Physical Activity, Coronary Heart Disease, and Inflammatory Response

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Background: We sought to estimate the risk for coronary heart disease (CHD) associated with leisure time physical activity (LTPA) and work-related physical strain (WRPS) after careful adjustment for other established risk factors and to elucidate the association of physical activity with various hemostatic and inflammatory markers.

Methods: Case-control study including 312 patients aged 40 to 68 years with stable CHD (angiographically confirmed) and 479 age- and sex-matched controls. Main outcome measures were odds ratio for CHD associated with LTPA and WRPS and associations of physical activity with inflammatory and other biochemical markers after adjustment for covariates.

Results: LTPA showed a clear inverse association with risk of CHD. Compared with subjects who reported no summer LTPA, the odds ratio for CHD was 0.85 (95% confidence interval [CI], 0.47-1.53) in the category <1 h/wk; 0.60 (95% CI, 0.38-0.95) in the category 1-2 h/wk; and 0.39 (95% CI, 0.26-0.59) in the category >2 h/wk, after full adjustment for covariates. Similar results were obtained for winter LTPA. By contrast, there was a strong positive association between WRPS and risk of CHD. Furthermore, levels of C-reactive protein, serum amyloid A, interleukin 6, and intercellular adhesion molecule 1 were inversely and independently associated with LTPA, but not with WRPS.

Conclusions: This study provides further evidence that LTPA, but not WRPS, is associated with a decreased risk of CHD, effective at even moderate levels. It further demonstrates that LTPA is associated with beneficial effects on the inflammatory response. This may represent one mechanism to explain the benefits of LTPA on coronary risk.

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CARDIOVASCULAR diseases still are the leading cause of disability and death in the United States and other developed countries, and half of all cases are directly attributable to coronary heart disease (CHD). Landmark observational studies such as the Framingham Study have established a number of determinants and risk factors for atherosclerosis. In addition, the beneficial effect of physical activity on cardiovascular morbidity and mortality, and all-cause mortality is widely acknowledged. Debate is still ongoing about the amount and intensity of physical activity needed to achieve these benefits and about the role of work-related physical strain (WRPS).

Convincing evidence suggests that CHD is an inflammatory process, and a variety of inflammatory and other biochemical markers potentially related to atherogenesis have been identified. Factors triggering this immunological response and the underlying mechanistic link are, however, yet unclear. Data relating the association of physical activity with various hemostatic markers and acute-phase proteins or cytokines are sparse and the current challenge is to investigate whether these markers act independent of other CHD determinants such as obesity, hypertension, smoking, alcohol consumption, and other established determinants of CHD. If so, this would present an important contribution to understand the underlying pathophysiology.

We analyzed data of a case-control study in patients with stable CHD to estimate the risk for CHD associated with leisure time physical activity (LTPA) and WRPS after careful adjustment for other established risk factors. Furthermore, we elucidated the association of physical activity with various hemostatic and inflammatory markers that may play a key role in the inflammatory response, characteristic for atherosclerosis.

METHODS

PATIENTS AND CONTROLS

German-speaking patients aged 40 to 68 years who underwent coronary angiography at the Cardiology Department of the University of Ulm between April 1996 and November 1997 and who showed at least 1 coronary stenosis of more than 50% of the luminal diameter were included in the study. Main exclusion criteria for...
patients were first medical diagnosis of CHD more than 2 years ago, unstable angina pectoris, acute myocardial infarction within the past 4 weeks, febrile infection within past 3 weeks, malignant disease, and anticoagulant therapy within past 2 weeks.

The control group consisted of 476 subjects who were occasional blood donors at the local Red Cross center serving the university hospitals of Ulm. All controls had no history of definite or suspected CHD, and did not report infections or surgery within the previous 4 weeks. Participation rates were 78% in eligible patients and 89% in eligible controls.

Frequency matching for age and sex was performed and a case-control ratio of 1:1.5 was intended. All subjects underwent standardized interviews conducted by trained interviewers. The primary objectives of the study were to assess the effect of various infective agents such as Helicobacter pylori on CHD risk (for details see Koenig et al)² and to investigate the role of other suggested CHD risk factors. The study was approved by the ethics committee of the University of Ulm.

