Physical exercise capacity is associated with coronary and peripheral vascular function in healthy young adults

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Hägg, Ulrika, Birger Wandt, Göran Bergström, Reinhard Volkmann, and Li-ming Gan. Physical exercise capacity is associated with coronary and peripheral vascular function in healthy young adults. Am J Physiol Heart Circ Physiol 289: H1627–H1634, 2005. First published June 3, 2005; doi:10.1152/ajpheart.00135.2005.—Short-term exercise training has been shown to improve cardiovascular function, whereas long-term effects of a physically active lifestyle, on coronary artery function in particular, are still not well studied. We explored possible relationships between physical exercise capacity and coronary and peripheral vascular function in healthy young adults. Twenty-nine healthy young male and female volunteers participated in the study. They underwent 1) basic clinical and echocardiographic characterization, 2) coronary flow velocity reserve (CFVR) measurement of the left anterior descending coronary artery (LAD), 3) common carotid artery (CCA) intima-media thickness (IMT) measurement, 4) assessment of CCA stiffness index (SI), 5) forearm flow-mediated vasodilation (FMD), and 6) submaximal exercise test. The calculated weight-adjusted maximal oxygen uptake capacity (Vo2max) was positively correlated to LAD CFVR and inversely correlated to IMT and SI. Also, subjects with high compared with moderate exercise capacity had higher FMD. In addition, subjects with LAD CFVR in the upper median had higher ratios between endotheium-dependent and -independent vasodilation in the forearm and lower SI in CCA. High exercise capacity due to a physically active lifestyle is associated with high coronary and peripheral artery function, indicating an early protective role of physical exercise for cardiovascular health.

coronary flow velocity reserve; stiffness; endothelial function; intima-media thickness; Doppler echocardiography

Physical exercise has beneficial effects on the occurrence and severity of coronary heart disease in animals (7) and humans (33). Cardiac (21) as well as vascular (5) function are improved in response to exercise. Recently, Hambrecht et al. (17) showed that moderate exercise is superior to primary percutaneous coronary intervention in patients with stable coronary artery disease (CAD). This interesting finding provides further evidence that exercise might exert direct beneficial effects on coronary artery function in humans.

Short- and long-term physical exercise have been shown to improve peripheral artery function, e.g., flow-mediated vasodilation (FMD) (9), and to reduce arterial wall stiffness index (SI) (37) in humans. However, peripheral arteries are considered to react differently than coronary arteries on increased workload (20). Also, arteriosclerosis and endothelial function in peripheral arteries as measured by, e.g., carotid artery intima-media thickness (IMT) and FMD, respectively, do not necessarily reflect the status of the coronary arteries. These major physiological and pathophysiological differences may demand distinct approaches to study function in various vascular beds.

CAD is the leading cause of atherosclerosis-related death. Because of methodological difficulties, coronary artery function and morphology are usually studied with invasive techniques. Hozumi and coworkers (22) were among the first to use high-frequency transthoracic Doppler echocardiography for assessment of coronary artery function. This method has been used successfully in detection of stenotic lesions in patients with coronary heart disease (23) and also in the assessment of coronary endothelial and smooth muscle cell function in healthy subjects (32).

In previous studies investigating possible relationships between cardiovascular state and physical exercise, measurements were made after periods of moderate to intensive training (14). Typically, exercise-induced improvement of vascular function is paralleled by beneficial metabolic effects. To study long-term cardiovascular effects of a physically active lifestyle and rule out the acute metabolic effects of exercise, we investigated coronary as well as peripheral artery function in healthy young individuals with various established exercise habits. Several well-established biomarkers including cholesterol, lipoprotein profile, and C-reactive protein levels were also measured.

We hypothesized that high exercise capacity due to an active lifestyle would entail high coronary flow velocity reserve (CFVR) and forearm FMD. We further hypothesized that high exercise capacity would be associated with lower IMT and arterial stiffness in young adults.

METHODS

Study Group

We recruited 29 healthy volunteers (16 men, 13 women) 20–40 yr of age. For participation in the study they had to be healthy nonsmokers not suffering from asthma or taking any medication. The study was approved by the local ethics committee of Göteborg University. Written informed consent was obtained from all subjects.

