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To the Graduate Council:

I am submitting herewith a dissertation written by Carolyn Albright entitled "Inflammatory Response Following Moderate and Vigorous Aerobic Exercise." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Education.

Dixie L. Thompson, Major Professor

We have read this dissertation and recommend its acceptance:

David R. Bassett, Edward T. Howley, Maureen Groer

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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Accepted for the Council:

Vice Chancellor and Dean of
Graduate Studies

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INFLAMMATORY RESPONSE FOLLOWING MODERATE AND VIGOROUS AEROBIC EXERCISE

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Carolyn Albright

August 2006

DEDICATION

This dissertation is dedicated to Mom, Dad, Jackie, Len, and Stephen. I thank you for your continual love and support in everything I have set out to accomplish.

"And what went wrong when other alchemists tried to make gold and were unable to do so?" "They were looking only for gold," his companion answered. "They were seeking the treasure of their personal legend, without wanting to actually live out their personal legend."

- Paulo Coelho

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ABSTRACT

The purpose of this study was to establish the effect of an acute bout of moderate and vigorous aerobic exercise on production of the inflammatory cytokine interleukin-6 (IL-6) and the acute phase protein C-reactive protein (CRP). Ten male recreationally trained cyclists (average age 30.3 $\pm$ 5.7 years) completed two 40-minute cycling bouts on two separate occasions. A moderate-intensity exercise bout was performed at 50% of VO_{2max} and a vigorous-intensity exercise bout was performed at 80% of VO_{2max}. Blood samples were taken before exercise, 30 minutes into exercise, and then 15, 30, 45, 60, 90, 120, 180, and 240 minutes post-exercise. Average percent of VO_{2max} for moderate and vigorous exercise was 52.7 $\pm$ 1.6 and 76.8 $\pm$ 5.0 percent, respectively. There was a significant increase in CRP during and following both moderate and vigorous exercise ($p < 0.05$). IL-6 was increased 15-minutes after moderate exercise, and during and for 1-hour following vigorous exercise ($p < 0.05$). The increase in IL-6 was greater following vigorous compared to moderate exercise ($p = 0.001$). Change in IL-6 during vigorous exercise was correlated with the change in CRP immediately following the exercise bout ($p = 0.003$, $r = 0.826$). These results show that an acute bout of moderate or vigorous exercise can result in an acute phase response during exercise. This acute phase response is related to the inflammatory response that occurs during exercise.

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CHAPTER 1

INTRODUCTION

The American Heart Association recommends increasing physical activity as one method for reducing heart attack risk.[20] Acute bouts of physical activity, however, can increase the risk for having a myocardial infarction (MI).[12] Vigorous physical exertion is associated with an increased risk for MI and the risk for MI is higher with vigorous-intensity compared to moderate-intensity exercise.[1, 12, 45] A meta-analysis examining the external triggers of MI found that the odds ratio for MI occurrence following heavy physical activity was 6.21 ($P < 0.001$), whereas the odds ratio for MI with moderate physical activity was 1.11 ($P = 0.45$).[12] The Myocardial Infarction Onset Study investigated the relationship between physical exertion and risk of acute MI.[45] Compared to performing less strenuous or no physical activity, the relative risk for MI following heavy physical exertion was 5.9. The average induction time for MI following heavy exertion was within one hour. Undergoing heavy physical exertion 2 to 5 hours prior to MI did not increase risk for MI. The Physician's Health Study also demonstrated a significant increased risk for the occurrence of a cardiac event following or during vigorous exertion. The relative risk for sudden death by cardiac causes during the one-hour period associated with vigorous exertion (30 minutes during and 30 minutes after) was 16.9 ($P < 0.001$) compared to any other time point.[1] The primary cause of sudden cardiac death following acute exertion is thought to be due to plaque rupture.[6, 83] The plaque rupture itself is not the exact cause of death, but the resulting platelet aggregation

and thrombosis that is a result of this rupture is what leads to acute myocardial infarction and sudden death.

Acute phase proteins and inflammatory cytokines may increase the risk for the occurrence of a cardiac event. During a stress response, C-reactive protein (CRP) and interleukin-6 (IL-6) enter into circulation. Once in circulation, the inflammatory molecules may produce a larger inflammatory response in other areas of the body by binding to sites such as fibrous caps present in atherosclerotic plaque. A higher concentration of inflammatory molecules located at this site will increase the risk for the cap to rupture, ultimately leading to vessel occlusion.[18, 69]

An acute-phase response occurs during exercise in response to skeletal muscle tissue damage. The first response to an exercise bout is the production of IL-6 in the exercising skeletal muscle.[57] This local inflammatory response results in a systemic reaction by stimulating additional IL-6 production in the liver and the release of CRP from the liver into circulation.[48, 52] CRP is an acute phase protein that serves both as a pro-inflammatory and anti-inflammatory molecule. The purpose behind the initial release of CRP is for this pro-inflammatory protein to initiate an inflammatory response at the site of skeletal muscle damage. This inflammatory response that CRP and IL-6 are responsible for consists of the regulation and the migration of neutrophils and monocytes to the skeletal muscle to initiate repair.[48, 52]

The earliest study showing an acute phase response to aerobic exercise was performed by Liesen et al.[40] Eight male subjects performed 3 separate treadmill bouts: 2 hours at 90% of aerobic-anaerobic threshold speed, 3-hours at 75% of aerobic-anaerobic

threshold speed, and 2 hours at 75% of aerobic-anaerobic threshold speed. Blood samples were taken before exercise, immediately after exercise, and 1, 2, 4, and 7 days following exercise. The study found a significant increase in CRP from rest to day 1 following exercise after all three running bouts, demonstrating an acute phase response within 24 hours of treadmill running.

