

## Cardiovascular Fitness and Vascular Inflammatory Markers After Acute Aerobic Exercise

**Eric P. Plaisance, J. Kyle Taylor, Sofiya Alhassan, Asheber Abebe, Michael L. Mestek, and Peter W. Grandjean**

Inflammatory markers such as C-reactive protein (CRP), fibrinogen, and white-blood-cell (WBC) count are strongly associated with cardiovascular disease. The authors' purpose was to compare the inflammatory response to a single aerobic-exercise session between individuals of high and moderate fitness. Ten apparently healthy highly fit and 11 moderately fit men expended 500 kcal at 70% of  $VO_{2peak}$ . Fasting blood samples were obtained on 2 consecutive days before and again at 24, 72, and 120 h postexercise. Blood samples were analyzed for CRP, fibrinogen, and WBC count. CRP was 76% lower at baseline in the highly fit group than in the moderately fit group ( $P = 0.03$ ). CRP, fibrinogen, and WBC count remained unaltered, however, in the days after exercise ( $P > 0.05$  for all). These findings suggest that markers of inflammation are stable in the days after a single session of moderate-intensity aerobic exercise in apparently healthy men of at least average fitness.

**Key Words:** C-reactive protein, fibrinogen, white-blood-cell count

Inflammation is involved in all stages of the development of atherosclerosis (38). Therefore, markers of inflammation such as C-reactive protein (CRP), fibrinogen, and white-blood-cell (WBC) count have been investigated as possible adjuncts to traditional risk factors to enhance prediction of the risk of cardiovascular disease (12). Comparisons of CRP and low-density lipoprotein cholesterol (LDL-C) suggest that CRP might be a stronger predictor of future cardiovascular events than LDL-C alone (36). Indeed, 46% of all cardiovascular events occur among women with LDL-C levels below 130 mg/dL (36). Recent findings that exercise reduces levels of CRP and fibrinogen provide evidence that at least part of the cardioprotective effects of exercise might be attributed to reduced vascular inflammation (15, 32, 40). This could help explain exercise-related reductions in cardiovascular-disease events in the absence of changes in more traditional risk factors such as total cholesterol and LDL-C (20).

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Plaisance, Mestek, and Grandjean are with the Dept of Health and Human Performance, and Abebe, the Dept of Mathematics and Statistics, Auburn University, Auburn, AL 36849. Taylor is with the Dept of Biology, Auburn University, Montgomery, Montgomery, AL 36117. Alhassan is with the Stanford Prevention Research Center, Stanford University, Stanford, CA 94305-5705.

The inverse relationship between exercise and levels of inflammatory markers is consistent and strong. Individuals accumulating greater amounts of self-reported exercise demonstrate 8–35% lower levels of CRP (7, 34, 35) and 4–10% lower fibrinogen and WBC levels (1, 14, 34, 47) than individuals who are sedentary. Differences in physical fitness provide further support that physical activity might reduce vascular inflammatory markers. In fact, highly fit individuals have been found to have CRP and fibrinogen levels 47–77% and 9% lower, respectively, than those of low fitness (6, 21, 22, 26). Longitudinal investigations also provide evidence that inflammatory markers are modified by exercise training (15, 27, 30, 32, 39, 40), although there are exceptions (17, 25). Although part of the reductions in inflammatory markers observed with exercise training might be a result of weight loss (42, 46), there is sufficient evidence to suggest that exercise training reduces inflammatory markers, independent of weight loss or differences in body composition (15, 27, 43).

