

Variation in Pulse Contour Markers on an Anesthetized Porcine During Pressure Perturbation: Association with Local and Regional Stiffness

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Abstract—Pulse contour analysis (PCA) provides detailed evaluations of the accelerative and decelerative phases of the arterial pulse waveform, potentially associated with large artery stiffness and vascular ageing. Previous studies have reported age-related associations (both structural and functional) with PCA markers and stiffness. However, changes in functional stiffness under a drug produced due to the interplay of blood pressure and heart rate were not explored. In this work, we investigate the variation of PCA markers derived from the second derivative of invasive pressure waveform recorded from the carotid artery of an anaesthetized porcine model under drug intervention. The variations in PCA markers are compared with the functional stiffness surrogates (pulse wave velocity (PWV) – regional and local), which are clinically relevant markers that vary with blood pressure and heart rate. Local and regional PWV was measured from pulse transit time, obtained from the carotid artery for the former and carotid-femoral artery for the latter. Group average local and regional PWV varied at least by 83.26%, and group average PCA markers by 25.19% for a 57.75% change in pulse pressure. PCA markers: b/a and c/a had statistically significant highest correlation ($r = 0.63$, $r = -0.93$ respectively, $p < 0.001$) with local PWV and pulse pressure ($r = 0.73$, $r = -0.97$ respectively, $p < 0.001$), whereas c/a and d/a had statistically significant highest correlation ($r = -0.96$, $r = -0.98$ respectively, $p < 0.001$) with regional PWV. The study helps understand the selective associations of PCA markers (through multivariate regression analysis) on local, regional stiffness and pulse pressure. Such PCA markers potentially provide information useful for developing vascular index matrices.

Keywords—pulse contour analysis, local PWV, regional PWV, pulse pressure, second derivative waveform, digital pulse volume, vascular ageing

I. INTRODUCTION

Vascular ageing is a consequence not solely due to structural elements and distending pressure but also due to the functional regulation of the blood vessel [1]. Functional abnormalities such as endothelial dysfunction are an underlying reason for large artery stiffening exacerbating cardiovascular risks of an individual; however, they may be potentially reversible. Functional impairment of the artery wall occurs before the structural changes, and detection methods for arterial functional assessments at central arteries

such as the carotid or aorta will prove to be a prognostic marker in cardiovascular risk stratification [2].

Abnormalities of vessel wall get manifested as variations in blood pulse (pressure, diameter, flow) morphology, which can be captured using pulse contour analysis (PCA). Arterial pulse contour analysis (PCA) is generally pursued in terms of an empirical comparison of physiological and clinical characteristics of the vasculature [3]. PCA using the second derivative waveforms obtained from digital volume pulses has been extensively studied in the past decades [4]–[8]. The second derivative waveforms corresponding to a pulse signal allow for detailed evaluations of the accelerative and decelerative phases. This analysis provides a more accurate recognition of the inflection points on the pulse contour. The terminology of definitions for various pulse contour markers derived from second derivative waveforms for peripheral volume or pressure signals is reported elsewhere [9]. The amplitudes of peaks and valleys of the second derivative waveforms are identified and labelled as a, b, c, d, e, as illustrated in Fig.1. PCA markers are defined as b/a, c/a, d/a, e/and (b-c-d-e)/a. Table I enlists the prominent PCA markers derived from the second derivative waveform along with its definitions [10]. If the mechanical property of the artery remains constant over a cardiac cycle, a change in the vessel diameter or volume bears a consistent relationship with its corresponding change in pressure. Therefore, a PCA on either of the pulse signals (volume or pressure) will have comparable information on the derived PCA markers [11].

Analysis of markers derived from PCA is reported to provide predictive information on large artery stiffening and vascular ageing [12], [13] limited to age-based associations. Such studies deal with structural and functional stiffness changes in the vessel walls due to ageing and cardiovascular diseases. However, the variation in PCA markers with instantaneous changes in the stiffness as a function of pressure and heart rate is less investigated. To understand the responses of PCA markers to functional stiffness changes by altering blood pressure and heart rate, we have performed a drug intervention study on an anaesthetized porcine model to emulate vascular ageing. The rationale for executing a study on an anaesthetized animal model was the limitation of

