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RELIABILITY OF OSCILLOMETRIC CENTRAL BLOOD PRESSURE RESPONSES TO SUBMAXIMAL EXERCISE

Running Title: Central Blood Pressure Response to Exercise

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Abstract

Central blood pressure responses to exercise may provide clinicians with a superior diagnostic and prognostic tool. However, in order to be of value in a clinical setting these assessments must be simple to conduct and reliable. **Objective**: Using oscillometric pulse wave analysis (PWA), determine the upper limit for between-day reliability of central systolic blood pressure (cSBP) and central pressure augmentation (AIx) responses to three progressive stages of submaximal exercise in cohort of young, healthy participants. **Methods:** Fifteen healthy males (25.8 y (SD 5.7), 23.9 kg/m^2 (SD 2.5)) were tested on 3 different mornings in a fasted state, separated by a maximum of 14 days. Central hemodynamic variables were assessed on the left arm. Participants underwent three progressive stages of submaximal cycling at 50W (low), 100W (moderate) and 150W (moderate-hard). **Results:** During low- and moderate-intensity exercise the ICC values for cSBP (0.79-0.80) and AIx (0.81-0.85) indicated excellent reliability (ICC >0.75). For the moderate-hard intensity AIx could not be computed, and the ICC for cSBP was adequate (0.72). **Conclusion:** Findings from this study suggest that, at least in a young health cohort, oscillometric PWA can be used to reliably assess central blood pressure measurements during exercise, up to a moderate intensity. While further work is required to validate these findings in clinical cohorts, these measurements may provide clinicians with a practical option for obtaining important hemodynamic information beyond that provided by resting peripheral blood pressure.

Introduction

The peripheral blood pressure response to submaximal exercise confers greater prognostic strength for future cardiovascular events than standard resting responses [1, 2]. 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 [3]. Therefore, a practical approach for assessing central pressures may provide clinicians and clinical research scientists with a superior diagnostic and prognostic tool. However, in order to be of value, particularly in a clinical setting, the following should be considered: (i) first, it must be determined whether the assessments are precise (reliable) under optimal operating conditions; (ii) the assessments must be relatively simple to conduct.

Central hemodynamic properties may be monitored with accuracy [4] and precision[5] 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 [6, 7]. 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 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 [8, 9] and direct aortic catheter assessments at rest [10-12] and during exercise [13].

In addition to being accurate (valid), an assessment tool must be precise (reliable) under the intended conditions. 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 [14]. While oscillometric PWA devices have been demonstrated to be highly reliable under standard resting conditions [8, 9, 15], to the best of our knowledge only one study has examined the reliability of PWA measurements during submaximal exercise [16]. The aforementioned study [16] 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 systolic blood pressure (cSBP) and central pressure augmentation (AIx) responses to three progressive stages of submaximal exercise in a healthy population.

Methods

Participants

To ascertain the upper limit of validity and reliability for oscillometric derived central hemodynamic parameters, fifteen healthy young men (25.8 y (SD 5.7), 23.9 kg/m^2 (SD 2.5)) were recruited. All participants were asymptomatic of any illnesses and were excluded if they reported any known cardio-metabolic disorders, were taking medications known to affect cardiovascular function, or reported cigarette smoking. Participants provided written informed consent prior to participating in the study, and institutional ethical approved was obtained from the Massey University Human ethics committee.

Experimental Procedure

Prior to 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 reported for testing following an overnight fast, consuming only water, and refraining from caffeine and supplement intake that morning. Participants also avoided strenuous physical activity and alcohol for 24 hours prior to experimentation. The maximum duration between the first and last study visit was 14 days (mean: 5.3 d (SD 4.0)). Baseline measurements were recorded following 15-20 minutes of quiet rest in an upright position. Participants then completed three stages of progressive intensity sub-maximal exercise, each lasting 10 minutes. Following exercise, participants rested in a seated upright position for 30 minutes.

Submaximal Cycle Protocol

Participants were placed on an electronically braked cycle ergometer (Velotron Racer Mate, Seattle, WA) and instructed to cycle at a cadence between 50-60 revolutions per minute (RPM). The exercise intensity for the three progressive stages were 50W (low intensity), 100W (moderate) and 150W (moderate-hard).

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 [17]. Each measurement cycle lasted approximately 60 seconds, consisting of a brachial blood pressure recording and then a 10 second sub-systolic recording. A corresponding aortic pressure waveform was generated using a validated transfer function [12], 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.

