Exercise Physiology

Vascular Endothelial Function and Leisure-Time Physical Activity in Adolescents

Katja Pahkala, MSc; Olli J. Heinonen, MD, PhD; Hanna Lagström, PhD; Paula Hakala, PhD; Olli Simell, MD, PhD; Jorma S.A. Viikari, MD, PhD; Tapani Rönnemaa, MD, PhD; Miika Hernelahti, MD, PhD; Lauri Sillanmäki, StudSocSc; Olli T. Raitakari, MD, PhD

Background—Exercise training improves endothelial function in high-risk adolescents, but the influence of habitual leisure-time physical activity on endothelial function in healthy adolescents is unknown.

Methods and Results—Brachial artery flow-mediated endothelial function and physical activity habits were assessed in 483 adolescents (13 years of age) participating in an atherosclerosis prevention study (Special Turku Coronary Risk Factor Intervention Project for Children [STRIP]). Endothelial function was examined with ultrasound; physical activity was assessed with self-administered questionnaires. A leisure-time physical activity index was calculated by multiplying mean weekly leisure-time exercise intensity, duration, and frequency [boys, 31.2±23.0 MET h/wk (mean±SD); girls, 24.0±20.9 MET h/wk; P for gender difference=0.0003]. Maximum flow-mediated dilatation (FMD) and total FMD response (the area under the dilatation curve 40 to 180 seconds after hyperemia) were calculated. In boys, maximum FMD and area under the dilatation curve 40 to 180 seconds after hyperemia were directly associated with leisure-time physical activity index in regression analyses adjusted for brachial artery diameter (maximum FMD, P=0.020; area under the dilatation curve 40 to 180 seconds after hyperemia, P=0.0055). These associations remained significant after further adjustments for body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, and systolic blood pressure. A difference of ≈50 MET h/wk corresponding to ≈10 hours of moderate intensity activity weekly between sedentary and active boys was associated with an ≈1% unit difference in maximum FMD.

Conclusions—Leisure-time physical activity is directly associated with brachial artery FMD responses in 13-year-old boys, providing evidence that physical activity beneficially influences endothelial function in healthy male adolescents. Lack of association in girls may reflect their overall lower physical activity level. (Circulation. 2008;118:2353-2359.)

Key Words: children • endothelium • exercise • ultrasound

The endothelium, the cell layer lining the blood vessels, plays a key role in a number of vascular functions.1 Brachial artery flow-mediated dilatation (FMD), induced by reactive hyperemia, is dependent on an intact endothelial layer and mediated by nitric oxide.2 Impairment of arterial endothelial function is an important early step in the atherosclerotic process.3 Brachial artery FMD is widely used as a marker of systemic arterial endothelial function. FMD is associated with coronary atherosclerosis4 and coronary artery endothelial function5 and predicts cardiovascular events.6 We have previously shown in healthy adults an inverse association between brachial artery endothelial function and carotid artery intima-media thickness, a subclinical marker of atherosclerosis.7

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Physical activity enhances endothelial function in conduit arteries, skeletal muscle arterioles, and coronary arterioles in adults.8–11 Ameliorated endothelial function associated with exercise training is not entirely mediated by changes in plasma lipoprotein, glucose and fibrinogen concentrations, blood pressure, waist-to-hip ratio, or body mass index (BMI).10,12 The mechanism mediating the beneficial effects of physical activity on arterial endothelial function is suggested to be an exercise-induced increase in blood flow, leading to augmented shear stress and cyclic stretch, further causing enhanced nitric oxide production.13 In overweight and obese children and adolescents, exercise training improves endothelial function even without concomi-
itant changes in body weight or BMI. 

Methods

Study Design and Subjects

This study is based on the ongoing prospective, randomized Special Turku Coronary Risk Factor Intervention Project for Children (STRIP), the design of which has been described. 

