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Title: Reproducibility of pulse wave velocity and augmentation index derived from non-invasive occlusive oscillometric tonometry analysis in adolescents

Year: 2019

Version: Accepted version (Final draft)

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Please cite the original version:

Haapala, E., Veijalainen, A., Kujala, U., & Finni Juutinen, T. (2019). Reproducibility of pulse wave velocity and augmentation index derived from non-invasive occlusive oscillometric tonometry analysis in adolescents. *Clinical Physiology and Functional Imaging*, 39(1), 22-28.
<https://doi.org/10.1111/cpf.12528>

**Reproducibility of pulse wave velocity and augmentation index
derived from non-invasive occlusive oscillometric tonometry
analysis in adolescents**

Short title: Reproducibility of oscillometric pulse wave analysis in youth

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Word count: 2656

Tables: 3

Figures: 1

ABSTRACT

The aim of this study was to investigate the short-term reproducibility of aortic pulse wave velocity (PWV_{ao}) and augmentation index (AIx%) assessed by the non-invasive oscillometric device. Altogether of 55 (19 boys, 36 girls) adolescents 16–19-years-of-age participated in the study. PWV_{ao} and AIx% were measured during the same laboratory visit at two minute intervals using the Arteriograph™ device. Peak oxygen uptake ($\dot{V}O_{2peak}$) was assessed by the maximal exercise test on a cycle ergometer and body fat percentage by bioelectrical impedance analysis. We studied reproducibility using intraclass correlation coefficients (ICC), coefficient variation with the root-means-square method expressed as percentages (CV%), and 95% limit of agreement (95% LA) and coefficient repeatability of the Bland-Altman plot. ICC for PWV_{ao} was 0.90, CV% 3.7 and the limits of agreement were -0.70 and 0.58 with a coefficient repeatability of 0.65. ICC for AIx% was 0.88, CV% 29.1%, and the limits of agreement were -6.8 and 7.1 with a coefficient repeatability of 6.9. No relevant differences in ICC, CV%, and coefficient repeatability for PWV_{ao} between adolescents with higher or lower $\dot{V}O_{2peak}$ or body fat percentage were observed. For AIx%, ICC was lower, CV% higher, and coefficient repeatability higher in adolescents with higher $\dot{V}O_{2peak}$ or lower body fat percentage than in adolescents with lower $\dot{V}O_{2peak}$ or higher body fat percentage. Short term reproducibility of Arteriograph™ derived PWV_{ao} was relatively good and was not affected by $\dot{V}O_{2peak}$ or adiposity. However, the reproducibility of AIx% was modest especially among adolescents with higher $\dot{V}O_{2peak}$ and lower body fat percentage.

Key words: arterial stiffness, youth, reliability, fitness, adiposity

INTRODUCTION

Arteriosclerosis has its origin in childhood and adolescence (Berenson et al., 1998; McGill et al., 2000). Arterial stiffness, referring to decreased distensibility and reduced buffering capacity of arteries against pulsatile cardiac load (Avolio, 2013), is one of the first signs of arteriosclerosis and arterial stiffening has been observed already in childhood (Veijalainen et al., 2013). Currently, pulse wave velocity (PWV) and augmentation index (AIx) as measures of arterial stiffness has been recognized as an independent risk factor for cardiovascular morbidity and mortality in adults (Vlachopoulos, Aznaouridis, & Stefanadis, 2010; Weber et al., 2004). Therefore, identification and intervening of individuals with increased arterial stiffness should begin already in childhood and adolescence. The American Heart Association also recommend that arterial stiffness should be measured in a standard clinical practice (Townsend et al., 2015).