TABLE I DESCRIPTION OF PCA MARKERS

PCA Marker	Description
b/a	An indicator of the LV ejection capacity and large artery compliance/elasticity
c/a	Reflects arterial stiffness and decreases with age, becomes more negative with aging
d/a	Indicates arterial stiffness, increasing negative value indicates constriction and/or stiffness in small arteries, useful to assess LV afterload and effects of vasoactive agents.
e/a	Decreases with age
(b-c-d-e)/a	Represents the ‘vascular age’, surrogate for arterial stiffness

silicone-based vascular phantoms in mimicking the actual hyperelastic behaviour and the incremental nature of the material properties seen in large arteries *in-vivo*. The hyperelastic nature helps to emulate the interplay between blood pressure and heart rate as seen with vascular ageing, which is otherwise difficult in an *in-vitro* phantom study. In order to compare the variations with clinically accepted markers, local and regional PWV [14]–[16] measured from carotid and carotid-femoral artery are employed in this study. Clinically, stiffness markers such as PWV have gained acceptance and have become part of hypertension management guidelines [17] and are an appropriate marker that changes with respect to functional stiffness. The subsequent sections describe in detail the animal preparation, experiment, and measurement procedure, followed by results and observations accompanying insights to future works.

II. MATERIALS AND METHODS

A. Animal Preparation, Experiment and Protocol

Two healthy female (non-pregnant and nulliparous) *Sus scrofa* swine (~ 70-80 kg) acquired from Tamil Nadu Veterinary & Animal Sciences University, Madras Veterinary College, Chennai, India, was used for this study. Institutional Animals Ethics Committee (IAEC) of the Palamuru Biosciences Pvt. Ltd., Telangana, India (Testing Facility) (Ref: PAL/IAEC/2020/5/01/08) has approved the experimental study. 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). The animals were fed a normal diet in the week leading to the study. Prior to surgery/experiment, the animal was fasted for 8-12 hours, prepared, and draped for the procedure. Electrocardiogram (ECG), respiration rate, heart rate, and oxygen saturation were monitored continuously during the procedure and recorded in addition to the invasive blood pressure (BP) measurements.

On the day of the experiment, anaesthesia was induced with an intravenous injection of Ketamine (dose: 40mg/kg, concentration: 50mg/ml). Followed by intravenous injection of propofol (dose: 10mg/kg, concentration: 0.5mg/ml), as and when required. Animals were intubated and maintained under anaesthesia with inhaled isoflurane (1.5% – 2.5%) during the study procedure. The mechanical ventilation was also

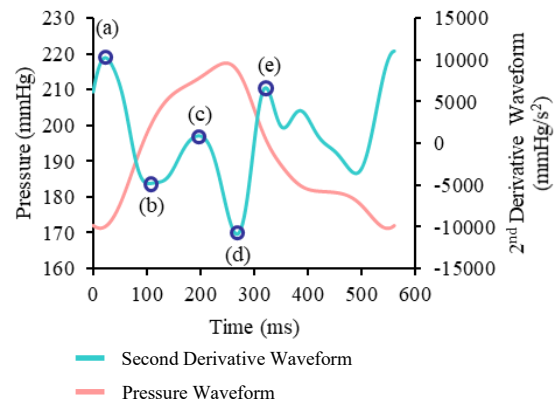


Fig.1. Pressure waveform and its second derivative with indications of all the pulse contour markers

arranged. Needle-stick method (Seldinger method) or cut down was performed at the groin/neck to expose the femoral/carotid artery. A sheath of size 6-8F was inserted into the femoral for delivery of a guiding/control pressure catheter to the carotid artery under fluoroscopic guidance. Heparin (80-120 IU/kg, IA) was administered prior to invasive blood pressure (BP) measurement. The animal was allowed to rest for 10 minutes at the start of the experiment, and baseline invasive BP measurements were recorded, followed by administering of a hypertensive drug (phenylephrine, mean cumulative dose of 10 mg/ml, at 1 mg/ml/min) to introduce blood pressure perturbations. The study period (baseline, drug intervention and recovery of baseline) was limited to less than 30 minutes per animal for a given day. Upon completion of the study procedure, the animals were allowed to recover.

