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Blood pressure-independent neurogenic effect on conductance and resistance vessels: a consideration for cuffless blood pressure measurement?

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Abstract— **Background: Pulse transit time (PTT) and pulse arrival time (PAT) are promising measures for cuffless arterial blood pressure (BP) estimation given the intrinsic arterial stiffness–BP relationship. However, arterial stiffness (and PTT) is altered by autonomically-driven smooth muscle tension changes, potentially independent of BP. This would limit PTT or PAT as accurate BP correlates, more so in resistance vessels than conductance arteries.**
Objective: To quantify if there is a measurable neurogenic effect on PAT measured using photoplethysmography (PPG) (path includes resistance vessels) and radial artery tonometry (path includes only conductance vessels) during physiologically induced BP changes.
Methods: PATs were measured continuously in participants (n=15, 35±15 years, 9 male) using an electrocardiogram and, simultaneously, a Finometer® PRO finger sensor, a finger PPG sensor and radial artery tonometer during seated rest, cold pressor test, cycling and isometric handgrip (IHG) exercise. ΔBP/ΔPAT was calculated for each sensor and each condition.
Results: All interventions significantly increased BP. A significant difference was observed in ΔBP/ΔPAT between cycling and both the cold pressor test and IHG exercise ($p<0.05$). ΔBP/ΔPAT did not differ whether measured via PPG or tonometry.
Conclusions: Under the conditions tested, autonomic function does not have a BP-independent effect on PAT where the path includes resistance vessels (PPG signal), likely due to the speed of the wave and the short path length of resistance vessels. Autonomic function therefore does not limit the ability for use of PPG as a signal for potentially estimating BP without a cuff.

Index Terms— **cuffless blood pressure; photoplethysmography; tonometry; pulse transit time; pulse arrival time; arterial stiffness; wearable devices**

I. Introduction

The arterial pulse carries a wealth of cardiovascular information and has the capacity to be used in methods to estimate arterial blood pressure (BP) without the use of a cuff. One proposed method of cuffless BP estimation relies on the relationship between BP and the stiffness of the artery. Fundamental Newtonian physics relates material stiffness to wave speed. Extrapolated to the geometry of a thin walled, fluid-filled tube (artery), the pulse wave speed, and therefore the pulse transit time (PTT), is related to vessel wall stiffness and, through interdependence, to BP [1], [2]. Whilst the estimation can be readily performed and has already been adopted into commercial, wearable health devices such as smartphones and smartwatches, estimation often ignores possible covariates of arterial stiffness and PTT that are partly independent of BP. These are potential contributing factors to the inaccuracies currently faced in cuffless BP estimation. Addressing such factors may prove advantageous for future wearable devices incorporating cardiovascular-based measurements.

In relation to the cardiovascular system, the sympathetic nervous system plays a dominant role in its regulation in order to meet metabolic demands and remain under homeostatic conditions. Whilst the influence of the sympathetic nervous activity has been extensively studied with respect to heart rate (HR) and its independent effect on arterial stiffness [3] and muscular sympathetic nervous activity [4], its particular direct influence over smooth muscle tone and arterial stiffness with resulting impact on PTT has not been studied. Due to regional differences in the smooth muscle content of vessels, it is likely that BP-independent sympathetic effects on PTT are greater where the arterial path includes resistance vessels than where the arterial path comprises only conductance vessels. Measurement of segmental arterial blood volume changes through the reflectance (or transmission) of light at certain wavelengths, as achieved through photoplethysmography (PPG), is one prominent method that has been widely adopted for the measurement of peripheral arterial signals. PTT assessed using a distal PPG signal encounters microvessels in the interrogated arterial path. As this path includes resistance vessels that are highly innervated, sympathetic effects may alter PTT as measured using PPG in a BP-independent manner. PTT measurement using the conducting arteries only, as performed with tonometry (force transduction), is unlikely to have the same degree of autonomic interference.