Arterial stiffness can be measured invasively by placing a catheter into the aorta but it is not a feasible method in clinical practice and especially in children and adolescents invasive methods have ethical constraints (Shirwany & Zou, 2010). PWV between carotid and femoral artery stands for the reference method for non-invasive assessment of arterial stiffness and it can be measured with multiple techniques (Laurent et al., 2006). However, many of these require highly educated assessors and are time consuming making them less feasible in clinical practice and especially in children and adolescents (Boutouyrie, Revera, & Parati, 2009). Arteriograph™, that is an automatic, brachial cuff-based oscillometric device analyzing pulse wave, may be an alternative user friendly and feasible method to assess arterial stiffness in clinical practice (Boutouyrie et al., 2009). A relatively good agreement ($r > 0.9$) between Arteriograph™ derived and invasively measured PWV and central blood pressure has been reported in adults (Horváth et al., 2010; Rossen et al., 2014). Furthermore,

PWV and AIx measured by Arteriograph™ has been found to have acceptable agreement with PWV and AIx measured by other commonly used non-invasive techniques (Jatoi, Mahmud, Bennett, & Feely, 2009).

Cardiorespiratory fitness has been associated inversely and adiposity directly with arterial stiffness in children and adolescents (Cote et al., 2015; Haapala et al., 2017; Veijalainen et al., 2016). However, the evidence on the modifying effect of peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) and body fat percentage on the reproducibility of the measures of arterial stiffness in adolescents is limited (Lowenthal et al., 2014).

Few studies have investigated the reproducibility of pulse wave analysis in youth (Simonetti, Eisenberger, Bergmann, Frey, & Mohaupt, 2008; Veijalainen, Tompuri, Lakka, Laitinen, & Lakka, 2011) and none of them have investigated the reproducibility of the measures of arterial stiffness assessed by the Arteriograph™ device among adolescents. Therefore, we investigated the reproducibility of aortic PWV (PWV_{ao}) and AIx derived from the non-invasive oscillometric pulse wave analysis using the Arteriograph™ device among healthy adolescents aged 16–19 years. We also investigated whether cardiorespiratory fitness or adiposity affect the reproducibility of these measures.

METHODS

Study design and participants

The present analyses are based on the baseline data collected in the Neural Effects of Exercise, Diet, and Sleep (NEEDS) Study (ISRCTN12991197) in 2016–2017. Altogether fifty five 16–19-year-old adolescents (19 boys, 36 girls) were recruited from high schools and vocational schools located in the city of Jyväskylä, Finland. The adolescents were eligible to participate in the study if they were apparently healthy and free of any cardiovascular disease,

untreated or poorly controlled type 1 diabetes, musculoskeletal trauma or disorder that would prohibit the safe participation in the study, or severe depression or anxiety. The protocol of the NEEDS Study was approved by the ethics committee of the University of Jyväskylä, Finland. All participants gave their written informed consent.

Assessment of body size and composition

Body weight, fat mass, and lean body mass were measured twice after of at least three hour fast with accuracy of 100 g and body fat percentage was estimated by bioelectrical impedance analysis by InBody 720 device (Biospace Co. Ltd. Seoul, South Korea). Stature was measured twice in the Frankfurt plane without shoes by a wall-mounted stadiometer with the accuracy of 1 mm. The mean of these two values were used in the analyses. Upper arm circumference was measured twice from the right arm with accuracy of 1 mm.

Assessment of aortic pulse wave velocity and augmentation index

PWVao and AIx were measured twice during a single laboratory visit. The protocol included a rest of ten minutes in a supine position and the oscillometric pulse wave analysis was performed twice from the right upper arm using Arteriograph™ device (Arteriograph; TensioMed Ltd., Budapest, Hungary) in the supine position at 2-minute intervals. The device measures automatically resting heart rate, systolic and diastolic blood pressure, pulse pressure, PWVao, and AIx. The device first measures automatically the actual systolic blood pressure and subsequently inflates the cuff 35 mmHg above measured systolic blood pressure and measures the oscillations in the brachial artery. The signals were passed on to a tablet computer, recorded, and analyzed as pulse waves. PWVao (meters/second) was calculated from the time difference between the first systolic wave (direct) and the second systolic wave (reflected) and was related to the distance from jugulum to symphysis. AIx% was computed

from the pressure difference between the first (P1) and second (P2) wave in relation to the pulse pressure by the formula ($AIx\% = [(P2-P1)/\text{pulse pressure}] \times 100$).