Despite the health-related benefits of a single session of aerobic exercise, there is little information regarding the effect of a single session of exercise on vascular inflammatory markers. CRP, fibrinogen, and WBC count were increased 5- to 20-fold immediately and up to 96 h after high-intensity exercise (4, 41, 43, 44, 48). Taylor and colleagues (41) observed 266% increases in CRP 24 h after a marathon returning to baseline by 48 h. Similarly, CRP and fibrinogen were increased 24 h after intense military maneuvers (4). Although CRP remained elevated for up to 96 h, fibrinogen returned to baseline by 48 h. In contrast, Castell et al. (5) observed only minor elevations in CRP concentrations immediately after a marathon, despite significant elevations in interleukin-6. Although these results provide evidence that inflammatory markers are elevated after high-intensity, long-duration exercise, it is unlikely that transient elevations in inflammatory markers increase the risk of cardiovascular disease (23); they are more likely to represent acute tissue damage (11, 45). Lower concentrations of vascular inflammatory markers would be expected in the days following moderate-intensity, moderate-duration aerobic exercise, because of reduced tissue damage when compared with high-intensity, long-duration exercise. Furthermore, highly fit individuals would be expected to experience less severe tissue damage and concomitantly lower concentrations of vascular inflammatory markers than less fit individuals when performing moderate-intensity aerobic exercise. Therefore, the purpose of this investigation was to simultaneously compare the effect of a single moderate-intensity aerobic-exercise session on CRP, fibrinogen, and WBC count in highly and moderately fit men in the days after exercise. We hypothesized based on available evidence that both highly and moderately fit individuals would experience an increase in inflammatory markers 24–72 h after an isocaloric exercise session but that the magnitude of increase would be lower for highly fit individuals.

## Methods and Materials

### Participants

Adult men between the ages of 25 and 45 y were recruited verbally and by posted flyer at Auburn University and in the Auburn, AL, community. Thirty-four volunteers responded to the posting. Eight were excluded because they did not meet

the fitness categories operationally defined by the investigators, and 5 participants discontinued the study because of a lack of time. A total of 21 participants met all criteria for the study. During their first visit to the lab, participants were informed of the risks and benefits of participating in the study and were asked to read and sign an institutionally approved informed consent. Each individual was then asked to complete a health history and physical activity questionnaire.

## Physiological Testing

After completion of the health history and physical activity questionnaire, anthropometric measurements including height, weight, waist circumference, and hip circumference were obtained. Percentage fat and lean body mass were calculated from body density using the sum of 7 skinfolds (18).

On the second visit to the laboratory, peak oxygen consumption ( $\text{VO}_{2\text{peak}}$ ) and work rate were determined using the standard Bruce protocol performed on a motor-driven treadmill (3). Blood pressure was determined manually using a mercury sphygmomanometer within the last minute of each stage. Heart rates were assessed during each minute of the protocol by Polar telemetry monitoring. Breath-by-breath analysis of  $\text{O}_2$  consumption and  $\text{CO}_2$  production were averaged over 30-s intervals using an automated system (Cardi $\text{O}_2$  Exercise Stress Testing System, Medical Graphics, Minneapolis, MN).  $\text{VO}_{2\text{peak}}$  was defined as the highest observed  $\text{O}_2$  uptake. An exercise test was considered maximal if at least 2 of the following criteria were met:

- 1) Respiratory-exchange ratio  $\geq 1.15$
- 2) Heart rate within 10 beats/min of age-predicted maximum
- 3) Rating of perceived exertion  $\geq 18$

Volunteers who achieved  $\text{VO}_{2\text{peak}}$  levels greater than or equal to the 80th percentile for fitness were classified as highly fit, and those who achieved  $\text{VO}_{2\text{peak}}$  values less than the 50th percentile were considered moderately fit (2).

## Dietary Records

Participants who met all criteria were invited to complete the study protocol and were subsequently asked to complete and return a 3-d dietary history reported 2 days during the week and on 1 weekend day. Dietary records were analyzed for total caloric intake and protein, carbohydrate, and fat composition using a commercially available software program (Food Processor for Windows, version 7.40, ESHA Research, Salem, OR). Participants were instructed to maintain dietary habits that were similar to the 3-d dietary history throughout the study period. Other than requesting that participants maintain caloric and nutrient intake, there was no attempt by the investigators to modify the diet of the participants. Participants were also instructed to avoid any strenuous physical activity, including exercise, for the 3 d before the experimental exercise session.

