

Research article

THE EFFECTS OF LONG-TERM REGULAR EXERCISE ON ENDOTHELIAL FUNCTIONS, INFLAMMATORY AND THROMBOTIC ACTIVITY IN MIDDLE-AGED, HEALTHY MEN

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ABSTRACT

As studying with population carrying no classical cardiovascular risk factors seems to be an advantage in isolating effects of regular exercise on endothelial functions, inflammatory and thrombotic activity; the present study was designed to evaluate the clear effects of long-term regular exercise in middle-aged, healthy men. A total of 32 regularly exercising (three times per week, 12.8 ± 6.8 years) men (Group I, mean age = 53.2 ± 6.1 yrs) and 32 sex- and age-matched sedentary subjects (Group II, mean age = 51.0 ± 7.7 yrs) were involved in the study. All participants were non-smokers and with no history of hypertension and diabetes. During one day preceding tests, the subjects refrained from training and maintained their normal diet. In all subjects, body mass index (BMI), percentage of body fat (% BF) and maximal oxygen uptake (VO_{2max}) were calculated. Serum uric acid, glucose, HbA1c, lipids, high-sensitive C-reactive protein (hs-CRP), fibrinogen levels, white blood cell (WBC) and platelet count were measured. Resting heart rates and blood pressures were recorded and standard exercise stress test was applied using the modified Bruce protocol. Flow-mediated and nitrate-induced dilatation (FMD and NID) of the brachial artery and carotid intima-media thickness (cIMT) were evaluated as markers of endothelial functions and early atherosclerosis. Mean BMI, % BF, systolic and diastolic blood pressures, WBC and platelet count, HbA1c, total and LDL cholesterol, hs-CRP and fibrinogen levels were similar between the groups. Group I had significantly lower serum glucose, uric acid and triglyceride ($p < 0.05$, $p < 0.005$ and $p < 0.05$, respectively) and higher HDL cholesterol levels ($p < 0.0001$) than in Group II. FMD values were significantly higher in Group I than in Group II ($p < 0.005$) while there were no significant differences in NID and cIMT measures between the groups. VO_{2max} and cIMT showed a negative correlation in Group I ($r = -0.463$, $p < 0.0001$). Negative correlations also existed between VO_{2max} and fibrinogen levels in both Group I and II ($r = -0.355$, $p < 0.05$ and $r = -0.436$, $p < 0.05$, respectively). These results are concordant with the concept of favorable effects of regular physical exercise on cardiovascular health based on enhancement of endothelial functions even in subjects who have low cardiovascular risk profile.

KEY WORDS: Physical activity, flow-mediated dilatation, nitrate induced dilatation, carotid intima-media thickness, C-reactive protein, fibrinogen.

INTRODUCTION

Regular physical activity is associated with decrease in all cause mortality, especially cardiovascular

disease (Johansson and Sundquist, 1999; Paffenbarger et al., 1993; J, Rosengren and Wilhelmsen, 1997; Wannamethee et al., 1998). Exercise promotes a healthy cardiovascular risk

profile by reducing adiposity, blood pressure, diabetes incidence, dyslipidemia, and inflammation, and enhancing insulin sensitivity, glycemic control, fibrinolysis, and endothelial function (Bassuk and Manson, 2003).

It is well documented with large sample studies that factors associated with increased coronary artery diseases are the causes of endothelial dysfunction at the same time. Dysfunction of the endothelium is presumed to play an initial part in the progress of atherosclerotic cardiovascular disease (Ross, 1999). Therefore, in attempts of prevention of cardiovascular health, improvement of endothelial dysfunction is targeted basically.

Aerobic regular exercise has been shown to improve endothelial functions in patients with chronic heart failure (Hornig et al., 1996) coronary artery disease (Kuvini et al., 2001), hypertension (Higashi et al., 1999), type 2 diabetes (Maiorana et al., 2001) and to prevent age-related declines in endothelial function (DeSouza et al., 2000). Many lines of evidence show that endothelial dysfunction is closely associated with inflammatory process. As a result of vascular biology and epidemiology research, investigators are agreed with serum inflammatory and thrombotic markers such as white blood cell, C-reactive protein and fibrinogen are predictive of future cardiovascular events (Danesh et al., 1998; Targher et al., 1996).