Assessment of cardiorespiratory fitness

Cardiorespiratory fitness was assessed by a maximal cardiopulmonary exercise test on an electromagnetically braked Monark 929E cycle ergometer (Monark Exercise Ab, Sweden). The protocol included 2-minute resting period sitting on an ergometer, a 2-minute warm-up without resistance, and an incremental exercise period with increase of workload by 1 W/3 seconds until voluntary exhaustion. The participants were asked to keep the cadence of 70–80 during the test. The test was terminated when the participant was unable to keep the cadence of 50 or required to stop. Participants were verbally encouraged to exercise until voluntary exhaustion.

Respiratory gas exchange was assessed directly by breath-by-breath method using calibrated metabolic cart (Vmax Encore, VIASYS ltd. USA) during the entire protocol and was averaged over 20-second periods. We defined peak cardiorespiratory capacity as the highest $\dot{V}O_2$ achieved in the exercise test ($\dot{V}O_{2\text{peak}}$) recorded during the last minute of the exercise test. Heart rate during the exercise test was recorded using Polar H7 heart rate sensor (Polar Electro, Kempele, Finland).

The exercise test was considered maximal if the primary and secondary objective and subjective criteria indicated maximal effort and maximal cardiorespiratory capacity (i.e. primary: a plateau of $\dot{V}O_2$ regardless of increasing workload, secondary: heart rate $>85\%$ of predicted, respiratory exchange ratio >1.05 , or perceived exertion in Borg 6–20 scale ≥ 18 , flushing, and sweating), and the exercise physiologist (EAH) supervising the exercise test considered the test maximal. To obtain physiologically relevant measure of cardiorespiratory fitness and to control for body size, we defined cardiorespiratory fitness as $\dot{V}O_{2\text{peak}}$ ml x kg

lean body mass⁻¹ x min⁻¹ (Graves et al., 2013). This approach was able to remove the association of $\dot{V}O_{2peak}$ with lean body mass ($r=0.06$, $p=0.660$) indicating the validity in scaling cardiorespiratory fitness. We also reported $\dot{V}O_{2peak}$ ml x kg body mass⁻¹ x min⁻¹ to allow comparison between studies.

Other assessment

Pubertal status was assessed according to self-reported testicular development in boys and breast development in girls on the basis of the 5-stage criteria described by Tanner (Taylor et al., 2001).

Statistical methods

We investigated the differences in PWV_{ao}, AIx%, $\dot{V}O_{2peak}$, and the measures of body composition between sexes by Student's t -test, Mann-Whitney U-test, or Chi Square test using the JASP Statistical software 0.8.2.0 (University of Amsterdam, the Netherlands). We studied reproducibility using intraclass correlation coefficients (ICC) and their 95% confidence intervals (CI), coefficient variation with the root-means-square method expressed as percentages (CV%), paired samples t-test or Wilcoxon test, and 95% limit of agreement (95% LA), coefficient repeatability, and line of equality with 95% CI of the Bland-Altman plot using the MedCalc Statistical Software version 17.8.6 (MedCalc Software bvba, Ostend, Belgium). We also investigated whether the agreement between two measurements in PWV_{ao} and AIx were proportionality related to the sample mean using the regression line of difference in the Bland-Altman plot. We investigated reproducibility of PWV_{ao} and AIx% among adolescents with \geq sex-specific median and $<$ sex-specific median of cardiorespiratory fitness and body fat percentage. The median of $\dot{V}O_{2peak}$ was 110 and 106 ml x kg lean body mass⁻¹ x min⁻¹ in boys and girls, respectively, and the median of body fat percentage was 11.2% in boys and 23.5% in girls.

RESULTS

Basic characteristics

Boys were taller, heavier, and had lower body fat percentage and more lean body mass than girls (Table 1). Boys also had higher absolute and body mass scaled $\dot{V}O_{\text{peak}}$, lower resting heart rate, higher systolic blood pressure, and a smaller AIx% than girls. We observed no difference in resting heart rate between the measurements but systolic blood pressure was lower in the second than in the first measurement ($p < 0.001$).

