Peak oxygen uptake, ventilatory threshold, and arterial stiffness in adolescents

Short title: Cardiorespiratory fitness and arterial stiffness in youth

Eero A. Haapala[1,2], Jari A. Laukkanen[1], Tim Takken[3], Urho M. Kujala[1], Taija Finni[1]

[1]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, FI-40014, Finland

[2]Institute of Biomedicine, University of Eastern Finland, Kuopio Campus, FI-70211, Finland

[3]Child Development and Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands

Address correspondence to: Eero A. Haapala, PhD, Sport and Exercise Medicine, Faculty of Sport and Health Sciences, University of Jyväskylä, PO Box 35, FI-40014 University of Jyväskylä, room VIV 247, email: eero.a.haapala@jyu.fi; telephone: +358408054210

ORCID

Eero Haapala: 0000-0001-5096-851X

Jari Laukkanen: 0000-0002-3738-1586

Tim Takken: 0000-0002-7737-118X

Urho Kujala: 0000-0002-9262-1992

Taija Finni: 0000-0002-7697-2813

ABSTRACT

Purpose

To investigate the associations of peak oxygen uptake ($\dot{V}O_{2peak}$) and $\dot{V}O_2$ at ventilatory threshold ($\dot{V}O_2$ at VT) with arterial stiffness in adolescents.

Methods

The participants were 55 adolescents (36 girls, 19 boys) aged 16–19 years. Aortic pulse wave velocity (PWVao) and augmentation index (AIx%) were measured by non-invasive oscillometric device from right brachial artery level. $\dot{V}O_{2peak}$ was directly measured during a maximal ramp test on a cycle ergometer. $\dot{V}O_2$ at VT was determined using the equivalents for ventilation ($\dot{V}_E$)/$\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$. $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT were normalised for body mass (BM) and lean mass (LM). Data were analysed using linear regression analyses and analysis of covariance adjusted for age and sex.

Results

$\dot{V}O_{2peak}$ normalised for BM (β=-0.445, 95% CI=-0.783 to -0.107) and $\dot{V}O_{2peak}$ normalised for LM (β=-0.386, 95% CI=-0.667 to -0.106) were inversely associated with PWVao. A higher $\dot{V}O_2$ at VT normalised for BM (β=-0.366, 95% CI=-0.646 to -0.087) and LM (β=-0.321, 95% CI=-0.578 to -0.064) were associated with lower PWVao. Adolescents in the lowest third of $\dot{V}O_{2peak}$ by LM (6.6 vs. 6.1 m/s, Cohen's *d*=0.33) and $\dot{V}O_2$ at VT by LM (6.6 vs. 6.0 m/s, Cohen's *d*=0.33) had a higher PWVao than those in the highest third of $\dot{V}O_{2peak}$ or VO_2 at VT by LM.

Conclusions

Higher $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT by BM and LM were related to lower arterial stiffness in adolescents. Normalising $\dot{V}O_{peak}$ and $\dot{V}O_2$ at VT for LM would provide the most appropriate measure of cardiorespiratory fitness in relation to arterial stiffness.

Key words: Cardiorespiratory fitness, physical fitness, vascular stiffness, arteriosclerosis, adolescent

Abbreviations: AIx = augmentation index; PWVao = aortic pulse wave velocity; VT = Ventilatory threshold; $\dot{V}O_{2peak}$ = peak oxygen uptake

INTRODUCTION

Arteriosclerotic process may originate already in childhood and adolescence (Berenson et al. 1998; McGill et al. 2000; Strong et al. 1997). Arterial stiffness, reflecting decreased compliance and distensibility against pulsatile pressure from the heart, is one of the first manifestations of early arteriosclerosis in children and adolescents (Avolio 2013). Arterial stiffening develops through multifactorial process that includes overproduction of collagen and diminished and fractured elastin and other cellular and molecular factors leading to smooth muscle media calcification, abnormalities in cell signalling, and endothelial dysfunction (Zieman et al. 2005).

Increased arterial stiffness has been linked to increased cardiovascular morbidity and mortality in adults independent of traditional cardiometabolic risk factors such as obesity, hyperlipidaemia, hypertension, and insulin resistance (Vlachopoulos et al. 2010). Furthermore, different interventions, such as exercise training, may improve arterial compliance and endothelial function and reduce the risk of cardiovascular morbidity without changes in traditional cardiometabolic risk factors (Thijssen et al. 2010).