## Experimental Design

$\text{VO}_{2\text{peak}}$  (L/min) obtained from the graded-exercise test data and a standard kilocalorie equivalent of 5 kcal/L of  $\text{O}_2$  were used to estimate the exercise intensity and

duration needed to elicit an energy expenditure of 500 kcal before the experimental exercise session (16). The rate of energy expenditure was estimated by multiplying the kilocalorie equivalent by the corresponding  $\text{VO}_2$  (L/min). Exercise duration was estimated by dividing 500 kcal by the estimated rate of energy expenditure. Participants were asked to warm up at 2.5 miles/h with a 2% incline on the treadmill for 3 min. After the warm-up, the treadmill speed and grade were increased to the predicted intensity of 70%  $\text{VO}_{2\text{peak}}$  for each participant. Respiratory-gas analysis and heart rates were obtained initially and at approximately 15-min intervals to verify energy expenditure and intensity. The speed and incline of the treadmill were adjusted to maintain exercise intensity. Exercise sessions ranged from 28 to 44 min in the highly fit group and 41 to 57 min in the moderately fit group to achieve the 500-kcal energy-expenditure requirements. Postexercise blood pressure and heart rate were measured 5 min after exercise with the participant in a seated position.

## Blood Sampling

Blood samples were obtained 24 h and immediately before the acute bout of exercise and 24, 72, and 120 h after exercise. All samples were obtained at the same time each morning after an 8- to 12-h fast. All blood samples were obtained from an antecubital vein into 2 chilled 7.0-mL ( $13 \times 100$  mm) serum Vacutainer tubes, one 4.0-mL ( $13 \times 75$ , 7.2 mg)  $\text{K}_2$ -EDTA tube, and one 4.5-mL ( $13 \times 75$  mm, 0.105 M) sodium-citrate tube, and immediately placed on ice. Serum was isolated within 2 h of collection by centrifugation at 1500 g for 20 min. Samples for CRP analysis were aliquotted and stored at  $-70^\circ\text{C}$  for later analyses.

## Analysis of Inflammatory Markers

Whole blood obtained from  $\text{K}_2$ -EDTA tubes was analyzed in duplicate for WBC count, hemoglobin, and hematocrit within 4 h of collection using a CELL-DYN 1700 autoanalyzer (Abbott Diagnostics, Abbott Park, IL). In brief, plasma is pumped through a von Behrens transducer, which determines WBC count by changes in electrical impedance as the cells pass through the transducer (19). Hematocrit and hemoglobin concentrations were used to evaluate changes in plasma volume after the exercise intervention according to the procedures of Dill and Costill (10). Plasma from sodium-citrate tubes was analyzed for fibrinogen within 4 h after collection using an STA compact analyzer (Diagnostica Stago, Inc, Parsippany, NJ). Fibrinogen concentrations were determined by adding 100  $\mu\text{L}$  of plasma to fibrinogen reagent according to the manufacturer's instructions. Serum samples were analyzed for CRP using an immunoturbidimetric autoanalyzer (Beckman Synchron CX@9 PRO, Fullerton, CA) (37). Supersensitive CRP reagents were obtained from Carolina Liquid Chemistries (Brea, NC). Intra-assay coefficients of variation were 4.0% for CRP, 1.4% for fibrinogen, and 2.5% for WBC count.

## Statistical Analysis

A 2-sample *t*-test was used to determine baseline differences in physiological and dietary variables between groups. No significant differences were noted between the 2 baseline blood samples for any of the dependent variables in either group. Therefore, the 24-h pre- and immediately preexercise samples were combined to represent baseline for statistical analysis.

Graphical and formal statistical tests revealed that CRP and fibrinogen levels were positively skewed while WBC count was normally distributed. A generalized linear model (GLM) with a gamma-link function was used to account for the exponential distribution, and generalized estimating equations accounted for correlation between repeated measures (28). As expected, correlational analyses revealed that baseline inflammatory markers and waist circumference were significant predictors of CRP and fibrinogen and were included in the model.

A more traditional analysis was also performed to compare the findings of the GLM. Differences between groups at all time points were analyzed using a Savage test (8) for exponentially distributed data for CRP and fibrinogen. Sign tests were then employed to determine changes from baseline within groups. A 2 (group)  $\times$  4 (time) ANOVA with repeated measures on time was used to analyze WBC count. There were no statistical differences in the results of the GLM equations and the more traditional statistical methods. The comparison-wise error rate was set at  $P < 0.05$ . Power analyses calculated for the GLM and Savage tests suggested that 10 participants would be required to meet statistical significance for each inflammatory variable at an effect size of 0.8 and an alpha level of 0.05. All statistical analyses were performed using the Statistical Analysis System (SAS for Windows, version 9.1, SAS Institute, Cary, NC).

