Markers of Inflammation Are Inversely Related to Physical Activity and Fitness in Sedentary Men With Treated Hypertension

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Background: Physical inactivity is an important risk factor for atherosclerotic disease. We studied the relationship between physical activity and physical fitness and soluble markers of atherosclerotic activity in men with drug-treated hypertension.

Methods: The participants (n = 177, 40 to 74 years of age), who were randomly recruited from the Hypertension High Risk Management Trial (HYRIM), were overweight and had sedentary lifestyles. The inflammatory markers high-sensitivity C-reactive protein (hs-CRP), soluble vascular cell adhesion molecule–1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble E-selectin (sE-selectin) and the hemostatic markers soluble thrombomodulin (sTM), von Willebrand factor (vWF), and tissue plasminogen activator antigen (tPAag) were measured. Physical activity was measured by use of a questionnaire. Time to exhaustion in a bicycle test was used as an expression of physical fitness.

Results: The hs-CRP showed a significant inverse relationship with physical fitness independent of major cardiovascular risk factors (P = .017) but was not related to physical activity. The sE-selectin was significantly related to physical activity, although only when other factors were taken into account (P = .033), and it had no significant association with physical fitness. In addition there were strong associations between hs-CRP and sICAM-1 and the Framingham Coronary Heart Disease risk score (P < .001).

Conclusions: The observed inverse relations between physical fitness and hs-CRP and between level of physical activity and sE-selectin in drug-treated, hypertensive sedentary men indicates a beneficial effect of good fitness status as well as activity of low intensity on vessel wall inflammation. Am J Hypertens 2006;19:669 – 675 © 2006 American Journal of Hypertension, Ltd.

Key Words: Hypertension, atherosclerosis, inflammation, hemostasis, physical activity.

Endothelial dysfunction, an early step in the atherosclerotic process, is characterized by increased expression of the cellular adhesion molecules (CAM) vascular cell adhesion molecule–1 (VCAM-1), intercellular adhesion molecule–1 (ICAM-1), and E-selectin, contributing to chronic subendothelial inflammation. Concurrently a rise in the endothelial secretion of von Willebrand factor (vWF) and plasminogen activator inhibitor type 1 (PAI-1) promotes thrombus formation. Elevated levels of soluble thrombomodulin (sTM), a component of the endothelial cell membrane, has been regarded a marker of endothelial cell damage. The soluble (s) forms of these endothelial related components are used as markers of inflammatory and hemostatic disturbances and endothelial injury, and hence of atherosclerotic activity. Furthermore C-reactive protein has emerged as a useful inflammatory marker and predictor of cardiovascular risk when measured by high sensitivity tests (hs-CRP). In addition CRP seems to promote inflammation itself, and has been shown to induce endothelial expression of CAM in vitro.

Physical inactivity and low physical fitness are both independent risk factors for cardiovascular disease (CVD). There is increasing evidence that the beneficial effect of increased physical activity is exerted partly by reducing vessel wall inflammation and prothrombotic activity.

Individuals with drug-treated hypertension are commonly met in everyday medical practice, and their high blood pressures are often accompanied by numerous other risk factors. Recent reports indicate that the prevalence of hypertension again is increasing in some western populations, partly because of the increase in obesity. It is well recognized that a broader intervention than treatment with
antihypertensive drugs alone is needed to be effective in preventing coronary heart disease (CHD) in this group. Nevertheless data on the effect of physical conditioning on biochemical markers of atherosclerosis among these patients are scarce.

The objective of the present study was to investigate the relationships between markers of inflammation and hemostasis and the level of physical activity and physical fitness among sedentary, drug-treated hypertensive men. Even occasional and moderate activity are associated with health benefits. Our hypothesis was therefore that despite a sedentary life, differences in fitness and energy expenditure resulting from everyday activities might influence the risk of developing atherosclerosis and hence might be reflected in levels of inflammatory and hemostatic variables.

We also wanted to study the relations between these biomarkers and traditional CVD risk factors as well as the Framingham CHD risk score (FCRS) in this particular population.