Cardiorespiratory fitness has been inversely associated with arterial stiffness (Haapala et al. 2017; Pahkala et al. 2013; Reed et al. 2005; Sakuragi et al. 2009), aortic and carotid intima media thickness (Ferreira et al. 2002; Pahkala et al. 2013; Melo et al. 2014), and endothelial function (Hopkins et al. 2009) in most but not all (Müller et al. 2016) studies in children and adolescents. Lower cardiorespiratory fitness during adolescence also has been related to increased risk of myocardial infarction later in life (Högström et al. 2014). Most previous studies have estimated cardiorespiratory fitness and peak oxygen uptake ($\dot{V}O_{2peak}$) utilising either indirect maximal exercise tests (Pahkala et al. 2013; Ried-Larsen et al. 2013) or 20 metre shuttle run test (Reed et al. 2005; Sakuragi et al. 2009). However, estimating $\dot{V}O_{2peak}$ from field tests may produce a significant error compared to measured $\dot{V}O_{2peak}$ (Léger et al. 1988; Ruiz et al. 2009). Furthermore, the evidence suggests that measured $\dot{V}O_{2peak}$ account less than 50% of the variance of the 20 metre shuttle run

test performance (Mayorga-Vega et al. 2015). Mayorga-Vega et al. also found that the validity of the 20 metre shuttle run test against measured $\dot{V}O_{2peak}$ was considerably lower in youth than in adults (Mayorga-Vega et al. 2015). Furthermore, the evidence on the associations between $\dot{V}O_{2peak}$ and arterial stiffness is still largely based on the data of $\dot{V}O_{2peak}$ normalised for body mass (BM) although such procedure is problematic because it may not eliminate the effect of body size on $\dot{V}O_{2peak}$ (Weslman et al. 1996). BM is also strongly correlated with fat mass (Tompuri et al. 2015a) that has been directly associated with arterial stiffness in youth (Cote et al. 2015). The inappropriateness of scaling of $\dot{V}O_{2peak}$ by BM has been demonstrated in studies showing that the inverse associations between $\dot{V}O_{2peak}$ normalised for BM and cardiometabolic risk factors are largely explained by fat mass (McMurray et al. 2011; Shaibi et al. 2005).

$\dot{V}O_{2peak}$ normalised for lean mass (LM) or fat free mass (FFM) has been suggested as the reference standard measure of cardiorespiratory fitness (Loftin et al. 2016) but few studies have utilised this approach to study the associations of cardiorespiratory fitness with arterial stiffness. Peak workload in Watts per LM (Veijalainen et al. 2016a) and $\dot{V}O_{2peak}$ by FFM (Haapala et al. 2017) have been inversely associated with arterial stiffness in children and adolescents. Furthermore, the allometric scaling of $\dot{V}O_{2peak}$ been proposed to remove the effect of body size on $\dot{V}O_{2peak}$ (Armstrong and Welsman 2008). Some studies (Ferreira et al. 2002, 2003) have observed a negative association of $\dot{V}O_{2peak}$ normalised for BM raised to theoretical allometrical exponent of 0.67 with carotid intima-media thickness and arterial stiffness. However, these previous studies did not report whether normalising for LM or FFM or utilising theoretical allometrical exponent successfully removed the influence of LM, FFM, or BM on $\dot{V}O_{2peak}$.

There are no previous studies on the associations between $\dot{V}O_2$ at ventilatory threshold (VT) with arterial stiffness. However, $\dot{V}O_2$ at VT has been negatively associated with blood pressure, cardiovascular, and all-cause mortality in adults (Kunutsor et al. 2017a, b). $\dot{V}O_2$ at VT, referring $\dot{V}O_2$ at the point where the rise in minute ventilation exceeds the increase in $\dot{V}O_2$ during

incremental exercise test, can used as an indicator of cardiorespiratory fitness in children and adolescents (Garofano 2018). The advantage of the assessment of $\dot{V}O_2$ at VT is that it can be obtained during submaximal exercise test making it safe and reproducible measure of cardiorespiratory fitness in children and adolescents (Garofano 2018; Hebestreit et al. 2000). Although $\dot{V}O_2$ at VT is positively related to $\dot{V}O_{2peak}$ (Hebestreit et al. 2000), $\dot{V}O_2$ at VT may better reflect the ability sustain prolonged submaximal exercise than $\dot{V}O_{2peak}$ (Basset JR and Howley 2000). Furthermore, while cardiac output is the primary limiting factor for $\dot{V}O_{2peak}$, $\dot{V}O_2$ at VT relies on the oxidative capacity of skeletal muscle suggesting that these two factors represent different aspects of cardiorespiratory fitness (Basset JR and Howley 2000). $\dot{V}O_2$ at VT also has been found to be more responsive to exercise training than $\dot{V}O_{2peak}$ in children and adolescents (Mahon and Vaccaro 1989). Finally, $\dot{V}O_2$ at VT may also be more ecologically valid measure of cardiorespiratory fitness in children and adolescents than $\dot{V}O_{2peak}$ because they rarely reach the intensity level near $\dot{V}O_{2peak}$ during habitual physical activity (Armstrong et al. 2011).

Different methods used to assess and normalise the measures of cardiorespiratory fitness might have obscured our understanding on the true relationship between cardiorespiratory fitness and arterial stiffness in paediatric populations. Therefore, we investigated the associations of $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT normalised using ratio standard and allometric procedures with arterial stiffness in high school and vocational school students aged 16–19 years. We hypothesised that $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT are inversely associated with arterial stiffness and that LM would be the most appropriate factor for normalising $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT.

