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Reliability of Pulse Waveform Separation Analysis: Effects of Posture and Fasting

Running Title: Reliability of Waveform Separation Analysis

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ABSTRACT

Oscillometric pulse wave analysis devices enable, with relative simplicity and objectivity, the measurement of central hemodynamic parameters. The important parameters are central blood pressures and indices of arterial wave reflection, including wave separation analysis (backward pressure component [Pb], reflection magnitude [RM]). **Objective**: This study sought to determine whether the measurement precision (between-day reliability) of Pb and RM: (i) exceeds the criterion for acceptable reliability; (ii) is affected by posture (supine, seated) and fasting state. Twenty healthy adults (50% F, 27.9 y, 24.2 kg/m^2) were tested on six different mornings: three days fasted, three days non-fasted. On each occasion participants were tested in supine and seated postures. Oscillometric pressure waveforms were recorded on the left upper arm. **Results:** The criterion intra-class correlation coefficient value of 0.75 was exceeded for Pb (0.76) and RM (0.77) when participants were assessed under the combined supine-fasted condition. The ICC was lowest for Pb in seated-non-fasted condition (0.57), and lowest for RM in the seated-fasted condition (0.56). For Pb, the smallest detectible change (SDC) that must be exceeded in order for a significant change to occur in an individual was 2.5 mm Hg, and for RM the SDC was 8.5%. **Conclusion**: Assessments of Pb and RM: (i) exceed the criterion for acceptable reliability, and (ii) are most reliable when participants are fasted in a supine position. The demonstrated reliability suggests sufficient precision to detect clinically meaningful changes in RM and Pb.

INTRODUCTION

Pulse wave analysis (PWA) devices enable clinicians and clinical scientists, with relative simplicity and objectivity,[1] to obtain important mechanistic diagnostic and prognostic information through the measurement of central hemodynamic parameters. [2-5] The important parameters are central blood pressures and indices of arterial wave reflection, including augmentation index (AIx) and the promising wave separation analysis. However, to be of value in a clinical setting, an assessment tool must also be precise (reliable) when used during normal clinical operating conditions.[6] This knowledge is required to gauge the critical difference in a parameter that must be exceeded between two sequential visits, when tested under a given set of conditions.[6]

Wave separation analysis is promising because it may provide a more accurate estimate of the effects of wave reflection on central blood pressure and centrally located organs than the more established AIx.[4, 7] The AIx, which is calculated by dividing the central augmentation pressure by the corresponding pulse pressure, is affected by the reflected wave transit time.[8, 9] Alternatively, by assuming a triangular or a physiologic flow waveform,[10] the aortic wave can be separated into its forward (Pf) component and timing-independent reflected component (Pb). Two large prospective studies [4, 5] suggest that wave separation analysis may be superior to AIx as a subclinical marker of cardiovascular disease, one reporting that Pb better predicts 15-year cardiovascular mortality than AIx,[5] the other that reflection magnitude (RM, Pb/Pf) better predicts cardiovascular events than AIx.[4]

In the clinical setting, the efficacy of a prescribed treatment can only be adequately assessed if the outcome of interest can measured with sufficient precision. Recently, our group published an article in the Journal of Hypertension which reported that oscillometric assessments of central blood pressures and AIx exceed the criterion for acceptable reliability when assessments were made under supine and fasted conditions.[11] However, a patient may report for clinical evaluation in a fasted or non-fasted state, and blood pressure is commonly measured with the patient in the seated or supine posture. We found that the precision of central blood pressure and AIx recordings was reduced when a participant was seated or non-fasted.

To the best of our knowledge, no previous study has assessed the precision of wave separation analysis, nor whether measurement precision is influenced by posture or the fasted state. Therefore, in order to facilitate guidelines for optimal assessments of Pb and RM, the data from our previous study[11] was re-analyzed to determine whether measurement precision (between-day reliability): (i) exceeds the criterion for acceptable reliability; (ii) is affected by posture (supine, seated) and fasting state.

METHODS

PARTICIPANTS

To ascertain the upper limit of validity and reliability for oscillometric derived central hemodynamic parameters, a relatively homogenous cohort of 20 young (19 – 35 y) and healthy participants (50% F) were recruited. Participants were excluded if they reported any known

cardio-metabolic disorders, were taking medications known to affect cardiovascular function, or reported cigarette smoking. Ethical approval was obtained from the Massey University Human Ethics Committee and all participants provided written informed consent prior to participating in the study.

