TITLE PAGE

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The acute effect of maximal exercise on central and peripheral arterial stiffness indices and hemodynamics in children and adults

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Arterial responses to acute maximal exercise

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Abbreviations:

ΔMAP   change in mean arterial pressure

ΔPP   change in pulse pressure

PWV   pulse wave velocity

ABSTRACT

PURPOSE: This study compared the effects of a bout of maximal running exercise on arterial stiffness in children and adults.

METHODS: Right carotid blood pressure and artery stiffness indices measured by pulse wave velocity (PWV), compliance and distensibility coefficients, stiffness index a and β (echotracking), and contralateral carotid blood pressure, upper and lower limb and central/aortic PWV (applanation tonometry) were taken at rest and 10 min following a bout of a maximal treadmill run in 34 children (7.38±0.38 years) and 45 young adults (25.22±0.91 years) having a similar aerobic potential. 2x2 repeated measures analysis of variance and covariance were used to detect differences with exercise between groups.

RESULTS: Carotid pulse pressure (PP; η^2=0.394) increased more in adults after exercise (p<0.05). Compliance (η^2=0.385) decreased in particular in adults and in those with high changes in distending pressure, similarly to stiffness index a and β. Carotid PWV increased more in adults and was related to local changes in PP but not mean arterial pressure (MAP). Stiffness in the lower limb decreased (η^2=0.115) but apparently only in those with small MAP changes (η^2=0.111). No significant exercise or group interaction effects were found when variables were adjusted to height.

CONCLUSIONS: An acute bout of maximal exercise can alter arterial stiffness and hemodynamics in the carotid artery and within the active muscle beds. Arterial stiffness and hemodynamic response to metabolic demands during exercise in children simply reflects their smaller body size and may not indicate a particular physiologic difference compared to adults.

Key Words:

Arterial compliance; pulse wave velocity; rest and recovery; height; distending pressure

INTRODUCTION

Large artery distensibility is physiologically important for cardiovascular efficiency. Distensible large arteries reduce impedance to systolic ejection and cardiac work, slows pulse wave velocity (PWV) so that the return of reflected pressure waves is delayed until after aortic valve closure, and favors coronary perfusion during diastole (Naka et al. 2003). Conversely, stiffening of the central arteries results in an elevation in systolic blood pressure (SBP) and a lowering of diastolic blood pressure (DBP) which, in turn, increases left ventricular afterload and alters coronary artery perfusion (Hamilton et al. 2007). These changes may result in left ventricular hypertrophy (Girerd et al. 1991) and increased fatigue of arterial wall tissues (Blacher et al. 1999), all of which substantially increase the risk of cardiovascular events (McEniery 2006).

Carotid stiffness increases throughout childhood and adolescence (Lenard et al. 2004; Senzaki et al. 2002). Interestingly, aortic capacitance also increases during this period, primarily as a function of increases in arterial size with age (Ahimastos et al. 2003; Senzaki et al. 2002). This appears to offset the increase in wall stiffness, preventing an increase in afterload that could adversely affect ventricular performance (Kingwell 2000; Kingwell et al. 1997; O'Rourke and Safar 2005).

The acute effects of exercise on both peripheral and central arterial distensibility in healthy adults have been examined (Heffernan et al. 2007d; Kingwell et al. 1997; Naka et al. 2003; Ranadive et al. 2012; Sugawara et al. 2004; Sugawara et al. 2003; Yan et al. 2014). Both acute aerobic and resistance exercise reduce arterial stiffness in the exercised limb, despite having no effect on arterial properties of

the non-exercised limb (Heffernan et al. 2006; Sugawara et al. 2003). As for central stiffness, it has been originally suggested that positive alterations were observed with aerobic exercise training whereas potentially negative alterations occur following resistance exercise training (Heffernan et al. 2007d). However, the varying exercise protocols used in these studies including incremental exercise to exhaustion (Heffernan et al. 2007d; Naka et al. 2003; Ranadive et al. 2012; Yan et al. 2014), moderate intensity continuous exercise (Kingwell et al. 1997; Mc Clean et al. 2007), brief low intensity exercise (Sugawara et al. 2004; Sugawara et al. 2003) and supramaximal exercise (Rakobowchuk et al. 2009; Rossow et al. 2010) showed that the effects of exercise in central stiffness are dependent on the intensity of exercise as well. High-intensity sprint exercise for instance, increases central artery stiffness (Rakobowchuk et al. 2009) similarly to the response following acute resistance exercise (DeVan et al. 2005; Heffernan et al. 2007d).

Acute increases in artery distensibility may be mechanistically linked to the increased arterial distensibility observed with chronic exercise training (Naka et al. 2003). To date no study has determined whether the physiological and morphological specificities of pre-pubertal children have an impact on their vascular responses to acute maximal exercise. It is conceivable that examination of the response of the arteries to physical stress, such as acute intense exercise, could offer additional critical information about vascular differences between healthy age groups, with possible clinical implications also for the understanding of the "unhealthy" child response. If changes in arterial stiffness indices following high-intensity exercise in adults are related to changes in blood pressure (Rossow et al. 2010), the arterial response may be different in children because they have lower SBP during maximal exercise compared to adults (Nottin et al. 2002). Whether the change in arterial stiffness indices following high-intensity exercise in children are a function of central or peripheral distending pressure is also unknown. Considering that central blood pressure may be different than standard brachial blood pressure (DeVan et al. 2005; Heffernan et al. 2008), it is essential that an appropriate central blood pressure is obtained.

The purpose of this study was to compare the effects of a bout of maximal running exercise on local, central and peripheral arterial stiffness indices and hemodynamic response in children and young adults, controlling for exercise induced changes (Δ) in distending pressure and body size differences.

MATERIALS AND METHODS

Thirty-four children 5 to 10 years of age and 45 young adults 18 to 36 years of age participated in this study between January 2013 and June 2014. All participants were healthy, free from cardiovascular, respiratory and metabolic diseases and none was considered to be a trained athlete. None were taking any medications known to affect heart rate or blood pressure. The Ethics Committee of the Faculty of Human Kinetics - University of Lisbon approved the study. Children provided assent for their participation and informed consent was obtained from their legal guardians. Informed consent was obtained from all adult participants.

Experimental design

Participants reported to the laboratory in the morning for a single day of testing, 3 h postprandial fasting as a minimum, and rested quietly for at least 15 min in the supine position before measurement. Adult participants were asked to refrain from vigorous activity and from alcohol or caffeine intake over the day before the protocol. The study was conducted with room temperature ranging from 22 to 25 °C.