B. Measurements and Data Processing

Intra-vascular blood pressure measurements at the carotid artery were recorded using high-fidelity dual pressure catheters (SPR 751S, Millar Instruments, USA) (specifications: 5F, 150 cm length, dual-sensor separated by 30 mm, sensitivity: 5 μ V/V/mmHg) and at femoral artery using a single pressure catheter (SPR 882, Millar Instruments, USA) (specifications: 3.5F, 140 cm length, sensitivity: 5 μ V/V/mmHg). Both catheters were inserted via the sheath at the femoral artery under fluoroscopic guidance. The tip-to-tip catheter distance between the one at the carotid artery to the one at the femoral artery was physically measured to be 735 mm. The carotid artery to aortic arch distance was obtained from X-Ray Angiogram as 126 mm. Therefore, the cumulative distance from the carotid artery to the femoral artery (pulse propagation length) was 609 mm. The overall measurement scheme is illustrated in Fig.2.

The pressure signals from the catheters were amplified using an analog front-end, designed based on an instrumentation amplifier and precision excitation voltage for the strain gauge pressure sensor using INA 125 (Texas Instruments, USA). The amplified signals from carotid and femoral arteries were simultaneously acquired in a synchronized manner at a 20 kHz sampling rate, through a 14-bit ADC channel of NI 6218 (Data Acquisition Card, National Instruments, USA) for further analysis and processing. Pressure measurements were recorded for the entire duration of the study (baseline, drug intervention and

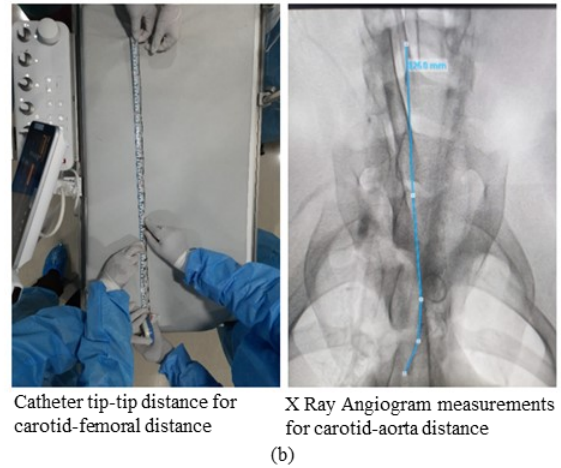
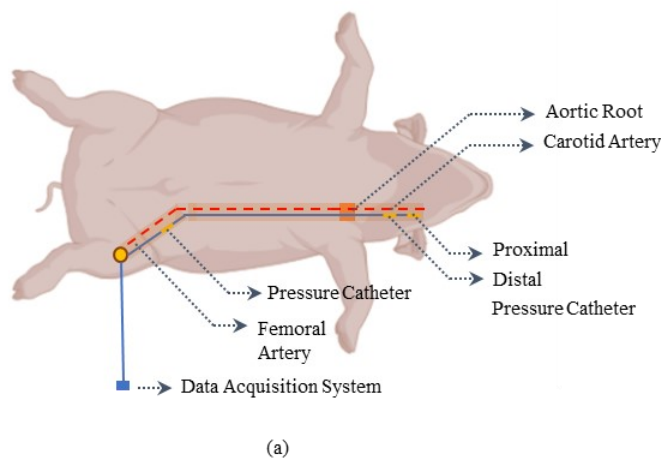


Fig.2(a). Measurement scheme and animal model, placement of pressure catheters, (b) measurement of distance for estimating PWV.

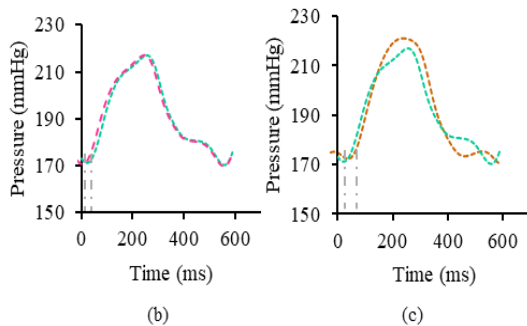
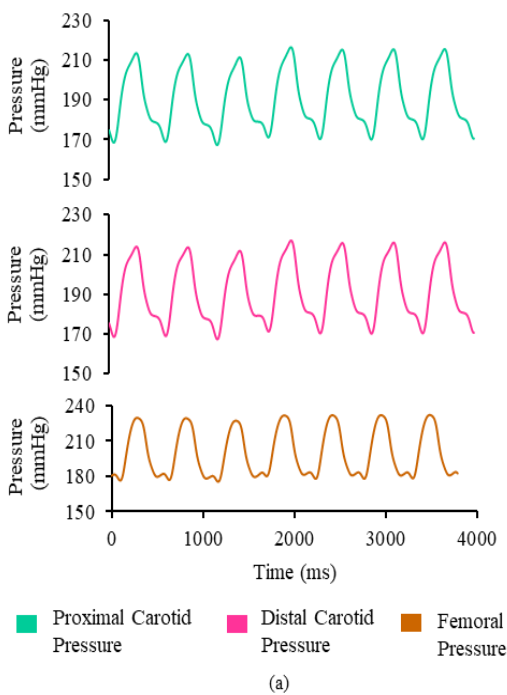