Beneficial effects of regular exercise also appear with mechanisms including direct effects on the cardiovascular system through an increase in stroke volume (Saltin, 1969; Wolfe et al., 1985) and an increase in maximal oxygen uptake (Morris and Froelicher, 1993). Regular physical activity and good cardiorespiratory fitness have been shown to be associated with reduced prevalence and progression of atherosclerosis as indicated by carotid intima-media thickness (cIMT) measurements (Lakka et al., 2001; Rauramaa et al., 1995).

Studying with population carrying no classical cardiovascular risk factors seems to be an advantage in isolating effects of regular exercise on endothelial functions, inflammatory and thrombotic activity. Therefore, the current study was planned to evaluate the clear effects of long-term regular exercise in middle-aged men with low cardiovascular risk profile.

METHODS

Subjects

A total of 32 regularly exercising middle-aged men (Group I, mean age = 53.2 ± 6.1 yrs) and 32 sex- and age-matched sedentary subjects (Group II, mean age = 51.0 ± 7.7 yrs) were involved in this study. Group

I subjects had been participating about 80 minute exercise sessions twice a week for a period of 12.8 ± 6.8 years. These sessions consisted of three parts. Warm-up period lasts about 20 min and includes jogging and light basketball game. The second part is a supervised exercise session which lasts about 45 min and includes activities such as walking, aerobic exercise, calisthenics, jogging, running, hopping and stretching drills. The last part consists of 15 min basketball game and 5 min stretching drills. Subjects were also exercising individually about one hour once a week including walking and running drills. None of the cases in the Group II have participated in regular physical activity. Subjects with history of smoking, diabetes, hypertension, metabolic syndrome, atherosclerotic vascular disease, heart failure and liver, renal or inflammatory disease were excluded.

The subjects were informed about testing procedures, possible risks and discomfort that might ensue and gave their written informed consent to participate in accordance with the Helsinki Declaration (WMADH, 2000).

During one day preceding tests, the subjects refrained from training and maintained their normal diet. Laboratory tests were carried out on the same day in similar conditions. Room temperature was 22-23° C and relative humidity was 50%. All the ultrasound studies were performed by a single experienced vascular sonographer who was unaware of the clinical and laboratory characteristics of the subjects.

Assessment of physical and performance characteristics

Body weight and height were measured with standard techniques and body mass index (BMI) was calculated as an index of total body mass.

Skinfold thickness at sites of abdomen, triceps, subscapular and supriliac were measured on the right side of the body using a Holtain caliper (Holtain Ltd, Crymych, UK) and for each subject; the average of two measurements was recorded. Percentage of body fat (% BF) was estimated using the equation of Yuhasz (Wilmore and Benhke, 1969).

Maximal oxygen uptake (VO_{2max}) values were obtained indirectly through the Astrand-Rhyming test (Åstrand, 1988) by cycle ergometry (Monark Ergomedic 828E, Sweden).

Biochemical analyses

Venous blood samplings were conducted in the morning following an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were assessed

enzymatically by autoanalyser (Bayer Diagnostics Dax 48, Toshiba, Japan) and low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula (Friedewald et al., 1972).

Serum glucose level was measured by the glucose oxidase technique (Biobak Laboratory Supplies Trade, Ankara, Turkey). HbA1c was measured via colorimetric method, white blood cell (WBC) and platelet count were determined using a Sysmex Cell Counter SE-9000 (Toa Medical Electronics, Tokyo, Japan) and high-sensitive C-reactive protein (hs-CRP) concentrations were assayed on a Hitachi 704 automatic analyzer using a turbidimetric method (Boehringer Mannheim GmbH, Mannheim, Germany). Fibrinogen levels were measured using a coagulometric assay according to Clauss method (Clauss, 1957) on an automatic analyzer Biomerieux-Option B.

Exercise testing

All participants underwent standard exercise stress test using the modified Bruce protocol. Blood pressures (BP), heart rate (HR) and 12-lead electrocardiograms were recorded at rest, at the end of test and three minutes after the test. The subjects were exercised until reaching their 90% of age-specific maximal heart rate (=220-years of age). Test was ended when the subjects reach target heart rate. Subjects who had abnormal exercise stress test were excluded from the study.