Reproducibility of aortic pulse wave velocity and augmentation index

ICC for PWVao was 0.90 (95% CI=0.84 to 0.94), CV% 3.7 (95% CI = 2.9 to 4.4) (Table 2), and the limits of agreement were -0.70 and 0.58 with a coefficient repeatability of 0.65 (95% CI=0.4 to 0.8) (Figure 1). The regression slope coefficient for the proportionality of difference was 0.066 (95% CI=-0.059 to 0.190, $p=0.296$). There was no statistically significant difference between the first and the second measurement in the PWVao or AIx% based on the Wilcoxon test (Table 2).

ICC for AIx% was 0.88 (95% CI=0.80 to 0.93), CV% 29.1% (95% CI=10.2 to 39.9) (Table 2), and the limits of agreement were -6.8 and 7.1 with a coefficient repeatability of 6.9 (95% CI=5.8 to 8.5) (Figure 1). The regression slope coefficient for proportionality of difference was not statistically significant (slope coefficient = 0.068, 95% CI=-0.061 to 0.211, $p=0.272$). There was no statistically significant difference between the first and the second measurement in the Wilcoxon test (Table 2). When boys and girls were analyzed separately, the results remained similar.

Reproducibility of aortic pulse wave velocity and augmentation index in relation to cardiorespiratory fitness and adiposity

No relevant differences in ICC, CV% and coefficient repeatability for PWVao between adolescents with higher cardiorespiratory fitness and those with lower cardiorespiratory fitness were observed (Table 3). For AIx%, ICC was lower, CV% higher, and coefficient repeatability higher in adolescents with higher cardiorespiratory fitness than in adolescents with lower cardiorespiratory fitness (Table 3).

ICC for PWVao was slightly lower in adolescents with lower body fat percentage than in adolescents with higher body fat percentage (Table 3). The Wilcoxon test also suggested a marginally significant difference in PWVao between the first and the second measurement among adolescents with lower body fat percentage but not among adolescents with higher body fat percentage. For AIx%, ICC was higher and CV% and coefficient repeatability were lower in adolescents with higher body fat percentage than those with lower body fat percentage (Table 3).

DISCUSSION

We found that short term reproducibility of PWVao was better than that of AIx%. We also found no marked differences in short term reproducibility for PWVao between adolescents varying levels of cardiorespiratory fitness and body fat percentage. However, we found weaker reproducibility of AIx% among adolescents with higher cardiorespiratory fitness or lower body fat percentage than among those with lower cardiorespiratory fitness or higher body fat percentage.

Few studies have investigated reproducibility of pulse wave analysis in children or adolescents and none of them have used Arteriograph™, a simple measurement procedure from brachial artery level. Simonetti et al. (Simonetti et al., 2008) found a CV of 7.5% of PWVao, measured by ultrasound probe between carotid and femoral artery during one laboratory visit, in children and adolescents aged 8–15, suggesting a worse reproducibility of

PWVao than was observed in our study. They also studied reproducibility of Stiffness Index measured by finger pulse wave analysis and found a CV of 4.0% that is comparable to our observations. Another study in children that also utilized finger pulse wave analysis in two laboratory visits separated by 5 to 14 days observed a worse reproducibility than in our study, with a CV of 6.3% (Veijalainen et al., 2011).

Reproducibility of AIx has also been studied rarely in children and adolescents and these studies have assessed AIx from radial artery level (Donald et al., 2014; Lowenthal et al., 2014). Previous studies have showed markedly better reproducibility with a CV of 4.1% in children and adolescents aged 7–17 years (Donald et al., 2014) or a slightly poorer reproducibility with ICC of 0.78 in children and adolescents aged 10–19 years (Lowenthal et al., 2014).