ASSESSMENT OF PHYSICAL ACTIVITY

Each participant was interviewed regarding physical activity during winter or summer. Both questions consisted of a 4-level graded scale for LTPA (none, <1, 1-2, >2 h/wk). In addition, a question evaluating physical strain at work was asked (none, light, medium, heavy), and we also asked for additional workday activity by bike or by foot (light, medium, heavy), and we also asked for additional workday activity by bike or by foot (<15, 15-30, 30-60, >60 minutes per workday). The questions related to LTPA and WRPS had been validated and used previously in a large, closely related, population sample.²

LABORATORY METHODS

Venous blood was drawn in the morning under standardized conditions and a complete blood cell count was done (Coulter STKS chamber; Coulter Co, Krefeld, Germany). Within 30 minutes, the remaining blood was centrifuged at 3000g for 10 minutes, immediately aliquoted, and frozen at −70°C until analysis. In cases, blood drawing was done before the angiographic procedure. The following markers of inflammation and hemostasis were determined by enzyme-linked immunosorbent assay: interleukin (IL) 6 and tumor necrosis factor α (Quintokine; R&D Systems, Wiesbaden, Germany); intercellular adhesion molecule 1 (ICAM-1) (Diaclone, Besancon, France); plasminogen activator inhibitor 1 activity (Immuno, Heidelberg, Germany); D-dimer (Dimentest Gold EIA; Agen Biomedical Ltd, Acacia Ridge, Australia); and von Willebrand factor (Haemochrom, Essen, Germany). In addition, C-reactive protein (CRP) determinations were done by an immunoradiometric assay (range, 0.05-10 mg/L) calibrated with the World Health Organization reference standard 85/506.² Fibrinogen was measured by immunonephelometry (Dade Behring, Marburg, Germany) and according to the Clauss method. Serum amyloid A was also determined by immunonephelometry (Dade Behring), and, finally, measurement of plasma viscosity was done in a viscometer (Harkness Coulter: Coulter Electronics, Luton, England). Interassay coefficients of variation were 7% for IL-6, 17.9% for tumor necrosis factor α, 14.2% for ICAM-1, 12% for CRP, 7.4% for serum amyloid A, 5% for fibrinogen, 11% for plasminogen activator inhibitor 1, 7.2% for D dimer, 15.8% for von Willebrand factor, and 2% for plasma viscosity. High-density lipoprotein cholesterol concentrations were determined by routine enzymatic methods. Lipoprotein Lp(a) and apoproteins were determined by immunoturbidimetry on an automated analyzer (WAKO R-30; WAKO Chemicals, Osaka, Japan). All laboratory analyses were done in a blinded fashion.

RESULTS

In total, 791 subjects were enrolled in the study (312 patients with stable CHD and 479 age- and sex-matched controls). Table 1 lists the main characteristics of the study population. Patients with CHD had more often a lower school education compared with control subjects and established cardiovascular risk factors were more unfavorably distributed in patients compared with controls.

Table 2 shows the self-reported LTPA in summer and winter and the WRPS in CHD patients and controls. With respect to LTPA, a larger proportion of patients with CHD reported no LTPA both in winter and in summer. This difference was statistically significant (P<.001 after adjustment for age and sex). However, with respect to work activity, the distribution was shifted toward heavy WRPS in CHD patients compared with control subjects. There were 10.6% of patients and only 5%
of controls who reported heavy WRPS and 11.3% of patients and 25.9% of controls reported no WRPS (P<.001 after adjustment for age and sex). With respect to additional workday activity by bike or foot, 23.4% of patients with CHD and 11.1% of controls reported less than 15 minutes a day and 45.2% and 42.6% more than 60 minutes a day, respectively (P<.001 after adjustment for age and sex).

The independent association between physical activity and risk of CHD was quantified by means of un-

conditional logistic regression analysis (Table 3). Compared with subjects who reported no LTPA in winter and in summer, there was a clear decreased risk of CHD already evident in the lowest category (<1 h/wk) (which however, did not reach statistically significance in summer LTPA in this category), and which was strongest in the category less than 2 h/wk. This clear risk reduction was similar in the partially adjusted model (adjusted for age and sex) and after full adjustment for other established risk factors for CHD.

