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# Evaluation of Vascular Pulse Contour Indices over the Physiological Blood Pressure Ranges in an Anesthetized Porcine Model

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***Abstract*— A series of physiological measures can be assessed from the arterial pulse waveform, which is beneficial for cardiovascular health diagnosis, monitoring, and decision making. In this work, we have investigated the variations in regional pulse wave velocity ($PWV_R$) and other pulse waveform indexes such as reflected wave transit time (RWTT), augmentation index (AIx), ejection duration index (ED), and subendocardial viability ratio (SEVR) with blood pressure (BP) parameters and heartrate on a vasoconstrictor drug-induced porcine model. Two healthy female (nulliparous and non-pregnant) *Sus scrofa* swine (~ 80 kg) was used for the experimental study. The measurement system consists of a catheter-based system with two highly accurate pressure catheters placed via the sheath at the femoral and carotid artery for acquiring and recording the pressure waveforms. The pulse waveform indexes were extracted from these recorded waveforms. Results from the pulse contour analysis of these waveforms demonstrated that Phenylephrine, as a post-synaptic alpha-adrenergic receptor agonist that causes vasoconstriction, produced a significant increment in the carotid BP parameters and heartrate. Due to the drug's effect, the $PWV_R$ and SEVR were significantly increased, whereas the RWTT, AIx index and ED index significantly decreased.**

***Clinical Relevance*— This experimental study provides the usefulness of the pulse contour analysis and estimation of various pulse waveform indexes for cardiovascular health screening and diagnosis.**

## I. Introduction

Identifying markers for early detection and their timely management is paramount to address the global health issue of cardiovascular diseases (CVD). The changes in the structural and functional property of the artery help in the early diagnosis of the CVD's. Hence, evaluating blood pressure (BP), arterial stiffness and monitoring its progression in the arterial system, especially at early stages, are recognized as a potential approach towards CVD risk stratification [1]. The arterial pulse waveform contains a wealth of data for cardiovascular health assessment and management [2]. Therefore, a series of physiological measures can be assessed from this pulse waveform, which is beneficial for cardiovascular health diagnosis, monitoring, and decision making. Among these, the frequently extracted pulse waveform indexes through pulse contour analysis are: BP parameters, heartrate, regional pulse wave velocity ($PWV_R$), reflected wave transit time (RWTT), augmentation index (AIx), ejection duration (ED) index and subendocardial viability ratio (SEVR) [3], [4].

The propagation velocity of arterial blood pulse waveforms along the arterial tree, referred to as $PWV_R$ – is a function of arterial vessel biomechanics and the hemodynamic of the circulatory system [4]. Typically, the $PWV_R$, an indicator of arterial stiffness, is calculated from pulse waveform successively obtained at a short time interval across two different arterial sites [5]. The $PWV_R$ estimation offers potential information on arterial structural dynamics, measures related to end-organ injury, transmural pressure exerted on the arterial walls, and the effect of biological ageing on arterial stiffness, even at the cellular level [6]–[8].

AIx specifies the combined effect of $PWV_R$, peripheral pulse waveform reflection and vascular function [9]–[11]. It is a commonly examined index of pulse contour analysis, with numerous studies demonstrating that AIx is independently predictive of adverse cardiac actions [12]. Patients with systolic dysfunction have a higher ED than individuals with diastolic dysfunction [4]. Further, SEVR, or the Buckberg index, is a myocardial oxygen supply and demand ratio. It is measured as the ratio of the diastolic area to the systolic area under the pressure curve. Also, subendocardial ischemia occurs when the SEVR value reduces from 50% [4], [13].

This work demonstrates the variations in pulse waveform indexes from pulse contour analysis within a cardiac cycle using a gold standard catheter-based technique on a porcine model in a controlled environment. We investigated the effect of continuously applied Phenylephrine, an α1-adrenergic receptor agonist [14], on BP, heartrate and pulse waveform indexes in a mechanically ventilated porcine model. Section II elaborates the experimental materials, methods and measurement techniques used to measure the pressure waveforms from a porcine model, followed by a discussion of

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extracting the pulse waveform indexes and their variations over the physiological BP changes. Finally, the study results with continuous variations in pulse waveform indexes over the physiological BP and heartrate are discussed in section III, followed by the conclusions in Section IV.