The sequence of measures was as follows: (1) total-body scans performed by dual-energy x-ray absorptiometry, (2) right brachial artery oscillometry, (3) right carotid artery stiffness measurement by means of echotracking, (4) contralateral brachial artery oscillometry, (5) arterial stiffness by applanation tonometry, (6) peak oxygen uptake exercise testing, and (7) recovery cardiovascular

measurements (2-5) within a 10 min immediately following a 3 min recovery protocol. This time point was chosen because previous research has shown that exercise substantially alters arterial stiffness 10 min following cessation of exercise (Heffernan et al. 2007b; Naka et al. 2003).

Anthropometry

Standing and sitting height were measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg on a scale with an attached stadiometer (model 770, Seca; Hamburg, Deutschland) wearing minimal clothing and no shoes. Leg length in children was calculated by subtracting sitting height from standing height.

Maturity

Maturity offset, that is, time before or after peak height velocity, was predicted in children 9-10 years of age with the equation of Mirwald et al (2002) using the following variables: leg length, sitting height, age, weight, and height.

Dual-energy X-ray absorptiometry

Total-body scans were performed by dual-energy x-ray absorptiometry and analyzed using an extended analysis program for body composition (Hologic Explorer-W, fan-beam densitometer, software QDR for windows version 12.4, Waltham, Massachusetts, USA) to determine whole body fat mass and lean soft tissue. The same technician positioned the subjects, performed the scans and completed the scan analysis according to the operator's manual using the standard analysis protocol. Quality control with spine phantom was made every morning, and with step phantom every week.

Brachial blood pressure

The right and left brachial SBP and DBP were measured following at least 15 minutes with the participants in the supine position using an automated oscillometric cuff (HEM-907-E, Omron, Tokyo, Japan). Two measurements were taken and if these values deviated by >5 mmHg, a third measurement was performed. The average of the two closest values was used. The mean arterial pressure (MAP) was calculated with the formula [DBP + 1/3 (SBP- DBP)].

Right carotid artery stiffness indices and blood pressure by vascular ultrasound

The right carotid artery stiffness measurement was conducted with the patient in the supine position after at least a 15 min resting period before and within 10 min immediately after the maximal exercise test. We used an ultrasound scanner equipped with a linear 13 MHz probe (MyLab One, Esaote, Italy) with Quality Arterial Stiffness technology, based on radio frequency signal in a common carotid artery segment ~1 cm before the bifurcation. The right carotid pressure waveform was calibrated to right brachial diastolic and MAP by iteratively changing the wall rigidity coefficient. This allows the calculation of carotid stiffness indices: PWV (m/s), distensibility coefficient (1/KPa), compliance coefficient (mm2/kPa), stiffness index a and β (Supplement S1).

 The coefficients of variation for repeated measurements in our laboratory for carotid PWV, distensibility, compliance, stiffness index a and β and carotid SBP are: 1.89%, 0%, 2.87%, 3.70%, 3.18% and 2.15%, respectively.

Contralateral pulse wave velocity and carotid blood pressure by applanation tonometry

PWV was measured by applanation tonometry immediately after ultrasound imaging. A single operator located the carotid, femoral, radial and distal posterial tibial arteries on the left side of the body and marked the point for capturing the corresponding pressure curves with two specific pressure sensitive transducers. The distance between the carotid and femoral, radial and distal posterial tibial arteries was measured directly and entered into the Complior Analyse software (ALAM Medical, Paris, France). Left brachial blood pressure was measured and entered into the software, and then signal acquisition was launched (Supplement S2) Values obtained from the carotid to femoral artery (aortic), carotid to radial artery (upper limb) and carotid to distal posterior tibial artery (lower limb) were taken as indices of central/aortic, upper and lower limb arterial stiffness, respectively. The quality of the PWV records was immediately evaluated by a second observer with considerable experience in this methodology. Whenever a continuous decrease before the sharp systolic upstroke was not clearly seen or tolerance was above 5ms, a second measure was taken.

Carotid SBP from the Complior Analyser was obtained from left carotid traces acquired during the PWV assessment. The waveforms were averaged and the mean values were extracted from 15 s window of acquisition. The carotid waveforms were calibrated with left brachial MAP, measured immediately before the acquisition.

The coefficients of variation for repeated measurements in our laboratory for aortic, upper limb and lower limb PWV and central/aortic SBP of young adult participants are: 2.95%, 9.10% and 4.11% and 2.45%, respectively.

Maximal Exercise Test

Peak oxygen capacity was determined using an individualized protocol on a motorized treadmill to exhaustion. The protocol started with a warm-up during 3 min in children and 5 min in adults, followed by 1 mph increments every 2 min for 4 min, after which 2.5% grade increments were added every minute until exhaustion. The speed of the treadmill in stage 1 was selected individually based on the participant's level of mobility and stride length. The protocol ended with a 1 min active recovery plus 2 min of passive recovery in the sitting position. Children had a treadmill training session before the test day.

Inspired and expired gases were continuously analysed, breath-by-breath, through a portable gas analyser (K4b^2, Cosmed, Rome, Italy) (Supplement S3). VO2peak was defined as the highest 20-second value attained in the last minute of effort provided 2 of the following criteria were met: (1) Attaining ~90% of predicted maximal heart rate (220-age); (2) Plateau in VO2 with an increase in workload (<2.0 mL.kg^{-1}.min^{-1}); (3) Rating of perceived exertion of $\geq$ 8 for children (1-10) or $\geq$ 18 for adults (6-20) and; (4) Respiratory exchange ratio of $\geq$ 1.05 for children and $\geq$ 1.1 for adults; 5) subjective judgment by the observer that the participant could no longer continue, even after encouragement.

Statistical analyses

All values were expressed as mean ± standard error of the mean. Normality was verified using the Shapiro-Wilk test in each variable. Baseline group characteristics were compared with one-way ANOVA. Repeated measures analysis of variance (ANOVA) was used to test for possible exercise and group interaction effects in non-adjusted and ΔMAP- or ΔPP and height- adjusted arterial stiffness indices. Additionally, repeated measures ANOVA was also used explore the interaction effects between exercise and ΔMAP (small/high), exercise and ΔPP (small/high) and exercise and height (small/high), when found significant in respective adjusted analysis. ΔMAP and ΔPP were calculated

as: [(value at recovery – value at rest) / value at rest]. Statistical significance level was set at p<0.05 for all tests. The statistical analyses were computed and analyzed using the SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the study groups are presented in Table 1.