**Methods**

**Study Population**

From the Hypertension High Risk Management Trial (HYRIM), a total of 177 men 40 to 75 years of age were randomly selected for inclusion in this substudy. They were all diagnosed with essential hypertension and were receiving drug treatment for hypertension before entering the study. Further inclusion criteria were a body mass index (BMI) between 25 and 35 kg/m² and a sedentary lifestyle, defined as <1 h of regular exercise per week. Individuals with clinical manifestation of atherosclerotic disease such as previous or present cerebrovascular or coronary heart disease were excluded. Cancer, impaired hepatic or renal function, and inability to perform physical exercise also led to exclusion, as did insulin dependent diabetes mellitus, total cholesterol (T-C) >8.0 mmol/L or s-triglycerides (TG) >4.5 mmol/L. None of the participants were taking lipid-lowering medication. The experimental protocol and the process for obtaining written informed consent were approved by the Regional Ethic Committee.

**Measurements**

Blood samples were drawn after overnight fasting, between 8 and 10 AM, to minimize diurnal variations. Vigorous physical activity was avoided the day before blood sampling, and smoking was avoided after midnight. Medications were taken as usual.

The sVCAM-1, sICAM-1, and sE-selectin were analyzed in serum with commercial enzyme-linked immunosassay methods (R & D Systems Europe, Abingdon, England). The vWF, sTM, and tissue plasminogen activator antigen (tPAag, considered mainly to reflect the concentration of PAI-1) were measured in citrated plasma by Asserachrom (Stago Diagnostica, Asnieres, France) and TintElize tPA (Biopool AB, Umeå, Sweden) respectively. The CRP was measured by a high-sensitivity immunoassay from Roche. All these samples were kept frozen at −70°C until analyzed. Serum lipids were measured by conventional enzymatic methods. The LDL-C was calculated according to the Friedewald formula.

The FCRS was calculated on basis of an individual’s age, blood pressure (BP), total cholesterol (T-C), HDL cholesterol (HDL-C), smoking, and diabetes status.

The BP was measured by an automatic device with the participant in supine position after resting for 5 min. The mean of two of the last three measurements was used.

After inclusion, the HYRIM Physical Activity Questionnaire (HPAQ) was used to estimate level of physical activity. The HPAQ was especially developed for HYRIM, giving a detailed assessment of daily life activities. A validity study has shown this questionnaire to be a reliable tool for measurement of total energy expenditure. The participant was asked by trained staff about the frequency, intensity, and duration of all types of activity related to work, transport, home, leisure time, hobbies, and regular exercise, as well as sedentary activities, during the previous 7 days. Each reported activity was given a predefined metabolic equivalent (MET) score and multiplied by the number of minutes spent on the activity. Total energy expenditure was estimated by multiplying the sum of MET values for all activities with the individual’s basal metabolic rate and time spent on each activity. We also calculated physical activity level, a measure of average daily activity level defined as total energy expenditure divided by basal metabolic rate.

Time to exhaustion in a bicycle exercise test was used as an estimate of physical fitness. After a warm-up phase of 7 min on 25 watts, the load increased with 15-watt/min until exhaustion. The Borg scale was used to evaluate degree of exhaustion. Tests terminated before maximal achievement were excluded from further analyses.

**Statistical Analyses**

One TG value (14.6 mmol/L) was omitted from the analyses because of nonfasting. When possible, both parametric and nonparametric tests were performed, without main differences in the results. The TG and CRP values were logarithmically transformed in parametric analyses because of skewed distributions. Because of one outlier (defined as >5 standard deviations from mean), the parametric analyses on sVCAM-1 were made both with and without this value, without considerable differences. All other measures were reasonably normally distributed in the population. Mean values in groups were compared using independent samples t and Mann-Whitney tests. Univariate correlations were made with the Pearson and Spearman correlation coefficients. Smoking status was modeled as current smoker (assigned the value 1) versus former or never smoker (assigned the value 0) and entered as an ordinal variable into Spearman correlation analysis.
Multiple regression analyses were performed in a backward stepwise manner to adjust for factors potentially linked to the inflammatory and hemostatic markers as well as activity level and fitness, such as age, BP, BMI, lipids, and smoking. The SPSS version 11.0 software package (SPSS Inc., Chicago, IL) was used for the statistical analyses. Significance level was set to 0.05. No adjustments for multiple tests were done.

Results

Table 1 shows characteristics of the study population. Of the subjects, 51% had a systolic blood pressure (SBP) ≥140 mm Hg, and 57% had a diastolic blood pressure (DBP) ≤90 mm Hg. In all, 51% used one single antihypertensive drug, 29% a combination of two, and the rest a combination of three or more drugs. There were no significant differences in markers of inflammation or hemostasis, or in physical activity or fitness, between users and nonusers of different drug classes (data not shown).