In brief, between February 1990 and June 1992, families of 6-month-old infants were recruited to the study at well-baby clinics in Turku, Finland. At 7 months of age, 1062 infants (56.5% of the eligible age cohort) were randomly allocated to a dietary intervention group (n=540) or to a control group (n=522). The intervention group received individualized dietary 

and antismoking counseling at least biannually. The study was approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital. Written informed consent was obtained from the parents.

Between June 2002 and November 2004, 565 adolescents 13 years of age were examined, and 560 completed a leisure-time physical activity questionnaire. Two adolescents were excluded because of congenital physical impairment, and 11 were excluded because of type 1 diabetes or familial hypercholesterolemia, leaving 547 adolescents (260 girls, 287 boys) in the study. The 11 adolescents with type 1 diabetes or familial hypercholesterolemia were excluded because these conditions may be associated with impaired endothelial function. 

Complete data on physical activity and ultrasound measures were available for 483 adolescents (88%) (230 girls, 253 boys). Unwillingness to participate, lack of time, fear of the study, and transportation problems were reasons for nonparticipation. 

Only one of the adolescents reported regular smoking.

Although 47% of the initially recruited families had discontinued participation during the 13 years of the study, there has been no difference in serum total cholesterol concentration or saturated fat intake between the children who remained in the study or discontinued participation, suggesting that discontinuation caused no or marginal bias to our study. Moreover, the mean BMI of the children who remained in the study at 13 years of age was similar to the mean BMI of those who had discontinued participation at the beginning of the study and at 13 months, 2 years, 5 years, and 10 years of age.

Physical Examination

Standing height was measured to the nearest 0.1 cm by a Harpenden stadiometer (Holtain, Crymych, Great Britain). Weight was measured with an electronic scale (Soehnle S10, Soehnle, Murrhardt, Germany) to the nearest 0.1 kg with the adolescent wearing underwear. BMI was calculated as weight divided by height squared (kg/m²). The children were classified as overweight if their BMI exceeded the international age- and sex-specific criteria.

Blood pressure was measured after 10 minutes of rest 3 times on the right arm with an automated sphygmomanometer during the ultrasound study (Omron M4, Omron Matsuaka, Matsuaka, Japan). The mean of the 3 measurements was used. Pubertal status was recorded according to Tanner staging as described.

Laboratory Measures

A fasting venous blood sample was drawn for the determination of serum lipid and lipoprotein concentrations. After clotting at room temperature for 30 to 60 minutes and centrifugation at 3400 g for 12 minutes, serum was separated and stored at −25°C. Serum cholesterol concentration was determined with a fully enzymatic cholesterol oxidase-p-aminoephazon method (CHOD-PAP, Merck, Darmstadt, Germany) with an AU 400 automatic analyzer (Olympus, Hamburg, Germany). Serum high-density lipoprotein cholesterol (HDL-C) concentration was analyzed after precipitation of low-density lipoprotein cholesterol (LDL-C) and very LDL-C with dextran sulfate 500 000. 

The interassay coefficients of variation of total cholesterol and LDL-C were 2.0% and 1.9% (intra-assay coefficients, 1.5% and 1.2%), respectively. Serum triglyceride concentrations were analyzed with the colorimetric GPO-PAP method (Merck) with an automatic Olympus AU 400 analyzer. The Friedewald formula was used to calculate LDL-C concentrations. 

High-sensitivity C-reactive protein (hs-CRP) concentration was assayed by a turbidimetric immunoassay (Wako Chemicals, Neuss, Germany). The sensitivity of the method was 0.06 mg/L. All analyses were done at the National Public Health Institute in Turku, Finland.

Physical Activity

Leisure-time physical activity habits were assessed at the 13-year visit with a self-administered questionnaire through which the frequency, duration, and intensity of habitual leisure-time physical activity were reported. 