A recent study by Scharhag et al. investigated the effect of moderate intensity cycling on immune cell function in competitive male athletes.[64] Twelve highly-trained men cycled for 4 hours on a 400 m track at 70% of their anaerobic threshold. Blood samples were taken before, immediately after exercise, 1, 2, and 19 hours post-exercise, and 1 day post-exercise. A significant increase in IL-6 occurred from before exercise (1.0 ± 0.5 pg/ml) to 1-hour post-exercise (9.6 ± 5.6 pg/ml). CRP increased significantly from before exercise (0.5 ± 0.4 mg/l) to 1-day post-exercise (1.8 ± 1.3 mg/l). A significant correlation was found between CRP and IL-6 over the exercise day ($r = 0.71$, $p < 0.01$). This study was able to demonstrate an acute phase response to moderate prolonged cycling, with almost a 10-fold increase in IL-6 and a 3- to 4-fold increase in CRP in well-trained competitive athletes.

Plaisance et al. sought to determine the inflammatory response to a single bout of moderate-intensity exercise.[60] Ten high-fit and 11 low-fit males performed treadmill exercise at 70% of VO_{2max} to expend 500 kcals. Blood samples were taken 2 consecutive days before and then 24, 72, and 120 hours post-exercise. No significant changes occurred in CRP following the exercise bout in either group. Although no changes were

seen 24-hours post-exercise, this study failed to determine if any immediate inflammatory response may have occurred following aerobic exercise.

A study that did measure CRP values immediately following an exercise bout was performed by Miles et al.[44] CRP and IL-6 were measured in men and women following a 20-mile off-road race. Blood samples were collected 0, 4, and 24 hours post-race. CRP levels were highest 4-hours post-race (women: 1.3 ± 1.9 to 2.7 ± 2.3 mg/l; men: 0.8 ± 0.8 to 4.6 ± 1.6 mg/l), with no significant gender by time interaction. This study does show an immediate inflammatory response, however, the vigorous nature and the long duration of the exercise bout would make it difficult to generalize the results to more normal exercise.

Henson et al. looked at the acute-phase response in 15 elite rowers (average VO_{2max} 4.1 ± 0.08 L/min) from the ARCO Olympic Training Center.[29] All women performed a 2-hour rowing session at moderate intensity (average 57% VO_{2max}). The athletes did not participate in any physical activity 12 hours prior to the practice period. Blood samples were taken pre-exercise, post-exercise, and 1.5-hr post-exercise. No significant changes in CRP or IL-6 were observed, suggesting that extended bouts of moderate exercise does not result in an increase in these inflammatory markers. However, the elite status of these subjects, as well no control over activity in the 48 hours prior to the study may have contributed to the lack of change in CRP and IL-6 following this activity.

Hubinger et al. showed no inflammatory response to level and downhill treadmill running. Subjects for this study averaged 20 years of age and participated in recreational

sport activities. The first part of the study had eight males perform 1 hour of level treadmill running at 90% HR_{max}. The second part of the study had three males and 3 females perform two 15-minute downhill runs, followed by one 10-minute downhill run with 5 minute seated recovery between each bout (-15% decline grade). Blood samples were taken immediately before, immediately after, and 1, 3, 5, and 7 days post-exercise. No changes in CRP were found following either protocol. Although a blood sample was taken immediately following the exercise bouts, there was no attempt to determine the inflammatory response in the immediate few hours following the exercise. Because of a potential lag time in release between IL-6 and CRP, an elevation in CRP directly following the exercise may not be expected, but may have occurred in the hours following.

Nieman et al. had women who reported walking at least 2 to 5 days per week perform a moderate walking bout at 60% of VO_{2max} for 30 minutes.[53] IL-6 levels immediately following and 1-hr post-exercise were significantly higher than pre-exercise values ($P < 0.001$). There was no difference between IL-6 levels measured immediately post- and 1-hour post-exercise. CRP was not analyzed in this study, so the effect of a moderate walking bout on this acute-phase protein is still unknown. The increase in IL-6 following the walking bout, however, did show that moderate intensity exercise can result in an inflammation response in some individuals.

Lack of consistency in this area makes it difficult to draw conclusions regarding the effects of a single aerobic exercise bout on the acute-phase response, primarily the production of CRP. Most studies were designed to investigate changes over a period of

days, failing to look at the hours immediately following the exercise bout. With CRP having a half-life of 19 hours, any change in this inflammatory marker within a few hours following exercise may not be captured if a sample is not taken until 24-hours post-exercise. Without studies sampling the first few hours following an exercise bout, one cannot determine if the aerobic exercise results in an immediate elevated inflammatory state and acute phase response.

