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**Original Scientific Paper**

# High, but not moderate frequency and duration of exercise training induces downregulation of the expression of inflammatory and atherogenic adhesion molecules

Thomas Peschel[a], Sebastian Sixt[a], Frido Beitz[a], Melanie Sonnabend[a], Gerhard Muth[a], Holger Thiele[a], Attila Tarnok[b], Gerhard Schuler[a] and Josef Niebauer[c]

Departments of [a]Internal Medicine/Cardiology, [b]Pediatric Cardiology, University of Leipzig, Heart Center and [c]Institute of Sports Medicine, Prevention and Rehabilitation, Paracelsus Medical University, Salzburg, Austria

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***Background*** **Lifestyle changes which include daily exercise training have been shown to slow the progression of coronary artery disease. We designed a study to examine the effects of a multifactorial intervention on atherogenic adhesion molecules on the surface of monocytes in patients with coronary artery disease.**

***Methods*** **We randomized 39 patients with coronary artery disease to (i) an intervention program which consisted of 4 weeks of daily 6 × 15 min ergometer training at submaximal intensity in addition to a 1 h/week group exercise session, followed by 5 months of home-based ergometer training of 30 min/day again in addition to a 1 h/week group exercise session or (ii) conventional therapy. All patients received a statin. Monocyte-bound cellular adhesion molecules LFA-1 (CD11a), MAC-1 (CD11b), VLA-4 (CD49d) and L-selectin (CD62L) were assessed by fluorescence activated cell sorting analysis.**

***Results*** **After 4 weeks the multifactorial intervention led to a significant improvement of maximal work capacity, lipid profile, body mass index, blood pressure, fasting glucose and hemoglobin A1c. This was associated with a reduced expression of MAC-1 and VLA-4. After 5 months of a home-based intervention the beneficial effects of the cardiovascular risk profile were still apparent, whereas the effects on the expression of adhesion molecules were blunted.**

***Conclusion*** **In patients treated with statins, 4 weeks of high frequency and long duration exercise training led to a diminished expression of atherogenic adhesion molecules MAC-1 und VLA-4. After 5 months of home-based exercise training of moderate frequency and duration, these effects were blunted. Our data suggest that our patients in cardiac rehabilitation programs might further benefit from the antiatherogenic effects of an even higher amount of exercise training.** ***Eur J Cardiovasc Prev Rehabil*** **14:476–482 © 2007 The European Society of Cardiology**

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**Keywords: adhesion molecules, coronary artery disease, diabetes mellitus type 2, exercise training**

## Introduction

Several studies have convincingly shown that a multifactorial intervention which focuses on exercise training and addresses all modifiable risk factors is very well capable of inducing improved endothelial function, slowed progression and in some patients regression of coronary artery disease [1–6]. The underlying molecular mechanisms of such interventions, however, are not yet fully understood [6].

It is evident that atherosclerosis manifests as a result of an inflammatory processes on the arterial vessel wall [7]. Monocyte adhesion to the endothelium occurs in

Correspondence to Professor Josef Niebauer, MD, PhD, Chair and Chief, Institute of Sports Medicine, Prevention and Rehabilitation
Professor of Internal Medicine, Cardiology and Sports Medicine, Paracelsus Medical University, Lindhofstr. 20, 5020 Salzburg, Austria
Tel: +43 662 4482 4270; fax: +43 662 4482 4274;
e-mail: j.niebauer@salk.at

1741-8267 

response to inflammation. Adherent monocytes migrate into the subendothelial space and take up lipids, which leads to the formation of foam cells [8]. Accumulation of lipid-laden macrophages form fatty streaks, which are the earliest microscopically visible state of atherosclerosis. Cellular adhesion molecules (CAMs) are the key players in the attachment of monocytes to the endothelium [9,10]. We and others have previously shown that their attachment can be reduced by shear stress and exercise training [11–14]. Furthermore, several studies which focused on lifestyle changes and physical exercise have shown a reduction in the expression of adhesion molecules such as soluble ICAM [14–18].