## II. Materials And Methods

### A. Animal Model, Preparation, and Study Protocol

The experimental procedures performed in this study was approved by the Institutional Animals Ethics Committee (IAEC) of the Palamur Biosciences Pvt. Ltd. test facility, Telangana, India (PAL/IAEC/2020/5/01/08). Two healthy female (nulliparous and non-pregnant) *Sus scrofa* swine (~ 80 kg) acquired from Tamil Nadu Veterinary & Animal Sciences University, Madras Veterinary College, Chennai, India was used for the experimental study. The animals were fed a normal diet. On the study day, anaesthesia was induced with an intramuscular injection of Ketamine (dose: 40mg/kg, concentration: 50mg/ml). Also, during the procedure, when the animals wake up, an intravenous injection of Propofol (dose: 10mg/kg, concentration: 0.5mg/ml) was induced. Animals were intubated and maintained under anaesthesia with inhaled Isoflurane (1.5% – 2.5%) during the study procedure. The mechanical ventilation was also arranged. The study was carried out according to the principles outlined in the Helsinki declaration of 1975, as revised in 2013 by the World Medical Association (WMA). After preparation and 10 minutes of rest, the baseline measurements of carotid and femoral pulse waveforms were recorded by placing 2 F pressure catheters (SPR-882, Miller Instruments, USA) via the sheath at the femoral and carotid artery, under the fluoroscopic guidance. Using the developed measurement system, the pressure waveforms were continuously acquired under baseline, followed by administering a hypertensive drug. A mean cumulative dose of 10 mg/ml, 1 mg/kg/min Phenylephrine, was administrated to the animals to increase the baseline BP values. Measurements were continued till the animals recovered back to the baseline/steady BP condition. Once the study procedure was completed, the animals were allowed for recovery.

### B. Measurements

The experimental setup with the hardware and software architecture is illustrated in Fig.1. For measurements, a catheter-based system mentioned earlier, with two highly accurate Mikro-Tip® 2F pressure catheters with a sensitivity of 5µV/V/mmHg, was placed via the sheath at the femoral and carotid artery. Due to their invasive nature, the catheter-based systems are not typically used outside the surgical settings; however, these allow the direct measurement of arterial pressure waveforms for pulse contour analysis. They were attached, with a tip-to-tip distance of 60.9 cm as the pulse propagation/sensor separation distance. The catheters were calibrated with a mercury manometer for pressure ranges of 0 mmHg to 300 mmHg. The MEMS pressure sensor inside the catheter is a strain gauge resistive network in a half-bridge. The half-bridge is excited with a precision voltage source of 5V. Their differential output voltage is expected from -0.5 mV to 7.5 mV, based upon the sensitivity at 5µV/V/mmHg and range of operation from -50 mmHg to 300 mmHg at 5V excitation as per the datasheet. This differential signal might

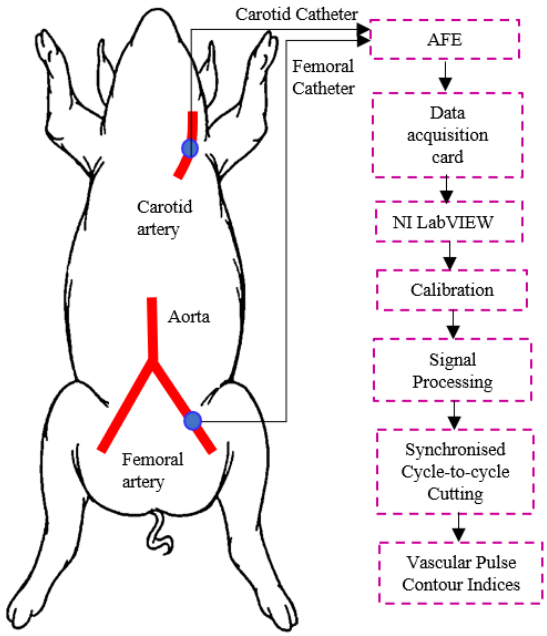


Figure 1. Schematic of the experimental setup with its analog front-end (AFE) circuitry, data acquisition unit and software architecture in the anesthetized porcine model.