Leisure-time physical activity constituted recreational and organized physical activity/sports outside school hours. The questionnaire has been widely used in studies involving children, adolescents, and adults, and it correlates modestly well with exercise capacity (women, r=0.49; men, r=0.53). A leisure-time physical activity index (PAI) was calculated as a multiple of the resting metabolic rate (MET; h/wk) by multiplying the frequency, mean duration in minutes, and mean intensity of weekly leisure-time physical activity as described; 

1 MET h/wk corresponds to ~12 minutes of moderate intensity activity weekly. From the PAI data, the tertile cut points were calculated, and the girls and boys were divided into Sedentary, Moderately Active, and Active groups. The PAI cut point was 19.5 MET h/wk for the Sedentary boys and 5.0 MET h/wk for the Sedentary girls, whereas the Active boys and girls exercised at least 32.6 and 31.3 MET h/wk, respectively.

Brachial Artery Ultrasound

All ultrasound studies were performed with an Acuson Sequoia 512 mainframe (Acuson, Mountain View, Calif) with a 13.0-MHz linear-array transducer as described. 

In brief, ultrasound studies were performed in silence in a temperature-controlled clinical research laboratory. Left brachial artery diameter was measured from B-mode ultrasound images at rest and during reactive hyperemia. A resting scan was performed and arterial flow velocity was measured with a Doppler signal. Increased flow was then induced by inflation of a blood pressure cuff placed around the forearm to a pressure of 250 mm Hg for 4.5 minutes, followed by release. A second continuous scan was recorded between 30 and 180 seconds after cuff deflation, including a repeated flow-velocity measurement during the first 15 seconds after cuff release. All ultrasound scans were performed and analyzed by the same experienced sonographer who was unaware of the clinical and laboratory characteristics of the adolescents. Vessel diameter was measured offline at a fixed position with ultrasonic calipers at end diastole, incident with the R wave on a continuously recorded ECG. Dilatation from baseline was measured at 10-second intervals between 30 and 180 seconds. From these data, maximum FMD (FMDmax; %), absolute FMD (mm), and FMD after 60 seconds of cuff release were measured. Furthermore, the total dilatation response, defined as the area under the dilatation response–versus-time curve between 40 and 180 seconds after hyperemia (FMDauc; %×s), was assessed. Hyperemia (%) indicates the percent increase in blood flow after cuff release. In our laboratory, the interobserver variation (coefficient of variation) of FMD measurements was 8.6%, and the between-study coefficient of variation was 9.3%.

Statistical Analyses

Because exposure of the child to dietary counseling and smoking prevention in the STRIP intervention group was not associated with
Table 1. Descriptive Data by Physical Activity Group and Association of PAI (1 MET h/wk~12 Minutes of Moderate-Intensity Activity Per Week) With Anthropometric Data, Serum Lipids and Lipoproteins, Blood Pressure Values, and Ultrasound Measures in 13-Year-Old Boys