Study Protocol

All physiological examinations were performed between 8 AM and 12 AM, on two different occasions, taking a maximum of 2 h each time. All blood samples were taken in the morning at rest, after at least 8-h fasting and before any examinations. Subjects were instructed to avoid caffeine and strenuous exercise for 24 h before the first occasion.

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when they were submitted to a cardiac echocardiographic examination followed by CFVR measurement in the left anterior descending coronary artery (LAD). On the second occasion, IMT, SI, FMD and physical exercise capacity were investigated.

**Cardiac Echocardiography**

A duplex ultrasound system (Acuson Sequoia 512, Mountainview, CA) equipped with a 4V1C transducer allowing color Doppler frequency of up to 2.5 MHz and pulsed-wave spectral Doppler frequency of 1.75 MHz was used. Imaging windows and measurements and calculations of left ventricle mass (LVM), ejection fraction, and cardiac output were performed according to recommendations from the American Society of Echocardiography (34).

**Coronary Flow Velocity Reserve in LAD**

Depending on the accessibility of the LAD we interchangeably used a 4V1C or a 7V3C transducer with 3.5- to 6-MHz color Doppler frequency and 3.5-MHz spectral Doppler frequency. A modified parasternal long-axis projection was used for Doppler recording of the blood flow velocity in the midpart of the LAD (Fig. 1). Baseline LAD flow velocities were recorded with an angle between the LAD course and the Doppler beam typically below 45°. Thereafter, 140 μg·kg⁻¹·min⁻¹ adenosine (ITEM Development, Stockenrud, Sweden) were administered intravenously to cause coronary hyperemia, and the hyperemic flow velocity was recorded at the same vascular segment. One operator performed all LAD flow velocity measurements. All subjects had continuous heart rate and ECG monitoring. Blood pressure was recorded at baseline and during adenosine infusion.

Another operator blinded to the identities of the subjects performed all evaluations off-line. Coronary flow velocity signals were averaged from three consecutive cardiac cycles, and CFVR was calculated as the ratio between the mean diastolic flow velocity during hyperemia and the baseline.

**Flow-Mediated Vasodilation**

Peripheral vascular function was assessed noninvasively, following the principles of Corretti et al. (10). Briefly, brachial artery diameter was recorded with a linear high-resolution probe (15 MHz) during rest, during hyperemia, and after intake of 0.5 mg of sublingual nitroglycerin (Nitromex, Dumex-Alpharma, Stockholm, Sweden). Baseline as well as hyperemic forearm flow velocities were measured to ensure adequate hyperemia.

One blinded operator performed all off-line analysis. Internal brachial artery diameter was measured according to the leading-to-leading edge approach from the near to the far wall at the R wave of the ECG signal. All values were averaged from three consecutive cardiac cycles. FMD or endothelium-dependent vasodilation (EDV) was presented as the percent change of the brachial artery diameter between baseline and hyperemic conditions. The percent change of the brachial artery diameter between baseline and after nitroglycerin administration was referred as endothelium-independent vasodilation (EIDV), and the ratio between EDV and EIDV (EDV/EIDV) was used to correct for possible differences in smooth muscle cell relaxation capacity (27).

**Intima-Media Thickness**

B-mode real-time ultrason was used to evaluate the arterial wall IMT in the common carotid artery (CCA) of subjects in the supine position. A linear high-resolution transducer (8 MHz) was used for the ultrasonic examination. The right CCA was investigated 1–2 cm proximal to the carotid bifurcation. The IMT is defined as the distance from the lumen-intimal interface to the medial-adventitial border (41). ECG-triggered B-mode images from at least three consecutive cardiac cycles were stored. Measurements were performed off-line by a blinded operator.

**Carotid Arterial Wall Stiffness Index**

Vessel stiffness was determined from diameter changes during the cardiac cycle recorded with ECG-triggered M-mode ultrasonography and two-dimensional carotid vessel cine loops. Vessel lumen diameter was measured with the leading-to-leading edge approach from the near wall to the far wall intimal echo. The maximal lumen diameter and vessel lumen diameter at the R wave were defined as systolic and diastolic diameter, respectively. To correct for the nonlinear relationship between blood pressure and vessel lumen diameter, the formula for stiffness index (β) according to Kawasaki et al. (24) was used: $β = \ln(\text{systolic blood pressure/diastolic blood pressure}) \cdot \text{diastolic diameter/systolic diameter} – \text{diastolic diameter}$.