be subjected to any offset, corrected by an offset correction pre-amp circuit. The offset correction circuit involves pre-amplifying the offset with a small gain using an instrumentation amplifier (INA125, Texas Instruments, USA) and subtracting the voltage at the inverting terminal of the second stage amplifier manually trimming it out using a 1 kΩ potentiometer, connected to a reference voltage. The gain of the second stage using the same instrumentation amplifier will amplify the signal to the required levels. The amplified voltage is then fed to a 14-bit ADC channel at a 20 kHz sampling rate of data acquisition device NI 6218 (National Instruments, USA) for analysis and recording. Using the developed measurement system, the pressure waveforms were continuously captured under baseline, followed by administrating a vasoconstrictive drug.

These recorded carotid and femoral pressure waveforms were later processed offline using NI LabVIEW 2017 (National Instruments, USA) for extracting the BP values, heartrate, $PWV_R$ and other pulse contour parameters. All the programming logic and digital signal processing were implemented in this LabVIEW environment, as depicted in Fig.1. The voltage signal is then calibrated to pressure signals. The pressure signals sampled at 20 kHz were filtered using a zero-phase 3rd order lowpass filter of 10 Hz cut-off frequency. The usage of zero-phase filters ensured no additional lags in the acquired waveforms. A cycle cutting algorithm was implemented to select the individual cycles from both the carotid and femoral pressure waveforms. These unique cycles are then used to analyze the beat-to-beat $PWV_R$ using the second derivative maximum method and to extract other pulse waveform parameters.

### C. Pulse Waveform Indexes Extraction

The pulse waveform indexes were extracted from the pressure waveforms. First, systolic blood pressure ($P_S$), diastolic blood pressure ($P_D$) and heartrate values were

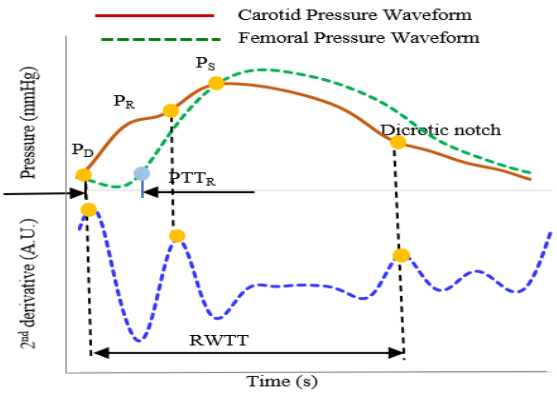


Figure 2. Pressure waveforms and second derivative to assess the fiducial points.

extracted from pressure pulse waveforms at the carotid arterial site. Second, regional pulse transit time ($PTT_R$), as illustrated in Fig.2, were measured along the carotid-to-femoral path by the extraction of the foot-to-foot transit time using the second-derivative maximum algorithm [15], [16]. Then $PWV_R$s were calculated as the ratio of the measured carotid-to-femoral path length to the estimated $PTT_R$.