Fig.3. (a) Continuous samples of pressure waveforms at carotid and femoral artery, (b) Evaluation of local PTT, (c) evaluation of regional PTT

recovery of baseline). The pressure catheters were calibrated from 0 to 300 mmHg against a standard pressure gauge before and after the experiment. The acquired carotid and femoral pressure signals were processed and analyzed offline using

programming logic and digital signal processing implemented in NI LabVIEW® (National Instruments, USA).

Simultaneously acquired pressure waveforms are filtered using a zero-phase 4th order Butterworth low pass filter of cut-off frequency 14 Hz. Before further analysis, any pressure waveforms exhibiting a baseline wandering were corrected by employing a linear baseline estimator. An automated cycle cutting based on the end-diastolic point of the pressure waveform was implemented. At least 40-50 individual cycles from baseline, intervention (when MAP was peaked) and recovery phase were saved for further analysis.

The required derivatives of the pressure waveform for the PCA is filtered using a Savitzky–Golay’s filter of 3rd order polynomial and 15 side points, ensuring a 3dB cut-off in the frequency spectrum of derivatives to be at 12 Hz [18]. The maxima and minima (both local and global), as per the definitions in Fig.1, are programmatically identified for each cycle in the baseline, intervention and recovery phase.

Local Pulse Transit Time (PTT) between the second derivative maxima point of the simultaneously acquired distal and proximal pressure waveforms are measured. The regional PTT between the simultaneously acquired proximal pressure waveform at the carotid artery and the pressure waveform at the femoral artery is measured. In both cases, PWV can be assessed by,

$$PWV \text{ (in m/s)} = \frac{PTT \text{ (s)}}{L} \quad (1)$$

where, L is the cumulative distance (in m) between the two-measurement arterial blood vessel sites. See Fig.2(b) for the measurement of L.

C. Statistical Analysis

Continuous variables are presented as mean \pm standard deviations. The similarity or difference between the different periods of the study (baseline, intervention, and recovery) was analyzed using Box-and-whisker plots constructed using median and interquartile ranges. The beat-to-beat coefficient of variation (CoV in %) in the measurements is calculated as the ratio of the standard deviation to mean expressed in percentage.

