Effect of six months' exercise training on C-reactive protein levels in healthy elderly subjects

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J. Am. Coll. Cardiol. 2004;44;2411-2413
doi:10.1016/j.jacc.2004.09.030

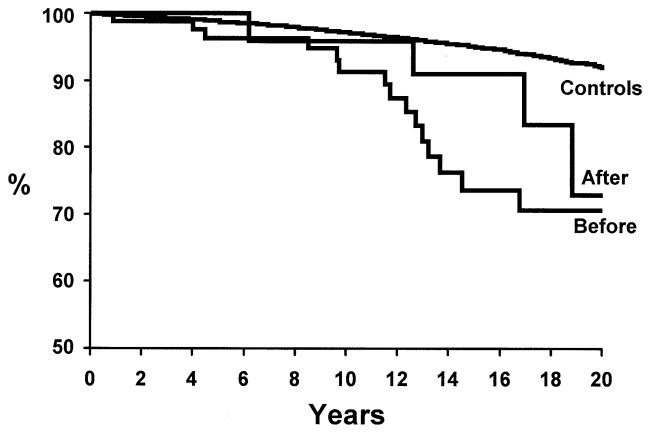

Figure 2. Observed survival in the thromboangiitis obliterans population before and after tobacco cessation compared with the expected survival in an age- and gender-matched U.S. population (controls). $p < 0.001$ by log-rank test.

would be in the interval of continued tobacco use from the time of diagnosis until he or she ceased smoking, at which point he or she would be placed in the interval of tobacco exposure cessation. In an analysis in which each amputation in persons with multiple amputations was considered a separate event, the amputation rate was 84.3 (confidence interval 68.4 to 102.7 amputations/person year × 1000) in the interval of continued tobacco use versus 30.6 (confidence interval 17.5 to 49.6 amputations/person year × 1000) in the interval of discontinued tobacco use.

Survival in the TAO cohort was compared with the expected survival in the U.S. population on the basis of age- and gender-specific mortality rates (Fig. 2). Fifteen of 111 subjects died in a median of 14.8 years of follow-up. The average age at death was 52.2 ± 8.9 years. The survival of the TAO cohort was significantly lower than that in the matched U.S. population ($p < 0.001$ by log-rank test). In univariate analysis, only older age at diagnosis and decade of diagnosis were associated with an increased risk of death. The risk of death was nearly identical in those subjects who continued to use tobacco and those who quit. In multivariate models, no variables were associated with risk of death.

The present TAO series is the first to report time-dependent event rates for major or any amputation and death. Our analyses have resulted in several novel observations: The risk of amputation continues in ongoing smokers up to a median of 14.8 years (mean, 15.6 years) after initial diagnosis. The risk of amputation in previous smokers is eliminated by 8 years after smoking cessation. In contrast to previous studies, we report an excessive late mortality in patients with TAO compared with the U.S. population (2,3).

Our data are limited in several ways. Not all patients had systematic evaluation for thrombophilia and autoimmune disease. The results of this study may not apply to patients with TAO in the community. The cause of death is not known for most patients. The ascertainment of nicotine cessation by chart review and survey may not accurately reflect actual smoking cessation. Those with mild addiction might be more likely than those with severe addiction to complete the survey. Finally, a substantial fraction of patients with TAO who reported smoking cessation may have continued to smoke.

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doi:10.1016/j.jacc.2004.09.029

Please note: the first two authors contributed equally to this work. Funded by a Mayo Foundation Protocol Grant.

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Effect of Six Months' Exercise Training on C-Reactive Protein Levels in Healthy Elderly Subjects

To the Editor: Nonspecific markers of inflammation such as C-reactive protein (CRP) are now recognized as major risk factors for cardiovascular events. General population studies have reported an inverse association between serum CRP levels and self-reported physical activity or physical fitness (1,2). These studies suggested that regular physical exercise might lower CRP levels by an anti-inflammatory action. However, an alternative explanation is that exercise lowers CRP levels by reducing total or abdominal fat. We performed a randomized controlled trial to assess the effects of six months' regular exercise training on serum CRP levels and body fat measured by dual-energy X-ray absorptiometry (DEXA) in a healthy elderly population.

Healthy elderly subjects age 60 to 85 years were recruited from the general population by newspaper advertisements. The exclusion criteria included inability to undertake an exercise-training program, current illness known to be associated with a systemic inflammatory response, a history of hypertension or diabetes, any current cardiovascular medication (including aspirin), or any evidence of cardiovascular disease on physical examination, electrocardiography, treadmill exercise testing, or echocardiography. The

Table 1. Baseline Characteristics

	Control Group (n = 31)	Exercise Group (n = 30)
Male gender (%)	14 (45)	13 (43)
Age (yrs)	66 ± 4	67 ± 5
Current smoker (%)	1 (3)	1 (3)
BMI (kg/m^2)	26 ± 4	25 ± 3
Body fat (%)	33 ± 9	33 ± 10
Trunk fat (%)	18 ± 5	17 ± 5
VO_2max (ml/kg/min)	28 ± 8	26 ± 6
Glucose (mg/dl)	90 ± 16	94 ± 13
LDL cholesterol (mg/dl)	139 ± 31	131 ± 29
CRP (mg/l)	1.5 [0.7 to 2.1]*	1.6 [0.5 to 2.9]*

*Numbers in brackets indicate interquartile range.
BMI = body mass index; CRP = C-reactive protein; LDL = low-density lipoprotein; VO_2max = maximum oxygen consumption during treadmill exercise.

study protocol was approved by the University of Auckland ethics committee, and all participants gave written informed consent.