Children and adults had similar total body fat, total lean soft tissue and abdominal fat (p>0.05), but differed in height (p<0.05). Total body fat was not significantly associated with changes in stiffness indices or hemodynamic variables (data not shown). All children were pre-pubertal (-1.87±0.38 years).

Adults reached a higher percentage of predicted maximal heart rate (91.45±0.76% vs 95.19±0.66%) in peak effort (p<0.05) but the aerobic aptitude was similar between age groups (p>0.05). Children had a faster heart rate recovery by the 3rd min (74.34±0.03% vs. 55.29±0.017%) (p<0.05).

Overall, the effects of a bout of maximal running exercise on arterial stiffness indices and hemodynamic response were not age or sex dependent within the group of children or the group of adults (data not shown).

Brachial blood pressure

Children had lower brachial SBP at rest and during recovery (p<0.05) (Figure 1). Brachial SBP increased (right/left: $\eta^2=0.456$/$\eta^2=0.108$) following exercise along with right brachial DBP ($\eta^2=0.097$). Exercise*group interaction effects were found in right brachial DBP ($\eta^2=0.100$) as the pressure increased in children following exercise compared to no change in adults. When measures were adjusted for participant's height, SBP at rest and after exercise were higher in children (p<0.05) (Table 1: Characteristics of the study groups.

	Children	Adults
Age	7.38 ± 0.38 [a]	25.22 ± 0.91

Sex	Girls/Boys	17 / 17			21 / 24	
Height	cm	127.59 ± 1.87 [a]			169.81 ± 1.34	
Total body fat	%	24.33 ± 1.15			21.62 ± 0.97	
Total lean soft tissue	%	72.35 ± 1.10			74.61 ± 0.95	
Abdominal fat	%	21.14 ± 1.43			21.06 ± 1.04	
Heart rate at rest	bpm	83.56 ± 1.78 [a]			59.33 ± 1.47	
Heart rate at peak	bpm	194.10 ± 1.47 [a]			185.44 ± 1.64	
Heart rate at recovery	bpm	114.39 ± 2.18			115.51 ± 2.63	
Peak oxygen consumption	bpm	46.92 ± 1.57			50.22 ± 1.26	
Peak respiratory exchange ratio	bpm	1.11 ± 0.01			1.15 ± 0.01	

Values are means and standard error of the mean. Statistical significance level was set at $p < 0.05$.

Legend: [a] Different from adults

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Table 2). No significant exercise or group interaction effects were found in the adjusted values.

Carotid blood pressure

Children had lower carotid blood pressure at rest and at recovery ($p<0.05$) (Figure 1). Carotid SBP (right/left: $\eta^2=0.617/\eta^2=0.075$) and PP (right/left: $\eta^2=0.394/\eta^2=0.066$) increased after exercise ($p<0.05$) regardless of the measurement technique. Significant exercise*group interaction effects were found in right carotid SBP ($\eta^2=0.068$) and DBP ($\eta^2=0.067$) and PP ($\eta^2=0.136$) as maximum pressure increased more in adults, together with no change in DBP. When measures were adjusted for participant's height, right carotid SBP and PP were higher in children at rest and during recovery ($p<0.05$) (Table 1: Characteristics of the study groups.

		Children			Adults		
Age		7.38	±	0.38 [a]	25.22	±	0.91
Sex	Girls/Boys	17	/	17	21	/	24
Height	cm	127.59	±	1.87 [a]	169.81	±	1.34
Total body fat	%	24.33	±	1.15	21.62	±	0.97
Total lean soft tissue	%	72.35	±	1.10	74.61	±	0.95
Abdominal fat	%	21.14	±	1.43	21.06	±	1.04
Heart rate at rest	bpm	83.56	±	1.78 [a]	59.33	±	1.47
Heart rate at peak	bpm	194.10	±	1.47 [a]	185.44	±	1.64
Heart rate at recovery	bpm	114.39	±	2.18	115.51	±	2.63
Peak oxygen consumption	bpm	46.92	±	1.57	50.22	±	1.26
Peak respiratory exchange ratio	bpm	1.11	±	0.01	1.15	±	0.01

Values are means and standard error of the mean. Statistical significance level was set at $p<0.05$.

Legend: [a] Different from adults

Table 2). Right PP significantly increased after exercise ($\eta^2=0.069$) in particular in taller participants ($\eta^2=0.111$; $p<0.05$).

Carotid artery stiffness indices

At both time points, children had higher compliance and distensibility, and a smaller carotid diameter coupled with lower stiffness index α and β, even when adjusted for ΔMAP or carotid ΔPP ($p<0.05$) (Figure 2; Table 3; Table 4). Significant main exercise effects were found in non-adjusted and ΔMAP-adjusted compliance ($\eta^2=0.385$; $\eta^2=0.345$), distensibility ($\eta^2=0.299$; $\eta^2=0.267$) and carotid diameter ($\eta^2=0.201$; $\eta^2=0.249$) as values decreased following exercise, but only for compliance when adjusted for ΔPP ($\eta^2=0.183$). Maximal exercise induced increases in stiffness index α ($\eta^2=0.065$) and β ($\eta^2=0.076$) but only when values were adjusted for ΔMAP. Exercise*group interaction effects were found in compliance ($\eta^2=0.088$) as it decreased more in adults. Significant exercise*ΔPP interaction effects ($\eta^2=0.432$) were found when compliance was adjusted to ΔPP. A deeper analysis showed that compliance ($\eta^2=0.80$) and distensibility ($\eta^2=0.07$) decreased more in those with high ΔPP. Significant exercise*group, exercise*ΔMAP and exercise*ΔPP interaction effects were also found in stiffness index α ($\eta^2=0.053$; $\eta^2=0.102$; $\eta^2=0.112$) and β ($\eta^2=0.059$; $\eta^2=0.115$; $\eta^2=0.135$), as only adults, those with small ΔMAP ($\eta^2=0.092$; $\eta^2=0.102$) or high carotid ΔPP ($\eta^2=0.102$; $\eta^2=0.0.112$) had increased stiffness following exercise. When measures were adjusted for participant's height, children had lower compliance at rest ($p<0.05$) (Table 4). There were no significant exercise, height or group interaction effects (Table 5).