METHODS

Study design, participants, and laboratory procedure

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. Exclusion criteria included any cardiovascular disease, untreated or poorly controlled type 1 diabetes, musculoskeletal trauma or disorder, 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.

In this study, the participants visited the laboratory once. The participants arrived at the laboratory in the morning or afternoon after of at least three hour fast. After emptying the bladder, body composition, and arterial stiffness were assessed. In the last part of the same day visit, the participants performed a ramp exercise test until voluntary exhaustion.

Assessment of body size and composition

BM, fat mass, and LM were measured twice with accuracy of 100 g after of at least three hour fast and body fat percentage was estimated by bioelectrical impedance analysis by InBody 720 device (Biospace Co. Ltd. Seoul, South Korea) (Stenman et al. 2017). In the present study, coefficient of variations for fat mass and LM were 2.3% and 1.0%, respectively. Stature was measured twice in the Frankfurt plane without shoes by a wall-mounted stadiometer with the accuracy of 1 mm. Waist circumference was measured twice after expiration at mid distance between the bottom of the rib cage and the top of the iliac crest by unstretchable measuring tape with accuracy of 1 mm. The mean of these two values was used in the analyses. Body mass index (BMI) was calculated as BM (kg) / stature $(m)^2$ and BMI-standard deviation score (SDS) was computed based on Finnish reference values (Saari et al. 2011).

Assessment of aortic pulse wave velocity and augmentation index

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 about 2-minute intervals (Haapala et

al. 2018). The mean of these two measurements were used in the analyses. The device measures automatically resting heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP), pulse pressure, aortic pulse wave velocity (PWVao), and augmentation index (AIx). The device first measures automatically the actual systolic blood pressure and subsequently inflates the cuff 35 mmHg above measured SBP and measures the fluctuations in the brachial artery. The signals were passed on to a tablet computer, recorded, and analysed as pulse waves. PWVao (m/s) 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)/pulse pressure] x 100. Age and sex-specific standard deviation scores (SDS) for PWVao and AIx% were calculated based on the data of over 4500 Caucasian children and adolescents (Hidvégi et al. 2012, 2015). We have previously reported a good short-term reproducibility for PWVao (intraclass correlation coefficient=0.90, coefficient of variation=3.7%) and moderate reproducibility for AIx% (intraclass correlation coefficient=0.88, coefficient of variation=29.1%) in adolescents (Haapala et al. 2018). Furthermore, Arteriograph-derived PWVao has acceptable agreement with invasively measured PWVao in adults (Horváth et al. 2010; Rossen et al. 2014).

Assessment of cardiorespiratory fitness

Cardiorespiratory fitness was assessed by a maximal ramp 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 (0 W), and an incremental exercise period with increase of workload by 1 W/3 seconds (totalling 20 W/minute) 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 encourage to exercise until voluntary exhaustion.

Respiratory gas exchange was assessed directly by breadth-by-breadth method using metabolic cart (Vmax Encore, VIASYS ltd. Conshohocken, USA) from the 2-minute resting period sitting on the ergometer until the voluntary exhaustion and were averaged over 20-second periods. The metabolic cart was calibrated according to the manufacturer's instructions. We defined maximal cardiorespiratory capacity as the highest $\dot{V}O_2$ achieved in the exercise test ($\dot{V}O_{2peak}$) averaged over 20 seconds recorded during the last minute of the exercise test. Beat-by-beat heart rate (HR) during the exercise test was recorded using Polar H7 HR sensor (Polar Electro, Kempele, Finland) and was passed to the laptop computer controlling the ergometer.

The exercise test was considered maximal if the primary and secondary objective and subjective criteria indicated maximal effort and maximal cardiorespiratory capacity (a plateau of $\dot{V}O_2$ regardless of increasing workload, HR >85% of predicted (Machado and Denadai 2011), respiratory exchange ratio >1.05, or perceived exertion in Borg 6–20 scale ≥18, flushing, and sweating), and the exercise physiologist supervising the exercise test considered the test maximal.

$\dot{V}O_{2peak}$ was defined as mL x kg LM^{-1} x min^{-1} because LM has been considered the most appropriate normalising factor (Graves et al. 2013). $\dot{V}O_{2peak}$ for mL x kg LM^{-1} x min^{-1} was not statistically significantly associated with LM (β = -0.140, 95% CI = -3.01 to 1.99, p = 0.68). We also utilised allometric scaling of $\dot{V}O_{2peak}$ to obtain power function ratio using regression model with sex, age, and log-transformed BM as independent variables and log-transformed $\dot{V}O_{2peak}$ as a dependent variable (Loftin et al. 2016). The scaling exponent b for power function ratio was identified from the slope between log-transformed BM and $\dot{V}O_{2peak}$ and the power function ratio was defined as $\dot{V}O_{2peak} = Y/X^b$, where Y is $\dot{V}O_{2peak}$ and X is the anthropometric scaling variable (BM). We found that the scaling exponent b for BM was 0.41 (95% confidence interval [CI] = 0.09 to 0.73). This

allometric procedure was able to remove the association with BM (β = -0.044, p = 0.68), indicating validity in scaling $\dot{V}O_{2peak}$.