**Assessment of Physical Activity History**

All participants reported the average amount of time spent weekly on high-intensity aerobic training (including jogging, swimming, participation in aerobics, football, etc.), daily activity (including walking or bicycling to work), and resistance training during the last year. Total self-reported physical activity was calculated as the sum of time spent weekly on high-intensity aerobic training and daily activity.

**Assessment of Exercise Capacity**

The physical condition of the subjects was assessed by submaximal cycling on an ergometer bicycle at 50 and 100 W and a speed of 60 rounds/min for 5 min at each load. ECG and heart rate were monitored continuously during exercise. The highest heart rate was recorded during the last minute of exercise. The weight-adjusted maximal oxygen uptake capacity ($\text{VO}_2\text{max}$) was estimated. For evaluation of exercise capacity, absolute values of $\text{VO}_2\text{max}$ were compared with a reference Swedish population, with respect to body weight, age, and sex. In this way, subjects were stratified into five different exercise capacity groups (reduced, moderately reduced, moderate, high, and very high) according to Astrand (2). However, because of the unequal distribution of subjects in each group and the fact that only two of the subjects had reduced and only one moderately reduced oxygen uptake capacity, we divided the whole population into two major groups: moderate, including subjects with reduced, moderately reduced, or moderate oxygen uptake capacity, and high, including subjects with...
high or very high oxygen uptake capacity. In female subjects, the $V_{O2 \max}$ cutoff values for high and moderate exercise groups were 43 and 41 ml·kg⁻¹·min⁻¹ for subjects 20–29 and 30–39 yr of age, respectively. The corresponding values for male subjects were 51 and 47 ml·kg⁻¹·min⁻¹.

### Biochemical Analyses

All biochemical analyses were performed with commercially available kits, according to the manufacturers’ protocols. Triglycerides and cholesterol in serum were measured with reagent systems from Roche (triglycerides/GB kit no. 12146029216, cholesterol kit no. 2016630, Roche Diagnostics, Mannheim, Germany). The assays were analyzed on a Cobas Mira analyzer (Hoffman-La Roche, Basel, Switzerland).

Apolipoprotein (apo)A1 and apoB concentrations were measured with a turbidimetric technique using polyclonal rabbit anti-human antibodies (Q 0496 and Q 0497, Daco Cytomation, Glostrup, Denmark). Concentrations of C-reactive protein were measured with a high-sensitivity reagent kit (CP 3847) from Randox Laboratories (Crumlin, UK).

### Statistics

Statistical analysis was performed with STATISTICA 7 for Windows (StatSoft, Tulsa, OK). Data are presented as means (SD). Clinical characteristics, $V_{O2 \max}$ values, rate-pressure products, heart rates, baseline and hyperemic LAD flow velocities, brachial artery diameters, as well as absolute and percent diameter changes were compared with a nonparametric Mann-Whitney test. Pearson’s correlation test was used to determine the relationship between $V_{O2 \max}$ and self-reported high-intensity aerobic training, self-reported total physical activity, CFVFR, IMT, and SI. After Pearson’s correlation test, a multivariate analysis model was used to adjust for age and sex. FMD in the high- and moderate-exercise-capacity groups as well as EDV/EIDV and SI in the upper and lower medians of LAD CFVFR were compared with a Mann-Whitney test. A $P$ value of $\leq 0.05$ was considered to be statistically significant.

### Results

#### Clinical and Echocardiographic Characteristics

Basic clinical and echocardiographic characteristics and serum levels of assessed biomarkers were similar in the groups. Values are summarized in Table 1.

#### Exercise Capacity

$V_{O2 \max}$ averaged 48.6 (SD 9.3) ml·kg⁻¹·min⁻¹ over the whole study population. Average $V_{O2 \max}$ was 54.0 (SD 7.5) and 42.0 (SD 6.8) ml·kg⁻¹·min⁻¹ ($P < 0.001$) in the high- and moderate-exercise-capacity groups, respectively.