EXPERIMENTAL DESIGN

Prior to beginning the study, participants were familiarized with all measurement procedures. Subsequently, participants were tested on 6 different days (over 2 weeks) between the hours of 7am and 10am: 3 days fasted (12 hr), having consumed only water, and 3 days non-fasted, having consumed their usual breakfast. To ensure an ecologically valid clinical model, meal consumption was not regulated, nor was the intake of caffeine. However, all participants were asked to refrain from supplement intake that morning, and to avoid strenuous physical activity and alcohol for 24 hours prior to experimentation. On each occasion the participant was tested in the supine and seated position, resulting in a total of 12 measurements per person, and a total of 240 data points. Two measurements were taken within a three-minute interval. If blood pressures differed by > 5 mmHg or AIx > 4%, a third recording was taken and the closest two recordings were averaged.[12]

PULSE WAVE ANALYSIS

Following 20 minutes of undisturbed rest, oscillometric pressure waveforms were recorded by a single operator on the left upper arm using a SphygmoCor XCEL device (AtCor Medical, Sydney, Australia), following standard manufacturer guidelines.[13] Each measurement cycle lasted

approximately 60 seconds, consisting of a brachial blood pressure recording and then a 10 sec

sub-systolic recording. A corresponding aortic pressure waveform (**Figure 1**) was generated

using a validated transfer function.[14] To enable direct comparison, the AIx data from the

previous study is re-reported.[11] The AIx is defined as the augmentation pressure (AP),

expressed as a percentage of central pulse pressure, where AP is defined as the maximum

systolic pressure minus the pressure at the inflection point. The aortic forward (Pf) and

backward (Pb) wave pressures were determined by assuming a triangular flow wave.[10, 15]

This method creates a triangular-shaped flow wave by matching the start, peak, and end of the

flow wave to the timings of the foot, inflection point, and incisura of the aortic pressure wave

(**Figure 1**). Thus, the forward and backward components of the pressure wave can be

constructed using the following equations:

$$Pf = [P + Zc \times Q]/2$$

$$Pb = [P - Zc \times Q]/2$$

where P is the synthesized aortic pressure wave, Q is the approximated pseudoflow wave, Zc is

the characteristic impedance, Pf is the forward pressure component, and Pb is the backward

pressure component. The RM was calculated as Pb/Pf. Because calculation of Pf and Pb involves

the product of flow (Q) and characteristic impedance (Zc), which itself has flow in the

denominator, calibration of the flow waveform is not needed.

SAMPLE SIZE

Sample size calculations were based on the primary outcome from the original study, cSBP, and assuming a typical error of 6.4 mmHg derived from a previous reliability study using healthy subjects.[16] Using magnitude-based inference [17] to estimate the sample size required to detect the smallest beneficial (or detrimental) in a cross-over study, with the maximum chances of a type 1 and 2 error set at 5% (i.e., very unlikely), approximately 8 participants are required to detect a 6 mmHg change (based on the smallest change reported in previous blood pressure studies.[18] We oversampled to account for the uncertainty with regards to the effect of fasting.

STATISTICS

Statistical analyses were performed using Statistical Package for Social Sciences version 21 (SPSS, Inc., Chicago, Illinois). All data are reported as means (SD), unless otherwise specified. Statistical significance was defined as $p<0.05$ (two tailed). The effects of (i) posture and (ii) fasting status on central hemodynamic parameters were assessed using analysis of variance (ANOVA) for repeated measurements with two within-subject factors (posture, fasting status). Effect sizes are reported using partial eta-squared η^2_p, where 0.01, 0.06, and 0.14 represent a small, medium, and large effect, respectively.[19]

Reproducibility of parameters was assessed by calculating the intra-class correlation coefficient (ICC), standard error of measurement (SEM), and smallest detectable change (SDC). The ICC was calculated according to the formula: $SD_b^2 / [SD_b^2 + SD_w^2]$, where SD_b^2 and SD_w^2 are the between and within-subject variance. In general, ICC values above 0.75 are considered to

indicate excellent reproducibility.[20] The SDC is defined as the critical difference in a parameter that must be exceeded between two sequential results in order for a statistically significant change to occur in an individual.[6] Absolute SDC was calculated using the formula: 1.96 x SEM x √2, where 1.96 corresponds to 95% confidence interval, and SEM was calculated using the equation: SD_b x √(1-ICC).[6]