Assessment of flow-mediated (FMD) and nitrate-induced dilatation (NID)

The noninvasive determination of endothelial dysfunction was performed according to the method described by Celermajer and co-workers (1992). Imaging studies of the brachial artery were performed using a high-resolution ultrasound machine (Hewlett-Packard SONOS 4500, Andover Massachusetts) equipped with a 3-11 MHz linear-array transducer. Vascular studies were performed in morning while the subjects were fasting, in a quiet and temperature controlled (22 °C) room. Brachial artery diameter was measured from B-mode ultrasound images. The brachial artery was scanned in longitudinal section 2-5 cm above the elbow and the center of the artery was identified when the clearest pictures of the anterior and posterior intimal layers were obtained. When a satisfactory transducer position was found, the skin was marked and the arm and transducer were remained in the same position throughout the study. Depth and gain settings were set to optimize images of the lumen/arterial wall interface, images were magnified using a resolution box function and the operating parameters were not changed during the

examination. Imaging of the left brachial artery was performed following 30 min. of rest. Baseline brachial artery diameter was measured. Endothelium-dependent vasodilatation (mediated by EDRF) was assessed by measuring the changes in the diameter of the brachial artery during reactive hyperemia created by an inflated cuff (250 mmHg for 5 min) on the upper-arm. The cuff was released after 5 minutes. The arterial diameter was measured at 60-90 seconds after deflation. Five cardiac cycles were analyzed and measurements were averaged. Twenty minutes later, a fourth scan was obtained to measure the endothelium-independent vasodilatation, 3 minutes after the sublingual administration of glycerol nitrate (400 µg). Images were recorded and brachial arterial diameters were measured by a single investigator. Measurements were taken from the anterior to the posterior interface between media and adventitia (m-line) at end-diastole (timed by QRS complex). FMD and NID were expressed as a percent increase of the baseline value of the diameter. Coefficients of variation of intra-observer FMD and NID measurements were 4.2% and 4.4%, respectively.

Assessment of carotid intima-media thickness (cIMT)

cIMT was assessed by B-mode ultrasound vasculography using a high-resolution ultrasound machine (Hewlett-Packard SONOS 4500, Andover Massachusetts) equipped a 3-11 MHz transducer. After having the subject rest for at least 10 min in the supine position with the neck in slight hyperextension, we evaluated an optimal visualization of the right common carotid artery 1 cm proximal to the bulb. The image was focused on the posterior (far) wall, and the resolution box function was used to magnify the arterial far wall. Two angles were used in each case for right common carotid IMT: anterior oblique and lateral. One end-diastolic frame for each interrogation angle was selected and analyzed for mean IMT. Five measurements of far-wall IMT were taken and the average values of these measurements were used in the analyses. Coefficient of variation of intra-observer cIMT measurements was 3.5 %.

Statistical analyses

The analyses were performed with SPSS for windows 11.0 (Chicago, IL, USA). Numerical values are expressed as mean \pm SD. Significant differences between groups were investigated using the t-test. Pearson's correlation test was used to evaluate the correlations among performance, endothelial function and biochemical data in each group.

Table 1. Baseline and clinical characteristics of the groups. Data are means (\pm SD).

	Group I (n=32)	Group II (n=32)
Age (yrs)	53.2 (6.1)	51.0 (7.7)
Height (m)	1.72 (.05)	1.72 (.07)
Weight (kg)	80.6 (9.6)	81.3 (10.3)
BMI (kg/m ²)	26.9 (2.4)	28.2 (3.1)
BF (%)	27.0 (5.6)	26.7 (7.2)
VO _{2max} (ml·min ⁻¹ · kg ⁻¹)	30.9 (6.0)	24.4 (6) ***
Systolic BP (mmHg)	124 (20)	118 (16)
Diastolic BP (mmHg)	74 (9)	78 (8)
Resting HR (bpm)	84 (13)	93 (13) *
Time spent reaching target HR (min)	9.59 (2.92)	8.00 (2.20) *

Group I = Regularly exercising subjects, Group II = Sedentary subjects, BMI = Body mass index, BF = Body fat, VO_{2max} = Maximal oxygen uptake, BP = Blood pressure.

* p < 0.05, *** p < 0.001

RESULTS

There were no significant differences in mean age, BP, BMI and % BF between the groups. However, Group I had higher VO_{2max} values (p < 0.0001) and time spent reaching target heart rate (p < 0.05) and lower resting heart rate (p < 0.05) than in Group II. Table 1 shows baseline and clinical characteristics of the groups.

Lower serum glucose (p < 0.05), uric acid (p < 0.005) and triglyceride (p < 0.05), and higher HDL cholesterol levels (p < 0.0001) were detected in Group I than in Group II. However, there were no significant differences in WBC and platelet count, HbA1c, total and LDL cholesterol, hs-CRP and fibrinogen levels between the groups. Table 2 presents biochemical and hematological markers of the groups.

