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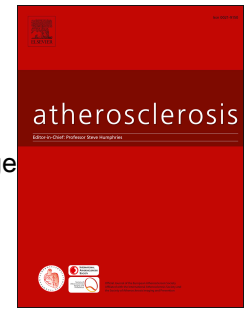

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RELIABILITY OF OSCILLOMETRIC CENTRAL HEMODYNAMIC RESPONSES TO AN ORTHOSTATIC CHALLENGE

Running Title: Reliability of Central Hemodynamic Responses

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ABSTRACT

Background: Monitoring central hemodynamic responses to an orthostatic challenge may provide important insight into autonomic nervous system function. Oscillometric pulse wave analysis devices have recently emerged, presenting clinically viable options for investigating central hemodynamic properties. The purpose of the current study was to determine whether oscillometric pulse wave analysis can be used to reliably (between-day) assess central blood pressure and central pressure augmentation (augmentation index) responses to a 5 min orthostatic challenge (modified tilt-table). **Methods**: Twenty healthy adults (26.4 y (SD 5.2), 55% F, 24.7 kg/m^2 (SD 3.8)) were tested on 3 different mornings in the fasted state, separated by a maximum of 7 days. Central hemodynamic variables were assessed on the left arm using an oscillometric device. **Results**: Repeated measures analysis of variance indicated a significant main effect of the modified tilt-table for all central hemodynamic variables (P<0.001). In response to the tilt, central diastolic pressure increased by 4.5 mmHg (CI: 2.6, 6.4), central systolic blood pressure increased by 2.3 (CI: 4.4, 0.16) mmHg, and augmentation index decreased by an absolute - 5.3 %, (CI: -2.7, -7.9 %). The intra-class correlation coefficient values for central diastolic pressure (0.83-0.86), central systolic blood pressure (0.80-0.87) and AIx (0.79-0.82) were above the 0.75 criterion in both the supine and tilted positions, indicating excellent between-day reliability. **Conclusion**: Central hemodynamic responses to an orthostatic challenge can be assessed with acceptable between-day reliability using oscillometric pulse wave analysis.

KEY WORDS: pulse wave analysis; orthostatic challenge; central blood pressure; arterial wave reflection; augmentation index

INTRODUCTION

Autonomic nervous system (ANS) dysfunction has been linked to a number of cardiovascular disturbances, including hypertension and stroke.[1, 2] The ANS function can be assessed using an orthostatic challenge, which results in pooling of blood in the sub-diaphragmatic venous system and subsequent vasoconstriction of the resistance and capacitance vessels.[3, 4] Thus, peripheral blood pressure is typically used to gauge the sympathetic response to an orthostatic challenge.[3] However, considering the marked differences in pulse pressure between the central aorta and peripheral limbs, peripheral blood pressure may not accurately reflect the effects of peak arterial blood pressure on centrally located organs.[5] For this reason, central hemodynamic assessments may provide a superior indication of ANS responses to an orthostatic challenge. However, in order to be of value in a clinical setting, these assessments must be accurate, precise, and relatively simple to conduct.

Central hemodynamic properties may be monitored with accuracy[6] and precision[7] using pulse wave analysis (PWA). Typically, the pressure waveform is non-invasively monitored at a peripheral site, and using a generalized transfer function, a corresponding aortic arterial waveform can be generated.[8, 9] Besides central blood pressure, the generated waveform is used to estimate central pressure augmentation (arterial wave reflection). Peripheral waveform recordings are typically collected using radial artery applanation tonometry. However, this technique requires some expertise, can be time consuming, and may be impractical for use in the clinical setting. Recently, oscillometric devices have emerged, which are operator independent, user-friendly, and have been validated against tonometric [10, 11] and direct aortic catheter assessments. [12-14]

In addition to being accurate (valid), a clinical setting assessment tool must be precise (reliable). Knowledge of reliability is required to gauge 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.[15] While oscillometric PWA devices have been demonstrated to be highly reliable under standard resting

conditions,[10, 11, 16] to the best of our knowledge only one study has demonstrated that PWA can be used to reliably assess central hemodynamic responses to an orthostatic challenge (ANS function).[17] The aforementioned study[17] utilized radial artery tonometry, which as previously stated may be unsuitable for clinical practice, and it is currently unknown whether user-friendly oscillometric devices provide acceptable reliability. Therefore, the purpose of the current study was to determine the between-day reliability of central blood pressure and central pressure augmentation responses to a modified tilt-table test, using oscillometric PWA.