Purpose

The optimal intensity of activity to decrease risk for cardiac events, but provide optimal health benefit is currently not known. There is debate surrounding the optimal intensity for prescribing exercise, with many feeling that vigorous exercise must be incorporated into daily physical activity. However, since vigorous activity leads to a greater risk for the onset of MI compared to moderate activity, a better understanding of the inflammatory response that may be responsible for triggering a MI should be established. Therefore, the purpose of this study is to characterize the inflammatory response, with regards to IL-6 and CRP production, during and immediately following moderate and vigorous exercise.

Hypotheses

1. There will be a significant increase in IL-6 following moderate-intensity activity.
2. There will be no change in CRP following moderate-intensity exercise.

3. There will be a significant increase in CRP and IL-6 following vigorous-intensity exercise.
4. The increase in IL-6 will be significantly greater following vigorous-intensity exercise compared to the increase measured with moderate-intensity exercise
5. A positive relationship will exist between changes in CRP and changes in IL-6 following vigorous exercise.

CHAPTER 2

REVIEW OF LITERATURE

Interleukin-6

Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced by lymphocytes, monocytes, fibroblasts, vascular smooth muscle cells, and endothelial cells. The release of IL-6 is stimulated by interleukin-1 (IL-1) and tumor necrosis factor-β (TNF-β).[46, 50] IL-6 can have a direct effect on the inflammation response by stimulating the hepatic acute phase response, macrophage production, platelet aggregation, proliferation of vascular smooth muscle cells, and expression of adhesion molecules and additional cytokines in endothelial cells.[22, 26, 32, 33, 49, 51]

When tissue injury occurs, either by infection or non-infectious causes, the body reacts using a local inflammatory response. This response includes the release of the pro-inflammatory cytokine IL-6, which further activates the vascular system and release of more inflammatory cells.[75] The additional cytokines and inflammatory cells then circulate throughout the bloodstream and are responsible for activating a systemic reaction.[25] As part of this systemic reaction, circulating IL-6 stimulates the acute phase response, resulting in the release of the acute phase protein C-reactive protein (CRP).[27]

Acute Phase Response and C-Reactive Protein

The acute phase response is a systemic reaction caused by infection, injury, or trauma.[23, 24] During the acute phase response cytokines stimulate the release of acute phase proteins including CRP, serum amyloid A (SAA), and haptoglobin (Hp) from

hepatocytes.[27, 28] Il-6 is the major mediator responsible for the secretion of acute phase proteins, predominantly CRP.[27]

CRP is an acute-phase protein that serves both as a pro-inflammatory and an anti-inflammatory molecule. In the pro-inflammatory state, the main function of CRP is to work as a protective mechanism by targeting pathogens and marking them for cellular destruction. In the anti-inflammatory state, CRP works to neutralize anti-inflammatory cytokines, proteases, and oxidants released during an inflammatory response to tissue damage.

In the pro-inflammatory state, CRP is capable of recognizing and targeting cells for destruction. CRP can target foreign pathogens and the phospholipid component of damaged cells by binding to phosphocoline. In normal functioning healthy cells, CRP is unable to bind to phosphocoline. However, when cells are in a damaged or dead state, this site becomes accessible, allowing CRP to bind to and target these molecules for destruction.[78] The elimination of targeted cells can also be initiated by CRP because of its ability to activate the complement system and bind to phagocytic cells, both important components of the host defense mechanisms.[78] Finally, CRP also functions in the pro-inflammatory state to modulate the function of monocytes by binding to and stimulating the release of inflammatory cytokines such as IL-1, IL-6, and IL-8 in addition to tumor-necrosis factor.[3]

The anti-inflammatory functions of CRP have been studied extensively in mice and show the protective function that CRP may play in the inflammation process. These findings can be applied to the inflammation response in humans because of the use of

CRP transgenic mice. In terms of CRP, these mice react in the same manner as a human because they have been given the 31-kb fragment of human DNA that contains the CRP gene, 50-and 30-flanking DNA encoding for the CRP promoter, and all of the known CRP gene regulatory elements.[9] By using CRP transgenic mice, Heuertz et al. was able to show that CRP is capable of inhibiting the adhesion of neutrophils to endothelial cells. This was found using the mouse model, in which higher CRP levels led to reduced lung injury by functioning to inhibit the influx of neutrophils into the lungs.[30] In addition to this study using mice, human model research has found that superoxide production by neutrophils is also inhibited by CRP.[5] This finding adds to the combined effects that CRP has on neutrophils to down-regulate the acute inflammatory response.[5]