FMD values were significantly higher in Group I than in Group II (p < 0.005) while there were no significant differences in NID and cIMT measures between the groups. Table 3 shows

endothelial functional markers of the groups.

There were no significant correlations between FMD and VO_{2max} values in both groups. A negative correlation was found between VO_{2max} and cIMT levels in Group I (r = -0.463, p < 0.0001) (Figure 1). Negative correlations also existed between VO_{2max} and fibrinogen levels in both Group I and II (r = -0.355, p < 0.05 and r = -0.436, p < 0.05, respectively) (Figure 2).

DISCUSSION

Regular physical activity reduces in both sexes and at all ages, coronary and cardiovascular morbidity and mortality (Gibbons and Clark, 2001). Furthermore, it has been demonstrated that inverse associations between regular physical activity and cardiovascular disease after adjustment for conventional risk factors (Yu et al., 2003). Multiple mechanisms can be responsible for cardio-protective effects of regular physical activity (Gibbons and Clark, 2001; Gielen and Hambrecht, 2001).

Table 2. Biochemical and hematological markers of the groups. Data are means (\pm SD).

	Group I (n=32)	Group II (n=32)
Glucose (mg·dl ⁻¹)	97.7 (9.6)	104.4 (12.7) *
HbA1c (%)	5.4 (.4)	5.5 (.4)
Total cholesterol (mg·dl ⁻¹)	213.7 (39.4)	205.2 (37.6)
HDL cholesterol (mg·dl ⁻¹)	50.6 (7.8)	43.3 (7.8) ***
LDL cholesterol (mg·dl ⁻¹)	140.5 (31.9)	132.5 (33.3)
Triglyceride (mg·dl ⁻¹)	112.6 (66.3)	157.0 (98.4) *
Uric acid (mg·dl ⁻¹)	5.40 (1.14)	6.37 (1.34) **
WBC (x10 ³ ·mm ⁻³)	6.21 (1.54)	6.74 (1.22)
hs-CRP (mg·dl ⁻¹)	.180 (.29)	.241 (.29)
Platelet count (x10 ³ ·mm ⁻³)	225.8 (43.6)	232.3 (41.8)
Fibrinogen (mg·dl ⁻¹)	308.0 (50.1)	294.7 (50.1)

Group I = Regularly exercising subjects, Group II = Sedentary subjects, HDL = High-density lipoprotein, LDL = Low-density lipoprotein, WBC = White blood cell, hs-CRP = High-sensitive C-reactive protein. * p < 0.05, ** p < 0.01 and *** p < 0.001.

Table 3. Markers of endothelial function and early atherosclerosis in both groups. Data are means (\pm SD).

	Group I (n=32)	Group II (n=32)
FMD (%)	11.66 (3.69)	8.16 (4.04) ***
NID (%)	14.98 (4.68)	13.78 (5.22)
cIMT (mm)	.67 (.14)	.70 (.12)

Group I = Regularly exercising subjects, Group II = Sedentary subjects, FMD = Flow-mediated dilatation, NID = Nitrate-induced dilatation, cIMT = Carotid intima-media thickness. *** $p < 0.001$.

Underlying mechanisms include direct effects on the cardiovascular system through an increase in stroke volume (Saltin, 1969; Wolfe et al., 1985) and an increase in maximal oxygen uptake (Morris and Froelicher, 1993). Exercise may also alter the distribution of the lipid fractions. Likewise, mean HDL cholesterol level was higher and triglyceride level was lower in Group I than in Group II. These findings are compatible with the meta-analyses reported by Leon and Sanchez (2001). High HDL cholesterol levels can improve endothelial functions. Furthermore, lower concentrations of thrombotic factors (Clauss, 1957) and inflammatory markers (Macy, 1997) are also proposed. Long term regular exercise regimens predispose the coagulation system toward fibrinolytic activity rather than thrombotic activity (Stratton et al., 1991).

Endothelial dysfunction is known as the first step of pathogenesis of atherosclerosis (Thompson et al., 2003). There is increasing evidence that the development of the endothelial dysfunction is associated with inflammatory process (Munro and Cotran, 1988; Ross, 1993; Tracy, 1997). Many studies demonstrated inverse relationships between

regular physical activity and serum concentration of inflammatory and thrombotic markers (Abrams, 2003; Chandra et al., 2004; Rosenson and Koenig, 2003). Kritchevsky and co-workers (2005) reported that systemic markers of inflammation appear useful for indicating elevated cardiovascular disease risk in middle-age. In our study, neither hs-CRP nor fibrinogen levels were different between the groups. Geffken et al. (2001) demonstrated that lower values of serum inflammatory markers and white blood cell count are associated with higher levels of physical activity. However, various exercise regimens may influence inflammatory markers differently and there is still lack of knowledge about the target exercise level leading optimum anti-inflammatory efficiency. In the current study, there were no correlation between physical activity and WBC count. However, it might be related to subtypes of WBC (leukocyte count e.g.) (Horne et al., 2005).