<table>
<thead>
<tr>
<th></th>
<th>Sedentary (n=95)</th>
<th>Moderately Active (n=79)</th>
<th>Active (n=79)</th>
<th>Total, n</th>
<th>β (SE) OR (CI)†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAI, MET h/wk</td>
<td>8.5±7.8</td>
<td>30.6±3.0</td>
<td>59.1±14.7</td>
<td>253</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>19.44±3.50</td>
<td>18.62±2.44</td>
<td>19.27±2.87</td>
<td>253</td>
<td>−0.0042 (0.0083)</td>
<td>0.61</td>
</tr>
<tr>
<td>Overweight, %§</td>
<td>18.9</td>
<td>11.4</td>
<td>15.2</td>
<td>253</td>
<td>0.996 (0.982–1.010)†</td>
<td>0.53</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.13±0.80</td>
<td>4.11±0.69</td>
<td>4.19±0.64</td>
<td>253</td>
<td>0.0021 (0.0020)</td>
<td>0.29</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.15±0.24</td>
<td>1.19±0.25</td>
<td>1.26±0.24</td>
<td>253</td>
<td>0.0021 (0.00067)</td>
<td>0.0015</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.59±0.64</td>
<td>2.54±0.59</td>
<td>2.60±0.57</td>
<td>253</td>
<td>0.00061 (0.0017)</td>
<td>0.71</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.80 (0.40)</td>
<td>0.70 (0.40)</td>
<td>0.60 (0.40)</td>
<td>253</td>
<td>−0.0018 (0.0012)</td>
<td>0.13</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>0.30 (0.47)</td>
<td>0.25 (0.36)</td>
<td>0.24 (0.37)</td>
<td>252</td>
<td>−0.0023 (0.0028)</td>
<td>0.41</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>107±7</td>
<td>108±8</td>
<td>109±9</td>
<td>245</td>
<td>0.032 (0.022)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>62±5</td>
<td>61±5</td>
<td>62±5</td>
<td>245</td>
<td>0.0027 (0.014)</td>
<td>0.84</td>
</tr>
<tr>
<td>Brachial artery baseline diameter, mm</td>
<td>2.99±0.32</td>
<td>3.03±0.29</td>
<td>3.07±0.32</td>
<td>253</td>
<td>0.0020 (0.00084)</td>
<td>0.016</td>
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<tr>
<td>FMDauc, %×s</td>
<td>671±482</td>
<td>721±480</td>
<td>811±555</td>
<td>252</td>
<td>3.67 (1.31)</td>
<td>0.0055</td>
</tr>
<tr>
<td>ΔFMD, mm</td>
<td>0.27±0.12</td>
<td>0.28±0.12</td>
<td>0.30±0.13</td>
<td>253</td>
<td>0.00083 (0.00034)</td>
<td>0.014</td>
</tr>
<tr>
<td>FMDmax, %</td>
<td>9.1±4.3</td>
<td>9.4±4.1</td>
<td>10.1±4.5</td>
<td>253</td>
<td>0.026 (0.011)</td>
<td>0.020</td>
</tr>
<tr>
<td>FMD at 60 s, %</td>
<td>7.2±4.4</td>
<td>7.7±4.4</td>
<td>8.4±4.8</td>
<td>251</td>
<td>0.032 (0.012)</td>
<td>0.0080</td>
</tr>
<tr>
<td>Hyperemia, %</td>
<td>334±132</td>
<td>341±135</td>
<td>333±134</td>
<td>246</td>
<td>−0.17 (0.37)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Descriptive data are given for physical activity groups as mean±SD or medians (interquartile range); triglycerides and hs-CRP.
*Regression coefficient (β) and standard error (SE) for a 1-unit change in PAI; linear regression analysis.
†Odds ratio (OR) estimate (95% CI) for a 1-unit change in PAI by logistic regression analysis.
§BMI >21.91 kg/m² at 13 years of age in boys.26
‡Adjusted for brachial artery baseline diameter.

the physical activity group26 or leisure-time physical activity level (PAI used as a continuous variable; P=0.48 for girls, P=0.13 for boys, ANOVA), the intervention and control boys were studied as 1 group, as were the intervention and control girls. The adolescents were analyzed by gender because of a difference in physical activity level between boys and girls (P=0.0003) and significant association between gender and FMDauc in linear regression analysis adjusted for PAI and brachial artery baseline diameter (P=0.0009). Association of PAI with anthropometric data, serum lipids and lipoproteins, blood pressure, and hyperemia was studied by univariate linear or logistic (weight status) regression analyses. Association of PAI with ultrasound measurements, excluding hyperemia, was studied with multivariate linear regression analyses in which brachial artery baseline diameter was used as a covariate. Furthermore, association of PAI with FMDmax and FMDauc was studied with multivariate linear regression analyses: BMI, HDL-C, LDL-C, triglycerides, hs-CRP, systolic blood pressure, and brachial artery baseline diameter were included in the model.