Sources of Inflammatory Markers with Exercise

Previous research has provided evidence of an inflammatory response to aerobic exercise.[53, 65, 68, 76] There is, however, conflicting evidence over what stimulates the production of inflammatory markers during and following an exercise bout. Possible sources include skeletal muscle, circulating mononuclear cells, or other body tissues.[65] The production of the inflammatory cytokine IL-6 directly within skeletal muscle has been demonstrated following an acute bout of exercise.[4, 57] Skeletal muscle responds to an exercise bout by locally producing cytokines including IL-6, TNF-α, and IL-1β . This local inflammatory response results in a systemic reaction by releasing additional IL-6 from the liver and initiating an acute phase response by stimulating the production of CRP.[48, 52] The newly formed CRP and IL-6 are then available to circulate through the

body and bind to damaged membranes and proteins to initiate or continue an inflammatory response. The inflammatory response that CRP and IL-6 are responsible for consists of the regulation and the migration of neutrophils and monocytes to the muscle to initiate repair.[47, 52]

Two early studies out of the Copenhagen Muscle Research Center investigated the inflammatory response to exercise by looking at IL-6 production in skeletal muscle and its relation to muscle damage following an exercise bout.[4, 57] Ostrowksi et al. used muscle biopsy samples before and after the Copenhagen Marathon to determine whether IL-6 was produced locally in exercising skeletal muscle following strenuous exercise.[57] Sixteen trained males, average age of 30 years and average VO_{2max} of 4.36 l/min, completed the Copenhagen Marathon. Muscle biopsies from the vastus lateralis of the quadriceps femoris and blood samples were taken in 16 men 1 week prior to the race, immediately following the race, and 2 hours post-race. Subjects refrained from exercise 2 days before the initial sample was taken one week before the race. Average running time for all participants was 3 hours and 17 minutes. Plasma IL-6 increased from pre- (1.5 $\pm$ 0.7 pg/ml) to post-exercise (94.4 $\pm$ 12.6 pg/ml), and although still greater than pre-race levels, declined 2 hours after the race (22.1 $\pm$ 3.8 pg/ml). Muscle biopsy results revealed no detectable mRNA for IL-6 pre-exercise, but four biopsies immediately post-race, and two biopsies 2 hours after the race detected IL-6 mRNA. There was no mRNA for IL-6 detected in blood mononuclear cells. Creatine kinase (CK) levels were still greater one (2360 U/l) and two (1193 U/l) days post-race compared to pre-race levels (225 U/l). The finding of IL-6 in the muscle but not in the blood mononuclear cells

(BMNC) suggests that IL-6 was locally produced in skeletal muscle in response to muscle damage and repair.

Bruunsgaard et al. studied the relationship between cytokine production and muscle damage in concentric versus eccentric exercise.[4] Nine men, average age 26 years and average VO_{2max} of 51.1 ml/kg/min were studied. All men were recreationally active and participated in exercise 1-5 days per week for 1-2 hours. The exercise protocol for this study included 30 minutes of concentric or eccentric cycling. The concentric cycling included normal cycling at 65% of VO_{2max}. The eccentric cycling protocol had subjects pedal in a reverse direction, at a predetermined speed, for 20 minutes at 150% followed by 10 minutes at 100% of the load eliciting concentric VO_{2max}. Blood samples were taken before, 2 hours after, and 2, 4, and 7 days following each cycling bout. Subjects were instructed not to perform any organized physical exercise for the 7 days after the cycling exercise. The results of this study found that IL-6 increased significantly 2-hours after the eccentric cycling compared to baseline levels, but not following the concentric cycling. Creatine kinase (CK) was also significantly elevated following the eccentric cycling at days 2, 4, and 7 compared to baseline levels. The authors chose to examine the relationship between IL-6 and CK by using the mean of days 4 and 7 since they did not know the exact peak value reached. There was a significant correlation ($r = 0.722$; $p = 0.028$) between IL-6 and CK following the eccentric cycling bout.

In contrast to those discussed above, some studies have found no association between muscle damage and inflammation, and therefore have proposed that other mechanisms are responsible for the increase in inflammatory markers found with

exercise.[11, 55, 56, 71] Jonsdottir et al. studied IL-6 production in rat skeletal muscle following eccentric and concentric exercise.[36] The study sought to determine whether the type of contraction, using eccentric contractions to produce skeletal muscle damage versus using concentric contractions without muscle damage, differed in terms of this cytokine response. Rat calf muscle was electronically stimulated at 100 Hz (4 x 10 contractions with 1 minute rest between the four series) for concentric or eccentric contractions. IL-6 mRNA was measured 30 minutes following contractions using reverse transcription-polymerase chain reaction (RT-PCR). The study found a significant increase in skeletal muscle IL-6 mRNA following both eccentric and concentric contractions, showing that cytokine mRNA is produced locally in the contracting skeletal muscle. The authors concluded that the similar increases in IL-6 mRNA found with both contractions indicate that IL-6 production is not due to muscle damage primarily seen with eccentric exercise, but was a result of muscle contraction. In addition to these results, measurements taken in the contralateral hind limb that was not stimulated showed no increase in the level of IL-6 mRNA. Also, the study found no difference in IL-6 mRNA increase between muscle fiber types.