The mean physical activity level of 1.52 confirms the sedentary nature of the population. The majority of the participants (53%) had an FCRS between 10% and 20%, which is considered to indicate a moderate risk of developing CHD during the next 10 years. The distribution of FCRS in the population is shown in Fig. 1.

Univariate Correlations

Univariate correlations between markers of inflammation and hemostasis, physical activity, physical fitness and CVD risk factors are displayed in Table 2. The sVCAM-1, sICAM-1, and vWF were inversely correlated with physical activity (P = .015, 0.002, and 0.030 respectively), whereas a positive correlation between tPAag and physical activity was noted (P = .033).

The s-ICAM-1 and hs-CRP were negatively correlated with physical fitness (P < .001 and P = .015) and were positively correlated with the FCRS (P < .001 and P = .006).

With the exception of s-E-selectin and hs-CRP, all markers were associated with age. sICAM and hs-CRP were the only markers significantly associated with current smoking (p = .032 and .030). The sICAM-1 showed a positive correlation with TG (P = .016). The s-E-selectin was positively correlated with DBP (P < .001), TG (P = .004), and BMI (P = .030). The hs-CRP was negatively correlated with HDL-C (P = .008), as was tPAag (P = .005). In addition tPAag was positively correlated with TG (P = .004).

Multiple Regression Analysis

Multiple regression analyses were performed with the inflammatory and hemostatic markers as dependent vari-

![FIG. 1. Distribution of Framingham coronary heart disease (CHD) risk score in the study population.](https://academic.oup.com/ajh/article-abstract/19/7/669/179270/b70270)
ables and with age, DBP, BMI, LDL-C, HDL-C, TG, and smoking status as independent variables. Physical fitness and physical activity were strongly intercorrelated ($r = 0.50$) and therefore included as independent variables in two separate regression models. The relationships between physical activity and physical fitness, respectively, and the inflammatory and hemostatic markers from these analyses are shown in Table 3. The inverse relation between hs-CRP and physical fitness was still significant ($P = .017$).

The sE-selectin now showed a significant negative association to physical activity ($P = .033$), whereas the univariate associations between sVCAM-1 and sICAM-1 and physical activity lost their significance when age was entered into the model. Similarly the relation between sICAM-1 and physical fitness was no longer significant when age was adjusted for. Neither were the relations between vWF and tPAag and physical activity statistically significant after adjustments for major risk factors.

The previously described relations between the measured biomarkers and traditional CVD risk factors were mainly unchanged when analyzed in these two regression models.

### Discussion

#### Physical Activity and Physical Fitness

In this study of sedentary men with treated hypertension and multiple cardiovascular risk factors, the main findings were a significant inverse relationship between hs-CRP and physical fitness and between sE-selectin and self-reported physical activity. The relationship between CRP and fitness was evident both univariately and after adjustments for age and other major risk factors. In contrast we found no association between CRP and level of physical activity. Inverse relationships between CRP and physical fitness$^{19,20}$ as well as self-reported activity level$^8,9$ have been demonstrated earlier, although in populations different from ours and not with both parameters examined simultaneously as in the present trial. That CRP in our study was related to only one of these strongly intercorrelated parameters was an intriguing finding that could indicate that this marker is more related to the effect of

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**Table 2.** Correlation coefficients between cardiovascular risk factors, physical activity, physical fitness, and markers of inflammation and hemostasis

<table>
<thead>
<tr>
<th>Variable</th>
<th>sVCAM-1</th>
<th>sICAM-1</th>
<th>sE-selectin</th>
<th>hs-CRP</th>
<th>sTM</th>
<th>vWF</th>
<th>tPAag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.23*</td>
<td>0.42*</td>
<td>—</td>
<td>0.19†</td>
<td>0.21†</td>
<td>0.22†</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>—</td>
<td>—</td>
<td>0.17†</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SBP</td>
<td>—</td>
<td>—</td>
<td>0.27*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DBP</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.15†</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.22*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HDL-C</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.20†</td>
<td>—</td>
<td>—</td>
<td>0.21†</td>
</tr>
<tr>
<td>TG</td>
<td>—</td>
<td>0.18†</td>
<td>0.22*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HbA1c</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PA</td>
<td>0.20†</td>
<td>0.24*</td>
<td>—</td>
<td>—</td>
<td>0.16†</td>
<td>0.16†</td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>—</td>
<td>0.28*</td>
<td>—</td>
<td>0.19†</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FCRS</td>
<td>—</td>
<td>0.40*</td>
<td>0.27*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Smoking</td>
<td>—</td>
<td>0.16†</td>
<td>—</td>
<td>0.16†</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