In cell culture and animal studies the distribution and function of CAMs have been studied in detail. CAMs, which play an important role in atherosclerosis, comprise the integrins LFA-1 (CD11a/CD18), MAC-1 (CD11b/CD18), VLA-4 (CD49d/CD29) and L-selectin (CD62L) on the mononuclear cell surface with their ligands, inter cellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 on the endothelial cell surface [10,11,15].

In humans, elevated levels of soluble CAMs have been associated with the presence of cardiovascular risk factors like diabetes and coronary heart disease. Most studies focused on soluble CAMs such as sICAM-1 and sVCAM-1, which may be shed from the endothelial cell surface [12,13]. To date no soluble form of any of the integrins LFA-1, MAC-1 or VLA-4 have been identified [13].

The fact that CAMs play a crucial role in atherosclerosis supports the hypothesis that interventions, which result in a reduction of atherosclerotic risk factors may also lead to a reduction not only in soluble CAMs but also in adhesion molecules on the surface of monocytes. As this would lend further evidence to the hypothesis, we set out to assess the effects of a multifactorial intervention which focused on physical exercise training on the expression of CAMs on the surface of monocytes in patients with coronary artery disease.

## Methods

### Participants

The study protocol was approved by the ethics committee of the University of Leipzig, and the study was carried out at the University of Leipzig-Heart Center. All participants gave written informed consent before study entry.

For inclusion in our study, patients had to have stable coronary artery disease and had to be able to exercise on a cycle ergometer. Exclusion criteria were unstable angina, myocardial infarction within the previous 3 months, chronic heart failure, which was defined as a left ventricular ejection fraction of $< 35\%$ or severe pulmonary disease.

Patients were randomized to a multifactorial intervention program for secondary prevention including regular physical exercise or conventional therapy, which was rendered by family physicians or cardiologists of the patients' choice. Randomization was carried out by drawing sealed envelopes.

Of the 39 patients who initially enrolled 6-month follow-up data were available in all but one patient who had to be excluded from the study owing to the diagnosis of cancer.

### Study design and multifactorial intervention program

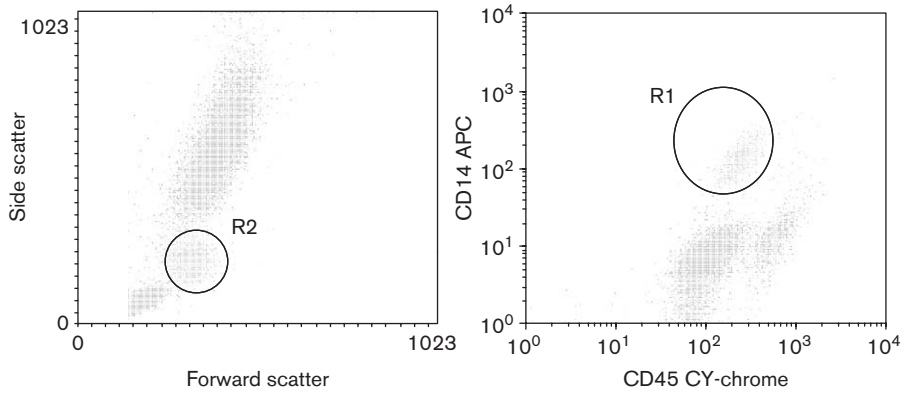
After informed written consent was obtained coronary angiography and maximal work capacity was performed by cycle ergometry. Fasting blood was drawn from a forearm vein between 0600 and 0800 h. for lipid profile [total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides], blood glucose, hemoglobin A1c, and flow cytometry assessment of CAMs. The blood samples for flow cytometry were immediately stored on ice and analyzed. Patients had to be free from acute infections as documented by a normal leukocyte count and erythrocyte sedimentation rate.

