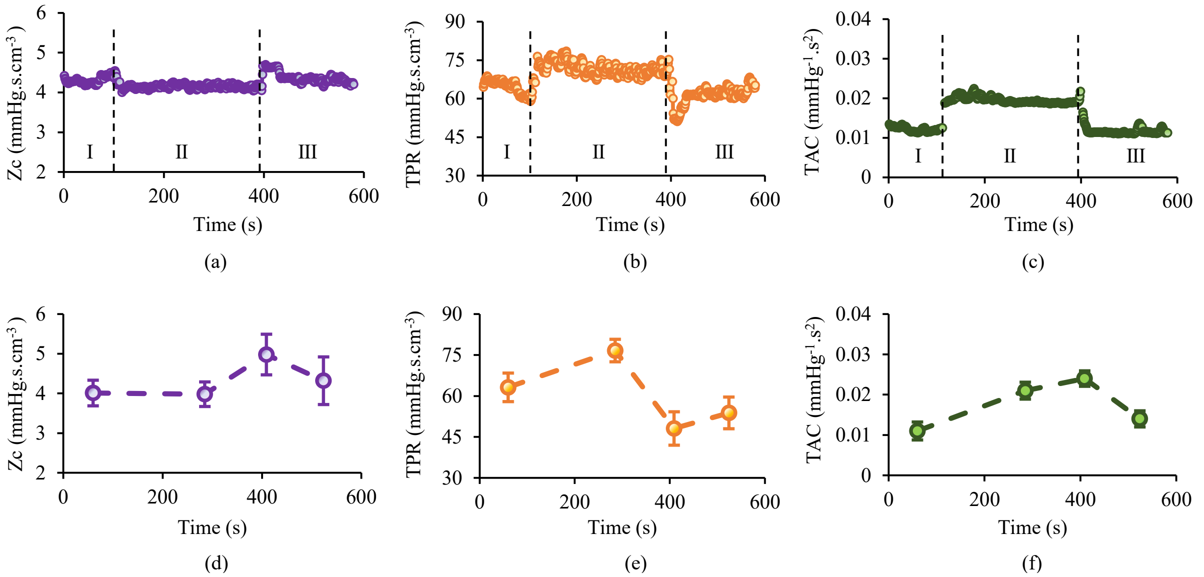
Fig 3. Group average of mean arterial pressure and flow velocity during baseline, ischemia, extrema and recovery

TABLE II. COV AND ICC OF THE INTER-DAY MEASUREMENTS

| Parameter | CoV (%) | ICC |
|---|---|---|
| Blood Pressure | 10.36 | 0.71 |
| Blood flow velocity | 9.66 | 0.78 |
| Zc | 9.43 | 0.75 |
| TPR | 10.39 | 0.69 |
| TAC | 11.03 | 0.66 |

## IV. LIMITATIONS AND FUTURE SCOPE

Reported observations should be taken in light of the study's limitations, like the use of a small sample size of 10 people. However, the data was collected through controlled experiments and can be expanded for future study to corroborate the given assumptions. Furthermore, the measurements were repeated over two consecutive days to check for reliability and repeatability of signals. Therefore, the provided observations are credible and strongly support the findings of related in-vivo study. Also, the steady-state behaviour of a lumped parametric model needs to be kept in mind while analyzing the time-response of impedance parameters. The response of each impedance parameter to RH



(a) (b) (c)

(d) (e) (f)

Fig 4. The time-series response of (a) Zc, (b) TPR and (c) TAC during baseline (I), intervention (II), and recovery (III) for a participant (male, 25 years). Group average of (d) Zc, (e) TPR and (f) TAC for the study population during baseline, ischemia, extrema and recovery

TABLE III. CoV AND ICC OF THE INTER-DAY ERA MEASUREMENTS

| **Parameter** | CoV (%) | ICC |
|---|---|---|
| FMD% | 17.43 | 0.54 |
| $ERA_{Zc}$ | 14.74 | 0.73 |
| $ERA_{TPR}$ | 15.23 | 0.69 |
| $ERA_{TAC}$ | 13.58 | 0.74 |

also requires a better understanding of the underlying haemodynamics. Image-free assessment of brachial artery diameter and flow with a higher frame rate may give a better insight[16], [17], [18].

## V. CONCLUSION

This work investigates the response of impedance parameters to an input shear stimulus. 10 healthy participants were recruited for the study for 2 consecutive days. $ERA_{IR}$ was estimated from the continuous pressure-flow cycles and compared with conventional FMD%. A significant change in impedance parameters exists in response to shear stress, and this needs to be explored in light of endothelial function. Repeatable measurements of diameter and flow velocity were ensured, and the corresponding $ERA_{IR}$ gave high repeatability as compared to FMD% (ICC > 0.64). A study on a larger cohort may further confirm the potential of arterial impedance-dependent vasodilation due to shear using simultaneous pressure-flow cycles.

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