BMI = body mass index; DBP = diastolic blood pressure; FCRS = Framingham coronary heart disease risk score; HbA1c = glycosylated haemoglobin; HDL-C = HDL cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = LDL cholesterol; PA = physical activity; PF = physical fitness; SBP = systolic blood pressure; sICAM-1 = soluble intercellular adhesion molecule-1; sTM = soluble thrombomodulin; sVCAM-1 = soluble vascular cellular adhesion molecule-1; TG = triglycerides; tPAag = tissue plasminogen activator antigen; vWF = von Willebrand factor.

Smoking is modelled as 0 (never or previous smoker) and 1 (current smoker).

* $P < .001$; † $P < .05$.

**Table 3.** Relationship between physical activity and fitness and biomarkers of inflammation and hemostasis after multiple regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>PA</th>
<th>PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>sVCAM-1</td>
<td>15.0 (9.0)</td>
<td>52.0 (94.0)</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>-3.9 (5.0)</td>
<td>45.4 (51.0)</td>
</tr>
<tr>
<td>sE-selectin</td>
<td>-2.5 (1.0)</td>
<td>-20.0 (12.0)</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.0023 (0.0)</td>
<td>-1.1 (0.0)</td>
</tr>
<tr>
<td>sTM</td>
<td>0.23 (1.0)</td>
<td>0.63 (7.0)</td>
</tr>
<tr>
<td>vWF</td>
<td>-0.51 (2.0)</td>
<td>-31.6 (25.0)</td>
</tr>
<tr>
<td>tPAag</td>
<td>0.22 (0.0)</td>
<td>-2.5 (4.0)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

Multiple linear regression coefficients B (SE) and $p$-values are listed. B for physical activity (PA) is given per 1000 kJ/day, and for physical fitness (PF) per 1000 sec. The following risk factors were adjusted for in the analyses: age, body mass index, diastolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglycerides and smoking status.

Adjusted $R$ square ($R^2$) is given when PA/PF remained significant after regression analysis: a: $R^2 = 0.173$, b: $R^2 = 0.053$. 
physical activity (ie, fitness) than to the activity level per se. Total energy expenditure was dominated by the sum of many daily-life activities of low intensity. Such activities will not improve oxygen consumption and exercise capacity, which may be necessary to affect levels of CRP. Moreover, physical fitness is not only determined by current activity level but also by factors such as genetic constitution and, to some degree, previous exercise habits. These factors may also influence the atherosclerotic process and hence the level of inflammatory markers. Finally, estimates based on self-reports are less objective and accurate than the method used for measurement of physical fitness, possibly affecting our ability to demonstrate a relationship between CRP and physical activity.

We found that sE-selectin was not significantly related to physical fitness. However, a negative relationship to physical activity ($P = .033$) occurred after adjustments for other risk factors. Both DBP and BMI showed unexpected positive relationships to activity level ($P < .001$ for both), possibly brought about by the selection of healthy hypertensive subjects with a wide age span. The younger subjects were characterized by a higher level of PA, but a more unfavorable risk profile (higher BMI and DBP, lower HDL-C) than the older subjects. The sE-selectin had a strong inverse correlation with both DBP and BMI, and these factors could easily confound the relationship between the marker and physical activity, becoming apparent only after adjustments for multiple risk factors. The finding of an association between sE-selectin and physical activity among these sedentary men may indicate that even low-intensity activity has a positive effect on the vascular inflammation process.

The mechanisms by which physical activity influences on vascular inflammation are only partly understood. Exercise raises the level of HDL-C, which has been shown to neutralize the proinflammatory effect of CRP, partly by inhibiting its induction of CAM on endothelial cells. In the present study, the inverse relationship between CRP and physical fitness was still significant after adjustments for HDL-C levels, indicating that other mechanisms are involved as well. Physical activity also increases the expression of endothelial NO synthase and thereby NO production. In turn NO has been reported to reduce the expression of CAM.

Inverse relations between CAM and self-reported physical activity has been demonstrated in two larger studies on healthy men and women. However the significance of these relations after adjustments for other major risk factors was not reported. In general, comparisons with other studies on self-reported activity are difficult because of differences in the questionnaires in use.