METHODS

PARTICIPANTS

To ascertain the upper limit of reliability, a relatively homogenous cohort of 20 young (19 – 35 y) and healthy participants were recruited. Participants were excluded if they smoked, reported any known cardio-metabolic disorders, or were taking medications known to affect cardiovascular function. 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 experimental procedures. Subsequently, participants were tested on 3 different days in a dimly-lit, climate controlled room between the hours of 7am and 10am. All participants were fasted, consuming only water, and refrained from caffeine and supplement intake that morning, and strenuous physical activity and alcohol for 24 hours prior to experimentation. The maximum duration between the first and last study visit was 7 days (mean: 3.2 d SD (1.8)), and women were tested on consecutive days to avoid the possible confounding influence of menstrual cycle hormones. Following a 10-min rest period in the supine posture, baseline PWA assessments were collected. The participant was then rapidly (~1 sec) tilted to a 60-degree upright position using a modified tilt-table for 5 min. During the tilt period, PWA assessments were collected at 2- and 5-min ($Tilt_2$,

$Tilt_5$). The participant was returned to the supine position for a 5-min recovery period during which PWA assessments were collected at 2- and 5-min (Rec_2, Rec_5).

PULSE WAVE ANALYSIS

Oscillometric pressure waveforms were recorded on the left upper arm by a single observer using the SphygmoCor XCEL device (AtCor Medical, Sydney, Australia), following standard manufacturer guidelines.[18] Each measurement cycle lasted approximately 60 sec, consisting of a brachial blood pressure recording and then a 10 sec sub-systolic recording. A corresponding aortic pressure waveform was generated using a validated transfer function,[14] from which central systolic, diastolic, pulse pressure (cSBP, cDBP, cPP), augmentation pressure (AP), and augmentation index (AIx) were derived. The AP is defined as cSBP minus the pressure at the inflection point, whereby the inflection point is the merging of the forward and reflected waves. The AIx is defined as the AP expressed as a percentage of cPP. AIx is influenced by heart rate, and thus an index corrected for a heart rate at 75 beats per minute (AIx75) was also calculated. At baseline, two measurements were taken, separated by a three-minute interval. If blood pressure differed by > 5mmHG or if AIx > 4% a third recording was taken and the closest recordings were averaged.[19] During the tilt and recovery conditions only 1 recording was taken at each time point.

STATISTICAL ANALYSIS

Statistical analyses were performed using Statistical Package for Social Sciences version 20.0 (SPSS, Inc., Chicago, Illinois). All data are reported as means and standard deviation (SD), unless specified. Statistical significance was defined as $P<0.05$ (two tailed). The effects of the orthostatic challenge central hemodynamic parameters were assessed using analysis of variance (ANOVA) for repeated measurements with one within-subject factors (time: base, $Tilt_2$, $Tilt_5$, Rec_2, Rec_5). 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.[20]

Reproducibility of parameters was assessed by calculating the intra-class correlation coefficient (ICC), standard error of measurement (SEM), and reproducibility coefficient (RC). 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.[21] The reproducibility coefficient (RC) 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.[15] Absolute RC 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* √(1-ICC).[15]

RESULTS

Data were successfully collected from all 20 healthy young men and women (26.4 y (SD 5.2), 55% F, 24.7 kg/m^2 (SD 3.8)).