These differences may be due to different methods and differences in age of the study samples but also differences in cardiorespiratory fitness and adiposity among study participants. None of the previous studies have reported the level of cardiorespiratory fitness or the modifying effects of cardiorespiratory fitness on reproducibility of or PWVao or AIx in children and adolescents. In contrast to our observations, the results of one study in children and adolescents found a positive correlation of body mass index to the intervisit difference in AIx (Lowenthal et al., 2014). One reason for this contrasting finding may be due to differences in the assessment of adiposity. Other reasons for these heterogeneous results may include the varying method assessing reproducibility and large variability of age groups studied. Taken together, although Arteriograph™-derived PWVao and AIx have been found to have relatively good agreement with those of other non-invasive devices (Jatoi et al., 2009), the evidence also suggest that different devices cannot be used interchangeably to estimate arterial stiffness. Therefore, in clinical practice and standard health care it is recommended to use same technique to follow-up changes in arterial stiffness.

We found that the reproducibility of PWV was better than that of AIx%. This observation may be due to the fact that PWVao is more dependent of structure of artery wall whereas AIx is not only a marker of arterial stiffness but also arterial tone, reflecting ventricular ejection and wave reflection and thus the pulse impedance mismatch between large conduit arteries and peripheral arteries, which is more variable by nature (London et al., 2001; Townsend et al., 2015). We also observed a positive correlation between change in AIx% and change in systolic blood pressure between measurements ($r=0.304$, $p=0.026$), which might reflect a change in vascular tone (Fahim, 2003). Cardiorespiratory fitness and adiposity has only minor effects on the reproducibility of PWVao. However, we observed a poorer reproducibility of AIx% between in adolescents with higher levels of cardiorespiratory fitness and lower body fat percentage than in other adolescents. An explanation for this finding may be that exercise training and adiposity affect particularly vascular tone (Fernandez-Alfonso, 2004; Green, Spence, Halliwill, Cable, & Thijssen, 2011).

The strengths of this study include the reproducibility analysis of the measures of arterial stiffness among adolescents with higher and lower levels of $\dot{V}O_{peak}$ and adiposity. We also investigated the reproducibility of PWVao and AIx among adolescents with relatively homogenous sample regarding age and pubertal status. Furthermore, in contrast to some previous studies (Veijalainen et al., 2011), we had no missing data because of incomplete pulse wave analyses suggesting that the Arteriograph™ device is feasible method to assess arterial stiffness in youth. Adolescents in our study sample had relatively high $\dot{V}O_{peak}$, which may have altered the results. Furthermore, we investigated only short term reproducibility within a single laboratory visit and therefore long-term reproducibility and day-to-day variability of Arteriograph™-derived PWVao and AIx% remains to be elucidated.

In conclusion, we found that the short term reproducibility of Arteriograph™ derived PWVao was relatively good and was not affected by cardiorespiratory fitness or adiposity. However,

the reproducibility of AIx% was modest especially among adolescents with higher cardiorespiratory fitness and lower body fat percentage. These results suggest that PWVao derived from the Arteriograph™ device can be utilized in follow-up and intervention studies investigating arterial stiffness. The results of AIx% in studies should be interpreted cautiously as its moderate reproducibility and being influenced by various factors.

ACKNOWLEDGMENTS

This study has financially been supported by the Jenny and Antti Wihuri Foundation and the Päivikki and Sakari Sohlberg foundation

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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FIGURE CAPTION