Repeated-measures ANOVA with covariates was used to study whether the magnitude of flow-mediated vasodilatory responses differed between Sedentary and Active girls and Sedentary and Active boys. In these analyses, time, interaction between activity group and time, and brachial artery baseline diameter were used as covariates. ANCOVA was used to study association of weight status with FMDmax. Brachial artery baseline diameter was used as a covariate in these analyses. Change in FMDmax in girls exercising 10 to 20 versus 40 to 60 MET h/wk to boys with the same activity criteria also was studied with ANOVA (gender-by-physical activity interaction). Values of P<0.05 were considered significant. SAS release 9.1.3 was used for the analyses (SAS Institute, Cary, NC).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

In boys, all markers of vascular endothelial function, ie, FMDmax, FMDauc, absolute FMD, and FMD after 60 seconds of cuff release, were directly associated with PAI in regression analyses adjusted for brachial artery baseline diameter (Table 1). In girls, no association between endothelial function and PAI was found (Table 2). Brachial artery baseline diameter increased with increasing PAI in boys but not in girls. An increase in blood flow after cuff release (hyperemia) was not associated with PAI in boys or girls. HDL-C was directly associated with PAI in both boys and girls. All other laboratory analytes and blood pressure were similar regardless of the activity level. In girls, but not in boys, the risk of being overweight decreased with increasing PAI. Descriptive data on BMI, prevalence of overweight, serum lipids and lipoproteins, hs-CRP, blood pressure, and ultrasound measurements by physical activity group are given in Tables 1 and 2. Data on pubertal status was available for 223 girls (97.0%) and 214 boys (84.6%). Puberty was ongoing (Tanner stage M/G2 to M/G4) in nearly all adolescents (girls, 93.3%; boys, 98.1%).

In boys, the direct association of FMDmax (Table 3) and FMDauc (Table 4) with PAI remained significant after adjustment for BMI, HDL-C, LDL-C, triglycerides, hs-CRP, systolic blood pressure, and brachial artery baseline diameter. In addition to PAI, brachial artery baseline diameter was inversely and BMI was directly associated with FMDmax; brachial artery baseline diameter also was inversely associated with FMDauc. Among girls, PAI was not associated with
Table 2. Descriptive Data by Physical Activity Group and Association of PAI (1 MET h/wk = 12 Minutes of Moderate-Intensity Activity Per Week) With Anthropometric Data, Serum Lipids and Lipoproteins, Blood Pressure Values, and Ultrasound Measures in 13-Year-Old Girls