CENTRAL BLOOD PRESSURE

In response to the modified-tilt table, there was a large main effect (η^2_p = 0.20 – 0.65) for all peripheral and central blood pressure variables (Table 1). The main variables of interest, cSBP and cDBP, increased in response to the tilt-table when compared to baseline, with the peak change in cSBP occurring at $Tilt_2$ (2.3 mm Hg, CI: 0.2, 4.4 mm Hg) and the peak change in cDBP occurring at $Tilt_5$ (4.5 mmHg, CI: 2.6, 6.4 mmHg). For all stages of the tilt-table test, the ICC values for cDBP and cSBP were above the criterion 0.75 (Table 2), indicating excellent between-day reliability. The RC values indicates that, for a given individual, in order for a significant change to have occurred between visits the cDBP at $Tilt_5$ (74 mmHg) must differ by 7.0 mmHg and the cSBP at $Tilt_2$ (103 mmHg) by 7.9 mm Hg.

SYSTEMIC ARTERIAL WAVE REFLECTION

In response to the modified-tilt table, there was a large main effect for AP, AIx and AIx75 (η^2_p = 0.21 – 0.67). The main variable of interest, AIx, decreased in response to the tilt-table when compared to

baseline, with the peak change occurring 2 min post-tilt (- 5.3 %, CI: -2.7, -7.9 %). For all stages of the tilt-table test, the ICC values for AIx were above the criterion 0.75 (Table 2). The RC indicates that the AIx value seen at $Tilt_2$ (5.2 %) must differ by an absolute 11.5 % between visits in order for a significant change to have occurred.

DISCUSSION

This study demonstrates that central hemodynamic response to an orthostatic challenge (modified tilt-table) can be precisely (reliably) assessed using oscillometric PWA.

CENTRAL BLOOD PRESSURES

A novel finding of the current study is the indication of comparable reliability estimates for oscillometric and tonometric derived assessments of cDBP and cSBP responses to an orthostatic challenge. The ICC values we observed for cDBP (0.83-0.86) and cSBP (0.80-0.85) responses to the orthostatic challenge exceed the criterion (0.75), and are consistent with previously reported ICC values for cDBP (0.80) and cSBP (0.74) measurements collected using tonometry.[17] Further, the RC, which is defined as the critical difference that must be exceeded in order for a significant change to occur in an individual,[15] was relatively low. Using cSBP as an example, the $Tilt_2$ would need to differ by 7.9 mmHg (or 7.7 %) between visits - or following a given perturbation or therapy. Collectively, these findings suggest that oscillometric PWA may be suitable for monitoring changes within an individual over time.

In response to the orthostatic challenge, cDBP increased by 4.5 mmHg and cSBP by 2.3 mmHg. These increases can be explained by the normal homeostatic mechanisms of blood pressure. For a young, healthy patient both heart rate and total peripheral resistance increase to maintain central blood volume and adequate perfusion to the brain.[4] The magnitude of change in cDBP we reported is consistent with the 3 mmHg response to 5 min head-up tilt previously reported in a healthy, albeit slightly older (33.9 y) cohort.[17] However, the cSBP response appears to be dependent on age; Tahvanainen *et al* [22] utilized head-up tilt

apparatus, reporting a small increase in cSBP (actual figure NR) for participants aged 20-29 y, but a progressive decrease in cSBP for participants aged 30-39 y, 40-49 y or 50-59 y. The progressive response was seen despite no systemic difference between age groups for change in cardiac output or total peripheral resistance, suggesting preserved cardiac and small artery function.

Further study is warranted to elucidate the mechanism(s) and clinical importance of changes in central blood during an orthostatic challenge. Previously, it has been demonstrated that peripheral blood pressure responses to submaximal exercise predict the future development of hypertension, independent of resting pressures.[23, 24] Whether or not central pressure responses to an orthostatic challenge can predict future cardiovascular complications warrants further attention.

SYSTEMIC ARTERIAL WAVE REFLECTION

The between-day ICC values we observed for the AIx (0.79-0.82) response to an orthostatic challenge are superior to the previously reported between-day ICC (0.70), but lower than the within-day ICC (0.95), derived from tonometric assessments.[17] However, while the RC for central blood pressures was small, the RC for AIx was relatively high (11.5 %) when compared to the mean. This may suggest that while AIx is potentially a sensitive marker for use in clinical studies, fairly large responses would be required to detect intra-individual variation, at least between-days.