A total of 18 recordings were taken per participant, per visit, for a study total of 810 recordings. At baseline, three measurements were taken, separated by three-minute intervals. For each exercise intensity recordings were taken at 4, 6 and 8 minutes during which participants were instructed to minimise movement while positioning and relaxing their left arm in an extended position on the bike handles. Following exercise, recordings were taken every 5 minutes for a period of 30 minutes.

Statistical Analysis

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. 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 reliability, 0.40-0.74 adequate reliability, and <0.40 poor reliability [18]. 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 [18]. 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) [18].

Results

Fifteen healthy young men (25.8 y (SD 5.7), 23.9 kg/m^2 (SD 2.5)) were recruited, and all successfully completed each test day. Table 1 summarises the mean values for central and peripheral hemodynamic variables reported at rest, during and post-exercise, and Table 2 summarizes the reliability data for each variable.

Baseline

The ICC values for MAP, DBP, SBP, and cSBP exceed 0.75, indicating excellent between-day reliability (Table 2). Of the calculated blood pressure variables only SBP-cSBP and DP exhibited excellent reliability. The ICC values for AIx and AIx75 indicate adequate reliability. The RC values indicate that the value that would need to be exceeded between visits for an individual is 6.5 mmHg for cSBP, and 13.3% for AIx75.

Exercise

For Ex2 and Ex3, blood pressure data was successfully recorded for each of the 3 test days for each participant. However, for Ex1 blood pressure data is missing for 1 of the test days for 1 participant (98% success rate). The AIx is automatically normalized to heart rate (AIx75) if the heart

rate is $\leq$110 bpm, which was exceeded for 8 of the subjects for Ex2 and all of the subjects for Ex3. Therefore, while the success rate for AIx75 was 91% for Ex1, it was 44% for Ex2, and 2% for Ex3.

The cSBP and AIx responses to exercise are depicted in Figure 1. With increasing exercise intensity cSBP progressively increased, while AIx marginally increased for Ex1 and then progressively decreased for Ex2 and Ex3. The ICC values indicate excellent reliability for all raw blood pressure parameters, AIx, AIx75, and DP for Ex1. For Ex2 the ICC values indicate excellent reliability for MAP, DBP, cSBP, DP and AIx75. For Ex3, only MAP and DP exhibited excellent reliability.

Recovery

All variables were recorded with a 100% success rate. The cSBP and AIx recovery responses are depicted in Figure 1. Following exercise cSBP rapidly decreased and returned towards baseline, whereas AIx rapidly increased above baseline, and was below baseline by 30 min post-exercise. The ICC values for AUC indicate excellent reliability for all blood pressure variables, DP and AIx75, but adequate reliability for AIx.

Discussion

This study demonstrated that oscillometric PWA can reliably estimate cSBP and AIx75 during exercise, at least during low to moderate exercise intensities. Furthermore, this study also demonstrates that oscillometric PWA can reliably estimate post-exercise cSBP and AIx75 responses, potentially providing an insight into integrative cardiovascular control.

Baseline

The current study demonstrates that cSBP can be recorded with acceptable reliability at rest (ICC: 0.85), consistent with a recent study using the same device (ICC: 0.82) [15]. However, the reliability of systemic arterial wave reflection (ICC: 0.68, AIx75: 0.70) was lower than previously reported (ICC: AIx 0.82, AIx75: 0.84) [15]. The inconsistent finding could be attributed to a smaller

sample size for the current study (15 versus 20 participants). Alternatively, this finding could be attributed to the effect of posture. In the present study participants rested in a seated up-right position, whereas in the previous study [15] participants rested in a supine position. An upright seated position increases heart rate and total peripheral resistance to maintain central blood volume and cerebral perfusion, integrating the cardiovascular system [15]. In addition, changes to mental state may have also contributed to the lower than expected reliability for AIx [19]. While we attempted to tightly control the laboratory environment, and asked participants to remain relatively still and quite, the participants may have experienced pre-exercise arousal and anxiety [20].

Exercise

This study found that during exercise, at least up to a moderate intensity, cSBP can be reliably (ICC: 0.79 -0.80) and simply measured using oscillometric PWA in young healthy participants. These findings are consistent with the findings of Holland et al [16] (ICC: 0.80 vs 0.85), the only other study to the best of our knowledge to investigate whether central hemodynamic responses to exercise can be reliably recorded using PWA. However, while Holland et al [16] utilized a tonometric device, the current study employed a more clinically viable oscillometric device. The equitable findings were evident despite some methodological differences. Holland et al [16] prescribed exercise intensities based on heart rate measurements (50%, 60% and 70%), while the current study utilised an absolute exercise intensity (50W, 100W & 150W) – although respective average heart rate recordings were 47%, 58% and 70% of predicted heart rate max.