<table>
<thead>
<tr>
<th></th>
<th>Sedentary (n=77)</th>
<th>Moderately Active (n=107)</th>
<th>Active (n=46)</th>
<th>Total, n</th>
<th>β (SE)*/OR (CI)†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAI, MET h/wk</td>
<td>3.1±1.9</td>
<td>25.2±2.8</td>
<td>56.1±15.7</td>
<td>230</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.25±3.63</td>
<td>19.16±3.21</td>
<td>19.25±2.70</td>
<td>228</td>
<td>-0.016 (0.010)</td>
<td>0.12</td>
</tr>
<tr>
<td>Overweight, %‡</td>
<td>25.3</td>
<td>10.3</td>
<td>19.9</td>
<td>228</td>
<td>0.978 (0.958-0.998)</td>
<td>0.036</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.28±0.67</td>
<td>4.28±0.77</td>
<td>4.22±0.75</td>
<td>228</td>
<td>-0.0093 (0.0023)</td>
<td>0.69</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.16±0.20</td>
<td>1.23±0.24</td>
<td>1.25±0.23</td>
<td>228</td>
<td>0.0015 (0.00072)</td>
<td>0.042</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.69±0.63</td>
<td>2.69±0.69</td>
<td>2.57±0.60</td>
<td>228</td>
<td>-0.0020 (0.0021)</td>
<td>0.34</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.80 (0.40)</td>
<td>0.70 (0.30)</td>
<td>0.80 (0.50)</td>
<td>228</td>
<td>-0.00062 (0.0013)</td>
<td>0.62</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>0.24 (0.42)</td>
<td>0.20 (0.24)</td>
<td>0.20 (0.42)</td>
<td>221</td>
<td>-0.0020 (0.0031)</td>
<td>0.52</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>106±8</td>
<td>105±8</td>
<td>105±8</td>
<td>226</td>
<td>0.0039 (0.026)</td>
<td>0.88</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>62±5</td>
<td>62±5</td>
<td>60±4</td>
<td>226</td>
<td>-0.020 (0.014)</td>
<td>0.17</td>
</tr>
<tr>
<td>Brachial artery baseline diameter, mm</td>
<td>2.81±0.27</td>
<td>2.79±0.28</td>
<td>2.74±0.27</td>
<td>230</td>
<td>-0.0010 (0.00088)</td>
<td>0.24</td>
</tr>
<tr>
<td>FMDauc, %×s</td>
<td>729±503</td>
<td>667±494</td>
<td>759±504</td>
<td>229</td>
<td>0.24 (1.57)</td>
<td>0.88</td>
</tr>
<tr>
<td>∆FMD, mm</td>
<td>0.28±0.12</td>
<td>0.26±0.11</td>
<td>0.29±0.13</td>
<td>230</td>
<td>0.00020 (0.00038)</td>
<td>0.60</td>
</tr>
<tr>
<td>FMDmax, %</td>
<td>10.0±4.2</td>
<td>9.3±4.2</td>
<td>10.6±4.8</td>
<td>230</td>
<td>0.00069 (0.014)</td>
<td>0.61</td>
</tr>
<tr>
<td>FMD at 60 s, %</td>
<td>7.9±4.4</td>
<td>7.2±4.6</td>
<td>8.4±5.0</td>
<td>229</td>
<td>0.0074 (0.014)</td>
<td>0.60</td>
</tr>
<tr>
<td>Hyperemia, %</td>
<td>363±145</td>
<td>384±156</td>
<td>340±128</td>
<td>228</td>
<td>-0.31 (0.47)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Descriptive data are given for physical activity groups as mean±SD or medians (interquartile range); triglycerides and hs-CRP.

*Regression coefficient (β) and standard error (SE) for a 1-unit change in PAI; linear regression analysis.
†Odds ratio (OR) estimate (95% CI) for a 1-unit change in PAI by logistic regression analysis.
‡Probability values are from regression analyses in which PAI has been treated as a continuous variable.
§BMI > 22.58 kg/m² at 13 years of age in girls.23

FMDmax (Table 3) or FMDauc (Table 4) in multivariate analyses. Furthermore, the results remained similar when physical activity energy expenditure (MET h/wk×weight [kg]) was used instead of PAI (data not shown).

Because of the direct association between BMI and FMDmax in boys, we studied whether being overweight was associated with FMDmax. Weight status was not associated with FMDmax in boys (P=0.31) or girls (P=0.16).

The temporal development of FMD responses measured between 30 and 180 seconds after cuff release followed a similar pattern over time in the Sedentary and Active boys, but the magnitude of the response was greater in the Active boys (Figure 1). Correspondingly, the temporal development of FMD responses followed a similar pattern over time in the Sedentary and Active girls, whereas there was no difference in the magnitude of response (Figure 2).

To explore gender differences in the association of PAI with endothelial function, we studied the change in FMDmax between girls exercising 10 to 20 MET h/wk (n=33) and 40 to 60 MET h/wk (n=36) compared with boys with same activity criteria. Mean±SD FMDmax was 8.9±4.9% in girls exercising 10 to 20 MET h/wk during leisure time and 10.1±4.7% in girls exercising 40 to 60 MET h/wk. The corresponding FMDmax measures were 9.3±4.7% for boys exercising 10 to 20 MET h/wk (n=37) and 10.1±4.8% for boys exercising 40 to 60 MET h/wk (n=67). The change in FMDmax was thus not affected by gender (P=0.78).