Patients randomized to the intervention group stayed in-hospital Monday to Friday for 4 weeks and received a low-fat, high-fiber diet of 1500 kcal/day. The program further consisted of optimal medical therapy with control of blood pressure (goal: $< 130/80$ mmHg), lipid profile (goal for LDL-cholesterol: $< 2.6$ mmol/l) and of blood glucose levels (goal: 3.3–6.1 mmol/l). Patients entered an intensive physical exercise program of $6 \times 15$ min cycle ergometer training a day under the supervision of an exercise specialist and a cardiologist. Exercise was performed at 70–80% of patients' individual maximal heart rate. In addition, patients participated in an 1-h group exercise session per week and on the weekends exercised at home on an ergometer for 30 min a day.

Patients in the control group received identical information and advice with regard to lifestyle changes and an optimized medical therapy before returning to their private physicians.

At baseline, 4 weeks, and after 6 months patients from the intervention and control group were reassessed by ergometry, and blood was drawn to analyze lipid profile, blood glucose, HbA1c and CAMs. Patients from the intervention group were discharged from hospital after 4 weeks and were asked to exercise for 30 min a day on a cycle ergometer (ERGO-FIT, Pirmasens, Germany) for

**Fig. 1**




An example of monocyte gating. Left: forward versus side scatter; right: CD45 vs. CD14. Events which were located in region 1 (R1) and region 2 (R2) were analyzed according to their CAM expression. CAM, cellular adhesion molecules.

the following 5 months. In addition, an 1 h group exercise session was held at the gym of the Heart Center. Compliance was assessed by log books kept by the patients as well as from data obtained from electronic chips of the cycle ergometer which contained information of the home-based exercise training. Furthermore, participation at weekly group exercise sessions was documented.

### Flow cytometry

The following CAMs were measured by flow cytometry: LFA-1, MAC-1 and VLA-4 (α-subunits CD11a, CD11b and CD49d) and L-selectin (CD62L). For staining, commercially available phycoerythrin (PE)-fluorescence dye-conjugated antihuman monoclonal antibodies were used in a saturating amount. To enable appropriate gating for selective analysis of the leukocyte subpopulations, allophycocyanin-conjugated anti-CD14 and Cy5 (Cy-Chrome; Becton Dickinson Biosciences, San Jose, California, USA)-conjugated anti-CD45 were added to each tube. PE-conjugated antimouse-IgG1 served as isotype control. Monoclonal antibodies were obtained from Pharmingen, Becton Dickinson Biosciences and Caltag (Hamburg, Germany).

For each of the CAMs 40 µl ethylenediaminetetraacetic acid (EDTA) anticoagulated whole blood was incubated with the corresponding monoclonal antibody for 10 min in the dark at room temperature. Red blood cells were lysed by diethylene glycol 30% and formaldehyde 10% (Becton Dickinson Biosciences). After centrifugation at 1400 r.p.m. for 5 min, cells were washed with phosphate-buffered saline (Sigma-Aldrich, Taufkirchen, Germany) and resuspended in 0.3 ml of *p*-formaldehyde 0.5% (Sigma-Aldrich) for fixation. Flow cytometry was performed using a dual-laser 4-color FACScalibur flow cytometer with the CellQuest software program (Becton Dickinson Biosciences). For each stain, data from 5000 monocytes were collected.

Monocytes were separated from the leukocyte population by gating from a bivariate plot of forward versus side scatter and another bivariate plot of CD45 versus CD14 (Fig. 1). The density of CAMs per monocyte, designated as molecules of equivalent PE (MEPE) was calculated by cross calibration of the mean fluorescence intensity of each PE-antibody to a standard curve, which was established using Spherotech Rainbow Calibration Particles (Spherotech, Libertyville, Illinois, USA). These particles contain a mixture of six similar size particles with determined numbers of fluorophores per particle. For each experiment an individual standard curve was established.