$\dot{V}O_2$ at VT was determined by one experienced assessor using the equivalents for $\dot{V}_E$ / $\dot{V}CO_2$ and $\dot{V}_E$ / $\dot{V}O_2$. $\dot{V}O_2$ at VT was defined as a rate of $\dot{V}O_2$ where $\dot{V}_E$ / $\dot{V}O_2$ begins to increase without an increase in $\dot{V}_E$ / $\dot{V}CO_2$. VT was defined as $\dot{V}O_2$ mL x kg BM^{-1} x min^{-1}, $\dot{V}O_2$ mL x kg LM^{-1} x min^{-1}, and percentage of $\dot{V}O_{2peak}$. We also used log-linear allometric modelling for normalising for BM and defined VT as $\dot{V}O_2$ at VT mL x kg $BM^{-0.54}$ x min^{-1}. $\dot{V}O_2$ at VT normalised for $BM^{-0.54}$ was not statistically significantly related to BM (β = -0.135, p=0.22).

Other assessment

Pubertal status was assessed according to self-reported genital development in boys and breast development in girls on the basis of the 5-stage criteria described by Tanner (Taylor et al. 2001). Years from peak height velocity was estimated using a sex-specific formula described by Moore et al. (Moore et al. 2015).

Statistical methods

All statistical analyses were performed using the JASP Statistical software 0.8.4.0 (University of Amsterdam, the Netherlands). Differences in basic characteristics, $\dot{V}O_{2peak}$, $\dot{V}O_2$ at VT, body size and composition, PWVao, and AIx% between sexes were investigated by Student's t -test or Mann-Whitney U-test for continuous variables or Chi Square test for categorical variables. The associations of $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT with PVWao and AIx% was investigated using linear regression analyses adjusted for age and sex. Differences in PWVao and AIx% between adolescents in the sex-specific thirds of $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT were investigated analyses of covariance adjusted for age and sex. All data were further adjusted for body fat percentage, waist circumference, resting HR, SBP, or years from peak height velocity. We found no evidence on modifying effects of sex on the associations of the measures of cardiorespiratory fitness with

arterial stiffness ($p>0.27$ for interaction). Therefore we performed all analyses with boys and girls combined. We estimated statistical power for our primary analyses using the G*Power software, version 3.1.9.2 (Faul et al. 2007, 2009). Fifty two observations was needed to observe a medium effect size of 0.2 (Cohen's f^2) in the four predictor multiple linear regression model at the power of 0.80 when alpha level was set at 0.05.

RESULTS

Basic characteristics

Boys were less mature as indicated by years from peak height velocity and they were also taller, heavier, and had less fat mass and more lean mass than girls (Table 1). Boys also had a higher absolute and body mass proportional $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT compared to girls. $\dot{V}O_{2peak}$ or $\dot{V}O_2$ at VT normalised for LM did not differ between boys and girls. There was no difference in PWVao between boys and girls, but boys exhibited a higher SBP and lower AIx% than girls.

Associations of the measures of cardiorespiratory fitness with arterial stiffness

$\dot{V}O_{2peak}$ mL x kg BM^{-1} x min^{-1} and $\dot{V}O_{2peak}$ mL x kg LM^{-1} x min^{-1} were inversely associated with PWVao (Table 2). However, $\dot{V}O_{2peak}$ mL x kg BM $mass^{-0.41}$ x min^{-1} was not statistically significantly related to PWVao. Further adjustment for body fat percentage, waist circumference, resting HR, SBP, or years from peak height velocity had no effect on these associations. The associations remained similar when PWVao-SDS and AIx%-SDS were used as outcome variables.

A higher $\dot{V}O_2$ at VT normalised for BM, $BM^{-0.54}$, and LM was associated with lower PWVao (Table 3). None of the measures of VT was associated with AIx%. After further adjustment for body fat percentage, waist circumference, resting HR, SBP, or years from peak height velocity, the inverse relationship between $\dot{V}O_2$ at VT and PWVao remained statistically significant. The proportion of VT from $\dot{V}O_{2peak}$ was not associated with PWVao or AIx%.

Differences in arterial stiffness between adolescents in the thirds of cardiorespiratory fitness

Adolescents in the lowest third of $\dot{V}O_{2peak}$ (mean difference=0.58 m/s, Cohen's *d*=0.33, Figure 1a) and $\dot{V}O_2$ at VT (mean difference 0.55 m/s, Cohen's *d*=0.33, Figure 1b) normalised for LM had a higher PWVao than those in the highest third. Further adjustment for body fat percentage, waist circumference, resting HR, SBP, or years from peak height velocity had no effect on the differences in PWVao between adolescents in the thirds of $\dot{V}O_{2peak}$. However, the difference in PWVao between adolescents with low and high $\dot{V}O_2$ at VT was no longer statistically significant after adjustment for resting HR (p=0.23, mean difference=0.31 m/s, Cohen's *d*=0.223). There were no differences in PWVao or AIx% among adolescents in thirds of $\dot{V}O_{2peak}$ or $\dot{V}O_2$ at VT normalised for BM.