## Results

$VO_{2\text{peak}}$  was significantly higher, whereas percentage fat, body-mass index, and waist circumference were significantly lower, in the highly fit group despite non-significant differences in body weight. Participant characteristics for the highly and moderately fit groups are presented in Table 1.

**Table 1 Physiological Characteristics and Dietary Data, Mean  $\pm$  SE**

	Highly fit group	Moderately fit group	<i>P</i>
Age, y	29 $\pm$ 6	33 $\pm$ 8	0.2983
Height, cm	177.1 $\pm$ 8.8	172.3 $\pm$ 6.4	0.1634
Weight, kg	78.3 $\pm$ 9.3	84.6 $\pm$ 14.1	0.2445
Body fat, %	13.5 $\pm$ 5	22 $\pm$ 5	0.0011 <sup>a</sup>
BMI, kg/m <sup>2</sup>	24.9 $\pm$ 1.9	28.4 $\pm$ 3.4	0.0102 <sup>a</sup>
Waist, cm	81.2 $\pm$ 6.9	90.1 $\pm$ 10.7	0.0470 <sup>a</sup>
Waist-to-hip circumference	0.84 $\pm$ 0.04	0.92 $\pm$ 0.06	0.0051 <sup>a</sup>
$VO_{2\text{peak}}$ , L/min	4.2 $\pm$ 0.4	3.0 $\pm$ 0.5	0.0001 <sup>a</sup>
$VO_{2\text{peak}}$ , mL $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup>	53.9 $\pm$ 7.0	39.3 $\pm$ 5.0	0.0001 <sup>a</sup>
Average caloric intake, kcal/d	3016 $\pm$ 349	2395 $\pm$ 243	0.1510
Average fat intake, g	88 $\pm$ 11	81 $\pm$ 13	0.7260
Average carbohydrate intake, g	458 $\pm$ 62	320 $\pm$ 34	0.0495 <sup>a</sup>
Average protein intake, g	105 $\pm$ 15	100 $\pm$ 40	0.8505

<sup>a</sup>Significant difference between highly and moderately fit groups,  $P < 0.05$  for all.

**Table 2 Inflammatory-Biomarker Responses to Exercise**

Biomarker, group	Baseline	+24 h	+72 h	+120 h
C-reactive protein, mg/L				
highly fit	0.25 ± 0.22 <sup>a</sup>	0.32 ± 0.20 <sup>a</sup>	0.18 ± 0.12 <sup>a</sup>	0.23 ± 0.09 <sup>a</sup>
moderately fit	1.06 ± 0.24	0.68 ± 0.17	0.82 ± 0.17	0.83 ± 0.23
Fibrinogen, mg/dL				
highly fit	269.5 ± 13.8	264.3 ± 18.2	269.0 ± 10.9	267.5 ± 10.0
moderately fit	291.5 ± 12.6	269.0 ± 20.3	289.0 ± 13.6	278.0 ± 13.6
White-blood-cell count, K/ $\mu$ L				
highly fit, <i>n</i> = 10	5.65 ± 0.41	5.34 ± 0.47	5.66 ± 0.43	5.55 ± 0.34
moderately fit, <i>n</i> = 11	6.05 ± 0.38	5.81 ± 0.36	5.88 ± 0.29	6.28 ± 0.33

<sup>a</sup>Significant group difference ( $P < 0.05$  for all).

Values are median ± SE for C-reactive protein and fibrinogen. Values are mean ± SE for white-blood-cell count.