### Data analysis

Nonparametric tests (Wilcoxon signed-rank test for intra-individual comparisons within groups and the Mann–Whitney *U* test for interindividual changes between groups) and $\chi^2$ test (for nominal variables) were used. Analysis of variance was performed to identify a significant difference among the mean values of a variable measured in more than two groups. When analysis of variance was significant, comparisons of the mean values were made by paired Student's *t* test with Fisher's exact test correction. $P < 0.05$ was considered statistically significant. Statistical analyses were performed with Microsoft Excel version 2003 (Microsoft Corp., Redmond, Washington, USA).

## Results

### Baseline data

The baseline characteristics of the study population are shown in Table 1. More smokers and more patients with a

history of myocardial infarction in the intervention group were present. The majority of the patients were male. A total of 61% of patients in the intervention group and of 60% in the control group had type 2 diabetes. Body mass index was $30.4 \pm 4.5\,kg/m^2$ in the intervention group and $29.3 \pm 4.4\,kg/m^2$ in the control group. Left ventricular function was preserved in both groups. All patients were already on a medication which included β-blockers, angiotensin-converting enzyme (ACE) inhibitors and aspirin. The vast majority of patients were on statins at study entry and statins were given to all patients in both groups throughout the study.

Baseline values of maximal work capacity, systolic blood pressure, lipid profile, blood glucose, HbA1c and CAMs were not statistically different between the training and intervention group (Table 2). A subgroup analysis of baseline values of the CAMs of diabetics versus nondiabetics showed no statistically significant differences.

**Table 1 Baseline characteristics shown in absolute numbers and percentage in brackets**

| Parameters | Intervention group ($n=18$) | Control group ($n=20$) |
|---|---|---|
| Age (years) | 61.4 ± 6.3 | 64.3 ± 6.9 |
| Sex (male) | 14 (78) | 15 (75) |
| Smokers, previous 2 years | 6 (33) | 3 (15) |
| Diabetes mellitus | 11 (61) | 12 (60) |
| Myocardial infarction | 7 (39) | 4 (20) |
| PCI | 13 (72) | 8 (40) |
| LVEF (%) | 62 ± 8.2 | 65 ± 10.4 |
| Hypertension | 18 (100) | 20 (100) |
| Nephropathy | 2 (11) | 2 (10) |
| Aspirin and/or clopidogrel | 18 (100) | 16 (80) |
| ACE-inhibitor and/or ARB | 18 (100) | 17 (85) |
| β-Blockers | 18 (100) | 16 (80) |
| Calcium blockers | 3 (17) | 7 (35) |
| Diuretics | 3 (17) | 7 (35) |
| Statins | 14 (78) | 15 (75) |
| Nitrates | 5 (28) | 3 (15) |
| Oral antidiabetics | 9 (50) | 5 (25) |
| Insulin | 6 (33) | 7 (35) |

Continuous data are expressed as mean ± SD. Percentage values of nominal data are in brackets. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

### Four-week in-hospital intervention

Results are shown in Table 2. After 4 weeks of a multifactorial intervention, a significant improvement of maximal work capacity (Fig. 2), body mass index and systolic blood pressure was documented. In diabetics fasting glucose and HbA1c was significantly reduced. This was associated with a reduction in total cholesterol and triglycerides (all $P < 0.05$). LDL-cholesterol at baseline was almost within the recommended range, which may explain why there was no further improvement after 4 weeks.

Monocytes showed a significantly lower expression of both MAC-1 and VLA-4 after 4 weeks of intervention (Figs 3 and 4). The expression of LFA-1 and L-selectin was virtually unchanged. The control group showed no significant changes in any of these variables.