The absolute -5.3% change in AIx during the modified-tilt is constant with, albeit smaller in magnitude, than the -12.2% response to 5 min head-up tilt previously reported in a slightly older (33.9 y) cohort.[17] However, similar to previous findings [17], the decrease in AIx opposes the increase in central blood pressure we saw. To determine the mechanism(s) for this conflicting finding, the sources of AIx must be decomposed. The AIx is thought to reflect the merging of forward and backward (reflected) pressure waves. Sources of the reflected wave reflection include large artery geometry [25, 26] and function,[27] and the tone of the small vessel beds.[28] Large artery geometry is unlikely to be notably influenced by an orthostatic

challenge, though endothelial function of lower-limb arteries may have been affected due to an altered shear stress profile. However, previous studies have demonstrated change in posture (supine to seated) to decrease shear stress and increase the vascular tone of these vessels,[29, 30] which would be expected to increase AIx. Similarly, previous studies have shown total peripheral resistance to increase during tilt-table testing, [17, 22] which would indicate increased tone of the small vessel beds.[31] The forward travelling wave is determined by cardiac function, including heart rate and stroke volume. Previous studies have demonstrated that AIx decreases by an approximate absolute 4% for each 10 b·min^{-1} increment in heart rate.[32] For the current study, heart rate increased by 3 b·min^{-1} during the tilt; the change in AIx after adjusting for heart rate, dropped from -5.3% to -3.4%. The remainder of the response may be explained by the large drop in stroke volume which occurs in response to an orthostatic challenge.[17, 22]

While not yet validated for use with oscillometric devices, the interpretation of future studies would be aided through the addition of the emerging wave reflection magnitude method,[33, 34] which includes decomposition of forward and backward pressure waves. The AIx and wave reflection magnitude are likely to provide complimentary information; AIx provides an integrated summary of the relations among reflected wave timing, amplitude, and ventricular function, whereas reflection magnitude is less likely to be influenced by confounding variables, including heart rate.[35] No known studies have assessed the relative importance of forward and backward traveling pressure waves to central pressure augmentation during an orthostatic challenge.

LIMITATIONS

Firstly, to ascertain the upper limit of reliability for oscillometric derived central hemodynamic parameters, we opted to recruit a homogenous cohort of young, healthy participants. Further study is required to generalize these findings in clinical populations of varying age and health states (e.g., those with cardio-metabolic disorders and risk factors). Second, the cohort was mixed-gender, and the possible confounding influence of menstrual cycle hormones on waveform morphology was not controlled for.

Considering the women were tested over three consecutive days this study limitation is unlikely to have substantially influenced intra-subject variation. While one previous study [36] reported acceptable reliability (ICC >0.80) for resting PWA assessments across the 3 phases of the menstrual cycle, it is unclear whether longer-term autonomic assessments would be equally reliable.

CONCLUSIONS

Findings from this study suggest that, at least in a young healthy cohort, oscillometric recordings of central heomdynamic responses to an orthostatic challenge exceed the criterion for acceptable between-day reliability. Oscillometric PWA presents an opportunity for providing the clinician or clinical research scientist with a practical option for obtaining important hemodynamic information beyond that provided by traditional peripheral blood pressure. In addition to being valid and reliable, the oscillometric PWA device employed in the current study is simple and quick to use (~1 min per recording), does not require extensive training for personnel, and could present opportunities for large-scale use in population-based research and clinical settings.

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None.

CONFLICT(S) OF INTEREST/DISCLOSURE(S)

None.

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TABLES

Table 1. *Mean values for peripheral and central hemodynamic responses to the modified tilt-table test*

Abbreviations: AP, augmentation pressure; AIx, augmentation index; AIx75, AIx normalized to a HR of 75 bpm; ICC; intra-class correlation coefficient; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure

Table 2. *Reliability of peripheral and central hemodynamic responses to the modified tilt-table test*

Abbreviations: AP, augmentation pressure; AIx, augmentation index; AIx75, AIx normalized to a HR of 75 bpm; ICC; intra-class correlation coefficient; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; RC, reliability coefficient; SBP, systolic blood pressure; SEM, standard error of measurement

Table 1.