DISCUSSION

The aim of this study was to investigate the associations of $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT normalised using ratio standard and allometric procedures with arterial stiffness in adolescents. Results showed that higher $\dot{V}O_{2peak}$ normalised for BM or LM was related to lower PWVao. We also observed that $\dot{V}O_2$ at VT regardless of normalising procedure was inversely associated with PWVao after further adjustments. Furthermore, adolescents in the lowest third of $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT normalised for LM had on average 10% higher PWVao than those in the highest thirds. Nevertheless, the relationships of $\dot{V}O_{2peak}$ normalised using allometric approach or $\dot{V}O_2$ at VT as a proportion of $\dot{V}O_{peak}$ with PWVao were not statistically significant. Finally, none of the measures of cardiorespiratory fitness were related to AIx%.

Few studies utilising the measures of cardiorespiratory fitness normalised for LM or FFM suggest that higher levels of maximal workload achieved in exercise test by LM (Veijalainen et al. 2016) and $\dot{V}O_{2peak}$ by FFM (Haapala et al. 2017) are related to lower arterial stiffness independent of body fat percentage (Haapala et al. 2017; Veijalainen et al. 2016). These studies may provide physiologically the most relevant information on the associations of cardiorespiratory fitness with

arterial stiffness because muscle mass is responsible for increased energy demands during exercise and it is also responsible for enhanced venous return maintaining left-ventricular end-diastolic volumes and cardiac output (Rowland 2013). In line with these previous results (Haapala et al. 2017; Veijalainen et al. 2016), we observed that $\dot{V}O_{2peak}$ normalised for LM was inversely associated with arterial stiffness. While adolescents in the lowest third of $\dot{V}O_{2peak}$ normalised for LM had higher PWVao than those in the highest third, similar differences were not observed when $\dot{V}O_{2peak}$ normalised for BM was used. Furthermore, $\dot{V}O_{2peak}$ normalised for LM had the narrowest 95% confidence interval limits compared to that of $\dot{V}O_{2peak}$ normalised for BM or allometric procedure. Taken together all these results, we suggest that cardiorespiratory fitness normalised for LM or FFM would provide the most appropriate measure of cardiorespiratory fitness in relation to arterial stiffness.

Consistently with previous studies (Ferreira et al. 2002, 2003; Pahkala et al. 2013; Reed et al. 2005; Ried-Larsen et al. 2013; Sakuragi et al. 2009) we found an inverse association between $\dot{V}O_{2peak}$ normalised for BM and arterial stiffness. However, normalising $\dot{V}O_{2peak}$ for BM may lead to spurious associations with arterial stiffness (Loftin et al. 2016) as BM also include fat mass, that has been directly related to arterial stiffness in youth (Cote et al. 2015). Fat mass has been observed to explain the inverse associations of cardiorespiratory fitness with insulin resistance, metabolic syndrome (Ahn et al. 2013; McMurray et al. 2011; Shaibi et al. 2005;) and arterial stiffness (Sakuragi et al. 2009; Ried-Larsen et al. 2013; Melo et al. 2014) in children and adolescents. Nevertheless, we found that higher $\dot{V}O_{2peak}$ by BM was associated with lower arterial stiffness even after adjustment for body fat percentage and waist circumference. These partly contrasting findings may be due to a relatively lean sample of young participants in the present study. Furthermore, $\dot{V}O_{2peak}$ scaled by allometric procedure for BM was not statistically significantly related to arterial stiffness. Although adjusting the data on $\dot{V}O_{peak}$ per BM for a measure of adiposity may add a confounding term to the dependent variable as denominator in $\dot{V}O_{2peak}$ by BM also include a

measure of adiposity (Armstrong et al. 2011), the utility of allometrically scaled $\dot{V}O_{peak}$ to identify increased arterial stiffness warrants further studies.

The explanation for inverse association between cardiorespiratory fitness and arterial stiffness may be that increased cardiorespiratory fitness is a result of sufficiently intense and frequent physical activity (Armstrong et al. 2011). Aerobic exercise training for 6 months has been observed to have beneficial effects on arterial stiffness, carotid intima media thickness, and systolic blood pressure in overweight and obese children (Farpour-Lambert et al. 2009). Furthermore, it is possible that lower arterial stiffness contributes to increased $\dot{V}O_{2peak}$ by increasing myocardial flow reserve (Roos et al. 2011) and myocardial perfusion (Roos et al. 2011), although the corresponding evidence in adolescents is lacking (Takken et al. 2017). Exercise training also has been found to improve myocardial flow reserve by lowering resting blood flow and increased coronary vasodilation capacity (Yoshinaga et al. 2006). Further explanation for the observed results may be that better arterial compliance enhances blood and oxygen flow to the working skeletal muscles or that cardiorespiratory fitness and arterial stiffness share a common genetic background.