Discussion

In our sample of nearly 500 adolescents, all studied markers of vascular endothelial function were directly associated with PAI in boys, whereas no association was found in girls. To the best of our knowledge, previous studies on vascular endothelial function and leisure-time physical activity in adolescents are lacking. In 45 children 5 to 10 years of age, total physical activity level assessed by an elegant stable isotope technique measuring total energy expenditure was positively correlated with brachial artery FMD.17 In that study, however, the association of endothelial function with...
physical activity was not examined by gender. We estimated that with this sample our study had >80% power to detect an association observed in boys ($r=0.15$) between FMDmax and PAI at the $P<0.05$ level in both genders. The fact that in our study endothelial function was not associated with PAI in girls may be due to the girls being physically less active than the boys. In adults, it has been suggested that a high volume of exercise training may be required to achieve beneficial effect on endothelial function in subjects with a priori normal vascular function, if possible at all. Indeed, when change in FMDmax was studied in girls and boys with the same activity level (10 to 20 versus 40 to 60 MET h/wk), there was no gender difference, suggesting that FMDmax response to exercise is similar in girls and boys. We thus suggest that the lack of association in girls is due to lower physical activity level rather than gender. Furthermore, the phase of the menstrual cycle may have affected the girls’ brachial artery FMD because endothelial function may vary in response to changing hormonal patterns. Taken together, the results of our study imply that brachial artery endothelial function improves with increasing leisure-time physical activity in 13-year-old boys. Girls with the same activity level as boys experience a similar increase in FMDmax.

Various exercise interventions among overweight and obese children and adolescents have resulted in improvements in endothelial function. Interestingly, the beneficial effect of exercise training was independent of changes in body weight or BMI and attenuated substantially after training cessation. Hence, it is likely that continuous training is needed to maintain the vascular benefits of physical activity. Exercise interventions also have been able to improve vascular endothelial function in healthy adults and in patients with coronary artery disease or type 2 diabetes. Data on the beneficial effect of exercise on endothelial health are most consistent in subjects with impaired endothelial function. Indeed, in a study by Maiorana and coworkers, exercise training did not enhance endothelial function in healthy adults. The discrepancy in the results of these studies on healthy adults may relate to differences in the intensity and amount of training. In addition to

<table>
<thead>
<tr>
<th>Physical activity index, MET h/wk</th>
<th>$\beta$</th>
<th>SE</th>
<th>$P$</th>
<th>$\beta$</th>
<th>SE</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys (n=243)</td>
<td>0.54</td>
<td>1.62</td>
<td>0.74</td>
<td>4.033</td>
<td>1.36</td>
<td>0.0032</td>
</tr>
<tr>
<td>Girls (n=214)</td>
<td>5.59</td>
<td>13.11</td>
<td>0.67</td>
<td>22.46</td>
<td>12.55</td>
<td>0.075</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>$-102.13$</td>
<td>164.77</td>
<td>0.54</td>
<td>$-182.39$</td>
<td>142.41</td>
<td>0.20</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>$-28.27$</td>
<td>52.37</td>
<td>0.59</td>
<td>58.53</td>
<td>52.48</td>
<td>0.27</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>121.15</td>
<td>92.16</td>
<td>0.19</td>
<td>-10.094</td>
<td>81.80</td>
<td>0.90</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>41.56</td>
<td>39.19</td>
<td>0.29</td>
<td>-35.49</td>
<td>32.23</td>
<td>0.27</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>$-7.058$</td>
<td>4.27</td>
<td>0.10</td>
<td>6.18</td>
<td>3.95</td>
<td>0.12</td>
</tr>
<tr>
<td>Brachial artery baseline diameter, mm</td>
<td>$-311.63$</td>
<td>133.41</td>
<td>0.021</td>
<td>$-739.57$</td>
<td>107.33</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Regression coefficients are for a 1-unit change in the covariate.

---

**Figure 1.** FMD responses in the active and sedentary boys 30 to 180 seconds after cuff release. Mean values are shown; error bars indicate SE. $P(\text{activity group*time})=0.0017$ indicates the significance for the interaction indicating the difference in FMD in the activity groups between time points.