A study looking at circulating levels of IL-6 from blood sampling, and not that measured through muscle biopsy, showed no relationship between changes in IL-6 and CK following treadmill running.[59] Peake et al. had 10 well-trained runners and triathletes perform 45 minutes of treadmill running at a negative 10% grade at 60% VO_{2max}. Blood samples were taken immediately before exercise, immediately following exercise, 1 hour post-exercise, and 24 hours post-exercise. The study found a significant increase in

plasma IL-6 immediately following exercise, and remained elevated only at 1 hour post-exercise, before returning to baseline levels at 24 hours post-exercise. Plasma CK levels, measured as a marker of muscle damage, were significantly increased at 24 hours post-exercise. However, there was no relationship between changes in IL-6 and changes in CK with exercise.

The earlier studies concluded that the increase in IL-6 was due solely to resulting muscle damage because the studies found increases in IL-6 and CK with eccentric exercise but not concentric exercise. However, studies showing an increase in IL-6 with concentric aerobic exercise provided evidence of an inflammatory response without significant skeletal muscle damage. It has therefore been concluded that there must be another mechanism for increased IL-6 production with exercise.[84] These other sources, including circulating mononuclear cells,[67] increased catecholamine production,[16, 66, 74] and exercise induced ischemia causing cytokine release from the splachnic bed,[2, 61] have all been found to be very minimal, and are not thought of as important sources of exercise-induced cytokine release.[65]

Although the exact mechanisms behind increased IL-6 production have not been established, it is known that aerobic exercise does result in increased circulation of this inflammatory cytokine.[65] The increase in IL-6 with acute exercise could then stimulate the following responses: acute phase reaction, HPA axis, and xanthine oxidase expression in the endothelium.

Inflammatory Response to Exercise

Research available on inflammatory response following aerobic exercise, with regards to increasing circulating levels of IL-6, has been consistent in its findings, with significant increases occurring immediately following exercise.[1, 53, 68, 76] Nieman et al. studied the immune response to a 30-minute bout of walking.[53] Fifteen women between the ages of 20 and 55 who had a history of walking at least 20-30 minutes, 2-7 days per week, for at least the previous 3 months were included in the study. The study was designed to test the immune response to a 30-minute walk with and without an exercise assist device (Body Bat). Both treadmill tests were performed at the same speed, which corresponded to 60% of VO_{2max}. Women also underwent a control day where they sat for 30 minutes. Blood samples were taken 15 minutes prior to exercise or sitting, immediately following, and 1 hour post-exercise or sitting. There was no difference in IL-6 response with and without the Body Bat. Both treadmill tests had significantly different changes in IL-6 values compared to sitting. IL-6 levels were significantly greater than pre-walk values both immediately following and 1-hour post exercise for both treadmill bouts, therefore showing an inflammatory response to a moderate bout of exercise.

Vassilakopoulos et al. compared the cytokine response to aerobic exercise before and after antioxidant supplementation.[76] Six untrained males, average age 33 years, cycled for 45 minutes at 70% of VO_{2max} on two separate occasions. Cycling bouts were performed before and after 60 days of antioxidant supplementation. Antioxidant supplementation included 200 mg of vitamin E, 50,000 IU of vitamin A, and 1,000 mg

vitamin C daily for 60 days, allopurinol 600 mg per day for 15 days, *N*-acetylcysteine 2 g per day for 3 days, and 800 mg on the morning before the second exercise bout. Subjects refrained from exercise or strenuous activity 24 hours prior to both testing days. Blood samples were taken before, immediately after, and 30 and 120 minutes following exercise. IL-6 was increased immediately following exercise and reached its peak 30 minutes post-exercise. Although still greater than resting levels, the IL-6 response following antioxidant supplementation was significantly lower compared to the exercise response before supplementation. These results led the authors to conclude that oxidative stress is a strong stimulator of cytokine production during exercise in healthy untrained men.

Starkie et al. also showed an increase in IL-6 production following cycling exercise. Seven endurance trained males cycled for 90 minutes at 70% of VO_{2peak} at either 15°C or 35°C.[68] Blood samples were collected pre-exercise, 45 minutes into exercise, immediately post-exercise, and 2 hours post-exercise. The study found a significant increase in IL-6 immediately following exercise at 35°C but no increases occurred with exercise at 15°C. The authors speculated that exercising in heat may have led to an increase in intramuscular glycogen use, which exacerbated IL-6 production in the skeletal muscle.

These studies have established that an inflammatory response is initiated following moderate and vigorous exercise. This response has also been found to occur in both trained and untrained individuals. An increase in IL-6 following a single bout of exercise, would make this inflammatory cytokine more readily available in circulation.

As already established, IL-6 could then continue a systemic inflammatory response by stimulating the production of additional inflammatory cytokines and by initiating an acute phase response.

Acute Phase Response to Exercise in Laboratory Studies

The time course for the stimulation of the acute phase response varies, and can occur within the first few hours of infection.[25] Studies have been able to establish that an acute phase response does occur following an acute bout of aerobic exercise,[37] however, the time course of this response following exercise is unknown. The shortest time period in which a significant increase in CRP has been shown, occurred immediately following a short bout of maximal aerobic exercise.[19] The studies discussed in this section have measured the release of CRP following varying exercise durations and intensities and used different blood sampling periods, therefore making it difficult to characterize specifically the acute phase response to exercise.