To the best of our knowledge, our study is the first investigating the associations of $\dot{V}O_2$ at VT with arterial stiffness in adolescents. Previous studies in adults have found that $\dot{V}O_2$ at VT was inversely associated with hypertension, cardiovascular, and all-cause mortality (Kunutsor et al. 2017a, b). The magnitude of the associations of $\dot{V}O_2$ at VT with arterial stiffness was lower than that of $\dot{V}O_{2peak}$, but the observed associations were more robust across different normalising procedures. These results suggest that low $\dot{V}O_2$ at VT may be a useful indicator of arterial stiffness in adolescents as it offers an indicator of submaximal exercise capacity independent of maximal effort. Reasons for these observations may include genetic characterises related both to $\dot{V}O_2$ at VT and arterial stiffness and physical activity habits during preceding months. High intensity interval training may be more effective at enhancing $\dot{V}O_2$ at VT in compared to moderate intensity exercise training in youth (McManus et al. 2005). High intensity exercise is also superior at improving endothelial function

than moderate intensity exercise training in adolescents (Bond et al. 2015a, b). However, we found no association between VT as a percentage from $\dot{V}O_{2peak}$ and arterial stiffness. This may be due to the fact that $\dot{V}O_2$ at VT as a percentage from $\dot{V}O_{2peak}$ is not a valid indicator of fitness level *per se* and it is also dependent on the effort of a youth performing maximal exercise test.

In conjunction with previous studies in children (Veijalainen et al. 2016), adolescents (Haapala et al. 2017), and young adults (Stöhr et al. 2012), we found no association between the measures of cardiorespiratory fitness and AIx% in adolescents despite the negative association of fitness with arterial stiffness. In contrast to the results among children and youth, $\dot{V}O_{2peak}$ normalised for BM has been inversely associated with AIx% in adults aged 50 years (Binder et al. 2006). Therefore, cardiorespiratory fitness may be stronger determinant of AIx among older individuals than in children, adolescents, or young adults. The reason for these age-related differences may be that the increase in AIx% during growth and maturation may be a normal physiological phenomenon while increased AIx% in older individuals may reflect pathological cardiovascular changes (McEniery et al. 2005). Another explanation for these weak associations between cardiorespiratory fitness and AIx% is that AIx% is a measure of arterial tone rather than arterial stiffness and it is also more variable in nature (Haapala et al. 2018).

The strengths of the present study include a valid and reproducible methods used to assess $\dot{V}O_{2peak}$, $\dot{V}O_2$ at VT, adiposity, and arterial stiffness. We also used ratio standard and allometric procedures to normalise $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT to adjust the effect of body size on the associations between cardiorespiratory fitness and arterial stiffness. While bioelectrical impedance has been show to provide valid estimates of LM in youth, it underestimates fat mass when compared to dual-energy x-ray absorptiometry that stands for the reference method in the body composition assessment (Sillanpää et al. 2014; Tompuri et al. 2015b). We also measured arterial stiffness from brachial artery level using oscillometric device. However, although oscillometric technique used in the current study has been shown to have reasonable agreement with invasive methods (Horváth et al.

2010; Rossen et al. 2014), PWV between carotid and femoral arteries has been considered the gold standard non-invasive method to assess arterial stiffness (Laurent et al. 2006). In addition, we did not utilise a supramaximal validation test for maximal $\dot{V}O_2$ and therefore it is possible that $\dot{V}O_{2peak}$ measured using the ramp protocol underestimated true maximal $\dot{V}O_2$ of some participants (Barker et al. 2011). We also had a relatively small sample of apparently healthy and fit adolescents which influences the generalisability of the results. However, the magnitude of the associations would probably have been larger if the study would have included more heterogeneous sample of low and high fit adolescents. Finally, cross-sectional study design does not allow any causal interpretation.