This study aims to quantify whether there is a different relationship between PTT (and more accurately pulse arrival time (PAT)) and BP when the arterial path includes resistance vessels than when it includes only conducting arteries, under conditions of varying autonomic control. This study addresses the hypothesis that where resistance vessels are encountered (e.g., using PPG), there may be a greater BP-independent effect on PTT/PAT. Knowledge of this effect and addressing this effect has the potential to improve cuffless BP estimation when using a PPG.

II. Methods

A. Participants

Participants were recruited from the university staff and student cohort, and associates of the study investigators. There were no exclusion criteria. The study was approved by

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the Macquarie University Human Research Ethics Committee and all participants provided informed, written consent.

B. Cardiovascular Measurements

Brachial arterial BP (OMRON HEM-907) was first measured following at least 5 minutes of seated rest. Continuous recordings were then performed with an electrocardiogram (ECG) in lead II configuration and the following devices connected to the non-dominant hand: a Finometer® PRO (Finapres Medical system, Amsterdam, Netherlands) on the middle or pointer finger for measurement of finger BP; a PPG sensor (ADInstruments, Dunedin, New Zealand) attached to the middle or ring finger for acquisition of a peripheral arterial blood volume waveform; a tonometer placed above the radial artery for acquisition of radial arterial waveform. Data was recorded using an ADInstruments data acquisition system at a sampling rate of 1 kHz. Continuous recordings were undertaken during three sequential stages (baseline, intervention, recovery) with the interventions as follows: cold pressor test, cycling and an isometric handgrip (IHG) exercise. Following 1 minute of baseline recordings individuals performed an intervention to induce a change in arterial BP. The cold pressor test required the participant to submerge the dominant hand into a container of ice-cold water (∼5°C, as measured by a temperature probe) for approximately 60-90 seconds. Cycling involved the participant to pedal on an ergonomic bicycle at a moderate pace (30-50% of maximum HR) continuously for 5 minutes in an upright seated position under a fixed load. Maximum HR was calculated as 220 minus the participants age. For the IHG exercise, participants were first required (prior to baseline measurements) to squeeze a dynamometer (force transducer) to determine their maximum grip strength. Once the maximum had been established, based on an average of three attempts, and after baseline measurements, the participant was then instructed to maintain ∼30% of their maximum hand grip for a duration of 3 minutes. At the completion of each intervention, 2 minutes of recovery recordings were taken. Participants performed all three interventions in a randomized order with an additional 5-10 minutes of recovery between each intervention.

C. Data analysis

Diastolic BP was extracted from the volume-clamp, vascular unloading, Peňáz technique (Finometer® PRO) signal. The PAT was measured as the time between the R-peak of the ECG and a fiducial point (peak of the second time derivative) on each of the following peripheral waveforms: Finometer® PRO; PPG; and radial tonometer. PAT was calculated automatically with a custom written code in CED Spike2 (version 7.20). As PAT adds the left ventricular pre-ejection period (PEP) to the PTT, PEP was estimated from HR based on Eq. 1, as previously described by Weissler *et al.* [5], and PTT calculated from PAT (Eq. 2).

$$\mathrm{PEP} = \begin{cases} \text{male} & -0.0004\times\mathrm{HR}+0.131 \\ \text{female} & -0.0004\times\mathrm{HR}+0.133 \end{cases} \quad (1)$$

$$\mathrm{PTT} = \mathrm{PAT} - \mathrm{PEP} \quad (2)$$

TABLE I
DEMOGRAPHICS

Parameter	Mean±SD	Range
Age (years)	35 ± 15	22–72
Height (cm)	169 ± 9	158–187
Weight (kg)	65 ± 15	39–91
HR (bpm)	75 ± 10	62–93
Seated SBP (mmHg)	115 ± 20	91–152
Seated DBP (mmHg)	65 ± 13	46–95

bpm: beats per minute; cm: centimetres; DBP: brachial diastolic blood pressure; HR: heart rate (seated); kg: kilograms; SBP: brachial systolic blood pressure; SD: standard deviation.