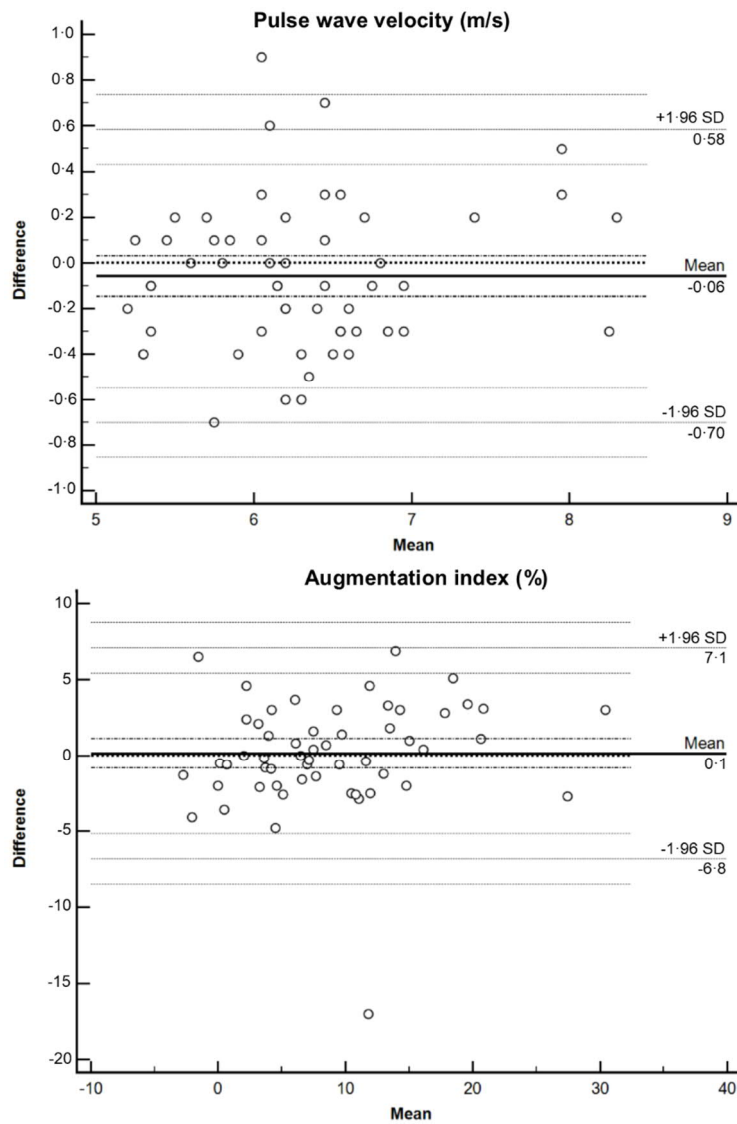


Figure 1. Bland–Altman plots of aortic pulse wave velocity and augmentation index with line of equality, mean difference (95% confidence intervals), and limits of agreement (95% confidence intervals). m/s = meters per second.

Table 1. Characteristics of participants

	All (N=55)	Boys (N=19)	Girls (N=36)	P for the difference
Age (years)*	17.3 (16.8–18.3)	17.2 (16.7–18.6)	17.3 (16.8–17.9)	0.866
Pubertal status (%) Stages 4–5	82.4	84.2	82.9	0.575
Stature (cm)	171.3 (7.6)	178.2 (5.6)	167.6 (5.8)	<0.001
Body weight (kg)	65.2 (9.7)	70.7 (9.3)	62.3 (8.6)	0.001
Fat mass (kg)*	12.8 (8.9–17.5)	7.8 (5.7–15.6)	14.5 (11.7–19.5)	<0.001
Body fat percentage (%)	20.8 (8.4)	12.9 (6.2)	24.9 (6.1)	<0.001
Fat mass index (kg/m ²)*	4.5 (3.2–6.5)	2.4 (1.7–4.9)	5.0 (4.1–6.8)	<0.001
Lean body mass (kg)	28.7 (5.2)	34.7 (3.2)	25.6 (2.6)	0.024
$\dot{V}O_{peak}$ (mL x min ⁻¹)	3038 (684)	3741 (492)	2667 (432)	<0.001
$\dot{V}O_{peak}$ (mL x kg lean mass ⁻¹ x min ⁻¹)	105.7 (13.5)	108 (15.2)	104 (12.5)	0.265
$\dot{V}O_{peak}$ (mL x kg body mass ⁻¹ x min ⁻¹)	46.9 (9.6)	53.8 (10.0)	43.2 (7.2)	<0.001
Resting heart rate (beats/min)				
First measurement	63.4 (9.0)	60.6 (8.8)	64.8 (8.8)	0.095
Second measurement	63.4 (11.9)	58.1 (15.6)	66.1 (8.4)	0.015
Resting systolic blood pressure (mmHg)				
First measurement	119.8 (10.3)	126.5 (9.3)	116.3 (9.0)	<0.001
Second measurement	116.4 (9.9)	121.8 (8.4)	113.5 (9.6)	0.003
Aortic PWV (m/s)*				
First measurement	6.2 (5.8–6.6)	6.4 (5.7–6.8)	6.1 (5.8–6.5)	0.435
Second measurement	6.3 (5.8–6.7)	6.3 (5.6–7.0)	6.3 (5.8–6.7)	0.529
Augmentation index (%)*				
First measurement	7.7 (3.5–14.2)	5.8 (2.1–8.3)	9.6 (3.7–15.7)	0.032
Second measurement	7.4 (3.7–12.8)	5.7 (1.0–7.8)	11.7 (4.4–15.5)	0.007

