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Title: THE AORTIC-FEMORAL ARTERIAL STIFFNESS GRADIENT DEMONSTRATES GOOD BETWEEN-DAY RELIABILITY

Running Title: aortic-femoral stiffness gradient reliability

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KEY WORDS

Carotid-femoral pulse wave velocity, femoral-ankle pulse wave velocity, pulse wave velocity ratio, repeatability.

INTRODUCTION

In a healthy cardiovascular system, arterial stiffness progressively increases from the elastic aorta to the muscular conduit arteries of the periphery. This *stiffness gradient* permits a gradual attenuation of the forward pressure wave into a smooth consistent blood flow, and prevents the transmission of pulsatile forces to the micro-circulation and end-organs[1]. However, aging and lifestyle factors may disrupt this beneficial phenomena.[2] In particular, the aorta tends to stiffen whereas changes in lower-limb arterial stiffness, for example, are less marked[2] .These differential changes in stiffness lead to a reversal of the stiffness gradient, increasing forward pressure transmission, and contributes to end-organ damage.[1,3] A recent study reported that the stiffness gradient between aortic and lower-limb arterial stiffness provided prognostic information beyond the criterion measure of arterial health, carotid-femoral pulse wave velocity (cfPWV)[4]. This measure provides a promising opportunity to gain meaningful insight into the hemodynamic integration of the vascular system. Though to be of value in clinical and research settings a measurement must confer acceptable precision (reliability). Therefore, the objective of this study was to estimate the between-day reliability of the aortic-femoral arterial stiffness gradient (af-SG).

METHODS

Following institutional ethical approval, twenty-five apparently healthy adults were recruited (15 male, 10 female) with a mean age of 22.6 ± 2.7 years, mean height of 172.2 ± 7.3 cm, mean weight of 71.1 ± 11.2 kg and a mean body mass index of 23.9 ± 2.8 kg/m^2. Participants completed an average of 4.1 ± physical activity sessions per week for an average of 51.3 ± 13.2 minutes. Following 20-min of supine rest, cfPWV and femoral-ankle PWV (faPWV) were determined using the SphygmoCor XCEL (AtCor Medical, Sydney, Australia) following recommended guidelines and as previously described[5] (**Figure 1**), on three separated days, separated by a maximum of 7 days. All PWV measures were recorded in triplicate, with the average of the closest two recordings being used. The af-SG was calculated as faPWV divided by cfPWV, emphasizing the model