Except for a small study on patients with heart failure, showing associations between sVCAM-1 and sICAM-1 and change in peak oxygen consumption after training, we have found no other reports on relationships between physical fitness and CAM.

In our study, the observed univariate correlations between physical fitness and sICAM-1, as well as between physical activity and both sVCAM-1 and sICAM-1, were no longer significant when age was taken into account, although resistant to adjustments for other relevant risk factors. These inflammatory variables increased with age, whereas physical activity and fitness decreased; hence the strong ability of this factor to act as a confounder on these relationships.

No independent associations between physical activity or fitness and the hemostatic markers were observed. Previous research in this field has yielded incomplete and conflicting results. Our findings are in accordance with other investigations showing no associations between markers of blood hemostasis and everyday leisure- or work-related activity.

### Classical CVD Risk Factors and FCRS

Both sICAM-1 and CRP increased significantly with increasing values of the FCRS ($P < .001$ for both). Previous investigations have shown associations between FCRS and CRP as well as s-selectin and vWF. Our findings of a relationship between FCRS and sICAM-1 support the hypothesis that increased expression of CAM are involved in the process through which established risk factors promote atherosclerosis.

The trial generally confirmed previous reports on associations between inflammatory and hemostatic variables and traditional CVD risk factors. Of special interest is the finding that sE-selectin was the only biomarker related to BP (ie, DBP) in this hypertensive population, independent of other risk factors and of drug class used. Other investigators have also reported a relation to BP specific for this adhesion molecule. Being exclusively expressed on endothelial cells, sE-selectin has been proposed to be a marker of endothelial activation, the first step in atherosclerotic development. The expression of sVCAM-1 and sICAM-1 seem to depend more on changes of the vessel wall appearing later in the development of atherosclerosis, which may explain their relationships to age, smoking, and risk scores found in our study. That sE-selectin was so closely related to the present BP level may suggest that BP reducing therapy directly decreases endothelial activation, as reflected in the expression of this particular CAM.

### Study Limitations

Because the study was based on men 40 to 75 years of age, the results may not be applicable to the general population. The fact that only sedentary persons were included diminished the ranges of physical activity and fitness. Moreover the group in some respects presented a more beneficial risk profile than expected: 51% had SBP $\leq$ 140 mm Hg, a level achieved by only 30% of this patient group in Norway. The number of smokers was low (16.4% vs 31% of the average male population), and
the education level high (53% more than high school). Thus individuals with a risk burden in the lowest as well as in the highest level were excluded, and this reduced range of risk may have led to an underestimation of the examined relationships.

Because little was known on the relations between our markers and physical activity and fitness, a meaningful prospective power calculation was difficult to perform. The statistical power of this study might therefore have been insufficient to detect existing associations.

Different types of activity, or the intensity with which they are performed, may have different effects on inflammatory markers.\(^\text{34}\) Because our parameter of PA summarizes all types and intensity levels of activity, the study could fail to reveal more specific responses.

The antihypertensive drugs taken by all our participants might have influenced the levels of the measured variables. Because the use of drugs was not randomized, the eventual effect of these agents cannot be evaluated. Studying effects of single drug classes would also have been difficult because of the many different combinations in use. However there were no significant differences in levels of either inflammatory or hemostatic biomarkers among users (either alone or in combination) and nonusers of the six drug classes. Even if we cannot exclude the possibility that some drug effects were present, we consider it unlikely to have affected our main findings.

In conclusion, the present study of drug-treated, sedentary hypertensive men revealed an inverse relationship between physical fitness and hs-CRP. This suggests that within a sedentary population a good fitness status has a beneficial effect on inflammation and hence on the progression of atherosclerosis. In addition the observed negative relation between self-reported physical activity and sE-selectin suggests an effect of activity of low intensity on vascular inflammation. Although statistically significant, the demonstrated relationships were rather weak, and the other measured markers of inflammation showed no clear associations with physical activity or fitness. Thus the relationship between physical activity and inflammation in this population is still somewhat unclear.

Our results suggest that markers of proinflammatory and prothrombotic activity in drug-treated hypertensive patients are related to classical cardiovascular risk factors, although the relationships generally are weak and other factors that are only partly known must contribute to an important degree. The study further indicates that different risk factors affect the atherosclerotic process through different mechanisms, as reflected by the variations in their influence on these markers of atherosclerotic activity. This underscores the need for a broad intervention including lifestyle counseling against the total risk burden to prevent atherosclerotic progression and disease among these patients.

References