#### Correlation Between Measured Exercise Capacity and Self-Reported Physical Activity

Average self-reported aerobic training averaged 2.0 (SD 1.7) h and was significantly correlated to $V_{O2 \max}$ ($P < 0.05$, $r = 0.43$). Also, total self-reported physical activity averaged 4.6 (SD 2.3) h and was significantly correlated to $V_{O2 \max}$ ($P = 0.01$, $r = 0.47$). Additionally, 13 of 29 subjects also performed regular resistance training for 1.5 (SD 0.9) h/wk, but no correlation was found between this parameter and $V_{O2 \max}$.

#### Effects of Exercise Capacity

**LAD CFVFR.** LAD CFVFR averaged 3.5 (SD 0.6) and was significantly correlated to $V_{O2 \max}$ ($P < 0.05$, $r = 0.41$). In a multivariate analysis model, the correlation remained significant even after adjustment for age and sex ($P < 0.05$; Fig. 2A).

**Intima-media thickness.** CCA IMT averaged 0.4 (SD 0.09) mm in this young population and was inversely correlated to $V_{O2 \max}$ ($P < 0.05$, $r = -0.45$). This inverse relationship was also significant after adjustment for age and sex and in a multivariate analysis model ($P < 0.05$; Fig. 2B).

**Carotid arterial wall SI.** The CCA SI averaged 3.7 (SD 0.9) and was inversely correlated to $V_{O2 \max}$ ($P < 0.05$, $r = -0.4$). The correlation was also age and sex independent ($P < 0.05$; Fig. 2C).

**Forearm FMD.** There was no significant correlation between the numerical values of FMD and $V_{O2 \max}$. However, when FMD between the moderate- and high-exercise-capacity groups was compared, FMD was significantly greater in the high- than in the moderate-exercise-capacity group (Table 2).

#### LAD CFVFR, Endothelial Function, and Arterial Stiffness

EDV/EIDV was significantly higher in subjects with a LAD CFVFR in the upper median compared with the lower median [upper vs. lower median: 21 (SD 13)% vs. 10 (SD 8.7)%, $P < 0.05$; Fig. 3A]. Similarly, subjects in the upper median of LAD CFVFR had significantly lower CCA SI than subjects in the lower median [upper vs. lower median: 3.4 (SD 0.8) vs. 4.1 (SD 0.9), $P < 0.05$; Fig. 3B].

### Discussion

In this study we demonstrate that steady-state $V_{O2 \max}$ in healthy young individuals is positively correlated to self-reported physical activity. Also, $V_{O2 \max}$ was positively correlated to LAD CFVFR and inversely correlated to IMT and CCA SI. These correlations were age and sex independent. In addition, subjects with high exercise capacity revealed greater FMD than subjects with moderate exercise capacity. Furthermore, individuals with LAD CFVFR in the upper median had...
significantly greater EDV/EIDV and lower CCA SI than individuals in the lower median. Steady-state physical exercise capacity does not impact on cholesterol, lipoprotein profiles, or C-reactive protein in this young population.

Coronary Artery Function

During recent years, high-resolution ultrasound has made it possible to noninvasively assess the blood flow velocities in proximal as well as middle and distal parts of the LAD. Compared with other invasive and semi-invasive methods, the advantages of this method are obvious. We and others (32) have shown a close to 100% success rate in assessing LAD flow velocity. By using positron emission tomography, Saraste and coworkers (36) have shown that coronary blood flow velocity is closely correlated to coronary blood flow. In patients with CAD, a CFVR cutoff value of 2 has been shown to predict significant coronary artery stenosis in the LAD. In healthy patients without CAD, CFVR seems to reflect coronary artery endothelial and smooth muscle cell function. Adenosine has been shown to exert its vasodilatory effects through both NO-dependent and -independent mechanisms (8). Furthermore, adenosine primarily dilates capillaries and arterioles. The FMD that takes place in the coronary arterioles requires intact endothelial NO-producing capacity (12). Interestingly, Otsuka et al. (32) showed that acute passive smoking induced endothelial dysfunction and reduced CFVR in healthy nonsmokers, which further supports the CFVR concept as a useful noninvasive method to assess coronary endothelial function.