In contrast, WRPS showed a different pattern. Subjects reporting light, medium, or heavy activity at work had a significantly increased risk of CHD compared with subjects with no reported physical strain; after adjustment for age and sex the odds ratio (OR) for CHD was 4.63 (95% confidence interval [CI], 2.42-8.89) in the group with heavy WRPS, and it increased slightly to 4.86 (95% CI, 2.34-10.12) after further adjustment for covariates. In contrast, additional workday activity by bike or foot again was clearly associated with a CHD risk reduction with increasing activity, both in the partly adjusted and in the fully adjusted model. Simultaneous inclusion of all the physical activities as listed in Table 3 in the fully adjusted model did not change the overall patterns and conclusions (data not shown).

To evaluate the physical activity pattern long before disease manifestation we also evaluated life-time physical activity (Table 4). Compared with subjects who reported rare LTPA between ages 20 and 39 years, the
not shown). When the analyses shown in Tables 5 and 6 were conducted controls only, similar patterns were seen (data not shown).

**Table 5. Relation of Winter and Summer LTPA With Various Markers of Inflammation, Hemostasis, and Lipids After Adjustment for Covariates: Results of Multiple Linear Regression**

<table>
<thead>
<tr>
<th>Marker (Unit of Measure)</th>
<th>Winter LTPA</th>
<th>Summer LTPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2 h/wk, β (SE)</td>
<td>&gt;2 h/wk, β (SE)</td>
</tr>
<tr>
<td>CRP (mg/L)‡</td>
<td>-0.259 (0.096)</td>
<td>-0.192 (0.112)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>-0.048 (0.052)</td>
<td>-0.115 (0.060)</td>
</tr>
<tr>
<td>Clauss method</td>
<td>-0.084 (0.051)</td>
<td>-0.099 (0.059)</td>
</tr>
<tr>
<td>Nephelometric</td>
<td>-0.005 (0.005)</td>
<td>-0.009 (0.006)</td>
</tr>
<tr>
<td>Plasma viscosity (mPa·s)</td>
<td>-0.120 (0.139)</td>
<td>-0.204 (0.161)</td>
</tr>
<tr>
<td>D dimer (ng/mL)‡</td>
<td>-0.264 (0.155)</td>
<td>-0.321 (0.180)</td>
</tr>
<tr>
<td>PAI-1 (activity U/mL)‡</td>
<td>-0.130 (0.086)</td>
<td>0.057 (0.078)</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)‡</td>
<td>-0.089 (0.129)</td>
<td>-0.099 (0.150)</td>
</tr>
<tr>
<td>SAA (mg/L)‡</td>
<td>-0.205 (0.065)</td>
<td>-0.251 (0.076)</td>
</tr>
<tr>
<td>vWF (activity %)</td>
<td>-5.892 (4.508)</td>
<td>-6.561 (5.208)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)‡</td>
<td>-0.165 (0.062)</td>
<td>-0.174 (0.071)</td>
</tr>
<tr>
<td>TNF-α (pg/mL)‡</td>
<td>-0.092 (0.044)</td>
<td>-0.094 (0.051)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>1.950 (0.915)</td>
<td>0.971 (1.059)</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; ICAM-1, intracellular adhesion molecule 1; IL-6, interleukin 6; Lp(a), lipoprotein a; LTPA, leisure time physical activity; PAI-1, plasminogen activator inhibitor 1; SAA, serum amyloid A; TNF-α, tumor necrosis factor α; vWF, von Willebrand factor.

†Reference categories are no winter and no summer LTPA. Models are adjusted for age, sex, smoked pack-years, alcohol consumption, years of school education, history of hypertension, body mass index, statin intake, and case-control status by multiple linear regression.

*Test for trend.

‡Log transformed.

OR for CHD was 0.50 (95% CI, 0.28-0.87) in the category “somewhat active” and 0.68 (95% CI, 0.41-1.15) in the category “very active” in the fully adjusted model. When asking about LTPA at age 40 to 50 years, the ORs were 0.60 (95% CI, 0.40-0.88) and 0.62 (95% CI, 0.42-0.92) in the respective categories.