RESULTS

Data were successfully collected from all 20 healthy young men and women (27.9 y (SD 4.9), 50% F, 24.2 kg/m^2 (SD 3.5)). **Table 1** summarizes the mean values for the central hemodynamic variables. For all central variables, no interaction effects were reported, and there was no main effect for posture. The fasted state did not significantly effect Pb, but had a large effect (η^2_p = 0.23 – 0.56) on Pf, RM, AP and AIx, increasing Pf by an estimated 1.3 (CI: 0.2, 2.4) mm Hg, and decreasing RM by -3.9 (CI: -2.3, -6.6) %, AP by -1.3 (CI: -1.9, -0.7) mmHg, and AIx by -4.0 (CI: -5.9, -2.2) %.

The between-day reliability values are reported in **Table 2**. The ICC values were lowest for all variables for the 'total' condition, i.e., across postural and fasted states. For Pf, the criterion ICC (0.75) was not exceeded for any test condition. For the remaining variables (Pb, RM, AP, AIx), the criterion ICC was only simultaneously exceeded for the combined supine-fasted condition.

DISCUSSION

This study demonstrates that pulse waveform separation analysis can be reliably assessed using oscillometric PWA. Oscillometric PWA recordings are most consistently reliable when the patient is in the supine posture and fasted. Fasting state influences the magnitude of RM readings (i.e., decreases RM), and the precision of Pb readings. Posture does not influence the magnitude of RM or Pb, but does reduce precision.

The ICC values we observed for Pb (0.76) and RM (0.77) in the supine-fasted condition are comparable to the ICC (0.79) we previously observed for AIx.[11] To put the value of Pb in to clinical perspective, we calculated the SDC to be 2.5 mm Hg. This SDC value is substantially less than the 1-SD (6 mm Hg) for Pb recorded from 1272 participants (47% women; mean age: 52 years; range: 30 to 79 years) in a previous prospective study.[5] This previous study found that a 6 mmHg higher Pb was associated with a 61% increase in cardiovascular mortality over 15 years. An additional study [4] assessed the relationship between central hemodynamic profiles and cardiovascular events in 5,960 participants (52% women; mean age: 62 years; range: 53 to 70 years). A 10% increase in RM (~8.4%), which is nearly equivalent to the SDC (8.5%) calculated for the current study, equated to an adjusted hazard ratio of 1.34. For both of these studies, the wave separation analysis variables were found to be superior to AIx. Thus, while AIx may have similar precision to Pb and RM, the later variables may be more clinically meaningful and, based on our finding, have high reliability in a fasted, supine state.

The non-fasted state may have significantly decreased RM and AIx, but not Pb, due to two potential sources of error: (i) the generalized transfer function used to generate the aortic

pressure waveform, and (ii) the reflected wave transit time. (i) The generalized transfer function may less faithfully reproduce the high-frequency components required for AIx computation than it does the low-frequency pressure harmonics required for Pb and Pf computation.[21] (ii) The AIx, as well as RM (as a function of Pf being the numerator), are both affected by the reflected wave transit time. The transit time is affected by the reflected wave timing, amplitude, and ventricular function, which in turn are known to be influenced by a number of factors, including heart rate.[8, 9] For example, in the current study, heart rate was 4.3 (CI: 1.9, 6.7) bpm higher in the non-fasted state and may have acted as an additional source of variability. Thus, the decreased AIx and RM in the non-fasted state may have not fully resulted from decreased wave reflection.

Our findings bear relevance to clinical research as well as clinical practice. There is growing public health interest in work place behaviours and cardiovascular health, including the influence of prolonged sedentary behaviour.[22-25] As such, there is interest in tracking the cardiovascular health of patients during the working day, during which they may sit and consume food. While posture and the fasted state does reduce the precision of central hemodynamic variables, including Pb, the magnitude of Pb does not appear to be influenced by these conditions. The Pb may be a robust variable for tracking vascular health during the working day.