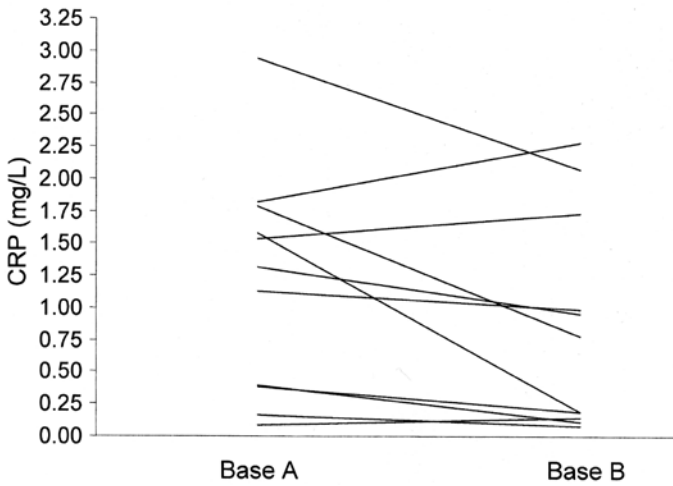
Estimated plasma volume was significantly increased in the days following the exercise session in both groups. Adjusting dependent variables for estimated shifts in plasma volume did not change the results of the analysis, however, so plasma-volume-uncorrected values of the inflammatory markers are provided (Table 2). CRP levels were 76% lower in the highly fit group than in the moderately fit group at baseline ( $P < 0.05$ ). Significant differences between groups for CRP were maintained at all time points ( $P < 0.05$ ), suggesting that the experimental intervention produced only minor fluctuations from baseline. Fibrinogen and WBC levels were not different between groups at baseline.

Mean daily variability was low for each of the inflammatory markers ( $P > 0.05$ ). The moderately fit group, however, demonstrated slightly greater individual variability for CRP than did the highly fit group (Figures 1 and 2).

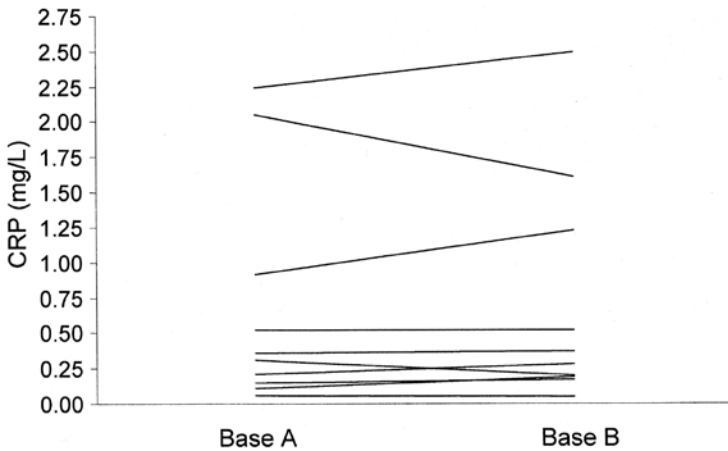
There were no statistically significant changes in any of the inflammatory markers in the days after the exercise session ( $P < 0.05$ ; Table 2). Waist circumference was positively associated with baseline levels of CRP ( $r = 0.47$ ), fibrinogen ( $r = 0.54$ ), and WBC count ( $r = 0.37$ ;  $P < 0.05$  for all) but did not influence the acute inflammatory response to exercise.

## Discussion

Regular aerobic exercise might be an effective intervention to reduce markers of inflammation (15, 27, 32). At least part of the health-related benefits of exercise training, however, are transient responses to the most recent bout of exercise performed (9). Furthermore, previous investigations suggest that cardiorespiratory fitness might influence blood lipid responses to a single session of exercise (9, 13). Therefore, we compared the effects of an acute moderate-intensity aerobic-exercise session in highly and moderately fit men to determine the effect of cardiorespiratory fitness on vascular inflammatory markers. We hypothesized that moderate fitness



**Figure 1** — Daily variation of C-reactive protein (CRP) as measured on 2 consecutive days in the moderately fit group. Base A indicates baseline blood sampling 24 h before exercise, and Base B, baseline blood sampling immediately before exercise.



**Figure 2** — Daily variation of C-reactive protein (CRP) as measured on 2 consecutive days in the highly fit group. Base A indicates baseline blood sampling 24 h before exercise, and Base B, baseline blood sampling immediately before exercise.

would be associated with a greater increase in markers of inflammation than would higher fitness after a single bout of exercise of similar caloric expenditure. Our findings indicate that baseline CRP, fibrinogen, and WBC concentrations are not significantly altered by a single session of moderate-intensity, moderate-duration aerobic exercise in apparently healthy men with at least average cardiorespiratory fitness.