We investigated the association of LTPA in winter and in summer and WRPS on various markers of inflammation, hemostasis, and lipids after adjusting for age, sex, pack-years of smoking, alcohol consumption, years of school education, history of hypertension, body mass index, and case-control status by means of multiple linear regression.

Table 5 shows the association of winter LTPA with these markers. We found a favorable profile associated with physical activity, which was statistically significant after adjustment for other covariates for serum amyloid A (P < .001), for IL-6 (P = .01), and for ICAM-1 (P = .005) and of borderline significance for CRP (P = .05).

These patterns were similar for summer LTPA. The relationship was statistically significant for CRP (P = .03), serum amyloid A (P = .04), and ICAM-1 (P = .005) after adjustment for covariates (Table 5).

By contrast, WRPS showed no statistically significant relationship with inflammatory markers (Table 6). When the analyses shown in Tables 5 and 6 were conducted controls only, similar patterns were seen (data not shown).

**COMMENT**

In this large case-control study including patients with angiographically confirmed and stable CHD, we found a strong and independent inverse association between LTPA and risk of CHD, already effective at moderate levels. In contrast, an increased risk of CHD associated with WRPS was seen. Furthermore, we demonstrated that LTPA is inversely and independently associated with several acute-phase proteins, proinflammatory cytokines, and circulating adhesion molecules (ICAM-1), suggesting a direct role of LTPA in triggering the immune response that is characteristic for atherogenesis.

The presented data are in accordance with previous epidemiological data1-13 (for a recent review see Wannamethee and Shaper19) and with the notion that LTPA is associated with decreased risk of CHD14 as recently also demonstrated in a cohort of women15 as well as in older men.16,17 Notably, our data, in line with other studies,15-19 suggest that these beneficial effects are seen even with moderate engagement in LTPA. Even simple activities such as low-intensity walking may lead to considerable reductions in mortality.10

The finding that WRPS was associated with an increased risk of CHD may be a surprise on the first look. However, a similar observation was made in a study conducted in a large population-based sample,6 which found an inverse association with plasma viscosity, a major determinant of microcirculatory flow, only with LTPA, but not with WRPS. Furthermore, a study in Finnish male twin pairs showed that only LTPA was able to prevent CHD, whereas occupational physical activity did not.20 The different characteristics of physical activity associated with work and LTPA might be one explanation for the opposite relations with CHD risk; the first is probably long-lasting and mainly static, whereas the latter is mainly short-lasting and dynamic in nature. However, despite careful control for possible confounding variables in multivariable analysis, we cannot rule out the possibility that some of the increased risk associated with heavy physical strain...
an acute-phase reactant produced in response to IL-6 and tumor necrosis factor

The present study provides additional evidence that LTPA is associated with plasma viscosity reported previously from a much larger study. Second, CHD was defined invasively by coronary angiography in cases, but for ethical reasons, no coronary angiogram could be obtained in controls. Although we excluded controls with a history or characteristic symptoms of CHD, the presence of asymptomatic CHD cannot be definitely ruled out; however, the prevalence of asymptomatic CHD cases seems to be very low in a middle-aged population. Furthermore, the choice of blood donors can be considered as suboptimal, as they might be healthier than the target population the cases were drawn from. We tried to minimize this potential bias by carrying out multivariate adjustments for a variety of covariates.

Furthermore, as always in case-control studies in which exposure and outcome are collected at one point in time it is difficult to assess whether behavior has actually preceded disease or vice versa and therefore, it is highly desirable to corroborate study results in a longitudinal study design. To assure that reported physical activity patterns represent levels before disease manifestation we also asked for lifetime physical activity. From comparison with these data it became evident that reported physical activity actually represented the typical individual behavior before diagnosis and disease manifestation; however, the distribution shifted to less physical activity with increasing age in cases as well as in controls. When assessing the role of LTPA at age 20 to 39 years and from age 40 to 49 or 50 years and older, similar associations with risk of CHD were observed.

The present study provides additional evidence that LTPA, but not WRPS, is associated with a decreased risk for CHD seen even at moderate levels. It further suggests that LTPA is associated with a beneficial effect on the inflammatory response potentially involved in atherosclerosis. These data therefore strongly support the recommendation of LTPA in the general population for the prevention of CHD.