In conclusion, we observed that higher $\dot{V}O_{2peak}$ normalised for BM or LM was related to lower arterial stiffness in adolescents aged 16–19 years. Furthermore, we found inverse associations of $\dot{V}O_2$ at VT with arterial stiffness. Based on our results, normalising $\dot{V}O_{peak}$ and $\dot{V}O_2$ at VT for LM would provide the most appropriate measure of cardiorespiratory fitness in relation to arterial stiffness. More evidence from prospective studies is needed to investigate whether changes in $\dot{V}O_{2peak}$ or $\dot{V}O_2$ at VT are related to arterial stiffness.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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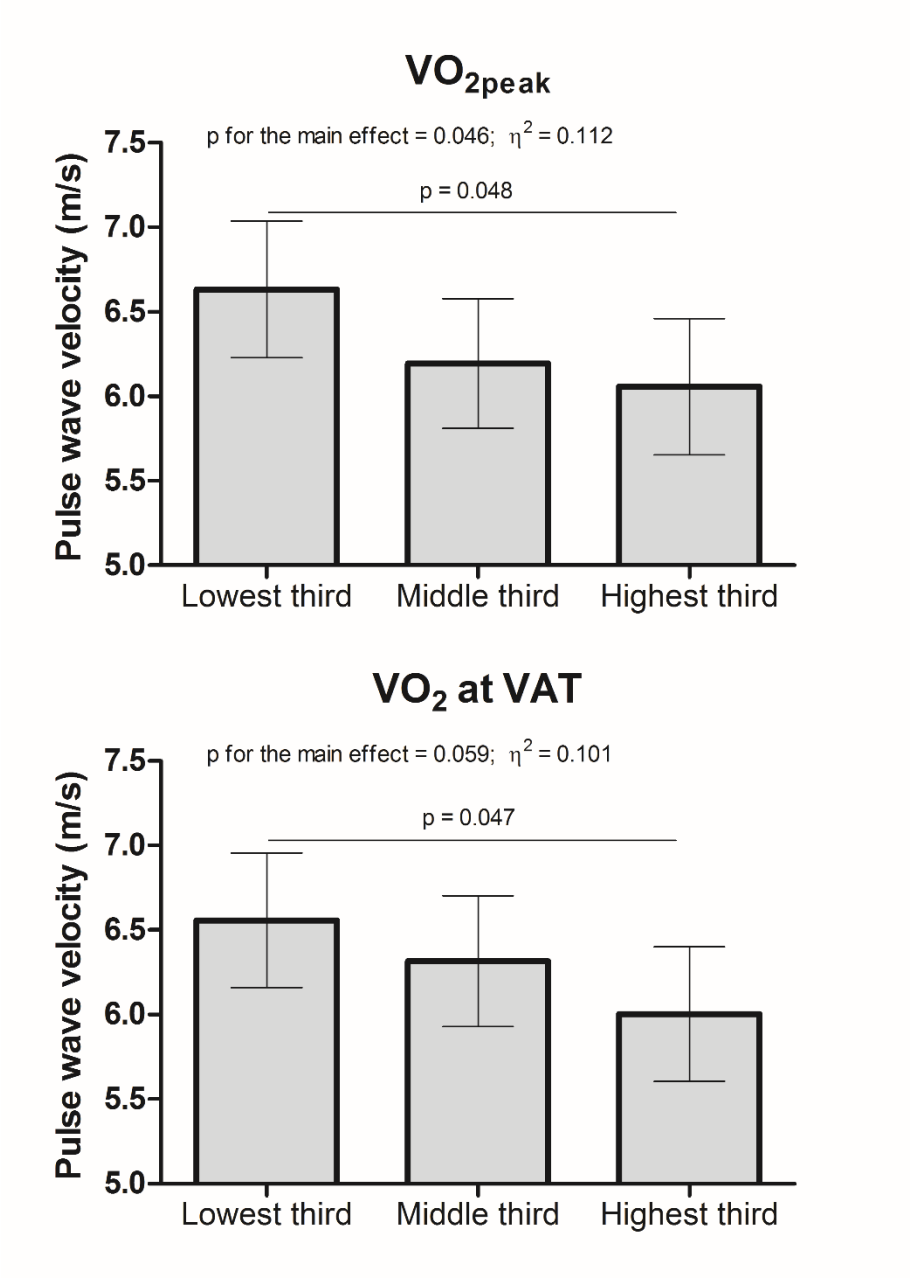

Figure caption

Figure 1. Differences in aortic pulse wave velocity between adolescents in the thirds of peak oxygen uptake ($\dot{V}O_{2peak}$) (a) and $\dot{V}O_2$ at ventilatory threshold (VT) (b) normalised for lean mass (LM). $\dot{V}O_{2peak}$ = girls: lowest third < 99.7; middle third 99.7–108.5; highest third >108.5 Boys: lowest third <101.8; middle third 101.8–117.3; highest third >117.3. $\dot{V}O_2$ at VT = girls: lowest third < 58.6; middle third 58.2–71.8; highest third > 71.8. Boys: lowest third < 59.4; middle third 59.4–80.4, highest third > 80.4.