There are several studies investigating the relationships between measures of physical activity and plasma fibrinogen. While most of the studies demonstrated significant inverse relationships (Elosua et al., 2005; Elwood et al., 1993; Folsom et

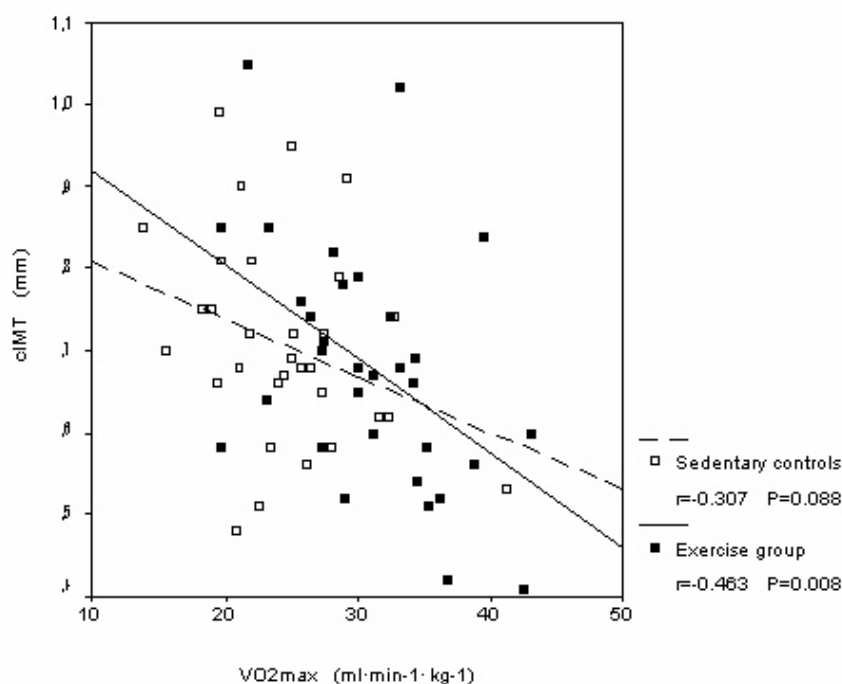


Figure 1. Correlations between VO₂max and cIMT in both groups.

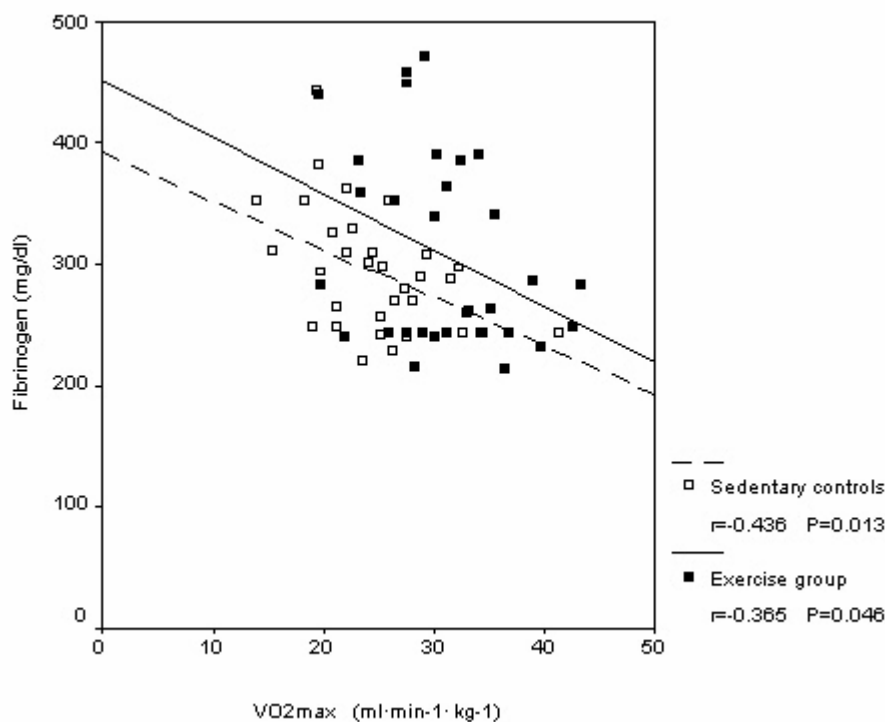


Figure 2. Correlations between VO_{2max} and fibrinogen in both groups.