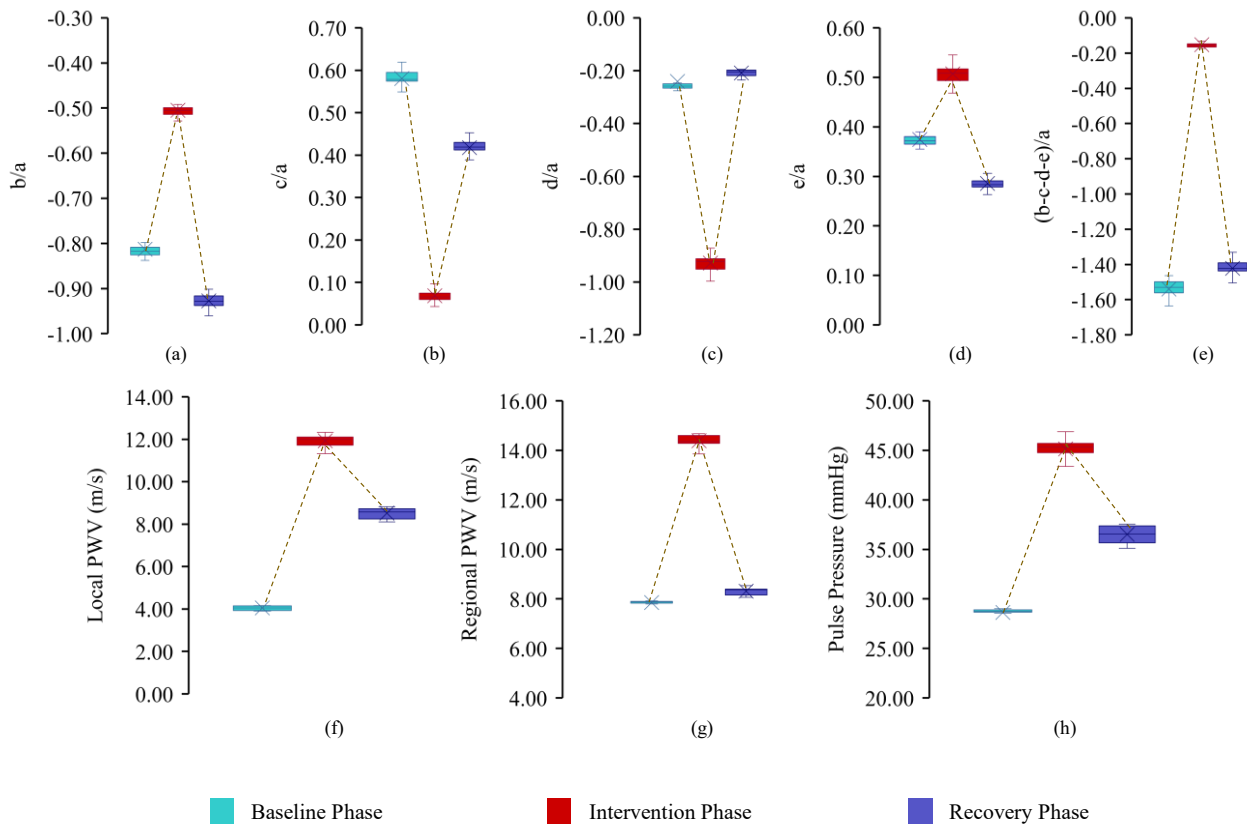


Fig.4. (a) – (e) Pulse contour markers derived from second derivative waveforms and their changes during intervention, (f)-(h) local and regional stiffness markers

III. RESULTS AND DISCUSSION

A. Reliability of Signals

The pressure waveforms acquired from the carotid and femoral artery were quasi-periodic and continuous. The signals had an SNR > 20 dB. Sampling rates of 20 kHz ensured reliable measurement of PTT for local and regional PWV assessment and fiducial point identification for PCA (with a resolution of 0.05 ms). The instrumentation induced measurement delays between different pressure channels (proximal and distal of carotid pressure and femoral pressure) were negligible, ensuring the accuracy of PTT (and PWV) be physiologically accurate.

The beat-to-beat repeatability of the identified fiducial points of the second derivative waveforms from baseline, intervention and recovery phase of the study were < 6%. The beat-to-beat repeatability of local PWV was < 5% and for regional PWV was < 3%. A continuous segment of the pressure waveforms exhibiting the PTT for the carotid artery and femoral artery is shown in Fig.3(a)-(c).

B. Measurement of PCA Markers

Baseline group average values obtained for PCA markers b/a , c/a , d/a , e/a and $(b-c-d-e)/a$ were -0.813 ± 0.022 , 0.580 ± 0.025 , -0.252 ± 0.035 , 0.374 ± 0.014 and -1.539 ± 0.074 respectively. The average CoV among the PCA markers was < 7%. The lowest CoV was observed for b/a (~2.61%), and the highest was observed for $(b-c-d-e)/a$ (~15.12%). Fig. 4 depicts the change observed in the PCA markers and stiffness markers during the intervention study. All the markers had a change > 25% from baseline phase to intervention phase and a change > 20% from intervention to the recovery phase.

Morphological changes in the pressure waveform under the effect of the hypertensive drug were faithfully captured in the pulse contour markers. The amplitudes of a , d , and e were observed to increase with pulse pressure, and amplitudes of b and c decreased, at par with the reported works in the literature on population-based studies [10].