The RC for cSBP was 12 mmHg during low-intensity exercise and 11 mmHg during moderate intensity exercise. Therefore, following an intervention 11-12 mmHg is the critical difference that must be exceeded in order for a significant change to occur in at an individual level [18]. While previous studies are limited, and have been limited to peripheral blood pressure responses in cohorts with chronic diseases, changes in peripheral SBP post an exercise intervention has been reported to exceed 11-12 mmHg [21]. For example, in patients with newly diagnosed transient ischemic attack (TIA), 8 weeks exercise intervention decreased the peripheral SBP response to light exercise by 11% (160 mmHg to 143 mmHg) - compared to a 7% reduction for resting blood pressure

[21]. While further work is warranted to determine critical thresholds for cohorts with chronic diseases, such as TIA, when coupled with previous work using peripheral blood pressures [1, 2]our initial findings suggest that cSBP responses to light-moderate intensity exercise may potentially provide clinicians with important diagnostic information beyond that provided by resting peripheral blood pressures.

In the present study AIx75 demonstrated excellent reliability during low (ICC: 0.81) and moderate (ICC: 0.85) exercise intensities. Likewise, Holland et al [16] reported similar responses during low (ICC: 0.90) and moderate (ICC: 0.83) exercise intensities. However, it is important to note that while AIx normalization to heart rate has been validated for heart rates up to 120 b.min. [22], the integrated software limits this normalization to a maximum of 100 b.min. For this reason, only 7 complete data sets were captured for the moderate-intensity exercise stage, and none were collected for the moderate-hard intensity stage. As such, heart rate normalized AIx responses, as an outcome of interest, may be limited to low-intensity exercise. Further, the absolute RC value for the AIx75 response to low-intensity exercise was relatively high at 15%. According of this RC statistic, AIx may be a suitable qualitative outcome in clinical research, but may not be suitable for assessing a given individual in clinical practice.

Recovery

A novel finding of the current study is that cSBP and AIx75 post exercise can be reliably (ICC: 0.90 & 0.82, respectively) recorded using oscillometric PWA. Consistent with previous studies [23-25],cSBP progressively increased during exercise and then rapidly decreased and returned to baseline (Figure 1). Further, AIx increased to above baseline at the lowest exercise intensity, then rapidly increased to above baseline post exercise (Figure 1). While the blood pressure responses have previously been well described [23-25], the AIx requires consideration. To determine the mechanism(s) 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 [26, 27] and function,[28] and the tone of the small vessel beds [29]. Large

artery geometry is unlikely to be notably influenced by acute exercise, though endothelial function

will likely be acutely improved due to increased anterograde shear stress.[30] However, improved

endothelial function would dampen the reflected wave and decrease the AIx [28], which opposes the

increase in AIx seen for the low intensity stage. Therefore, it is likely that this initial exercise response

is linked to the constriction of peripheral small vessel beds, which act to prevent blood from pooling

in the lower extremity and ensure adequate venous return. Likewise, following exercise, to counter the

elevated cardiac output the peripheral small vessels would constrict to prevent venous pooling and

hypotension [31]. Following the recovery of cardiac output, the relaxation of the peripheral small

vessels and the acutely elevated endothelial function would result in dampened wave reflection,

leading to decreased AIx [28].

Clinical Perspective and Future Direction

While further study is required to generalize these findings to clinical populations of varying

age and health states (e.g., those with cardio-metabolic disorders and risk factors), the current findings

indicate potentially promising clinical utility. Peripheral blood pressures responses to submaximal

exercise have been shown to better predict cardiovascular events [1, 2], including one study which

reported that an exaggerated blood pressure response to submaximal exercise was associated with a 2-

to 4-fold risk for new-onset hypertension [1]. However, peripheral blood pressure may not accurately

reflect the effects of peak arterial blood pressure on centrally located organs [3]. Therefore, whether

or not central pressure responses to exercise can better predict future cardiovascular complications

clearly warrants further attention. Further study is also required to determine the clinical utility of

post-exercise central blood pressure and wave reflection responses, which may reflect integrative

cardiovascular control.