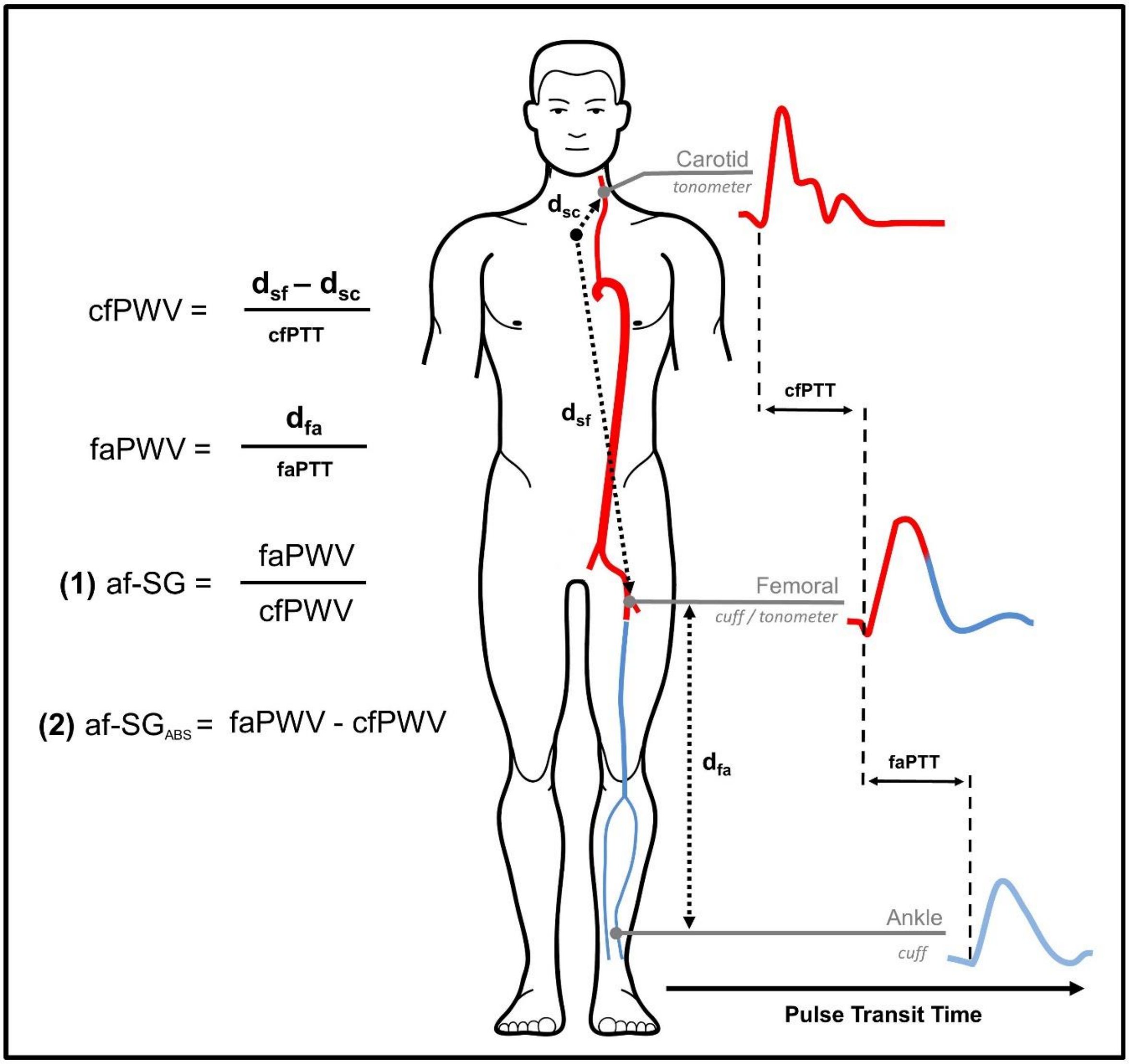

Figure 1 Determination of relative (1) and absolute (2) aortic-femoral arterial stiffness gradient measures from carotid-femoral pulse wave velocity and femoral-ankle pulse wave velocity assessments. ***Abbreviations:*** *cfPWV, carotid-femoral pulse wave velocity; faPWV, femoral-ankle pulse wave velocity, af-SG, relative aortic-femoral stiffness gradient, af-SG_{ABS}, absolute aortic-femoral stiffness gradient; d_{sf}, sternal notch to femoral distance; d_{sc}, sternal notch to carotid distance; d_{fa}, femoral to ankle distance; cfPTT, carotid to femoral pulse-transit time; faPTT, femoral to ankle pulse transit time.*

arterial system, whereby arterial stiffness increases between central and distal arteries[1]. Additionally, we calculated the absolute difference between faPWV and cfPWV segments (af-SG_{ABS})[6].

Measures over the three visits are reported as pooled averages and standard deviations (SD). Between-day reliability was determined by calculating the intra-class correlation coefficient (ICC), standard error of measurement (SEM), and minimal detectable change (MDC). The ICC was calculated as: SDb^2 / [SDb^2+SDw^2], where SDb^2 and SDw^2 are the between and within-subject variance, respectively. The SEM was calculated as: SD* $\sqrt{(1\text{-ICC})}$ and the MDC calculated as: 1.96*SEM*$\sqrt{2}$. MDC% was calculated as (MDC/mean) x 100, where the mean is the mean score of all trials. The ICC was used to interpret the strength of between-day reliability: poor (<0.5), moderate (0.5), good (0.75), and excellent (>0.9)[7].

RESULTS

Reliability estimates for PWV and af-SG measures between-visits are presented in **Table 1**. There was no missing participant data. Although cfPWV and faPWV measures demonstrated greater reliability than both af-SG and af-SG_{ABS}, all PWV measures demonstrated good between-day reliability (ICC: 0.77-0.84). However, whilst cfPWV, faPWV and af-SG demonstrated comparable MDC%, the af-SG_{ABS} demonstrated an MDC% that was more than twice as large as the other arterial stiffness markers.

DISCUSSION

This study is the first to report the between-day reliability of af-SG, a novel marker of systemic arterial health. Our finding of ‘good’ reliability for the af-SG (ICC: 077) contrasts the ‘moderate’ reliability reported by Beltrami[6] for the aortic-brachial stiffness gradient (ICC: 052). This disparity is likely due to the use of different peripheral arterial segments and their inherent differences in measurement error. Individually, our central and peripheral arterial stiffness measures, cfPWV and faPWV, both demonstrated good reliability (ICC: 0.84), consistent with that reported in existing literature[8,9]. In contrast to the good reliability for faPWV, reported reliability estimates for the peripheral arterial stiffness marker used by Beltrami[6], carotid-radial PWV (crPWV), are

Table 1 Between-day reliability of pulse wave velocity and arterial stiffness gradient measures.