### Six-month follow-up

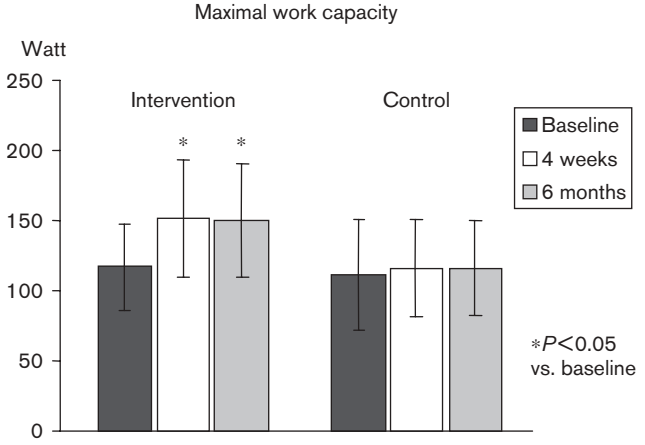
After 5 months of home-based exercise training, maximal work capacity remained as high as after 4 weeks of in-hospital exercise training. Body mass index was not as low as at 4 weeks but still significantly lower than at baseline. Triglycerides remained significantly reduced, whereas systolic blood pressure, total cholesterol, LDL, glucose and HbA1c were lower in absolute numbers than at baseline but failed statistical significance. This was also the case for MAC-1 and VLA-4; LFA-1 and L-selectin, which remained unchanged as compared with baseline and 4 weeks. In the control group, there were again no significant changes observed.

**Table 2 Influence of the intervention on body mass index, maximal work capacity, systolic blood pressure, lipid profile, blood glucose, HbA1c and the expression of CAMs**

| | Intervention group ($n=18$) | | | Control group ($n=20$) | | |
|---|---|---|---|---|---|---|
| | Baseline | 4 weeks | 6 months | Baseline | 4 weeks | 6 months |
| Max. work capacity (watts) | 117 ± 31 | 152* ± 41 | 150* ± 41 | 112 ± 39 | 116 ± 35 | 116 ± 34 |
| BMI ($kg/m^2$) | 30.4 ± 4.8 | 29.3* ± 4.4 | 29.8* ± 4.4 | 29.3 ± 4.5 | 29.6 ± 4.6 | 29.5 ± 4.6 |
| SBP (mmHg) | 139 ± 20 | 120* ± 18 | 129 ± 23 | 141 ± 15 | 138 ± 21 | 136 ± 19 |
| Cholesterol (mmol/l) | 4.96 ± 1.23 | 4.34* ± 1.48 | 4.49 ± 0.65 | 5.00 ± 0.87 | 4.82 ± 0.88 | 4.70 ± 1.13 |
| HDL-cholesterol (mmol/l) | 1.37 ± 0.45 | 1.26* ± 0.36 | 1.54* ± 0.47 | 1.26 ± 0.46 | 1.31 ± 0.45 | 1.36* ± 0.46 |
| LDL-cholesterol (mmol/l) | 2.79 ± 1.23 | 2.70 ± 1.51 | 2.44 ± 0.61 | 2.99 ± 0.88 | 2.93 ± 0.93 | 2.80 ± 1.1.19 |
| Triglycerides (mmol/l) | 2.73 ± 1.75 | 1.46* ± 0.69 | 1.47* ± 0.97 | 1.87 ± 1.32 | 1.74 ± 0.65 | 1.93 ± 0.88 |
| Fasting glucose (mmol/l) | 7.3 ± 3.4 | 5.5* ± 0.9 | 6.5 ± 1.8 | 7.2 ± 2.6 | 7.2 ± 1.5 | 7.4 ± 1.7 |
| HbA1c (%) | 6.5 ± 1.4 | 5.7* ± 0.9 | 5.9 ± 0.8 | 6.6 ± 1.1 | 6.3 ± 1.1 | 6.6 ± 1.4 |
| LFA-1 (ME) | 16 200 ± 2943 | 15 951 ± 2827 | 14 938 ± 2732 | 16 658 ± 4469 | 15 811 ± 3418 | 17 081 ± 3818 |
| MAC-1 (ME) | 38 461 ± 9663 | 30 070* ± 8665 | 32 341 ± 12 122 | 36 379 ± 11 958 | 35 454 ± 11 200 | 38 335 ± 13 584 |
| VLA-4 (ME) | 10 150 ± 2616 | 8069* ± 1944 | 9696 ± 2880 | 9283 ± 2120 | 8912 ± 1927 | 9246 ± 2122 |
| L-selectin (ME) | 40 150 ± 10 553 | 41 398 ± 12 438 | 35 949 ± 8471 | 44 515 ± 14 351 | 42 750 ± 14 845 | 44 742 ± 14 329 |