Considering that the reliability of baseline AIx was lower than previously reported, it is

recommended that baseline values are recoded in the supine posture and on a separate day to remove

the influence of pre-exercise arousal. Further, reliability is not necessarily synonymous with validity.

One study has validated the generalized transfer function used by AtCor in 30 older (mean: 56 years)

patients during exercise. However, the exercise intensity was relatively light, eliciting a mean change in heart rate from 64 to 79 b.min. Additionally, a pacing study has validated the generalized transfer function for heart rates up to 120 b.min [22]. However, 120 b.min was exceeded by 80% of the participants during moderate-hard intensity exercise and by 20% of the participants during moderate-intensity exercise. As such, caution should be applied if using exercise intensities beyond low-moderate until the generalized transfer function has been validated under high stress conditions.

Lastly, 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 [32, 33], 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 [34]. No known studies have assessed the relative importance of forward and backward traveling pressure waves to central pressure augmentation during and following exercise.

Conclusion

Findings from this study suggest that, at least in a young health cohort, oscillometric PWA devices can reliably assess central blood pressure measurements at rest and up to moderate exercise intensity. In addition to being valid and reliable, the oscillometric PWA device employed in the current study is simple to use and operator-independent. Therefore these devices, when coupled with an exercise paradigm, may potentially provide clinicians with a practical option for obtaining important hemodynamic information beyond that provided by resting peripheral blood pressure.

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Tables and Figures

Figure 1. Aortic pulse pressure waveform.
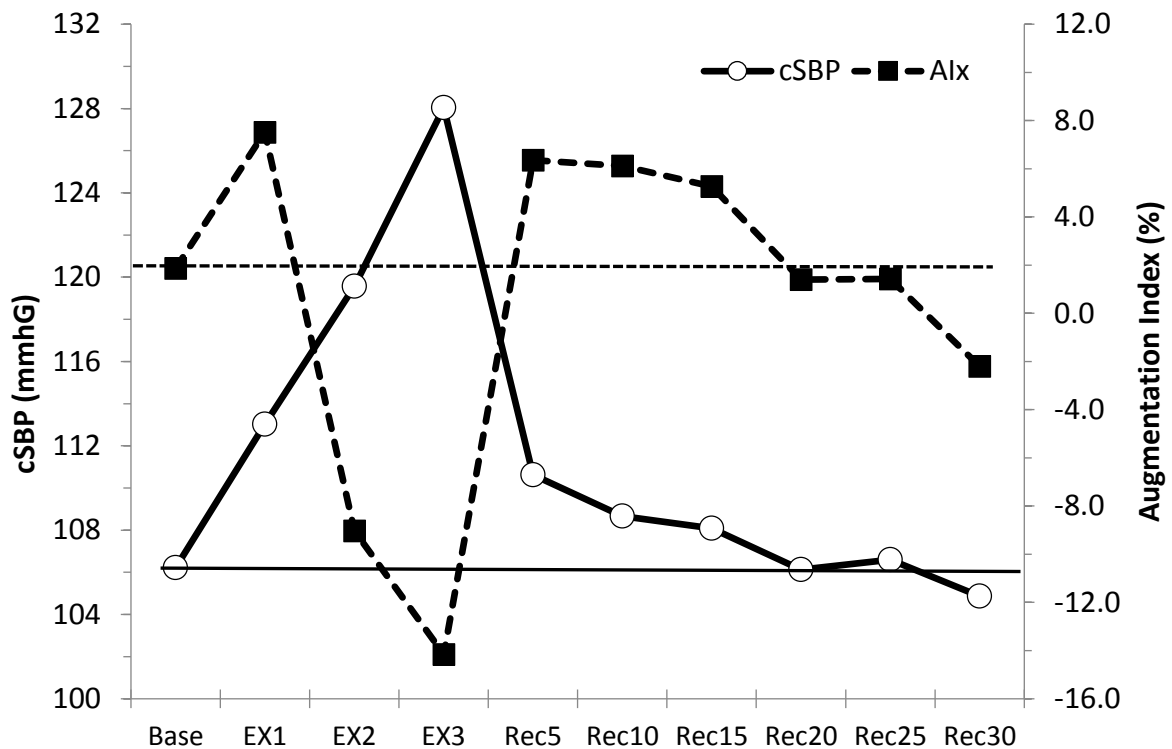
Systolic and diastolic pressures are the peak and trough of the waveform. Augmentation pressure is the additional pressure added to the forward wave by the reflected wave. Augmentation index is defined as the augmentation pressure (AP) as a percentage of pulse pressure (PP).