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The study was partly funded by grants from the Medical Faculty of the University of Ulm; ASTRA, Wedel, Germany; and MEDAC, Wedel, Germany. We thank the University of Ulm blood bank staff for their help, and all patients and voluntary blood donors for their participation in the study.

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Table 6. Relation of Work-Related Physical Strain With Various Markers of Inflammation, Hemostasis, and Lipids After Adjustment for Covariates: Results of Multiple Linear Regression

<table>
<thead>
<tr>
<th>Marker (Unit of Measure)</th>
<th>Light or Medium, β (SE)</th>
<th>Heavy, β (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)‡</td>
<td>0.072 (0.107)</td>
<td>-0.092 (0.182)</td>
<td>.90</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>-0.029 (0.058)</td>
<td>-0.002 (0.098)</td>
<td>.82</td>
</tr>
<tr>
<td>Nephelometric plasma viscosity (nPa-s)</td>
<td>-0.006 (0.056)</td>
<td>-0.119 (0.095)</td>
<td>.20</td>
</tr>
<tr>
<td>Leukocyte count (&gt;10⁹/µL)</td>
<td>-0.218 (0.154)</td>
<td>-0.273 (0.260)</td>
<td>.31</td>
</tr>
<tr>
<td>D dimer (ng/mL)‡</td>
<td>-0.074 (0.172)</td>
<td>-0.360 (0.291)</td>
<td>.32</td>
</tr>
<tr>
<td>PAI-1 (activity U/mL)‡</td>
<td>-0.060 (0.075)</td>
<td>-0.249 (0.075)</td>
<td>.10</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)‡</td>
<td>-0.038 (0.143)</td>
<td>0.312 (0.242)</td>
<td>.45</td>
</tr>
<tr>
<td>SAA (mg/L)‡</td>
<td>0.028 (0.073)</td>
<td>-0.036 (0.124)</td>
<td>.97</td>
</tr>
<tr>
<td>vWF (activity %)</td>
<td>2.107 (4.990)</td>
<td>-2.429 (4.443)</td>
<td>.95</td>
</tr>
<tr>
<td>IL-6 (pg/mL)‡</td>
<td>0.028 (0.069)</td>
<td>-0.142 (0.117)</td>
<td>.50</td>
</tr>
<tr>
<td>TNF-α (pg/mL)‡</td>
<td>-0.026 (0.048)</td>
<td>0.023 (0.082)</td>
<td>.97</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td>-3.060 (14.130)</td>
<td>-12.830 (23.940)</td>
<td>.85</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>-0.585 (1.010)</td>
<td>3.150 (1.710)</td>
<td>.33</td>
</tr>
</tbody>
</table>

*Reference category is no work-related physical strain. Model is adjusted for age, sex, smoked pack-years, alcohol consumption, years of school education, history of hypertension, body mass index, statin intake, and case-control status by multiple linear regression. For explanation of abbreviations, see the footnote to Table 5.
†Test for trend.
‡Log transformed.

at work may be due to residual confounding by a low occupational class or other associated risk.

Systemically measurable markers of low-grade inflammation are important predictors of CHD risk and are increased in patients with stable CHD. According to a meta-analysis fibrinogen, CRP, albumin, and leukocyte count are consistently associated with CHD risk, indicating an important role in pathogenesis of CHD, although the mechanisms are still unclear. C-reactive protein has been shown to be an important predictor of CHD in various clinical and epidemiological studies. It is an acute-phase reactant produced in response to IL-6 stimulation. Among other effects, CRP induces the expression of ICAM-1, an adhesion molecule that regulates attachment and transmigration of leukocytes across the vascular endothelium, an important early step in the pathogenesis of atherosclerosis.

The present study provides further evidence of an inverse association of LTPA with inflammatory response; sedentary subjects had a higher inflammatory response compared with physically active subjects. When assessing the role of LTPA at age 20 to 39 years and from age 40 to 49 or 50 years and older, similar associations with risk of CHD were observed.

The present study provides additional evidence that LTPA is associated with a decreased risk for CHD seen even at moderate levels. It further suggests that LTPA is associated with a beneficial effect on the inflammatory response potentially involved in atherosclerosis. These data therefore strongly support the recommendation of LTPA in the general population for the prevention of CHD.

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REFERENCES