The earliest study demonstrating an acute phase response to aerobic exercise was performed by Liesen et al.[40] The study included eight male subjects, ages 21 to 29 years. Blood samples were collected before, immediately after, and 1, 2, 4, and 7 days following exercise. Exercise bouts included a 3-hour treadmill run or two 2-hour treadmill runs. Running speed for the first 2-hour test was at 90% of aerobic-anaerobic threshold speed. Average running speed for the 3-hour and second 2-hour test was 75% of the aerobic-anaerobic threshold speed. All running bouts resulted in a significant increase in CRP from rest to 1 day following exercise. This led the authors to conclude that an acute

phase response does occur within 24 hours following exercise in response to different running durations and intensities.

A more recent study by Scharhag et al. studied the effect of moderate intensity cycling on immune cell function in competitive male athletes.[64] Twelve men, average age of 26 years, who had been cycling for 6.5 years and had trained on average 11 hours per week during their season participated in the study. The men cycled for 4 hours on a 400 m track at 70% of their anaerobic threshold. Blood samples were taken immediately before exercise, immediately after exercise, 1,.2, and 19 hours post-exercise, and 1 day post-exercise. All men also underwent a control day in which blood samples were taken at the same time points. There were no significant changes in IL-6 and CRP over the control day. A significant increase in IL-6 occurred from before exercise (1.0 ± 0.5 pg/ml) to 1-hour post-exercise (9.6 ± 5.6 pg/ml). CRP increased significantly from before exercise (0.5 ± 0.4 mg/l) to 1-day post-exercise (1.8 ± 1.3 mg/l). A significant correlation was found between CRP and IL-6 over the exercise day ($r = 0.71$, $p < 0.01$). This study was able to demonstrate that an acute phase response to moderate prolonged cycling, with almost a 10-fold increase in IL-6 and a 3- to 4-fold increase in CRP, does occur in well-trained competitive athletes.

The inflammatory and acute phase response to a 5-km run was studied by Drenth et al.[17] Ten competitive runners (3 females, 7 males), age 17-36 years, completed the running event. Average run time was 20.5 ± 1.5 min and average exercise intensity was 94% of heart rate reserve. Blood samples were taken immediately before, immediately after, and 3, 24, and 48 hours after the run. CRP was significantly greater 24-hours after

the run compared to baseline ($p = 0.015$) and then declined to baseline levels by 48-hours. IL-6 was only detected in 2 of the 10 subjects. The IL-6 levels immediately following the race were 20 pg/l and 18 pg/l for the two runners. Although IL-6 is the principal stimulator of CRP, this study found a 1.5-fold increase in CRP, but no detectable changes in IL-6. The authors believe that the immunoassay may have been too insensitive to detect significant changes in IL-6, therefore, making it difficult to draw any conclusions about the IL-6 and CRP association following a 5-km run.

Sacheck et al. sought to determine whether age had an effect on the inflammatory and acute phase response to exercise.[63] Sixteen physically active young men (18-35 years of age) and 16 elderly men (65-80 years of age) participated in the study. Subjects performed 45 minutes of downhill treadmill running at 75% of VO_{2max}. Running was done in three 15-minute intervals with a 5-minute rest period between each interval. Blood samples were taken before exercise, immediately following exercise, and at 6, 24, and 72 hours post-exercise. In both young and elderly men, CRP was approximately 2-fold higher 24 hours following exercise ($p < 0.001$). IL-6 was increased in both groups at 6-hours post-exercise, but returned to baseline levels by 24-hours. There was also a significant correlation ($r^2 = 0.31$, $p < 0.01$) between IL-6 and CRP at 24-hours. The authors concluded that a bout of eccentric exercise can result in a similar acute phase response in both young and elderly men.

A study designed to test the acute immune response to exercise performed at different ambient temperatures was carried out using laboratory treadmill running.[54] Seven men who were competitive runners performed two separate 60-minute treadmill

bouts at 75% of VO_{2max}. Running bouts were performed at temperatures of 18°C and 28°C. Subjects were told to refrain from vigorous training 5 days prior to the first run and between runs. Blood samples were taken before, immediately after, and 30 minutes, 3 hours, 24 hours, and 48 hours after the end of each run. There was no difference in IL-6 or CRP response between temperatures. IL-6 was significantly greater immediately following and 30 minutes post-exercise compared to pre-exercise values. There was no change in CRP at any time following exercise. These men trained on average 9 hours per week and had an average VO_{2max} of 66.3 ml/kg/min. Therefore, highly trained runners may experience an inflammatory response to running at a vigorous intensity for 60 minutes, however, this response may not be great enough to initiate an acute phase response.