Pulse Wave Velocity

Children had lower carotid, aortic and lower limb in non-adjusted and ΔMAP- adjusted PWV at rest and at recovery ($p<0.05$) (Figure 3; Table 3). Following exercise, stiffness increased in the carotid artery ($\eta^2=0.444$) and decreased in the lower limb ($\eta^2=0.115$) even when adjusted to ΔMAP ($\eta^2=0.363$; $\eta^2=0.276$). Exercise*group interaction effects were found in non-adjusted, ΔMAP- or ΔPP adjusted carotid PWV ($\eta^2=0.125$; $\eta^2=0.113$; $\eta^2=0.031$) meaning that carotid PWV increased more in adults and

that ΔMAP did not add to the explanation. However, carotid PWV increased more in participants with high carotid ΔPP. Exercise*ΔMAP interaction effects were found in lower limb PWV (η^2=0.111) as only those with small ΔMAP decreased lower limb PWV following exercise (η^2=0.111). When measures were adjusted for participant's height, only upper limb PWV was different between children and adults at rest and recovery ($p<0.05$) (Table 4). No significant exercise, height or group interaction effects were found (Table 5).

DISCUSSION

The key findings of this study were: a) carotid distending pressure increased immediately following exercise in children and adults; b) a single bout of maximal exercise increased carotid stiffness indices whilst decreasing stiffness in the exercised limb; c) the changes in stiffness may be related to the hemodynamic response; d) children and adults did not differ in vascular or hemodynamic responses at a comparable intensity level once adjusted to height; e) central/aortic PWV by applanation tonometry and local carotid PWV by echotracking should not be used interchangeably in the measurement of central stiffness and central hemodynamics.

The physiologic response to acute exercise is complex and may be mechanistically linked to the increased arterial distensibility observed with chronic exercise training. To date, cardiovascular adaptations in children have been assessed with cardiac output, stroke volume, left ventricular dimensions and heart rate kinetics in relation with the work rate or oxygen uptake (Nottin et al. 2002; Rowland et al. 1997; Vinet et al. 2002). Most have included boys only, and few studies have investigated cardiovascular responses to exercise in young boys and girls (<10 years old). This is the first study comparing local, aortic and peripheral stiffness indices, following acute maximal treadmill exercise in children from the age of 5 and young adults, and sheds light on our understanding of the

exercise-mediated signals for arterial adaptations. Herein, we have evidenced in 2 distinct age groups that an acute bout of maximal exercise can alter arterial stiffness in the carotid artery and within the active muscle beds. Given that localized exercise training does not exert systemic effects on the vasculature (Ranadive et al. 2012), it is possible that there is a threshold for hemodynamic forces and circulatory factors that may only be reached when exercise involves large muscle groups (Padilla et al. 2011). In addition, our findings indicate that a lower stiffness and hemodynamic response to metabolic demands during exercise in children appear to reflect their smaller size which may explain why arterial stiffness gradually increases throughout childhood (Doyon et al. 2013; Novo et al. 2013).

Central and peripheral hemodynamic response

The carotid SBP in children and adults were similar to reference values reported in literature (Elmenhorst et al. 2014; Herbert et al. 2014) showing an increase in central blood pressure with age. However, our data also show that differences in height may be the major reason for these age differences. This finding is consistent with previous work (Elmenhorst et al. 2014).

Several studies have shown that an acute bout of aerobic exercise leads to an immediate drop in brachial artery (Ciolac et al. 2009; Terblanche and Millen 2012), central/aortic (Heffernan et al. 2009; Kingsley et al. 2011; Yan et al. 2014) and carotid blood pressure (Sun et al. 2014). Interestingly, this pattern was found to be much less consistent in normotensive individuals (Forjaz et al. 2000; Wang et al. 2014). In our study, maximal exercise induced a 3.92% (adults) to 8.47% (children) increase in right brachial MAP, and 14.98% (children) to 38.49% (adults) increase in carotid PP. The changes in PP were greater in adults due to greater increases in carotid SBP following exercise. The inconsistency in findings in post exercise hypotension between studies may be due in part to the intensity of the stimulus as hemodynamic after-effects of exercise apparently depend on the severity of the load (Piepoli et al. 1994); to the duration of the effort and the health status of the study population as shorter bouts of exercise elicit inconsistent changes in arterial pressure in normotensive but not in hypertensive

individuals (Halliwill 2001) and; to the time of measure (Piepoli et al. 1994; Tordi et al. 2010). DeVan et al. (2005) have shown that although peripheral SBP remained constant following exercise, central SBP was significantly elevated above baseline levels immediately after exercise. Our data are consistent with these findings and those of Rossow et al. (2010). In addition, our results show that the response patterns of central and peripheral blood pressure to exercise are not age-dependent once the values were adjusted for body size.

Carotid artery stiffness indices

Carotid stiffness indices at rest increased with age in accordance with previous studies (Doyon et al. 2013; Novo et al. 2013). Stiffness in the carotid artery also increased following maximal exercise. Early post-exercise, the carotid artery decreased in diameter, consistent with vasoconstriction in both children (1.6%) and adults (3%). The mechanism of the post-exercise carotid vasoconstriction is not clear, but strenuous dynamic exercise is associated with high levels of sympathetic vasoconstrictor activity and plasma noradrenaline concentrations (Dimsdale et al. 1984; Rowell and O'Leary 1990), and the carotid artery smooth muscle is known to be innervated by sympathetic efferents and to express a1 adrenergic receptors (Thomas 2011). Thus sympathetically mediated vasoconstriction may have contributed. Alternatively, Studinger et al. (2003) showed that at high work intensities the elevated arterial pressure induces a strong myogenic response in the carotid smooth muscle (Olesen et al. 1995). When exercise is terminated and the intraluminal distending pressure suddenly drops, the myogenic smooth muscle contraction is left unopposed, causing a transient vasoconstriction. Myogenic vasoconstriction results in baroreceptor unloading and consequent sympathetic excitation (Studinger et al. 2003). Compliance and distensibility in children and adults decreased following exercise as both coefficients are largely influenced by local pressure (denominator). Our data indicates that changes in compliance and distensibility following maximal exercise were mediated primarily by local changes in distension pressure as shown by the significant exercise*ΔPP interaction

effect found, and that the measurement of peripheral blood pressure during exercise recovery provides little insight into the central vascular burden associated with high-intensity dynamic exercise (Rossow et al. 2010). Moreover, there was no change in the stiffness index α and β after the exercise bout further supporting the importance of local pressure. Interestingly, when we controlled both indices for local and systemic distending pressures we witnessed an exercise*distending pressure interaction effect, meaning that changes in stiffness are related to changes in pressure.