FUTURE DIRECTION

While the SDC values for RM and Pb are at a level previously reported to be clinically meaningful,[4, 5] further study is required to confirm our findings in clinical populations of varying age and health states. In the current study, to ascertain the upper limit of reliability for oscillometric derived central hemodynamic parameters, we opted to recruit a homogenous cohort of young, healthy participants. Additionally, the maximum duration between the first and last testing sessions was 11 days, which is long enough to shift phases of the menstrual cycle and may have added a source of error to our findings. While subgroup analysis for the supine-fasted data revealed that the SDC values for women compared to men were actually marginally superior for Pf (5.2 mmHg vs. 3.0 mmHg, respectively), Pb (2.8 mmHg vs. 2.0 mmHg, respectively), and RM (4.0 % vs. 2.0 %, respectively), further study is required to determine the influence of the menstrual cycle on waveform morphology. Lastly, to ensure an ecologically valid clinical model, meal consumption was not regulated, nor was the intake of caffeine. The non-standardization of caffeine consumption likely added an additional source of error variance to AIx and RM, as both of these parameters are known to be influenced by heart rate.[8, 9] The known relationship between these parameters and heart rate further indicates the need to standardize testing conditions.

CONCLUSIONS

Findings from this study suggest that assessments of Pb and RM: (i) exceed the criterion for acceptable reliability, and (ii) are consistantly reliable when participants are evaluated while fasted and in a supine position. The SDC values for RM and particularly for Pb are sufficiently small to detect differences of clinical meaningfulness. These findings lend support to the use of

oscillometric PWA in the clinical setting, and Pb in particular may be an important adjuvant to central blood pressure recordings.

CONFLICT(S) OF INTEREST/DISCLOSURE(S)

None.

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FIGURES

Figure 1. Aortic pulse wave analysis.

Using the generated aortic pressure waveform (top panel), augmentation index (AIx) is calculated by expressing augmentation pressure (AP) as a percentage of the central pulse pressure (cPP). The AP is the additional pressure added to the forward wave by the reflected wave, and is defined as the maximum central systolic pressure minus the pressure at the inflection point. Using a physiologic flow waveform (middle panel), the aortic wave can be separated (bottom panel) into its forward (Pf) and reflected (Pb) waves and reflection magnitude (RM) can be computed (Pb/Pf).

TABLES

Table 1. Mean values for central hemodynamic variables

AIx, augmentation index; AP, augmentation pressure; MAP, mean arterial pressure; Pb, aortic forward wave pressure; Pf, aortic forward wave pressure; RM, reflection magnitude. Bold indicates significant at P<0.05.

Table 2. Reliability of central hemodynamic variables

AIx, augmentation index; AP, augmentation pressure; ICC, intraclass correlation coefficient; Pb, aortic forward wave pressure; Pf, aortic forward wave pressure; RM, reflection magnitude; SEM, standard error of measurement; smallest detectable change (SDC).
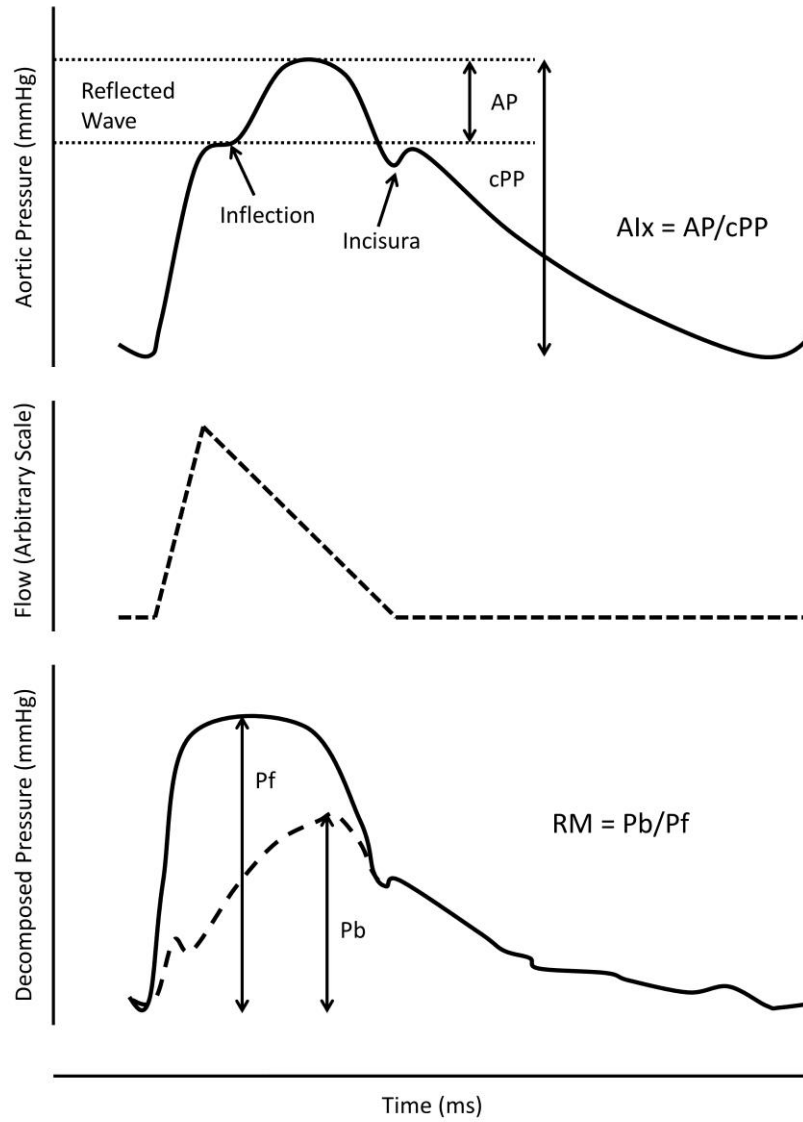
Figure 1.