In this healthy population, intravenous adenosine caused significant increase in heart rate similarly in all study subjects. Because of the potential influences of adenosine-induced heart rate increase on hyperemic myocardial blood flow (29), the hyperemic mean diastolic flow velocity and therefore also the CFVR values could be slightly misjudged. Although this was the case for both high- and moderate-exercise groups, caution

Table 2. Baseline and hyperemic characteristics of CFVR and FMD examinations

<table>
<thead>
<tr>
<th>Variables</th>
<th>Moderate Exercise Capacity (n = 13)</th>
<th>High Exercise Capacity (n = 16)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD flow velocities, m/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.18 (SD 0.04)</td>
<td>0.15 (SD 0.03)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>0.59 (SD 0.12)</td>
<td>0.57 (SD 0.09)</td>
<td>NS</td>
</tr>
<tr>
<td>Ratio (CFVR)</td>
<td>3.3 (SD 0.5)</td>
<td>3.8 (SD 0.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>FMD measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm</td>
<td>3.7 (SD 0.58)</td>
<td>3.6 (SD 0.55)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperemia, mm</td>
<td>3.7 (SD 0.61)</td>
<td>3.8 (SD 0.53)</td>
<td>NS</td>
</tr>
<tr>
<td>Change, mm</td>
<td>0.06 (SD 0.17)</td>
<td>0.17 (SD 0.13)</td>
<td>NS (P = 0.08)</td>
</tr>
<tr>
<td>Change, %</td>
<td>2.0 (SD 4.6)</td>
<td>5.3 (SD 4.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>66 (SD 8)</td>
<td>66 (SD 11)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>88 (SD 13)</td>
<td>87 (SD 12)</td>
<td>NS</td>
</tr>
<tr>
<td>Rate-pressure product, beats/min×10^3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.0 (SD 0.9)</td>
<td>7.5 (SD 1.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>10.0 (SD 1.5)</td>
<td>9.5 (SD 1.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means (SD) for n subjects. LAD, left anterior descending coronary artery; CFVR, coronary flow velocity reserve; FMD, flow-mediated vasodilation.

Coronary Artery Function

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In this healthy population, intravenous adenosine caused significant increase in heart rate similarly in all study subjects. Because of the potential influences of adenosine-induced heart rate increase on hyperemic myocardial blood flow (29), the hyperemic mean diastolic flow velocity and therefore also the CFVR values could be slightly misjudged. Although this was the case for both high- and moderate-exercise groups, caution
should still be taken when comparing our absolute values of CFVR to those of other studies.

Endothelial Function

An impaired NO pathway has been recognized as a major contributing factor underlying endothelial dysfunction and has been demonstrated in patients with cardiovascular risk factors (43). Several investigators have demonstrated an increase in reactive oxygen species after exercise training (11). To overcome exercise-induced oxidative stress, there is accumulating evidence that physical exercise endows the vascular wall with higher NO-producing capacity, as well as antioxidative capacity (16). Indeed, using quantitative angiography, Windecker et al. (42) showed that coronary endothelium-dependent vasodilation was significantly improved after endurance exercise training for 5 mo.

During exercise, increased hemodynamic load in terms of increased flow and shearing force on the endothelium has been shown to upregulate a number of endothelial mediators involved in vascular antiatherogenic defense. Among others, the vascular NO pathway has been shown to be upregulated on shear stimulation (15). We demonstrated here that subjects with high exercise capacity had greater FMD. Furthermore, we also found that subjects with CFVR values in the upper median demonstrated a greater EDV/EIDV in the forearm. Together, a well-functioning endothelium, associated with a physically active lifestyle, could be one of the crucial mechanisms associated with a better coronary vasodilatory response in the high-exercise-capacity group.

In the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) study, invasively assessed CFVR values have been shown to comprise prognostic information for patients undergoing percutaneous coronary intervention (1). Furthermore, Blair et al. (3) showed in a large prospective population study that physical exercise capacity is associated with low risk of cardiac death in individuals not yet showing any manifestation of CAD. With the use of physical exercise as an intervention, improved CFVR has been shown after periods of vigorous exercise in healthy subjects (42) as well as in patients with CAD (18). In line with these previous studies, we showed in the current work that high physical exercise capacity is associated with greater coronary artery function. Thus improved CFVR may be an important physiological mechanism mediating the long-term cardioprotective effects of physical exercise.