al., 1991; Lakka and Salonen, 1993) others did not (Carroll et al., 2000; Verdaet et al., 2004). In the present study, despite finding of no significant differences in thrombotic markers between the groups, there were negative correlations between VO_{2max} and fibrinogen levels in both groups. Discrepancies between these study results can be due to differences in study design and methodology.

FMD is endothelium-dependent and can be a useful marker of the presence of endothelial dysfunction while NID is endothelium-independent and may not reflect endothelial function. In our study, FMD values were significantly higher in Group I than in Group II while there were no significant differences in NID values between the groups. Although reports exist in the literature indicating positive correlations between FMD and exercise capacity (Hagg et al., 2005; Palmieri et al., 2005), there was no relationship in the current study.

These findings indicate that different mechanisms may play an important role on endothelial functions. For instance, in a recent study (Elosua et al., 2005) moderate-high physical activity in men and light and moderate-high physical activity in women are reported to be associated with lower levels of uric acid. Similarly, regularly exercising subjects had lower uric acid concentrations compared to sedentary controls in the present study. This issue might be an indicator of reduced total oxidative stress in regular exercisers. Consequently, low oxidative stress may contribute endothelial functions positively. In addition, exercise causes

various kinds of mechanical, chemical and thermal stresses on the endothelial cell. Chronic and repetitive exposure to these stresses may precondition the endothelial cell to future stresses through a number of different mechanisms (Marsh and Coombes, 2005). Shear stress increases during exercise and elevates free radical production, up-regulates protective mechanisms such as antioxidant enzymes and heat-shock proteins and down-regulates proapoptotic factors in the endothelial cell (De Keulenaer et al., 1998; Dimmeler et al., 1999; Takeshita et al., 2000). Furthermore, shear stress is known to influence the in situ morphology of endothelial cells that reinforces the architecture of the vascular wall and decreases the turbulence of blood flow (Reidy and Langille, 1980). Finally, Taddei et al. (2000) showed that regular exercise protects the endothelium from aging-related deterioration via availability of nitric oxide which known to improve endothelial functions and inhibit endothelial cell apoptosis.

Increased cIMT has been shown to be predictive of the development of coronary atherosclerosis, CHD, and stroke (Bots et al., 1997; O'Leary et al., 1999). According to epidemiologic studies, the existence of ≥ 1 mm cIMT is significantly associated with increased risk of myocardial infarcts and cerebrovascular disease at all ages (Sinha et al., 2002). Dietary cholesterol, insoluble fibre, BMI and smoking are known significant predictors of cIMT progression (Markus et al., 1997). Moreover, it has been demonstrated an

inverse relationship between cardiorespiratory fitness and cIMT progression (Lakka et al., 2001). VO_{2max} has also suggested as a new independent predictor of cardiovascular events (Myers et al., 2002; Ridker et al., 2002). Yu et al. (2003) indicated that VO_{2max} had strong, inverse, and graded associations with 4-year increases in maximal cIMT after adjustments for age and cigarette smoking. Despite the cross-sectional design of our study, cIMT values were not significantly different between the groups. Furthermore, we found no values of cIMT equal or over 1 mm in both groups. This may probably be the result of low cardiovascular risk profile of subjects. However, there was an inverse relationship between VO_{2max} and cIMT values in regularly exercising subjects. This finding suggests that good cardiorespiratory fitness may be associated with slower progression of atherosclerosis.

CONCLUSION

Favorable effects of regular physical exercise on cardiovascular health seem to be based on enhancement of endothelial functions. The results suggest that regular exercise promotes better endothelial functions even in subjects who have low risk for cardiovascular disease.

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KEY POINTS

- The present study results suggest that regular exercise is effective on endothelial functions even in subjects who have low risk for cardiovascular disease.
- Therefore, regular exercise is feasible in improving endothelial functions independently from cardiovascular risk profile.

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KEY POINTS

- The present study results suggest that regular exercise is effective on endothelial functions even in subjects who have low risk for cardiovascular disease.
- Therefore, regular exercise is feasible in improving endothelial functions independently from cardiovascular risk profile.

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