The data are mean (standard deviations), median (interquartile range)*, or percentages and the P-values from the t-test for independent samples for continuous variables with normal distribution and Mann-Whitney U-test for continuous variables with skewed distribution, or Chi-square for categorical variables. LM=lean body mass

Table 2. Reproducibility of aortic Pulse wave velocity and Augmentation index 55 adolescents.

	ICC (95% CI)	CV%	95% LA	CR	p-value from Wilcoxon test
Aortic Pulse wave velocity (m/s)	0.90 (95% CI=0.84 to 0.94)	3.7% (95% CI = 2.9 to 4.4)	-0.70 0.58	0.6 (0.5 to 0.8)	0.080
Augmentation index (%)	0.88 (95% CI=0.80 to 0.93)	29.1% (95% CI=10.2 to 39.9)	-6.8 7.1	6.9 (5.8 to 8.5)	0.428

ICC = intraclass correlation coefficient; 95% CI = 95% confidence interval; CV% = coefficient variation, 95% LA = 95% limits of agreement; CR = coefficient of repeatability

Table 3. Reproducibility of aortic Pulse wave velocity and Augmentation index (Aix%) among 55 adolescents with higher and lower cardiorespiratory fitness and body fat percentage.

	ICC (95% CI)	CV%	95% LA	CR	p	ICC (95% CI)	CV%	95% LA	CR	p	
		≥ median of cardiorespiratory fitness					< median of cardiorespiratory fitness				
PWV _{ao}	0.90 (0.80 to 0.95)	3.47 (2.18 to 4.39)	-0.64	0.6 (0.5 to 0.8)	0.189	0.89 (0.8 to 0.95)	4.0 (2.67 to 5.0)	-0.77	0.7 (0.6 to 1.0)	0.223	
Aix%	0.82 (0.64 to 0.91)	36.5 (0.0 to 52.9)	0.54	8.1 (6.4 to 10.9)	0.829	0.94 (0.88 to 0.97)	18.7 (10.5 to 24.3)	0-64	5.4 (4.3 to 7.4)	0.156	
			-8.7					-4.4			
			7.6					6.1			
		≥ median of body fat percentage					< median of body fat percentage				
PWV _{ao}	0.92 (0.83 to 0.96)	3.7 (2.6 to 4.5)	-0.70	0.66 (0.5 to 0.9)	0.511	0.83 (0.67 to 0.92)	3.8 (2.3 to 4.9)	-0.71	0.64 (0.5 to 0.9)	0.07	
Aix%	0.95 (0.89 to 0.98)	22.76 (6.76 to 31.5)	0.64	4.5 (3.6 to 6.1)	0.276	0.78 (0.58 to 0.89)	39.2 (8.9 to 54.7)	0.54	8.6 (6.8 to 11.6)	0.909	
			-4.2					-8.8			
			4.9					8.7			

ICC = intraclass correlation coefficient; 95% CI = 95% confidence interval; CV% = coefficient variation, 95% LA = 95% limits of agreement; CR = coefficient of repeatability; median of $\dot{V}O_{2peak}$ was 110 and 106 ml x kg lean body mass⁻¹ x min⁻¹ in boys and girls, respectively. Median of body fat percentage was 11.2% in boys and 23.5% in girls.