		Base	Tilt2	Tilt5	Rec2	Rec5	*P*	η^2_p
MAP (mmHg)	X	81	85	85	79	80	<0.001	0.63
	SD	*6*	*7*	*7*	*5*	*6*		
SBP (mm Hg)	X	113	116	116	112	113	<0.001	0.38
	SD	*8*	*8*	*8*	*8*	*8*		
DBP (mm Hg	X	68	73	73	67	68	*<0.001*	0.67
	SD	*5*	*6*	*7*	*5*	*6*		
PP (mm Hg)	X	45	44	43	45	46	0.002	0.20
	SD	*7*	*6*	*6*	*7*	*7*		
cSBP (mmHg)	X	100	103	102	98	99	*<0.001*	0.39
	SD	*7*	*7*	*8*	*7*	*8*		
cDBP (mm Hg)	X	70	73	74	68	68	*<0.001*	0.65
	SD	*5*	*6*	*7*	*5*	*6*		
cPP (mm Hg)	X	31	29	28	31	31	*<0.001*	0.31
	SD	*5*	*4*	*4*	*5*	*5*		
Heart rate (bpm)	X	60	63	63	59	60	*<0.001*	0.58
	SD	*9*	*9*	*9*	*9*	*9*		
AP (mmHg)	X	3.4	1.8	1.7	2.2	2.0	*0.001*	0.21
	SD	*3.2*	*3.9*	*3.1*	*3.1*	*3.3*		
AIx (%)	X	10.5	5.2	5.6	7.0	5.7	*<0.001*	0.23
	SD	*9.3*	*11.8*	*9.8*	*9.8*	*9.3*		
AIx75 (%)	X	3.2	-0.2	0.2	-0.7	-1.1	*<0.001*	0.67
	SD	*11.2*	*14.2*	*12.2*	*11.7*	*11.7*		

Table 2

	Base			Tilt2			Tilt5			Rec2			Rec5		
	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC
MAP (mmHg)	0.88	2.1	5.7	0.85	2.6	7.3	0.87	2.6	7.3	0.73	2.8	7.7	0.82	2.7	7.5
SBP (mm Hg)	0.84	3.0	8.4	0.84	3.1	8.7	0.75	3.9	10.9	0.83	3.2	8.8	0.79	3.6	10.0
DBP (mm Hg	0.85	2.0	5.7	0.84	2.5	6.8	0.87	2.4	6.7	0.73	2.6	7.2	0.78	2.7	7.4
PP (mm Hg)	0.84	2.7	7.6	0.76	2.8	7.9	0.61	3.5	9.7	0.73	3.4	9.4	0.77	3.3	9.0
cSBP (mmHg)	0.87	2.5	7.0	0.85	2.9	7.9	0.80	3.3	9.3	0.84	2.8	7.7	0.82	3.2	8.8
cDBP (mm Hg)	0.83	2.1	5.7	0.83	2.5	7.0	0.86	2.5	7.0	0.72	2.5	7.0	0.78	2.6	7.2
cPP (mm Hg)	0.85	2.0	5.5	0.74	2.0	5.5	0.64	2.2	6.2	0.73	2.4	6.7	0.77	2.2	6.1
Heart rate (bpm)	0.87	3.2	8.8	0.89	3.0	8.3	0.88	3.2	8.7	0.86	3.3	9.0	0.86	3.3	9.2
AP (mmHg)	0.80	1.5	4.1	0.81	1.7	4.7	0.83	1.3	3.5	0.74	1.6	4.4	0.74	1.7	4.6
AIx (%)	0.79	4.3	11.8	0.79	5.4	14.9	0.82	4.2	11.5	0.78	4.6	12.7	0.78	4.4	12.1
AIx75 (%)	0.82	4.8	13.3	0.84	5.7	15.9	0.88	4.2	11.6	0.81	5.0	14.0	0.82	4.9	13.7

- Autonomic nervous system function may be assessed using an orthostatic challenge
- Central hemodynamics can be simply assessed using oscillometric pulse wave analysis
- Oscillometric pulse wave analysis reliably assesses orthostatic challenge responses