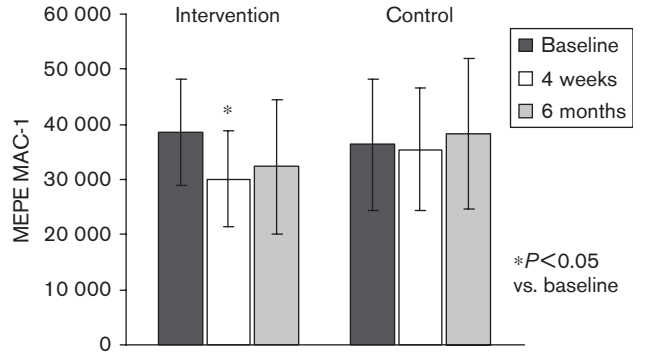
Data are expressed as mean ± SD. *$P<0.05$ vs. baseline. BMI, body mass index; CAM, cellular adhesion molecules; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density protein; ME, molecules of equivalent; SBP, systolic blood pressure.

**Fig. 2**



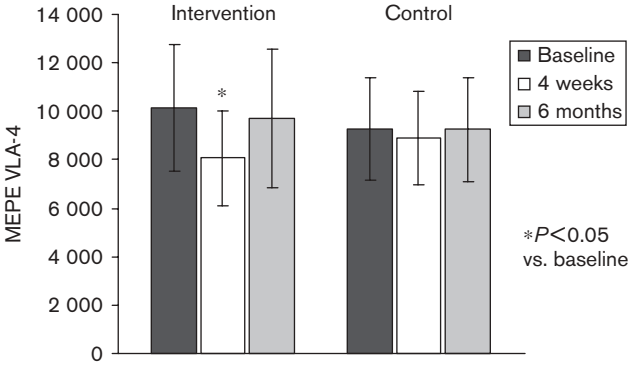

Effects of a multifactorial intervention on maximal work capacity (mean ± SD).

**Fig. 3**




Changes in MAC-1 during the study (mean ± SD).

**Fig. 4**




Changes in VLA-4 during the study (mean ± SD).

## Discussion

The goal of a multifactorial intervention is to reduce all modifiable atherosclerotic risk factors through an optimal medication and a change in lifestyle. Hypertension, diabetes mellitus, hyperlipidemia, obesity, physical inactivity, smoking and high contents of saturated fat in foods have been identified among others as modifiable cardiovascular risk factors [19].

In this study, patients with coronary artery disease followed a 4-week in-hospital and a subsequent 5-month home-based multifactorial intervention program, which focused on daily exercise training. During the first 4 weeks patients exercised 90 min/day at a submaximal intensity on cycle ergometers in addition to a 1-h group exercise session. This was associated with an improvement in modifiable risk factors and a reduction of the expression of MAC-1 and VLA-4. Interestingly, these effects on CAMs were achieved in patients who already received an optimal medical therapy, which included β-blockers, ACE inhibitors, aspirin and statins. As a result, LDL levels were almost optimal at baseline and remained so throughout the study.