The average  $\text{VO}_{2\text{peak}}$  of the highly and moderately fit groups was  $53.9 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and  $39.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , respectively, placing them in the 90th and 40th percentiles for fitness, respectively. Both groups consisted of primarily young white men with no known medical conditions, acute or chronic infection, or musculoskeletal injuries. The highly fit group had significantly lower levels of body fat, body-mass index, and waist circumference than the moderately fit group. Body-fat percentage in the highly fit group was 9% lower, and waist circumference, 10% lower, than in the moderately fit group.

Waist circumference was positively associated with baseline levels of each of the inflammatory markers. The positive association between baseline inflammatory markers and other estimates of body composition, such as body-mass index, has previously been reported (22, 26). Our findings suggest that waist circumference is associated with baseline levels of inflammatory markers but not with the response to a single bout of moderate-intensity aerobic exercise in young healthy men.

Although the highly fit group had a greater number of individuals with CRP levels  $<1.0 \text{ mg/L}$ , only 7 of 21 participants had values greater than  $1.0 \text{ mg/L}$ . Furthermore, none of the participants in either group had CRP values greater than  $1.7 \text{ mg/L}$ , which is currently recognized as indicating moderate risk for cardiovascular disease (33). The relatively young age and health status of participants might help explain the low CRP levels in the current investigation. Despite the relatively low CRP levels, CRP was 76% higher in the moderately fit group than in the highly fit group, suggesting that even low CRP levels can be influenced by fitness. In contrast, there were no significant differences between groups for fibrinogen and WBC count, suggesting that exercise training has less impact on these factors.

Baseline blood samples were collected on 2 consecutive days before exercise to determine daily variation in the markers of inflammation. There was no statistically significant variation in any of the inflammatory markers within either group. More individuals in the moderately fit group, however, demonstrated a larger degree of variation than those in the highly fit group. There has been little work conducted to date on the day-to-day variability of inflammatory markers. Macy and colleagues (24), however, examined CRP levels in 4 participants taking part in a 7-wk study in which blood was sampled twice per week. CRP levels were consistently maintained with only minor fluctuations during the investigation. Ockene and colleagues (31) demonstrated minor seasonal fluctuations in CRP that are similar to those reported for serum total cholesterol. Although there is little evidence regarding the daily variability of fibrinogen and WBC levels, we found only minor daily variation, providing additional evidence that these are also stable markers of inflammation even after exercise.

There were no statistically significant fluctuations in any of the inflammatory markers 24–120 h after a single bout of moderate-intensity aerobic exercise in the current investigation. In contrast, others have shown that CRP, fibrinogen, and WBC count can be increased 5- to 20-fold immediately and up to 96 h after high-intensity aerobic exercise (4, 41, 43, 44, 48). CRP was increased 266% 24 h after a marathon but returned to baseline by 48 h (41, 48). Similarly, CRP and fibrinogen were increased 24 h after intense military maneuvers (4). Our results suggest that fibrinogen and WBC count are unaltered by moderate-intensity and -duration aerobic exercise (15). The change in CRP and inflammatory markers observed after intense and prolonged exercise, but not moderate intensity, moderate-duration



exercise, might be partly attributed to greater mechanical forces, tissue damage, and glycogen depletion after high-intensity or prolonged exercise (11, 29). It is likely that the exercise completed in the current investigation required lower mechanical forces and resulted in less tissue damage and glycogen depletion than in previous studies, which might, in part, explain the differences in inflammatory responses noted here and in previous investigations.

In summary, previous investigators have reported significant increases in inflammatory markers in the hours and days after high-intensity or long-duration exercise. Our findings suggest that exercise of moderate intensity and duration does not appreciably alter markers of inflammation in young healthy men of at least average fitness. Although high and moderate fitness had no effect on the inflammatory response to exercise, it is possible that less fit populations would respond differently to a single bout of aerobic exercise. It is also possible that the relatively young age of our participants influenced our findings. The results of this investigation might be useful for clinicians because a single session of moderate-intensity and -duration exercise appears to have little impact on markers of inflammation. Additional work will be required to determine the mechanism by which intensity and duration affect the acute inflammatory response to exercise.

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