Hubinger et al. studied the response of acute phase reactants to both level and downhill grade treadmill running.[31] The first portion of the study included eight males, ages 17 to 19 years, whose activity level included participating solely in weekend recreational sports. Subjects performed 1-hour of level treadmill running at a speed that elicited 90% of maximal heart rate (HR_{max}). The second portion of the study included males and females, 21 years of age, who again participated only in weekend recreational sport activities. These subjects performed a downhill treadmill protocol chosen because it was known to induce skeletal muscle damage. The running protocol for this portion of the study included two 15-minute and one 10-minute downhill runs, with a 5-minute seated recovery between each run. Runs were performed at a 15% negative incline and at a speed eliciting 75-80% of HR_{max}. Subjects for both study portions had been fasted for

12 hours and refrained from alcohol and exercise for 48 hours prior to testing. Blood samples for both tests were taken before, immediately after exercise, and then 1, 3, 5, and 7 days after testing. Subjects were told not to exercise during the 7-day period following the run when blood samples were still being taken. There were no significant increases in CRP at any of the sampling times for either running protocol. To note, CK levels were significantly increased for both tests, with levels being highest 1-day following both runs. The authors concluded that neither treadmill protocol was able to produce significant skeletal muscle injury and/or inflammation to induce an acute phase response.

The effect of fitness level on the inflammatory response to moderate exercise was studied by Plaisance et al.[60] Subjects included 10 high-fit (VO_{2max} = 53.9 $\pm$ 7.0 ml/kg/min; 29 $\pm$ 6 years of age) and 11 low-fit (VO_{2max} = 36.0 $\pm$ 5.0 ml/kg/min; 33 $\pm$ 8 years of age) males. Treadmill exercise included walking or jogging at 70% VO_{2max} to expend a total of 500 kcals. Blood samples were taken two consecutive days before, and 24, 72, and 120 hours post-exercise. The study found no change in CRP during any of the sampling times. Using results from this study one could conclude that both trained and untrained individuals do not experience an acute phase response on the days following vigorous treadmill exercise. However, the response was not measured within the first 24-hours following exercise.

A study by Henson et al. tested the effect of carbohydrate beverage ingestion on the inflammatory response to rowing.[29] The study included 15 elite female rowers training at the ARCO Olympic Training Center. At the time of the study, women were averaging 12-13 training sessions per week, with each session averaging 90-120 minutes

in length. The research design included three consecutive testing days: one baseline sample day and two exercise days. On day 1, a blood sample was taken after a 9 hour fast and subjects had not exercised in the previous 12 hours. On days 2 and 3, subjects reported to the testing site following a 9 hour fast, and ingested either a carbohydrate or placebo beverage. Subjects then performed a normal 2-hour training bout while continuing to drink the respective beverage every 15 minutes. To determine exercise intensity, all subjects wore a heart rate monitor and a subset of subjects had their VO_2 measured with a Cosmed K4 B-2 metabolic unit for a 10 minute period during exercise. Blood samples were collected within 10 minutes following exercise and 1.5 hours following exercise. During the 1.5 hours following exercise, subjects continued to drink the carbohydrate or placebo beverage every 15 minutes. Subjects averaged 57% of VO_{2max} during the 2-hour row. No differences in CRP or IL-6 were detected following exercise. Results of this study showed that highly trained females do not experience an acute phase response within the first 1.5 hours following moderate activity, regardless of carbohydrate supplementation.

To date, studies have used a variety of exercise modes, durations, and intensities, in an attempt to establish the inflammatory and acute phase response to a single bout of aerobic exercise. An inflammatory response to exercise, regardless of intensity, has been shown to occur within 60 minutes of aerobic exercise.[53, 64, 68, 76] An acute phase response has also been found to occur within 24 hours of a vigorous-intensity exercise bout.[17, 40, 63, 64] However, additional studies using vigorous- or moderate-intensity exercise have failed to see any inflammatory or acute phase response after an acute bout of aerobic exercise.[29,

[31, 54, 60] Although IL-6 is the primary stimulator of the acute phase response, and some studies have found an association between IL-6 and CRP following exercise,[63, 64] consistent evidence linking these markers of inflammation following moderate and vigorous exercise has not been provided. A timeframe for IL-6 and CRP release following an acute bout of moderate and vigorous exercise has also yet to be established.

Acute Phase Response to a Maximal Aerobic Test

Two studies have found conflicting results for the acute phase response immediately following a maximal aerobic exercise test.[13, 19] The use of aspirin therapy on CRP release following a short maximal exercise bout was studied by Feng et al.[19] Thirty-two men, average age 29 $\pm$ 6 years, performed a Bruce maximal protocol test, before and after 7 days of aspirin therapy. Blood samples were taken immediately before and after the test. The study found no effect for aspirin therapy on CRP response. CRP did significantly increase 13 percent from pre- (0.81 + 0.13 mg/l) to post-test (0.92 + 0.13 mg/l)). The results showed that an individual can experience an acute phase response immediately following a short maximal aerobic exercise bout, and that the use of anti-inflammatory medication does not attenuate this response.

In contrast to results found by the previous study, Czarkowska-Paczek et al. found that an inflammatory response, but not an acute phase response, occurs following a maximal aerobic power test. Fourteen trained male cyclists, average age 18 $\pm$ 0.5 years, participated in the study. The average VO_{2max} for all participants was 65.7 $\pm$ 4.8 ml/kg/min. The exercise protocol included cycling on an exercise track until exhaustion.