Finally, the other indexes of the arterial stiffness were calculated from the carotid pressure waveform (RWTT, AIx, ED and SEVR/Buckberg index). The RWTT was calculated as the time delay between the incident and the reflected pulse waveform along the carotid artery and is inversely proportional to $PWV_R$ as depicted in Fig.2 [17]. AIx was calculated as the ratio of augmentation pressure (AP), attributed to the reflected wave, to the pulse pressure (ΔP), expressed as a percentage [18]. The augmentation pressure (AP) was estimated by subtracting the reflection pressure of the carotid pulse waveform ($P_R$) from the systolic carotid BP ($P_S$). The approach considered to assess landmarks on the acquired pressure waveform, which are indicative for the return of the reflected wave, was based on the second-order derivative, aiming to detect the inflection point timing [19], as

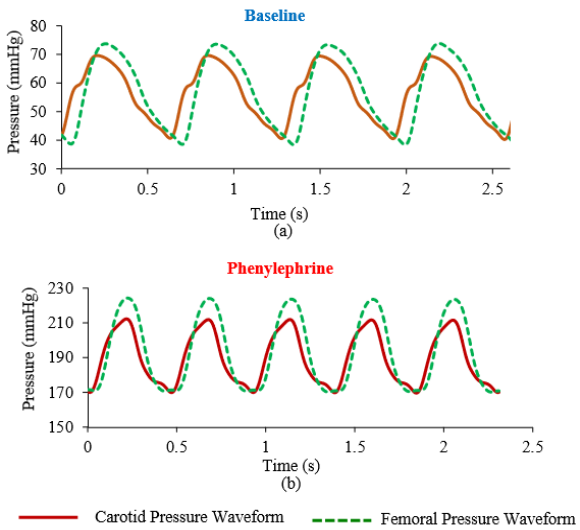


Figure 3. The typical traces of the effects of a vasoconstrictor drug on the pulse waveform obtained from the carotid and femoral arteries from a specific porcine model.

illustrated in Fig.2. ED index was estimated as the ratio of the systolic ejection period to the total period of a cardiac cycle. Finally, the SEVR was calculated as the ratio of the diastolic time integral to the systolic time integral [4].

## III. Results And Discussions

The representative traces of the effects of a vasoconstrictor drug on the pulse waveform acquired from the carotid and femoral arteries are shown in Fig.3 (a)-(b). The pre-drug baseline values of all the extracted pulse waveform indexes with their beat-to-beat variations are summarized in Table 1. The coefficient of variation of these different pulse waveform indexes demonstrates a high level of repeatability with their potential to be included in the routine cardiovascular assessment of ambulatory patients. Later, the vasoconstrictor drug induction efficiently perturbed the baseline BP parameter and heart rate levels in the porcine model. During their post-drug administration, the beat-to-beat variation in BP parameters, heartrate and extracted pulse contour indexes were continuously recorded. The time courses of variations in the extracted carotid arterial BP parameters, heartrate, $PWV_R$ and other pulse contour parameters by vasoconstrictor drug administration are illustrated in Fig.4 (a)-(g). Due to the effect of Phenylephrine, as a post-synaptic alpha-adrenergic receptor agonist that causes vasoconstriction, a significant increment was observed in the BP parameters and heartrate. The baseline $P_S$ and $P_D$ were statistically elevated approximately to 215 mmHg ($p < 0.001$) and 172 mmHg ($p < 0.001$), respectively. About 142 bpm ($p < 0.001$) statistical increment was observed in the baseline heartrate.

Due to the drug's effect, the $PWV_R$ and SEVR were increased, whereas the RWTT, AIx index and ED index were decreased. The $PWV_R$ and SEVR were statistically increased by approximately 15 m/s ($p < 0.001$) and 200% ($p < 0.001$), respectively. The RWTT, AIx index and ED index were significantly decreased by about 0.25 s ($p < 0.001$), 9% ($p < 0.001$) and 53.5% ($p < 0.001$), respectively.

TABLE I. Baseline Measurement Repeatability of Extracted Pulse Contour Indexes

| Parameters | Mean ± SD | Coefficient of variation (%) |
|---|---|---|
| $P_S$ (mmHg) | 65.76 ± 1.71 | 2.6 |
| $P_D$ (mmHg) | 38.75 ±1.02 | 2.63 |
| Heartrate (bpm) | 88.73 ± 2.26 | 2.54 |
| $PWV_R$ (m/s) | 7.94 ± 0.28 | 3.49 |
| AIx (%) | 33.5 ± 0.94 | 2.8 |
| ED (%) | 67.25 ± 0.84 | 1.26 |
| RWTT (s) | 0.45 ± 0.006 | 1.48 |
| SEVR (%) | 86.98 ± 4.17 | 4.79 |

Therefore, the measurement of all these pulse wave indexes and the $PWV_R$ will provide crucial information on quantifying arterial stiffness and BP in patients. Also, it was noted that the RWTT has a higher correlation ($R^2 = 0.97$) with the $PWV_R$, signifying that it is an indicator of large artery stiffness.