Subjects were assigned randomly to either an exercise group or a control group. The participants in the control group were asked to maintain their usual level of physical activity. The exercise group underwent six months' exercise training, consisting of three supervised sessions and one unsupervised session each week. Exercise intensity was monitored by heart rate response. The training intensity was increased gradually so that by the fourth month, participants were training for 45 min at a heart rate of 80% of their current estimated maximum oxygen consumption (VO_2max).

At the start and end of the study, the patients' VO_2max was measured during graded treadmill exercise, body mass index (BMI) was calculated (weight/height^2 [kg/m^2]), and total body fat and trunk fat composition were determined by DEXA scanning using a Lunar DPX-IQ scanner (GE Medical Systems, Waukesha, Wisconsin). Venous blood samples were collected for measurement of CRP levels at least 24 h after the last exercise session. In participants with any illness or injury associated with an acute phase response, blood sampling was delayed for two weeks. The samples were stored at −80°C before being analyzed as a single batch using a high-sensitivity assay (Dade Behring, Inc., Deerfield, Illinois).

Because the distribution of CRP levels was skewed, natural-log-transformed CRP was used for statistical analysis. The Pearson correlation coefficient was used to assess the association between natural-log-transformed CRP and other baseline variables. Changes in CRP levels and other variables were compared between groups using a Mann-Whitney *U* test. All analyses were performed using SAS Release 8.0 Software (SAS Institute Inc., Cary, North Carolina).

Two participants were lost to follow-up, leaving a final cohort for analysis of 30 exercise subjects and 31 control subjects. Analyses were performed on an intention-to-treat basis and included all subjects with follow-up data. A sensitivity analysis (excluding four dropouts from the exercise program) did not alter the study findings.

The baseline characteristics of the exercise and control groups were similar (Table 1). Greater physical fitness (VO_2max) was associated with a lower BMI ($r = -0.27$, $p = 0.03$), less body fat ($r = -0.61$, $p < 0.001$), and less trunk fat ($r = -0.55$, $p < 0.001$). C-reactive protein levels correlated with measures of adiposity, including the BMI ($r = 0.40$), body fat percentage ($r = 0.46$), and trunk fat percentage ($r = 0.48$, $p \leq 0.001$ for all). In contrast, there was only a weak trend toward lower CRP levels with greater fitness ($r = -0.22$, $p = 0.09$).

At six months, there was an 18% improvement in cardiorespiratory fitness in the exercise group and no change in the control group (Table 2). There were no significant changes in body weight, body fat percentage, lipid profile, or serum glucose levels in either group. Considerable individual variability in CRP levels existed between baseline and six months but, on average, serum CRP levels did not change in either group. In addition, no association between changes in fitness and changes in CRP levels during the six-month trial was found. The results were similar for men and women.

In this study, six months' exercise training in healthy elderly participants did not lower serum CRP levels despite a significant improvement in their cardiorespiratory fitness. This finding contrasts with those of several large epidemiologic studies that reported an inverse association between serum CRP levels and regular physical activity (1,3,4) and/or physical fitness (2,5). There are several possible explanations for this difference. The association between exercise and inflammatory markers observed in epidemiologic studies may not be causal. Poor health of any severity may cause inflammation, as well as decreasing regular exercise and physical fitness. Alternatively, the cumulative effects of exercise may influence serum CRP levels over the course of many years, although not by shorter-term changes in exercise levels. This possibility is consistent with the hypothesis that physical exercise acts predominantly by reducing body fat. It is supported by the strong inverse association between physical fitness and body fat percentage observed in this study and the results of clinical trials that have reported reductions in CRP levels after weight loss (6). Although observational studies that reported an association be-

Table 2. Changes in Fitness, BMI, Body Fat, and Serum Levels of CRP, Glucose, and Lipids Between Baseline and Six Months