Table 1. Characteristics of participants

	All (N=55)	**Boys (N=19)**	**Girls (N=36)**	**P**
Age (years)*	17.3 (16.8–18.3)	17.2 (16.7–18.6)	17.3 (16.8–17.9)	0.87
Pubertal status (%)				0.42
Stages 3	18.5	15.8	17.4	
Stage 4	31.5	36.8	28.6	
Stage 5	50.0	47.4	54.0	
Years from peak height velocity (years)	4.3	3.5	4.6	<0.001
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)*	4.5 (3.2–6.5)	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
Body mass index	21.7 (20.2–23.8)	21.6 (19.7–25.2)	21.9 (20.2–23.8)	0.97
Body mass index standard deviation score	0.2 (0.8)	0.1 (0.6)	0.3 (0.9)	0.26
Lean body mass (kg)	28.7 (5.2)	34.7 (3.2)	25.6 (2.6)	0.024
$\dot{V}O_{2peak}$ (mL x min^{-1})	3038 (684)	3741 (492)	2667 (432)	<0.001
$\dot{V}O_{2peak}$ (mL x kg lean $mass^{-1}$ x min^{-1})	105.7 (13.5)	108 (15.2)	104 (12.5)	0.27
$\dot{V}O_{2peak}$ (mL x kg body $mass^{-1}$ x min^{-1})	46.9 (9.6)	53.8 (10.0)	43.2 (7.2)	<0.001
$\dot{V}O_{2peak}$ (mL x kg body $mass^{-0.41}$ x min^{-1})	548 (113)	656 (93.4)	491 (74.2)	<0.001
$\dot{V}O_2$ at VT (mL x min^{-1})*	1880 (1494–2339)	2420 (1919–2789)	1663 (1406–2020)	<0.001
$\dot{V}O_2$ at VT (mL x kg LM^{-1} x min^{-1})	66.2 (57.8–80.0)	67.2 (57.8–80.6)	66.1 (57.8–76.6)	0.59
$\dot{V}O_2$ at VT (mL x kg BM^{-1} x min^{-1})	27.9 (24.5–35.3)	32.1 (26.8–76.6)	26.7 (23.2–32.3)	0.004
$\dot{V}O_2$ at VT (mL x kg $BM^{-0.54}$ x min^{-1})	198 (162–243)	244 (196–288)	175 (157–214)	<0.001
Percentage of $\dot{V}O_2$ at VAT from $\dot{V}O_{2peak}$ (%)	64.9 (10.6)	63.4 (10.6)	64.4 (11.0)	0.83
Peak respiratory exchange ratio	1.3 (0.1)	1.3 (0.1)	1.2 (0.1)	<0.001
Peak heart rate	190 (7.8)	191 (8.5)	190 (7.5)	0.54
Resting heart rate (beats/min)	63.4 (9.7)	59.3 (11.2)	65.5 (8.2)	0.02
Resting systolic blood pressure (mmHg)	118 (9.8)	124 (8.5)	114 (9.0)	<0.001
Mean of aortic PWV (m/s)*	6.2 (5.8–6.6)	6.2 (5.9–6.9)	6.2 (5.8–6.5)	0.47
PWV-SDS	0.06 (-0.06–0.82)	0.13 (-0.87–1.23)	0.06 (-0.67–0.81)	0.88
Mean of augmentation index (%)*	7.5 (3.7–13.4)	6.1 (2.2–7.7)	10.4 (4.1–14.7)	0.01
Augmentation index - SDS	0.45 (-0.63–0.83)	0.4 (-0.2–0.6)	0.5 (-0.8–0.9)	0.78

Data are from the Student t-test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables and are displayed as means (SD), medians (interquartile range*), or percentages (%). P values refer to statistical significance for differences between boys and girls. VT = ventilatory threshold, SDS = standard deviation score

Table 2. Associations of the measures of peak oxygen uptake ($\dot{V}O_{2peak}$) with arterial stiffness

	Aortic pulse wave velocity (m / s)			Augmentation index (%)		
	β	95% CI	P	β	95% CI	P
$\dot{V}O_{2peak}$ (mL x min^{-1})	-0.199	-0.625 to 0.277	0.35	-0.336	-0.735 to 0.063	0.10
$\dot{V}O_{2peak}$ (mL x kg BM^{-1} x min^{-1})	-0.445	-0.783 to -0.107	0.01	-0.174	-0.515 to 0.167	0.31
$\dot{V}O_{2peak}$ (mL x kg $BM^{-0.41}$ x min^{-1})	-0.355	-0.756 to 0.045	0.08	-0.300	-0.685 to 0.085	0.12
$\dot{V}O_{2peak}$ (mL x kg LM^{-1} x min^{-1})	-0.386	-0.667 to -0.106	0.01	-0.035	-0.322 to 0.252	0.81

The data are standardised regression coefficients and their 95% confidence intervals (CI) adjusted for age and sex.

Table 3. Associations of the measures of ventilatory threshold ($\dot{V}O$ at VT) with arterial stiffness

	Aortic pulse wave velocity (m / s)			Augmentation index (%)		
	β	95% CI	P	β	95% CI	P
$\dot{V}O_2$ at VT (mL x kg BM^{-1} x min^{-1})	-0.366	-0.646 to -0.087	0.01	-0.098	-0.382 to 0.186	0.49
$\dot{V}O_2$ at VT (mL x kg $BM^{-0.54}$ x min^{-1})	-0.334	-0.634 to -0.030	0.03	-0.132	-0.431 to 0.167	0.38
$\dot{V}O_2$ at VT (mL x kg LM^{-1} x min^{-1})	-0.321	-0.578 to -0.064	0.02	-0.016	-0.277 to 0.245	0.90
$\dot{V}O_2$ at VT from $\dot{V}O_{2peak}$ (%)	-0.162	-0.446 to 0.121	0.26	0.032	-0.242 to 0.307	0.81

The data are standardised regression coefficients and their 95% confidence intervals (CI) adjusted for age and sex.