Figure 2. (A) Central systolic blood pressure (cSBP) and (B) augmentation index (AIx) response during baseline, exercise and recovery. Error bars are standard deviation. The dashed line represents baseline values.

Table 1. Mean values for peripheral and central hemodynamic variables.

		Base	EX1	EX2	EX3	AUC
MAP (mmHg)	X	86	95	102	110	553
	SD	7	9	9	11	47
DBP (mm Hg	X	74	78	82	89	465

	SD	8	8	9	9	42
SBP (mm Hg)	X	122	131	144	155	756
	SD	6	11	12	17	46
cSBP (mmHg)	X	106	113	120	128	657
	SD	6	10	9	11	42
SBP-cSBP (mmHg)	X	16	18	24	27	100
	SD	3	3	5	6	18
pPP (mmHg)	X	49	51	62	66	292
	SD	6	16	9	11	38
cPP (mmHg)	X	32	32	35	35	184
	SD	4	13	5	6	22
PPA (ratio)	X	1.5	1.6	1.8	1.9	9.5
	SD	0.1	0.1	0.1	0.2	0.5
Heart rate (bpm)	X	59	90	111	136	471
	SD	7	7	11	14	54
AP (mmHg)	X	1.3	2.6	-2.7	-7.8	4.1
	SD	2.9	4.3	3.0	5.4	15.2
AIx (%)	X	1.9	7.5	-9.0	-14.2	13.1
	SD	9.6	12.7	11.4	19.1	49.4
AIx75 (%)	X	-5.6	13.2	4.4		18.6
	SD	8.7	12.4	11.8		60.2
DP	X	6323	9996	13319	17418	52325
	SD	1013	1859	1965	2797	8106

Abbreviations: AP, augmentation pressure; AIx, augmentation index; AIx75, AIx normalized to a HR of 75 bpm; AUC, area under the curve; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; DP, double product; MAP, mean arterial pressure; PP, pulse pressure; PPA, pulse pressure amplification; SBP, systolic blood pressure

Table 2. Between-day reliability of peripheral and central hemodynamic variables during and post exercise.

	Base			EX1			EX2			EX3			AUC		
	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC
MAP (mmHg)	0.92	2.05	5.69	0.81	3.82	10.58	0.83	3.62	10.03	0.77	5.13	14.23	0.94	11.7	32.5
DBP (mm Hg)	0.90	2.50	6.92	0.79	3.53	9.77	0.81	3.78	10.47	0.63	5.37	14.88	0.92	11.5	31.9
SBP (mm Hg)	0.82	2.67	7.39	0.77	5.46	15.14	0.72	6.16	17.09	0.70	9.39	26.02	0.89	15.2	42.2
cSBP (mmHg)	0.85	2.34	6.49	0.79	4.46	12.37	0.80	4.00	11.08	0.72	6.09	16.88	0.90	12.9	35.8
SBP-cSBP (mmHg)	0.82	1.60	4.45	0.69	2.63	7.30	0.67	3.39	9.38	0.67	4.45	12.33	0.89	7.2	20.1
pPP (mm Hg)	0.72	3.30	9.16	0.66	9.18	25.45	0.55	6.02	16.67	0.38	8.82	24.46	0.83	15.9	44.1
cPP (mm Hg)	0.62	2.68	7.42	0.69	7.31	20.26	0.57	3.36	9.31	0.35	4.69	13.01	0.76	10.6	29.4
PPA (ratio)	0.58	0.06	0.17	0.52	0.09	0.24	0.66	0.06	0.17	0.72	0.11	0.29	0.78	0.2	0.7
Heart rate (bpm)	0.85	2.94	8.16	0.64	4.50	12.49	0.89	3.45	9.57	0.87	5.22	14.48	0.91	15.8	43.9
AP (mmHg)	0.59	1.82	5.05	0.69	2.40	6.66	0.51	2.12	5.88	0.81	2.37	6.57	0.71	8.2	22.6
AIx (%)	0.68	5.43	15.05	0.77	6.06	16.80	0.66	6.66	18.47	0.58	12.44	34.47	0.69	27.3	75.7
AIx75 (%)	0.70	4.79	13.28	0.81	5.37	14.88	0.85	4.53	12.56	-	-	-	0.82	25.6	70.9
DP	0.88	353	977	0.78	880	2440	0.88	687	1904	0.84	1114	3088	0.93	2201	6102

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