In our study, there was no correlation between the numerical levels of $\dot{V}_O^2_{max}$ and FMD. This could be due to methodological variations in assessment of FMD. A diameter change of 0–10% (10) between baseline and hyperemia is expected when using the FMD method. This, in comparison with the CFVR method, where a 500% change can be achieved, may introduce substantial experimental variations, which in themselves could be limited to some extent by experienced operators. The lack of direct correlation between FMD and $\dot{V}_O^2_{max}$ could be due to a limited sample size in the current study, especially in light of the considerable methodological variation.

Intima-Media Thickness

CCA IMT is a well-established surrogate marker for atherosclerosis. However, the association between exercise and IMT is disputed in the literature (13, 38). These conflicting data may be due to different study designs as well as characteristics of the subjects. Rauramaa et al. (35) showed an inverse relationship between exercise capacity and carotid bifurcation IMT in a population aged 50–60 yr, which partially supports the data from the current study, although we measured CCA IMT in an even younger population.
Generally, IMT > 1.20 mm is considered to be abnormal and an early sign of atherosclerosis. In our young healthy volunteers, IMT averaged ~450 μm, which is far below the pathological IMT level. It is now recognized that IMT is a composite surrogate marker for various cardiovascular diseases rather than atherosclerosis burden per se. Interestingly, Liuba et al. (28) showed thickening of IMT in children after acute infection with concomitant elevation of anti-oxidized LDL antibodies. Evidence is now also accumulating that many of the proatherogenic risk factors, including limited NO bioavailability and systemic inflammation, could be involved in vessel wall thickening. Green et al. (15) showed that exercise increased vascular NO production not only in the exercised muscles but also in vascular beds feeding metabolically inactive tissue. This is assumed to be the result of pulse pressure dynamics stimulating the endothelium throughout the circulation (15). Thus one may speculate that beneficial systemic hemodynamic effects associated with an active lifestyle may account for the lower CCA IMT in subjects with high exercise capacity.

In this study population, subjects in the high-exercise-capacity group tended to have lower blood pressure than those in the moderate-exercise-capacity group. Because blood pressure is a known vascular hypertrophic factor (31), we tested the possible impact of blood pressure on the relationship between exercise capacity and IMT in a multivariate analysis model, which confirmed the correlation to be blood pressure independent.

**Arterial Stiffness**

Aging is known to progressively cause a redistribution of elastin-collagen composition (26), resulting in stiffer arteries. It is plausible that this mechanism can be affected by long-term aerobic exercise training. It has further been suggested that the increased pulse pressure and mechanical distension during exercise sessions stretches collagen fibers and modifies their cross-linking, thereby increasing arterial compliance (6). Kingwell et al. (25) reported lower arterial stiffness in trained athletes than in their sedentary peers. Interestingly, we showed recently (16) that in vivo arterial wall compliance, as assessed with tissue Doppler imaging technique, was increased in spontaneously hypertensive rats after 5 wk of voluntary exercise training.

Increased arterial wall stiffness reduces the windkessel function of the large conduit vessels, which may in turn cause a detrimental diastolic flow pattern in the coronary arteries. Indeed, arterial stiffness has been identified as an independent predictor for CAD as well as future cardiovascular events (37).

We showed here that subjects with high coronary artery function had lower CCA SI. This finding further supports a pathogenic link between peripheral conduit vessel mechanical properties and coronary artery function.

**Exercise Capacity According to Åstrand**

Åstrand’s (2) submaximal exercise test is a well-established method of assessing exercise capacity. It is suitable for all subjects independent of sex and exercise habits. However, to avoid environmental influence on maximal heart rate, we performed the submaximal test on the second occasion when subjects were habituated with the facilities and special caution was taken to create a calm and stress-free environment. The significant correlation between self-reported exercise habits and objectively assessed exercise capacity through the submaximal test indicates that the measured exercise capacity indeed reflects daily exercise habits.