Pulse wave velocity

Our results show a considerable increase in resting PWV with age along the arterial tree, indicating an increase in arterial stiffness with age (Avolio et al. 1985). The aortic PWV values in both groups were slightly higher than optimal values reported in literature (Collaboration 2010; Elmenhorst et al. 2014).

Maximal aerobic exercise bout triggered a 4%-7% decrease in stiffness in the arteries of the exercised limb in children and adults. The magnitude of the lower limb vascular response to exercise is similar between modes of leg exercise such as treadmill and cycling (Naka et al. 2003; Ranadive et al. 2012). Contradictory to the carotid artery response to exercise discussed above, the decrease in stiffness in the lower limb is likely due to the vasodilatory response to the exercise, presumably transferring stress from the less extensible collagenous elements in the wall to the more elastic elastin fibers (O'Rourke and Nichols 2005). In addition, the mechanical compression of the arteries during muscular contraction reduces arterial stiffness of the exercised limb (Heffernan et al. 2007c). This may explain why there was a significant decrease in PWV in the exercised limb as compared to no significant change in large central/aortic arterial properties after a maximal exercise bout (Heffernan et al. 2007b; Phillips et al. 2012; Ranadive et al. 2012; Vlachopoulos et al. 2010).

Carotid and central/aortic PWV can be both considered measures of central stiffness, but our results show these arteries yield different values at rest and following exercise. Carotid PWV increased 6% to 12% following exercise in both groups whereas no significant change was observed in aortic PWV.

Although both the carotid artery and the aorta are classified as elastic vessels, the ultrastructure of the carotid artery is more like the abdominal aorta than the ascending aorta. Discrepancies between carotid and aortic arteries could also result from inaccurate measurements. Aortic PWV is generally considered the gold standard for the direct measurement of aortic stiffness (Pannier et al. 2002). However, the distance between the carotid and femoral sites is measured manually and may differ from the true length of the arterial pathway because of anatomic particularities. An identical method would be difficult to apply to the carotid artery because of the short vessel path (10 to 15 cm) and subsequent short time lag (5 to 15 ms) (Paini et al. 2006). Therefore, carotid PWV is determined cross-sectionally from local changes in pressure and artery diameter. PWV may also be influenced by heart rate (Liang et al. 1999) although only heart rates above 120 bpm appear to affect PWV measures (Callaghan et al. 1984).

Considering the high interdependence of arterial stiffness and arterial pressure (Filipovský et al. 2005; O'Rourke and Nichols 2005), it would be understandable to suspect that disparate blood pressure responses between groups confounded the results. There were no main exercise effects in left brachial MAP following exercise, however the exercise*ΔMAP interaction effect in ΔMAP adjusted analysis showed that those participants with small ΔMAP decreased lower limb PWV more following exercise, suggesting that the mechanisms responsible for the alteration in PWV may be related at least in part to the hemodynamic response (Donley et al. 2014). Other studies found reductions in stiffness after acute aerobic exercise (Heffernan et al. 2007a; Kingwell et al. 1997), and increases in stiffness after acute resistance exercise (DeVan et al. 2005), with no change in brachial mean blood pressure. However, they did not go further on adjusting the analysis for changes in distending pressure and used longer time of recovery (20-60 min following exercise).

The noninvasive assessment of PWV is critically dependent on the measurement of the travel distance of the arterial pulse wave (Weber et al. 2009). Travel distance is proportional to body height

(Vermeersch et al. 2009). Wang et al (2010) recognized the problem and adjusted the hazard ratios expressing the risk of death related to a pulse wave reflection index for body height in adults. Doyon et al. (2013) observed in children that growth abnormalities need to be considered in the assessment of arterial distensibility given that children who are very short or tall for age might be assessed more accurately by height-normalized reference values. Although biologically it is possible that age-related changes in resting arterial stiffness noted in this study reflect the precedents of vascular ageing, since it may be affected by structural factors like the composition of the arterial wall including the contents of the extracellular matrix (Olivetti et al. 1980), an alternative or additional mechanism underlying the observed changes from childhood to adulthood might be adaptive remodeling of the vessel walls in response to physiological developmental changes in body dimensions or/and blood pressure (Doyon et al. 2013). Whereas our data cannot conclusively answer the question whether vascular aging or changing body dimensions are more relevant for the vascular differences observed, we showed that there were no significant differences in PWV at rest or following exercise when measures were adjusted to the height of the participants.

LIMITATIONS

The estimates of normal MAP in the literature for adults may not be valid for young children or for altered heart rates. Vasodilation could potentially cause an overestimation of MAP for any given cardiac output, and at higher heart rates MAP is more closely approximated by the arithmetic average of systolic and diastolic pressure because the shape of the arterial pulse changes as the period of diastole shortens more than does systole (Klabunde 2011). However, this method provides a valid estimation of MAP over a wide range of exercise intensities in adults (MacDougall et al. 1999) and this should not have influenced our conclusion regarding the relative changes in children.

The experimental nature of this study would be enriched if we had employed a separate day to serve as a time control. It would also be helpful to have tested both sides of the body simultaneously, apply additional exercise intensities, exercise modes and time points in the recovery phase.

Menstrual cycle variation was not controlled in adult female subjects. We recognize that while it has been reported that elastic properties of central arteries do not fluctuate significantly with the phases of the menstrual cycle (Hayashi et al. 2006; Robb et al. 2009; Willekes et al. 1997; Williams et al. 2001), and that artery wall properties are not affected by oral contraceptive use (Willekes et al. 1999), this is not a universal finding (Hayashi et al. 2006). In our study, both male and female participants had similar PWV at rest and at recovery irrespective of the segment measured (p>0.05; data not shown), suggesting that there were no sex differences in the arterial response to acute maximal exercise. These findings are supported by previous reports suggesting that men and women have similar arterial responses to acute perturbations (Heffernan et al. 2007c; Heffernan et al. 2006; Ranadive et al. 2012).

Some children were not tested for vascular assessment in the morning. Although they were asked to respect the same pre-requisites this may have been an unavoidable source of bias. However, data obtained from a postprandial and post-exercise study show that there were no consistent differences in PWV under fasting or post-prandially in adults (Tripkovic et al. 2014).