C. Association of PCA Markers with Local & Regional Stiffness Markers

A statistically significant and moderate correlation ($r > 0.63$, $p < 0.001$) was observed between b/a , c/a and local PWV and pulse pressure. PCA markers d/a , e/a and $(b-c-d-e)/a$ showed statistically insignificant p -value ($p > 0.05$) with local PWV and pulse pressure. However, with regional PWV, a statistically significant and strong negative correlation ($r > -0.9$, $p < 0.001$) was observed for c/a and d/a , with other markers being statistically insignificant. Table II summarises the multivariate regression analysis for local PWV, regional PWV and pulse pressure as a function of the identified five pulse contour markers.

The recovery of stiffness markers (local and regional PWV) and pulse pressure responded differently to the intervention study. Regional PWV has recovered back to its baseline levels in the recovery phase. However, the local PWV and pulse pressure calculated at the carotid have returned to a level slightly higher than that of the baseline. A similar trend was also observed for b/a , c/a , e/a . For the ratio d/a and $(b-c-d-e)/a$, the trend was like regional PWV. Although there is a robust correlation of PCA markers with local, regional PWV and pulse pressure ($r > 0.9$, $p < 0.001$), only a few of the PCA markers have a statistically significant correlation, as highlighted in Table II. The ratio c/a was the

TABLE II SUMMARY OF MULTIVARIATE REGRESSION ANALYSIS

Stiffness Markers	Pulse Contour Markers	Coefficients	p-value	CI: Lower 95%	CI: Upper 95%
Local PWV Multiple r = 0.98 Adjusted r = 0.95 p < 0.001	b/a	-16.790	0.001	-26.665	-6.915
	c/a	-13.705	0.002	-22.123	-5.287
	d/a	-3.031	0.441	-10.893	4.831
	e/a	-0.769	0.915	-15.217	13.679
	(b-c-d-e)/a	2.540	0.455	-4.257	9.339
Regional PWV Multiple r = 0.99 Adjusted r = 0.99 p < 0.001	b/a	2.049	0.345	-2.277	6.375
	c/a	-5.798	0.003	-9.486	-2.110
	d/a	-3.782	0.032	-7.227	-0.338
	e/a	1.388	0.661	-4.942	7.718
	(b-c-d-e)/a	0.096	0.949	-2.882	3.074
Pulse Pressure Multiple r = 0.99 Adjusted r = 0.98 p < 0.001	b/a	-17.601	0.022	-32.583	-2.619
	c/a	-26.518	0.001	-39.290	-13.746
	d/a	-10.376	0.087	-22.305	1.553
	e/a	-18.004	0.105	-39.925	3.917
	(b-c-d-e)/a	2.563	0.619	-7.752	12.877

only marker that had consistent statistical significance with all the three stiffness markers. The ratio c/a reflects the late systolic phase, which is very sensitive to arterial reflections, and augmented pressure. The increase in BP causes the inflection point to shift between the late systolic phase and early diastolic phase, causing variations in c/a, and d/a. The trends are similar to population-based studies reported in the literature [19], [20].

The confounding effect of heart rate, respiratory rate, and ECG is not investigated in this current study. The advent of wearable platforms enables continuous monitoring of ECG [21], [22], heart rate [23], respiratory rate [24], [25] when combined with conventional markers, which would provide further insights into the dynamics of PCA markers. The applicability of PCA markers on diameter waveforms [26], [27] has potential for large scale screening using non-invasive instrumentations [28], [29] for understanding central haemodynamics.

IV. CONCLUSION

In this work, we have demonstrated the application of pulse contour markers derived from second derivative waveforms of arterial pressure waveform obtained invasively at the carotid artery of a porcine animal model. The invasive measurement scheme of recording simultaneous pressure waveforms from carotid and femoral arteries was implemented. The dual pressure measurement from the carotid ensured reliable estimation of local PWV and carotid to femoral PWV. The association of PCA markers with local and regional stiffness (PWV) and pulse pressure were investigated during a drug intervention study. All the PCA markers had an observational change in the mean values from baseline to intervention and back to recovery. However, a very strong correlation was obtained between stiffness markers with PCA markers. A multivariate regression analysis was performed to understand the dependency of PCA markers on local PWV, regional PWV and pulse pressure. A major limiting factor of this study is that it was performed on small sample size. Further, the influence of blood pressure and heart rate are not individually assessed in this study. This would require specific protocols to induce

pressure independent or heart rate independent drugs and individual influence on PCA markers.

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