The baseline period was selected as the average of the first 50 pulses whilst the intervention period was calculated as the average of 8 pulses surrounding the period where systolic BP (SBP) was the greatest during the intervention, ensuring that those periods were in sinus rhythm and free of Finometer® PRO recalibration periods. Pulses were decided arbitrarily on the basis that it would encapsulated a particular region of sustained alterations in haemodynamic parameters. The slope was calculated as the change in diastolic BP (DBP) between the intervention and baseline period divided by the respective change in either PAT or PTT (Eq. 3):

$$\mathrm{slope}_{\mathrm{DBP}} = \frac{\mathrm{DBP}_{int} - \mathrm{DBP}_{baseline}}{\mathrm{TT}_{int} - \mathrm{TT}_{baseline}} \quad (3)$$

whereby 'int' denotes the intervention period and 'TT' denotes transit time (PAT or PTT). The slope term allows normalization of the PAT changes with respect to the BP changes in order to compare between sensors and interventions. DBP was used as that was the pressure pulse point from which transit time was calculated.

D. Statistical Analysis

Statistical analyses were performed using MATLAB (version R2020a) and R (version 4.0.5). Baseline participant hemodynamic data was defined using an average of the initial seated oscillometric brachial arterial BP measurements. A repeated measures 3-way analysis of variance (ANOVA) was performed using the linear model function 'lm' in R on both the transit times (data not presented) and the slope (ΔBP/ΔPAT) to determine if there were statistical differences between the respective reference and intervention sections. Normality of the model was assessed by a Sharpio-Wilk test and graphically through a QQ plot of the residuals. Differences are presented as mean±standard deviation (SD). A difference of $p<0.05$ was deemed statistically significant.

The ΔBP/ΔPAT was calculated for each sensor during each intervention. Points were deemed as statistical outliers if they fell outside mean±3× the interquartile range (IQR). An additional repeated measures 3-way ANOVA was performed whereby these outliers had been excluded on the basis of mean$\pm 1.5 \times$IQR. These results did not show any significant differences compared to when data was excluded using $\pm 3 \times$ IQR. The final analysis presented is that with outliers excluded using mean$\pm 3 \times$ IQR.

TABLE II
AVERAGE CHANGES IN HAEMODYNAMIC PARAMETERS FOLLOWING INTERVENTIONS

Intervention	Parameter	Mean±SD	p
Cold Pressor	ΔHR (bpm)	1±6	0.845
	ΔSBP (mmHg)	41±19	<0.001
	ΔDBP (mmHg)	21±9	<0.001
Cycling	ΔHR (bpm)	41±15	<0.001
	ΔSBP (mmHg)	68±25	<0.001
	ΔDBP (mmHg)	16±9	0.002
IHG	ΔHR (bpm)	5±6	0.329
	ΔSBP (mmHg)	36±16	<0.001
	ΔDBP (mmHg)	20±8	<0.001

bpm: beats per minute; DBP: diastolic blood pressure; HR: heart rate; IHG: isometric handgrip; SBP: systolic blood pressure; SD: standard deviation.

III. RESULTS

Participant demographics (n=15, 9 males) are displayed in Table I. Data collected in two individuals during the cold pressor test was removed from the analysis due to the participants being unable to complete a sufficient amount of the manoeuvre. Additionally, because of complications with the ECG measurement collected in a separate individual during the cycling manoeuvre, data was excluded from analysis due to inability to calculate PAT. All other data collected in individuals was included in the analysis (270 observations total, 18 of these observations were excluded due to missing data). Changes in HR, SBP and DBP are presented in Table II. On average all interventions significantly increased both SBP and DBP ($p<0.05$). Only cycling significantly increased HR ($p<0.001$).