**Figure 2.** FMD responses in the active and sedentary girls 30 to 180 seconds after cuff release. Mean values are shown; error bars indicate SE. $P(\text{activity group*time})=0.97$ indicates the significance for the interaction indicating the difference in FMD in the activity groups between time points.
the effects of relatively short-term training interventions on endothelial function, long-term endurance training counteracted the loss of endothelium-dependent vasodilatation associated with aging.8

The vascular endothelium produces numerous paracrine substances, including nitric oxide, which help to maintain the health of the vascular wall and regulate vasomotor function.33 Exercise training may improve endothelial function by upregulating endothelial nitric oxide synthase expression15,39 and activation of the endothelial nitric oxide synthase via kinase Akt-dependent phosphorylation.39 The signals produced by exercise initiating these adaptations are suggested to be increased vascular shear stress and cyclic stretch.13 The amount and intensity of exercise needed to improve endothelial function remain obscure.33

Obesity is associated with endothelial dysfunction in children and adolescents.40 In this study, however, BMI was directly associated with FMDmax in boys; ie, FMDmax improved with increasing BMI. We also have previously found this unexpected association between BMI and brachial artery endothelial function in 24- to 39-year-old adults.7 In the Cardiovascular Risk in Young Finns cohort,7 we showed that the association of BMI with FMD may be curvilinear rather than linear, and an upward slope of this relation was observed. Thus, an increase in body size within the nonobese range in a population of healthy subjects may be associated with physiological changes that lead to enhanced FMD responses and overcome the opposing influences of larger vessel size and increased oxidative stress associated with higher BMIs.7 Indeed, when the association between overweight and FMDmax was studied, weight status was not associated with FMDmax in either gender. However, only a minority of the adolescents in this study were overweight or obese; hence, the influence of obesity on endothelial health is difficult to assess in this population.

The major strengths of our study are that we had a substantially larger sample size of nearly 500 adolescents than in previous studies of endothelial function and physical activity in children. Furthermore, physical examination, laboratory, and ultrasound data were assessed with well-established methods. A limitation is that we used a subjective method, a questionnaire, to assess physical activity level. In addition, the questionnaire has not been validated against other physical activity measures, and only leisure-time physical activity habits in contrast to total physical activity were studied. The fact that we found an association between endothelial function and PAI with a simple tool to assess habitual leisure-time physical activity level suggests, however, that the questionnaire was precise enough to indicate physical activity habits in this rather large sample of adolescents. Another limitation is that we did not have data on the girls’ menstrual cycle phase at the time of the ultrasound measurements or on the adolescents’ last bout of exercise. We also were unable to measure smooth muscle–dependent vasodilatation of the brachial artery.

Conclusions

We found that leisure-time physical activity has a beneficial effect on endothelial function in adolescent boys. We did not find a significant association in girls, which may be due to the girls being considerably less physically active than the boys.

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Disclosures

None.

References

CLINICAL PERSPECTIVE

The onset of cardiovascular diseases lies in childhood. Impairment of arterial endothelial function is an important early observation in the atherosclerotic process. Brachial artery flow-mediated dilatation, a marker of systemic arterial endothelial function, can be measured with a feasible noninvasive ultrasound method already in childhood. In overweight and obese children and adolescents, exercise training improves endothelial function. Our results in adolescents representing the general population further suggest that leisure-time physical activity beneficially affects endothelial function. This effect was clearly found in boys, and with the same level of physical activity, girls experience a similar increase in maximum flow-mediated dilatation. Keeping in mind that physical activity also has several other positive health effects, clinicians should discuss physical activity habits with children and adolescents. Especially with sedentary children, enjoyable ways to be physically more active should be given attention. In addition to encouraging physical activity in children, clinicians could advise parents to exhibit a physically active role model.

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Katja Pahkala, Olli J. Heinonen, Hanna Lagström, Paula Hakala, Olli Simell, Jorma S.A. Viikari, Tapani Röninemaa, Miika Hernelahti, Lauri Sillanmäki and Olli T. Raitakari

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