Other studies investigated the effects of regular exercise and lifestyle-intervention on the expression of CAMs. In obese men who received a low-fat diet and performed daily aerobic exercise training a reduction was found in sICAM-1 (indicator of endothelial activation), serum-stimulated monocyte adhesion and monocyte chemotactic activity [20]. Another trial from the same group showed similar results in diabetics [21]. A recent study found that an intensified lifestyle change in young first-degree relatives of patients with premature coronary heart disease led to a reduction in E-selectin and in those who quit smoking to a decrease in sICAM-1 [22]. It has also been shown to reduce sICAM-1, but not VCAM-1 in postmenopausal women with multiple risk factors for coronary heart disease after a 14-day residential diet and exercise intervention [23]. One study found an inverse correlation of physical fitness with levels of sICAM-1 and sVCAM-1 [24].

Some potential mechanisms exist, which may lead to an altered expression of CAMs after exercise. Such mechanisms include differential trafficking from or to various sources, mechanical deformation of the cells, effects of cytokines or catecholamines, or changes in induction of adhesion molecules [25]. These effects, however, have mainly been assessed by single exercise studies but not by long-term exercise training. In a study, which measured the surface expression of LFA-1, MAC-1 and VLA-4 in healthy individuals, a decrease of LFA-1 and VLA-4 on monocytes was seen after a submaximal exercise of 3 h running, whereas MAC-1 remained

unchanged [26]. In addition, a significant decrease in the expression of integrins could be demonstrated on monocytes in exercising individuals. Another study found that MAC-1 expression was increased after a treadmill run at submaximal intensity, whereas a treadmill run of high intensity downregulated the expression of MAC-1 [27]. The results of other studies differ depending on the type of exercise [25].

The majority of exercise studies used soluble CAMs, which may be shed from the cell surface. The relationship between plasma levels of soluble CAMs and their cell surface activity still remains unclear [10].

To the best of our knowledge, this is the first study, which assesses the effects of a multifactorial intervention including physical exercise on the expression of integrin CAMs on the monocyte surface.

In this study we found after 4 weeks of intervention that LFA-1 and L-selectin remained unchanged, whereas MAC-1 and VLA-4 improved significantly to fail statistical significance after 6 months. This may be due to the reduced frequency and duration of exercise training. Our findings are in keeping with another randomized trial, which compared the effect of a vigorous, hospital-based exercise training program and a following home-based exercise program on coronary endothelial function. It was found that there were more pronounced effects after hospital-based than home-based exercise training, although part of the salutary effects of training on coronary vasomotion could be maintained throughout the 6-month study period [28]. This and other studies demonstrate that the positive effects of a multifactorial intervention are difficult to maintain when patients return home and fall back to their old behavior. Strategies must be developed to help patients maintain a high level of compliance and high enough exercise intensity to achieve long-lasting anti-inflammatory and thus anti-atherogenic effects.

Diabetes mellitus is one of the most prominent atherosclerotic risk factors. In our study, about 60% of patients were diabetics. In an animal study, it was shown that both diabetes and hypertension led to increased monocyte adhesion to the endothelium [29]. In patients with metabolic syndrome, sICAM-1 has been found to be elevated [30]. In our cohort of patients, CAM expression on monocytes at baseline and after exercise was not different between diabetics and nondiabetics, which might be due to the high rate of statin use in our study and the successfully controlled lipid and glycemic profile already at baseline.

It is well known that smoking cessation leads to a normalization of inflammatory markers. As all smokers in both groups refrained from smoking throughout the study period, smoking cessation may have contributed to the anti-inflammatory effects in our patient cohort. It, however, seems unlikely that smoking cessation alone has led to the reported improvement, as CAM expression at 6 months was higher than that at 4 weeks.

In conclusion, we could demonstrate an improvement in the cardiovascular risk factor profile after a multifactorial intervention, which was associated with a reduction of the proinflammatory and atherogenic adhesion molecules MAC-1 and VLA-4. On the molecular level, this provides in-vivo evidence for the beneficial antiatherogenic effects of a multifactorial intervention. Our data further suggest that findings of improved endothelial dysfunction and slowed progression of coronary artery disease could be even more pronounced if we were to implement programs that would have patients exercise at a higher frequency and longer duration than currently recommended.

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