The ΔBP/ΔPAT values are displayed in Fig. 1. It can be observed that there is larger variability apparent between the IHG intervention compared to the cold pressor test and cycling. The 3-way repeated measures ANOVA (F=6.35, $p<0.001$, adjusted R^2=0.28) included 239 observations. A total of 31 data points were excluded based on missing data (n=18 observations) or being deemed as outliers (n=13 observations). The results of the ANOVA showed a statistically significant difference between the slope calculated for cycling compared to the cold pressor test (p=0.0002) as well as a significant difference between the transit time type (PAT and PTT) for the IHG intervention ($p<0.05$). Slopes for the respective transit times were not significantly different across sensors ($p>0.05$).

IV. DISCUSSION

This study assessed the transit time changes with respect to DBP (ΔBP/ΔPAT) following various interventions to alter BP. All interventions increased BP to varying degrees. Cycling increased systolic BP the most (68±25 mmHg) whilst cold pressor test and IHG exercise increased DBP the most (21±9 mmHg and 20±8 mmHg, respectively). Despite the significant changes in BP during the cold pressor test and IHG, HR changes were minimal ($p>0.05$). Pulse wave velocity and consequently transit time are both partly dependent on HR [3], [6]. This dependency is quite minimal, and may be considered a negligible confounder with small HR changes, such as that observed with the cold pressor test and the IHG. However, considering the degree of HR change during cycling, HR cannot be dismissed as a potential confounder of the transit time measurement.

HR changes have shown to be correlated with sympathetic activity [7] and therefore vascular tone. This is a plausible factor as to why there were no significant differences between transit time measured by the different sensors. However, a previous study by Victor *et al.* [8] observed a dissociation in the response between muscle sympathetic nerve activity and HR during a cold pressor test, indicating that HR alone is not a strong indicator of sympathetic activity. This observation for the cold pressor test might not extrapolate to other interventions that influence the cardiovascular system in a slightly different manner. This notion may be supported through the idea that the mechanisms controlling sympathetic outflow vary between cardiac muscle and smooth muscle under different interventions [9].

In the present study, transit time was strictly measured as PAT, calculated based on the R-peak of the ECG and the second derivative of the peripherally acquired waveform. Despite the convenience of this measurement and as mentioned previously, PAT includes a period of electrical activity prior to the mechanical opening of the aortic valve, the PEP. This additional time period is a confounder of the transit time as a correlate of BP as PEP does not necessarily change in a correlated fashion with BP. In an attempt to correct for this, PEP was estimated based on the regression models described previously Eq. 1 and 2 to arrive at an estimated corrected PTT [5]. Whilst this approach may address some inherent error present in the PAT measurement, it is limited as it is a generalized equation that has been generated based on data collected in resting individuals and therefore does not consider other cardiovascular factors that change following alterations in BP. A more reliable solution to this limitation would be to measure the PEP, and consequently the actual PTT, as achievable using an ultrasound, phonocardiogram or ballistocardiogram.

Stemming from the influence of sympathetic activity on the vasculature, Colombo *et al.* [9] previously performed a study on gravitationally induced sympathetic activity changes measured with a PPG sensor. Despite the small sample size, they showed that indices of the PPG were capable of measuring autonomic modulation, as correlated with HR variability analysis. With this in mind, perhaps in conjunction to measuring transit time these indices should be considered as potential influencing factors.

That the slope term was higher during cycling than during cold pressor or IHG might indicate a sympathetic effect on PAT and PTT, should it be considered the sympathetic tone is different during cycling than the other challenges. However, this effect occurred regardless of the site of measurement, with large conduit vessels (measured by radial tonometry) showing the same effect as pathways with resistance vessels (PPG measurement). Alternatively, the higher slope term during cycling may be a direct BP effect. The SBP and pulse pressure change was greater during cycling than the other