**Serum Biomarkers**

apoA1 and apoB have been shown to be better biomarkers than LDL and HDL in predicting fatal myocardial infarction (40). Also, high-sensitivity C-reactive protein (4) has been shown to be a powerful biomarker reflecting the inflammatory status and comprising predictive values for future cardiovascular events. These biomarkers and lipid profiles were analyzed in the present study to address possible metabolic mechanisms of action of a physically active lifestyle. In this healthy young population, these biomarkers do not seem to be related to cardiovascular status. However, cellular and molecular adaptations in the vascular wall, as shown, e.g., by us in a voluntary rat exercise study (16), cannot be addressed in the human setting. It is also conceivable that a larger and less homogeneous study population, mainly regarding physical exercise capacity, may be able to shed some more light on this interesting issue.

**Mechanistic Considerations**

At steady state, there are no differences between subjects with high and moderate exercise capacity regarding lipid profiles and low-degree inflammation, in terms of C-reactive protein levels. Using a voluntary rat exercise model, we showed upregulated antioxidant capacity in the aortic tissue (16), which suggests that vessel wall-specific mechanisms are of great importance in exercise-induced beneficial vascular effects. Furthermore, the lack of obvious correlations among CFVR, FMD, IMT, and SI may also suggest that these physiological biomarkers address distinct aspects and mechanisms within the vascular wall, and different vascular beds may benefit differently from physical exercise.

Interestingly, self-reported resistance training activity in our study does not seem to contribute to VO2max or to any other vascular effects studied in the present study. Indeed, various types of exercise training have been shown to exert distinct effects on the cardiovascular system, i.e., decreased vascular compliance has been reported after resistance training (30).

Data from the present study may suggest that aerobic training as well as low-intensity daily activity rather than resistance training are associated with beneficial cardiovascular effects, probably due to positive vascular responses to increased shear load during aerobic training as discussed above.

The supraphysiological dose of adenosine in the present study has been shown to cause maximal hyperemia, where coronary endogenous autoregulation is ruled out and a linear relationship between coronary blood flow and perfusion pressure is created (20). Thus it is unlikely that different adenosine sensitivity could account for the improved CFVR.

Hildick-Smith et al. (19) showed nicely supranormal coronary flow reserve in athletes compared with sedentary controls. Because of the significantly lower rate-pressure product in the athletic subjects and similar LVM-corrected hyperemic coronary flow between athletes and control subjects, the authors suggested that endothelium-independent mechanisms were responsible for the supranormal coronary flow reserve in these athletes.
top athletes. In the present study, we observed significantly lower baseline coronary flow velocities in subjects with high exercise capacity. This was independent of resting rate-pressure product and LVM, which does not really support the interpretation that the altered myocardial metabolism is the key mechanism accountable for the higher CFVR. Most likely, the low resting coronary flow velocity was a consequence of an exercise-induced coronary artery lumen increase, which has been shown nicely by Windecker et al. (42) with quantitative angiogram. This exercise-induced vascular outward remodeling process is known to be NO dependent (39).

Furthermore, given that the epicardial vessel lumen is increased in high-exercise-capacity subjects, the similar hyperemic flow velocity values may imply higher hyperemic flow per ventricular mass, which is similar in both groups. This may indicate an improved myocardial vasodilatory capacity. Also, the higher FMD in the high-exercise-capacity group, as well as the higher EDV/EIDV and lower SI in subjects with high CFVR, may indirectly support a role of the endothelium in the observed improvement of CFVR. Interestingly, different intensities of exercise seem to exert distinct effects on endothelium-dependent vasodilatory capacity. Gotto et al. (14) showed beneficial endothelial effects after moderate- but not high-intensity exercise. Thus it is conceivable that top athletes acquire a supranormal CFVR via endothelium-independent mechanisms as suggested by Hillick-Smith et al. (19), whereas in subjects with moderate exercise habits, a high endothelial function might contribute to the higher CFVR, as shown in the present study.

In conclusion, high exercise capacity due to a physically active lifestyle is associated with high coronary and peripheral artery function, indicating an early protective role of physical exercise for cardiovascular health.

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