Maturation was assessed non-invasively using sex-specific equations (Mirwald et al. 2002). Application of the equation was recommended for children 10–18 years (Mirwald et al. 2002) but we recognize that predicted age to peak height velocity is influenced by chronological age and actual maturity status (Malina and Kozieł 2014a; Malina and Kozieł 2014b).

CONCLUSION

An acute bout of maximal exercise can alter arterial stiffness and hemodynamics in the carotid artery and within the active muscle beds. In addition, our findings indicate that arterial stiffness and hemodynamic response to metabolic demands during exercise in children simply reflects their smaller body size and may not indicate a particular physiologic difference compared to adults.

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TABLES

Table 1: Characteristics of the study groups.

		Children			Adults		
Age		7.38	±	0.38 [a]	25.22	±	0.91
Sex	Girls/Boys	17	/	17	21	/	24
Height	cm	127.59	±	1.87 [a]	169.81	±	1.34
Total body fat	%	24.33	±	1.15	21.62	±	0.97
Total lean soft tissue	%	72.35	±	1.10	74.61	±	0.95
Abdominal fat	%	21.14	±	1.43	21.06	±	1.04
Heart rate at rest	bpm	83.56	±	1.78 [a]	59.33	±	1.47
Heart rate at peak	bpm	194.10	±	1.47 [a]	185.44	±	1.64
Heart rate at recovery	bpm	114.39	±	2.18	115.51	±	2.63
Peak oxygen consumption	bpm	46.92	±	1.57	50.22	±	1.26
Peak respiratory exchange ratio	bpm	1.11	±	0.01	1.15	±	0.01

Values are means and standard error of the mean. Statistical significance level was set at $p<0.05$.

Legend: [a] Different from adults

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Table 2: Height adjusted carotid and brachial blood pressures at rest and after a single bout of maximal exercise in children and adults.

		Children						Adults					
		Rest			Recovery			Rest			Recovery		
Right brachial SBP	(mmHg)	115.97	±	2.91 [a]	127.39	±	3.73 [a]	103.73	±	2.18	110.30	±	2.79
Right brachial DBP	(mmHg)	58.43	±	2.81	62.23	±	2.81	63.57	±	2.10	64.73	±	2.10
Right brachial MAP	(mmHg)	77.35	±	3.01	78.50	±	3.05	78.53	±	1.58	78.74	±	1.59
Right carotid SBP	(mmHg)	112.10	±	3.69 [a]	129.30	±	4.60 [a]	94.99	±	2.27	108.11	±	2.82
Right carotid DBP	(mmHg)	58.71	±	3.24	60.75	±	3.06	63.63	±	2.23	66.30	±	2.11
Right carotid PP [b, c]	(mmHg)	52.94	±	3.72 [a]	69.16	±	5.26 [a]	31.32	±	2.33	40.93	±	3.29
Left brachial SBP	(mmHg)	120.55	±	2.94 [a]	120.87	±	3.40 [a]	102.68	±	1.98	107.24	±	2.28
Left brachial DBP	(mmHg)	61.76	±	3.01	62.28	±	3.03	63.52	±	2.02	63.04	±	2.04
Left brachial MAP	(mmHg)	81.07	±	2.64	82.12	±	2.85	77.06	±	1.67	77.81	±	1.80
Left carotid SBP	(mmHg)	110.61	±	4.46	109.26	±	5.05	104.54	±	2.29	108.85	±	2.60
Left carotid DBP	(mmHg)	61.82	±	3.46	61.96	±	3.48	65.35	±	1.96	63.94	±	1.97
Left carotid PP	(mmHg)	50.03	±	5.47	47.92	±	6.13	38.56	±	2.86	44.60	±	3.20

Values are estimated marginal means and standard error of the mean. Statistical significance level was set at $p < 0.05$. Covariates appearing in the model are evaluated at the following values: 152.70 to 158.49 cm

Legend: [a] Different from adults; [b] main exercise effect; [c] main exercise*group interaction effect; [d] main exercise*height interaction effect.

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Table 3: ΔMAP adjusted arterial stiffness indices at rest and after a single bout of maximal exercise in children and adults.

		Children						Adults					
		Rest			Recovery			Rest			Recovery		
Carotid PWV [b, c]	(m/s)	3.912	±	0.115 [a]	4.160	±	0.124 [a]	4.791	±	0.096	5.374	±	0.104
Aortic PWV	(m/s)	5.161	±	0.289 [a]	5.560	±	0.321 [a]	6.963	±	0.218	6.791	±	0.243
Upper Limb PWV	(m/s)	10.367	±	0.398	9.816	±	0.493	9.368	±	0.301	8.987	±	0.373
Lower Limb PWV [b, d]	(m/s)	6.727	±	0.233 [a]	6.103	±	0.225 [a]	7.947	±	0.176	7.467	±	0.170
Compliance [b, c]	(1/Kpa)	1.612	±	0.078 [a]	1.466	±	0.075 [a]	1.278	±	0.063	0.971	±	0.060
Distensibility [b]	(mm^2/kPa)	0.071	±	0.004 [a]	0.060	±	0.003 [a]	0.042	±	0.003	0.034	±	0.002
Alpha Stiffness [b, d]		2.126	±	0.107 [a]	2.080	±	0.112 [a]	2.684	±	0.088	2.810	±	0.091
Beta Stiffness [b, d]		4.520	±	0.219 [a]	4.427	±	0.225 [a]	5.647	±	0.179	5.929	±	0.184
Carotid Diameter [a]	(mm)	5.70	±	0.09 [a]	5.58	±	0.10 [a]	6.201	±	0.07	6.03	±	0.07
Distension	(mm)	0.75	±	0.03	0.73	±	0.04	0.67	±	0.02	0.70	±	0.03

Carotid PWV was obtained by echotracking whereas, central/aortic, upper and lower limb PWV were obtained by applanation tonometry. Values are estimated marginal means and standard error of the mean. Statistical significance level was set at p<0.05. Covariates appearing in the model are evaluated at the following values: 0.015 to 0.067.

Legend: [a] Different from adults; [b] main exercise effect; [c] main exercise*group interaction effect; [d] main exercise*ΔMAP interaction effect.

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Table 4: ΔPP adjusted carotid elastic function at rest and after a single bout of maximal exercise in children and adults.