$AIx = AP/cPP$

$RM = Pb/Pf$

Table 1.

		Total	Supine		Seated		Interaction		Posture		Fasted	
		X	Fast	Non	Fast	Non	P	η^2_p	P	η^2_p	P	η^2_p
MAP (mmHg)	X	84.1	81.4	82.4	86.3	86.1	0.154	0.10	**<0.001**	0.56	0.489	0.03
	SD	5.49	5.51	7.07	5.36	6.24						
Heart rate (bpm)	X	64.4	59.5	64.5	64.9	68.5	0.060	0.17	**<0.001**	0.58	**0.002**	0.42
	SD	9.66	8.26	10.2	10.1	12.1						
Pf (mmHg)	X	24.8	24.0	25.3	24.3	25.5	0.743	0.01	0.548	0.02	**0.027**	0.23
	SD	2.61	2.54	3.92	2.29	3.28						
Pb (mm Hg)	X	12.3	12.4	11.9	12.5	12.4	0.297	0.06	0.329	0.05	0.128	0.12
	SD	1.42	1.82	1.91	1.34	1.61						
RM (mm Hg)	X	49.4	51.1	47.3	51.7	47.6	0.753	0.01	0.682	0.01	**<0.001**	0.56
	SD	4.8	6.4	6.5	4.5	5.6						
AP (mmHg)	X	1.79	2.22	1.12	2.68	1.16	0.316	0.05	0.603	0.01	**<0.001**	0.54
	SD	2.75	3.05	2.44	3.26	3.36						
AIx (%)	X	6.08	7.25	3.92	8.94	4.19	0.207	0.08	0.537	0.02	**<0.001**	0.52
	SD	8.59	9.15	7.65	10.1	11.0						

Table 2.

	Total			Supine-F			Supine-NF			Seated-F			Seated-N		
	ICC	SEM	SDC	ICC	SEM	SDC	ICC	SEM	SDC	ICC	SEM	SDC	ICC	SEM	SDC
Pf (mmHg)	0.48	1.89	5.24	0.66	1.48	4.11	0.67	2.25	6.22	0.55	1.54	4.27	0.62	2.01	5.56
Pb (mm Hg)	0.47	1.03	2.86	0.76	0.90	2.48	0.69	1.06	2.93	0.57	0.88	2.43	0.56	1.07	2.97
RM (%)	0.48	3.48	9.64	0.77	3.08	8.54	0.80	2.95	8.16	0.56	2.97	8.24	0.75	2.81	7.78
AP (mmHg)	0.62	1.69	4.70	0.78	1.45	4.01	0.69	1.36	3.77	0.81	1.44	3.99	0.80	1.50	4.15
AIx (%)	0.63	5.24	14.5	0.79	4.22	11.7	0.71	4.10	11.4	0.82	4.32	12.0	0.81	4.73	13.1