	Exercise Group		Control Group		Exercise vs. Control p Value
	Median Change*	% Change*	Median Change*	% Change*	
VO_2max (ml/kg/min)	3.7 [1.3 to 8.3]	18 [4 to 37]	0.05 [−2.2 to 3.0]	0 [−7 to 14]	0.004
BMI (kg/m^2)	−0.14 [−0.6 to 0.3]	−1 [−3 to 1]	−0.07 [−0.07 to 0.2]	0 [−3 to 1]	0.98
Body fat (%)	−0.7 [−2.8 to −0.1]	−2 [−10 to 0]	0 [−1.7 to 1.3]	0 [−7 to 4]	0.43
Trunk fat (%)	−0.9 [−1.7 to −0.5]	−6 [−10 to −2]	−0.8 [−1.9 to 0.6]	−4 [−15 to 3]	0.54
CRP (mg/l)	−0.12 [−0.8 to 0.3]	−6 [−34 to 33]	−0.06 [−0.4 to 0.5]	−4 [−30 to 52]	0.30
Glucose (mg/dl)	0.9 [−9.0 to 5.4]	1 [−9 to 7]	1.8 [−10.8 to 5.4]	2 [−11 to 7]	0.95
LDL cholesterol (mg/dl)	−2.2 [−4.5 to 2.3]	−6 [−10 to 8]	−3.4 [−5.7 to 0.0]	−7 [−15 to 0]	0.21

Changes are six-month levels minus baseline levels. *Numbers in brackets indicate interquartile range.
Abbreviations as in Table 1.

tween physical activity or fitness and serum CRP levels adjusted for BMI or waist girth (1,2), these measures of body fat are relatively imprecise, and residual confounding is possible. In the current study, the more precise DEXA scanning method was used to measure body fat and trunk fat. These DEXA measures correlated more strongly than BMI with both CRP levels and physical fitness. A limitation of the current study was variability in serum CRP levels. This variability reduced the statistical power of the study and, therefore, a small effect of improved physical fitness on CRP levels, independent of changes in body fat, cannot be excluded. Few previous studies have reported the effects of exercise training on CRP levels. Mattusch et al. (7) found a significant reduction in CRP levels after nine months of marathon training in 12 athletes. Smith et al. (8) reported a trend toward lower CRP levels in 43 volunteers after six months of exercise training. These studies did not include a control group and did not measure body fat. In conclusion, our findings suggest that the association between greater physical fitness and lower serum CRP levels is explained, at least in part, by long-term regular exercise reducing body fat.

Acknowledgments

The authors thank Roy The, BSc, for CRP analysis, Teena West, MSc, for statistical input, Charlene Nell for secretarial assistance, and Anna Breckon, ELS, for editorial assistance.

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doi:10.1016/j.jacc.2004.09.030

Please note: this work was supported by Project Grant No. 990 from the National Heart Foundation of New Zealand (Auckland, New Zealand) and by the generous loan of a CRP autoanalyser from Dade Behring Diagnostics Limited (Auckland, New Zealand). Dr Hammett was the recipient of a Cardiac Society of Australia and New Zealand/Merck Sharp and Dohme Fellowship.

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Gender as a Risk Factor in Young, Not in Old, Women Undergoing Coronary Artery Bypass Grafting

To the Editor: Women have a higher early mortality after coronary artery bypass grafting (CABG) compared with men in most studies (1,2). The influence of gender and age on early mortality and age- and gender-dependent risk factors have only been analyzed in a single U.S. study (1). Because demographic variables and therapeutic strategies may be different in the U.S. and Europe, analyses from European countries also are needed.

Patients undergoing CABG are increasingly older, and women undergoing CABG are older than men. The risk for myocardial infarction (MI) differs in women and men, as well as the pattern of coronary artery disease and myocardial remodeling. Acute MI has a worse prognosis, especially in younger women (3). Similar risk factors may influence mortality after MI and CABG.

We therefore analyzed in our large patient cohort whether early outcome after CABG was worse in women, whether the interaction between female gender and mortality was age dependent, and which preoperative parameters acted in a gender-specific manner. Using on our quality control database, we analyzed 17,528 consecutive patients (4,278 women and 13,250 men) who underwent CABG in the Deutsches Herzzentrum Berlin from 1993 to 2001. Standard statistical procedures, including multivariate testing, receiver-operated command analysis, and the Breslow-Day test, were used (1,4).

The percentage of women who underwent CABG increased with age, from 14% in the cohort younger than 50 years to 49% in that cohort older than 80 years (Fig. 1). In the mean, women had better left ventricular ejection fraction (LVEF) than men (55% women vs. 53% men); previous MI and previous CABG were less frequent (55% vs. 59% and 20% vs. 22%, respectively), and hypertension and diabetes (77% vs. 67% and 39% vs. 27%, respectively) were more frequent. In contrast, non-elective surgery was more frequent in women than in men (31% vs. 27%; $p < 0.001$ for all).

Mortality in women was significantly higher than in men, with the greatest differences in the youngest and no differences in the older age groups (Fig. 2). Female gender was an independent risk factor for mortality (hazard ratio 1.236; 95% confidence interval 1.008 to 1.56). In addition, age, impaired LVEF, and number of diseased vessels were independent predictors of early mortality in women. In men, priority of surgery and renal dysfunction were significant predictors of outcome.

The optimal cutoff value for age as a predictor of mortality was calculated as 70.5 years by receiver-operated command analysis. In the younger cohort, gender, age, number of affected vessels, LVEF, priority of surgery, and renal dysfunction were predictors of outcome. Previous MI was a significant risk factor in younger

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