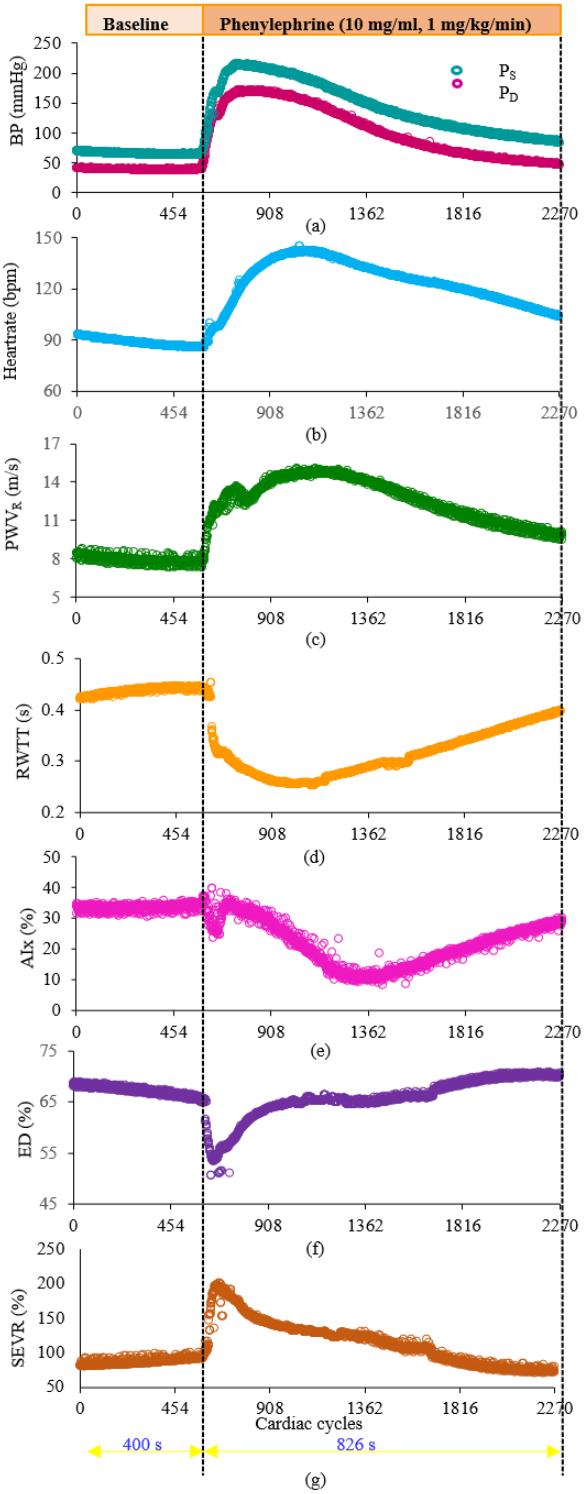


Figure 4. The time courses of the effects of a vasoconstrictor drug on the carotid arterial BP, heartrate, $PWV_R$ and the other extracted pulse contour parameters of a specific porcine model.

## IV. Conclusion

This work demonstrated the variations in pulse waveform indexes from pulse contour analysis within a cardiac cycle using a gold standard technique on a porcine model. Using this direct measurement method, this measurement technique provided evidence for the continuous intra-cycle variation of regional $PWV_R$, RWTT, AIx index, ED index, and SEVR with BP parameters and heartrate. These pulse waveform indexes assessment can be incorporated into routine clinical cardiovascular diagnostics and screening.

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