		Children		Adults	
		Rest	Recovery	Rest	Recovery
Carotid PWV [b, c]	(m/s)	3.912 ± 0.115 [a]	4.160 ± 0.124 [a]	4.791 ± 0.096	5.374 ± 0.104
Compliance [b, d]	(1/Kpa)	1.549 ± 0.087 [a]	1.281 ± 0.069 [a]	1.252 ± 0.062	0.987 ± 0.049
Distensibility [c, d]	(mm^2/kPa)	0.068 ± 0.004 [a]	0.053 ± 0.003 [a]	0.041 ± 0.003	0.035 ± 0.002
Alpha Stiffness [d]		2.162 ± 0.119 [a]	2.117 ± 0.128 [a]	2.708 ± 0.089	2.818 ± 0.096
Beta Stiffness [d]		4.593 ± 0.242 [a]	4.519 ± 0.257 [a]	5.696 ± 0.181	5.940 ± 0.192
Carotid Diameter [b]	(mm)	5.729 ± 0.087 [a]	5.606 ± 0.097 [a]	6.183 ± 0.065	6.016 ± 0.072
Distension [d]	(mm)	0.75 ± 0.04	0.76 ± 0.04	0.66 ± 0.03	0.68 ± 0.03

Values are estimated marginal means and standard error of the mean. Statistical significance level was set at $p < 0.05$. Covariates appearing in the model are evaluated at the following values: 0.3162 to 0.3281.

Legend: [a] Different from adults; [b] main exercise effect; [c] main exercise*group interaction effect; [d] main exercise*ΔPP interaction effect; PWV – pulse wave velocity

Table 5: Height adjusted arterial stiffness indices at rest and after a single bout of maximal exercise in children and adults.

		Children						Adults					
		Rest			Recovery			Rest			Recovery		
Carotid PWV	(m/s)	4.726	±	0.191	5.051	±	0.204	4.223	±	0.140	4.752	±	0.151
Aortic PWV	(m/s)	6.370	±	0.438	6.852	±	0.518	6.019	±	0.329	5.798	±	0.388
Upper Limb PWV	(m/s)	11.092	±	0.691 [a]	10.792	±	0.786 [a]	8.251	±	0.532	8.017	±	0.605
Lower Limb PWV	(m/s)	7.516	±	0.390	6.682	±	0.375	7.052	±	0.307	6.942	±	0.296
Compliance	(1/Kpa)	1.079	±	0.134 [a]	0.946	±	0.127	1.625	±	0.093	1.309	±	0.088
Distensibility	(mm^2/kPa)	0.048	±	0.007	0.039	±	0.005	0.058	±	0.005	0.049	±	0.003
Alpha Stiffness		2.502	±	0.202	2.323	±	0.212	2.431	±	0.145	2.647	±	0.152
Beta Stiffness		5.332	±	0.413	4.995	±	0.427	5.099	±	0.296	5.546	±	0.306
Carotid Diameter	(mm)	5.93	±	0.15	5.73	±	0.17	5.99	±	0.11	5.87	±	0.12
Distension	(mm)	0.80	±	0.06	0.87	±	0.07	0.63	±	0.04	0.61	±	0.05

Carotid PWV was obtained by echotracking whereas, central/aortic, upper and lower limb PWV were obtained by applanation tonometry. Values are estimated marginal means and standard error of the mean. Statistical significance level was set at $p < 0.05$. Covariates appearing in the model are evaluated at the following values: 151.64 to 158.10 cm.

Legend: [a] Different from adults; [b] main exercise effect; [c] main exercise*group interaction effect; [d] main exercise*ΔPP interaction effect; PWV – pulse wave velocity

FIGURES

Figure 1: Central and peripheral blood pressure measures at rest and at recovery after maximal exercise in children and adults.
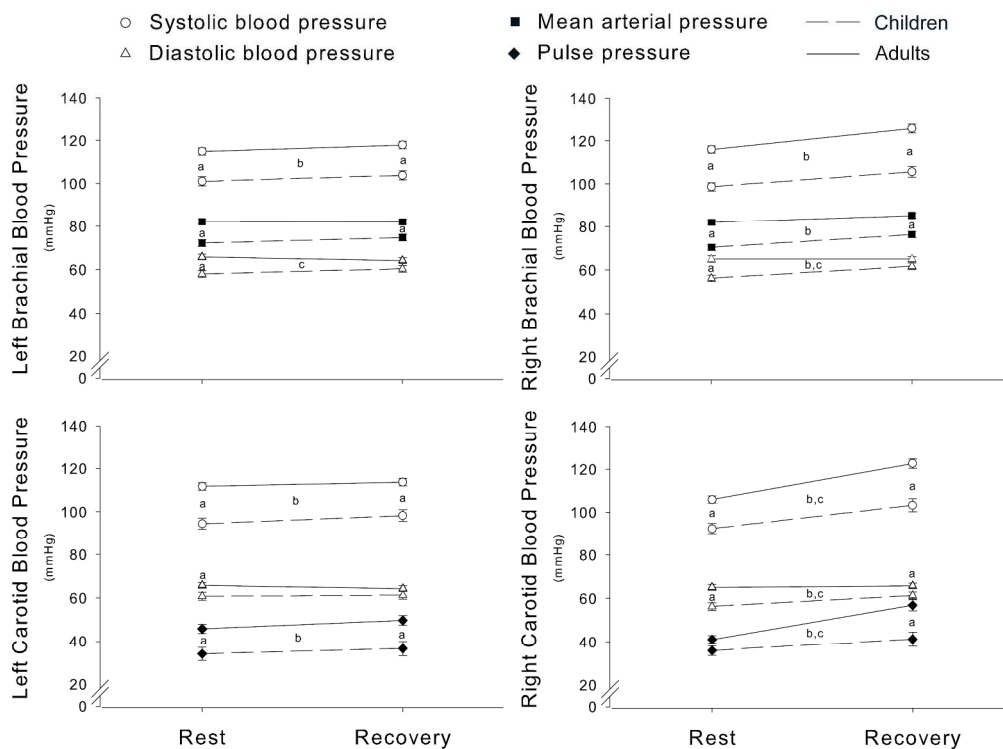
Left carotid blood pressure was obtained by applanation tonometry whereas right carotid blood pressured was obtained by echotracking. Values are expressed as mean and standard error of the mean. Statistical significance level was set at $p < 0.05$. Legend: [a] Different from adults; [b] main exercise effect; [c] main exercise*group interaction effect.

Figure 2: Right carotid stiffness indices at rest and at recovery after maximal exercise in children and adults.