	Visit 1		Visit 2		Visit 3		Between visit		Reliability Coefficients							
	Mean	SD	Mean	SD	Mean	SD	MD	SD	ICC (95% CI)		SEM (95% CI)		MDC (95% CI)		MDC% (95% CI)	
cfPWV (m/s)	5.72	0.92	5.51	0.68	5.54	0.72	0.12	0.36	0.84	(0.67- 0.93)	0.29	(0.19- 0.41)	0.79	(0.53- 1.15)	14.19	(9.56- 20.51)
faPWV (m/s)	8.84	1.02	8.59	1.08	8.71	1.03	0.09	0.38	0.84	(0.68- 0.93)	0.38	(0.26- 0.55)	1.05	(0.71- 1.52)	12.08	(8.13- 17.48)
af-SG	1.57	0.22	1.56	0.15	1.59	0.19	-0.01	0.10	0.77	(0.54- 0.89)	0.08	(0.05- 0.11)	0.22	(0.15- 0.31)	13.79	(9.39- 19.54)
af-SG_{ABS} (m/s)	3.13	0.94	3.08	0.81	3.17	0.83	-0.03	0.43	0.78	(0.56- 0.90)	0.36	(0.24- 0.51)	0.99	(0.68- 1.41)	31.78	(21.60- 45.14)
SBP (mmHg)	116	10	117	9	115	10	0.7	3.9	0.83	(0.64- 0.92)	3.73	(2.52- 5.37)	10.34	(6.98- 14.88)	8.93	(6.03- 12.84)
DBP (mmHg)	66	7	66	5	65	6	0.8	3.6	0.74	(0.48- 0.88)	2.72	(1.86- 3.81)	7.53	(5.16- 10.57)	11.33	(7.76- 15.91)
MAP (mmHg)	83	7	83	5	82	7	0.8	3.1	0.80	(0.56- 0.91)	2.55	(1.73- 3.64)	7.07	(4.79- 10.08)	8.53	(5.78- 12.16)

Abbreviations: cfPWV, carotid-femoral pulse-wave velocity; faPWV, femoral-ankle pulse-eave velocity; af-SG, aortic-femoral arterial stiffness gradient, af-SG_{ABS}; absolute aortic-femoral arterial stiffness gradient; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; MD, mean difference; CI, confidence interval; ICC, intra-class correlation coefficient; SEM, standard error of measurement; MDC, minimum detectable change.

moderate (ICC: 0.56-0.66)[6,9]. The greater variability of crPWV compared to faPWV is likely due to the upper-limb arteries being more susceptible to the impact of symapthovagal balance on vascular tone, but also because the shorter carotid to radial pulse wave propagation time inherently increases absolute error[2].

Estimates of MDC permit practitioners to evaluate whether changes in PWV for a given individual are true, or beyond measurement variation. Our study suggests that the af-SG must increase or decrease by 0.22 (unitless) to exceed measurement variation. Importantly, the relative change required for af-SG (13.8%) in the present study was similar to cfPWV (14.2%), a criterion measure. As a final consideration, the arterial stiffness gradient can be calculated as the relative[3,4] or absolute[6] difference between central and peripheral arterial stiffness. Although af-SG_{ABS} demonstrated a comparable ICC, it had an MDC% more than two-fold larger than that of af-SG. This finding is consistent to that reported for the ab-SG[6] and suggests that relative measures of the arterial stiffness gradient are preferred to absolute measures.

Regardless of approach, both the present study and that of Beltrami[6] reported lower reliability for arterial stiffness gradient measures than for the segmental PWV measures from which they were derived. A lower reliability is likely a consequence of the additional random and measurement error, as well as biological variability, that arises from combining PWV measures. Awareness of this phenomena is important, as although cfPWV and faPWV demonstrate good reliability in young healthy adults, their reliability has been reported to be poorer in older adults[10]. Indeed, a limitation of this study is the recruitment of a relatively homogeneous group of young, healthy participants, limiting the overall generalizability of our findings to populations of varying age and health states. However, prior to clinical use, it is imperative to identify whether any inherent variability is caused by the technique itself and not a consequence cardiovascular pathology. A major strength is that this is the first study to determine the between-day reliability of the af-SG, a novel marker of arterial health.

Acceptable reliability of arterial health assessment tools is critical to accurate CVD risk stratification. The current study found that the af-SG, a novel marker of arterial health, demonstrates good reliability. Whilst further research is needed to identify if the reliability is impacted by age or health states, the af-SG is a promising tool that may assist clinicians and epidemiological researchers in the identification and stratification of CVD risk.

CONFLICT OF INTEREST

None.

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FIGURE CAPTIONS

Figure 1. Determination of relative (1) and absolute (2) aortic-femoral arterial stiffness gradient measures from carotid-femoral pulse wave velocity and femoral-ankle pulse wave velocity

assessments. **Abbreviations:** cfPWV, carotid-femoral pulse wave velocity; faPWV, femoral-ankle pulse wave velocity, af-SG, relative aortic-femoral stiffness gradient, af-SG_{ABS}, absolute aortic-femoral stiffness gradient; d_{sf}, sternal notch to femoral distance; d_{sc}, sternal notch to carotid distance; d_{fa}, femoral to ankle distance; cfPTT, carotid to femoral pulse-transit time; faPTT, femoral to ankle pulse transit time.