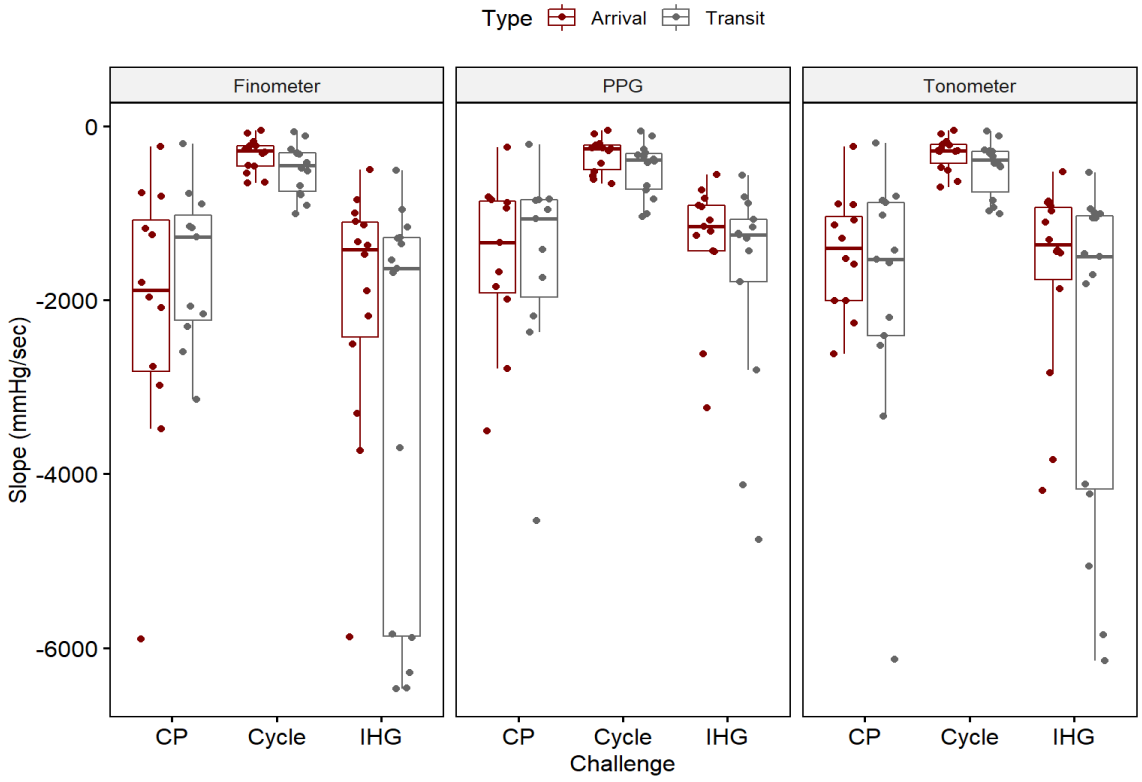

Fig. 1. The slope (ΔBP/ΔPAT) calculated for each intervention (CP = cold pressor, cycle, IHG = isometric handgrip) for each sensor (Finometer® PRO, PPG = photoplethysmography, radial tonometer) for both pulse arrival time (PAT, red) and the estimated pulse transit time (PTT, grey). Data was excluded if the slope value lied outside $\pm$3xIQR.

challenges. Whilst the BP - arterial stiffness relationship is considered linear for small changes in BP, it is not linear over larger changes [10]. This non-linearity may cause the greater slope term during cycling, as a result of the different BP change, compared to the other challenges, independent of any sympathetic differences.

V. Conclusions

The current study showed no apparent neurogenic effect that is measurable through PAT or PTT changes using PPG finger-tip sensor or radial tonometry during various BP altering interventions. Whilst there was a notable difference between cycling and IHG and the cold pressor test, along with the transit time type (PAT or PTT), this is likely a consequence of the larger systemic change in both HR and BP, indicating a non-linear relationship with pressure and/or HR changes. Rather than using an average of pulses, a beat-to-beat investigation may provided further insight. This study indicates that in estimating BP from PTT, autonomic effects are small to the point that they can be ignored, regardless of the pulse acquisition modality. However, HR effects and the non-linear PTT-BP relationship are factors that may need to be taken into account.

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