Values are expressed as mean and standard error of the mean. Statistical significance level was set at $p < 0.05$. Legend: [a] Different from adults; [b] main exercise effect; [c] main exercise*group interaction effect; PWV – pulse wave velocity

Figure 3: PWV at rest and at recovery after maximal exercise in children and adults.
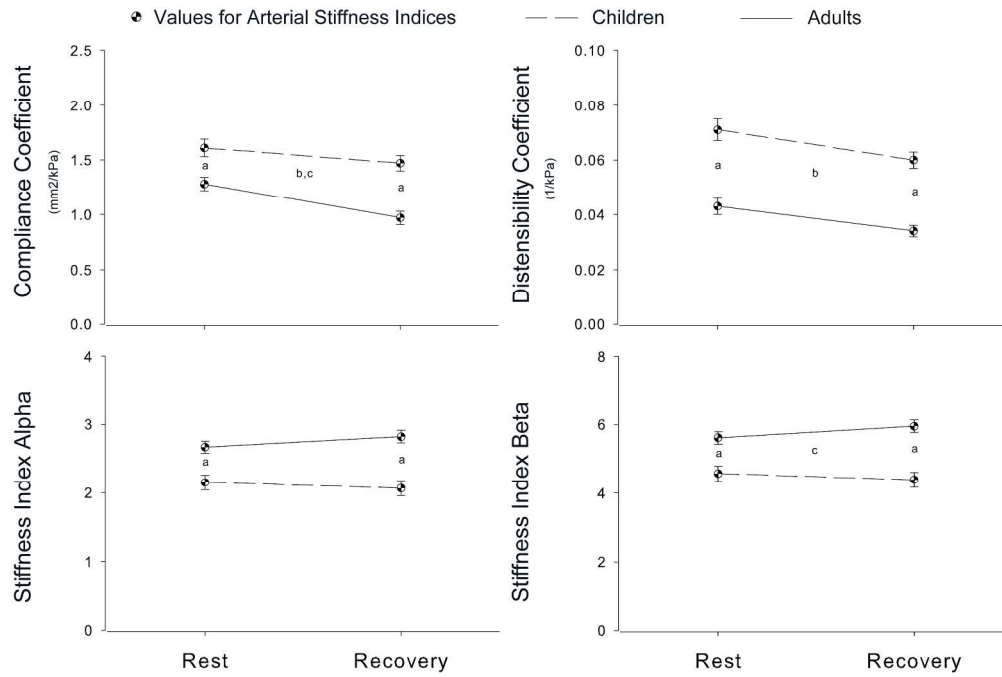
Carotid PWV was obtained by echotracking whereas, central/aortic, upper and lower limb PWV were obtained by applanation tonometry. Values are expressed as mean and standard error of the mean. Statistical significance level was set at $p < 0.05$. Legend: [a] Different from adults; [b] main exercise effect; [c] main exercise*group interaction effect; PWV – pulse wave velocity

Central and peripheral blood pressure measures at rest and at recovery after maximal exercise in children and adults.
Left carotid blood pressure was obtained by applanation tonometry whereas right carotid blood pressured was obtained by echotracking. Values are expressed as mean and standard error of the mean. Statistical significance level was set at p<0.05. Legend: a Different from adults; b main exercise effect; c main exercise*group interaction effect.

212x156mm (300 x 300 DPI)

Right carotid stiffness indices at rest and at recovery after maximal exercise in children and adults. Values are expressed as mean and standard error of the mean. Statistical significance level was set at p<0.05. Legend: a Different from adults; b main exercise effect; c main exercise*group interaction effect; PWV – pulse wave velocity
217x144mm (300 x 300 DPI)
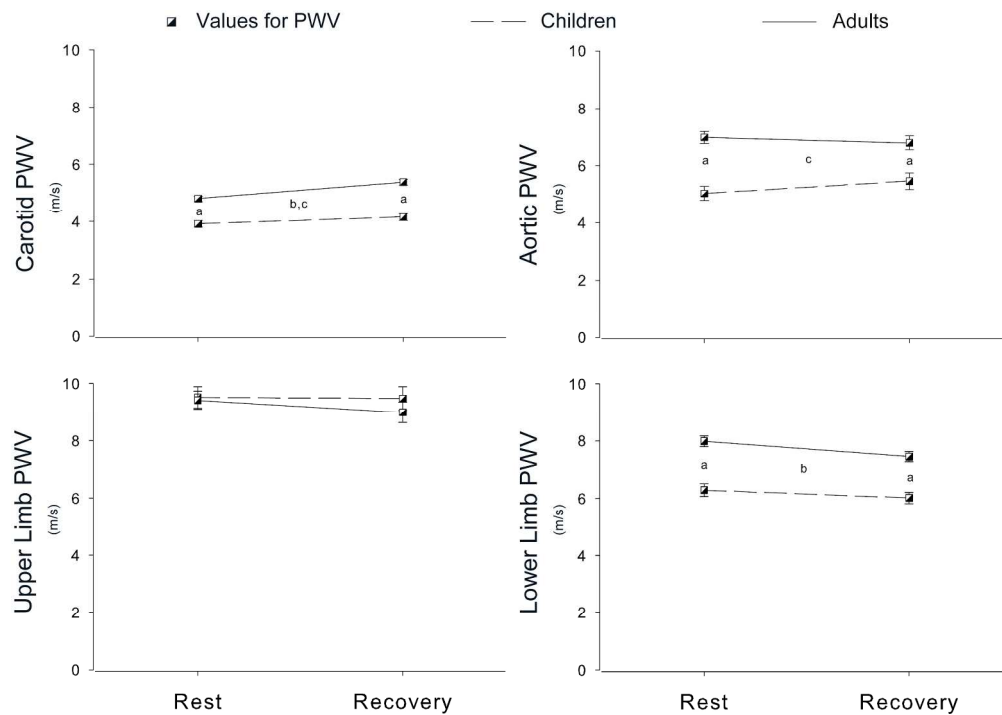
PWV at rest and at recovery after maximal exercise in children and adults.
Carotid PWV was obtained by echotracking whereas, central/aortic, upper and lower limb PWV were obtained by applanation tonometry. Values are expressed as mean and standard error of the mean. Statistical significance level was set at p<0.05. Legend: a Different from adults; b main exercise effect; c main exercise*group interaction effect; PWV – pulse wave velocity
207x146mm (300 x 300 DPI)