Participants cycled at 20 km/hr, while the grade of the track was increased every 3 minutes. Blood samples were taken before, immediately after, and 2 hours after exercise. No significant change in CRP was detected over the 2 hours of sampling. IL-6 levels immediately following (1.214 $\pm$ 0.566 pg/ml) and 2 hours post-exercise (10.071 $\pm$ 14.43 pg/ml) were significantly higher than pre-exercise levels (0.482 $\pm$ 0.309 pg/ml). There was no correlation found between IL-6 and CRP levels following the exercise test. Using only these findings, the authors concluded that IL-6 must not be the principal stimulator of acute phase proteins in the liver following strenuous exercise, and that after this type of activity it may only exert a metabolic effect and not an inflammatory or immunological effect.

With lack of information regarding the fitness level of men in the Feng study, it is difficult to draw any conclusions regarding the acute phase response to a maximal aerobic power test. The average length of time of each test was also not provided, so it can not be concluded that exercise duration was also a factor in stimulating an acute phase response.

Acute Phase Response to Competitive Endurance Events

Additional studies have provided information regarding the acute phase response to physical activity performed outside of a controlled laboratory setting. Although these studies will be mentioned, the extreme nature of the physical activity in terms of duration and intensity leads one to take discretion when generalizing the results to all populations or to the acute phase response with more general exercise.

Byrne et al. studied the acute phase response following a 48-hour military exercise (ME) in 200 military recruits.[8] All subjects had just completed a 10-week basic training program prior to undergoing the final exercise. Six different groups provided blood samples at different time points following the 48-hour exercise: group 1 at 12 hours, group 2 at 24 hours, group 3 at 48 hours, group 4 at 3 days, group 5 at 4 days, and group 6 at 6 days. A significant increase in CRP concentration occurred in group 1 (12 hours), and a significant decrease in CRP was found in groups 5 (4 days) and 6 (6 days) following the exercise bout. Lack of control over subjects' activity following the ME may have had an effect on CRP levels found in groups whose samples were taken from 24 hours to 6 days post-exercise. The authors admit that CRP data may have been compromised by undeclared exercise prior to the 48-hour exercise bout and intramuscular injections, not described in detail by the authors, which were later found to have been administered throughout the basic training program.

Strachan et al. sought to determine whether the extent of the acute phase response to physical activity was dependent on running distance.[70] Thirty-eight volunteers from five separate long distance races were studied. Pre- and post-race blood sampling times were not the same for all races. Six runners from each event were studied following 15 and 21 km races. Blood samples taken before and 24 hours post-race showed a small increase in CRP after both racing distances. Six runners had blood samples taken immediately before, immediately after, and every 24 hours for 5 days following a 56 km race. Compared to pre-race levels, CRP for this race was not increased immediately post-race but did reach the highest measured levels 1 day following the race. Twelve runners

who completed the 88 km ultra-marathon had blood samples taken immediately before, immediately after, and every 24-hours for 10 days following the race. CRP was elevated immediately post-race, peaked by day 1, and then returned to pre-race levels by day 10. Eight runners who ran a 42 km marathon had blood samples taken every three days for a week preceding the race, immediately before, and immediately after the race. Additional samples were taken every 12 hours for two days following the race, and then for 24 hours for an additional 2 days. CRP was elevated immediately post-race, and then peaked 24 hours post-race. CK levels for all subjects were also analyzed to get a measure of tissue injury for each racing distance. There was no correlation between CK and CRP following any of the races. Exact values for CRP and CK were not provided by the authors. Although the magnitude changes in CRP are not compared between different events, the research does show an acute phase response to various running durations, regardless of the extent of skeletal muscle damage.

The inflammatory response to a 32.3-kilometer trail race was measured in 27 male and female endurance-trained runners.[10] Runners who had run in at least three previous ridge runs or at least 2 ridge runs and at least one ultra-endurance event were grouped as experienced (n = 9). All other runners were grouped as novice (n = 18). Average race time was 5.9 $\pm$ 1.2 hours for experienced runners and 6.2 $\pm$ 1.3 hours for novice runners. Blood samples were taken the afternoon before the race, and 0, 4, and 24-hours post-race. There was no difference in IL-6 response between groups, with a significant increase occurring from pre- to immediately post-race. The novice group increased from 0.93 $\pm$ 1.05 to 33.26 $\pm$ 23.94 pg/ml and the experienced group increased

from 1.01 ± 0.55 to 32.22 ± 12.38 pg/ml. Both groups significantly increased CRP from pre-race to 24-hours post-race ($p < 0.001$), with the experienced runners (2.15 ± 1.95 to 36.27 ± 27.16 mg/l) having a significantly greater increase than the novice runners (0.69 ± 0.73 to 14.91 ± 7.49 mg/l). CK activity also increased at 0, 4, and 24 hours post-race. The highest measured CK values occurred at 4-hours, with no difference in CK values at anytime between groups. Although this study did show an extremely high increase in CRP following this type of endurance event, correlations between CK and CRP were not provided to determine if there was a relationship between skeletal muscle damage and the inflammatory response.

A study by Miles et al. investigated the difference in CRP and IL-6 production in men compared to women following a 20-mile race.[44] Blood samples were collected from 8 men and 8 women 12-16 hours pre-race, and 0, 4, and 24 hours post-race. Average running time for men and women were 6.0 ± 1.5 and 6.5 ± 1.2 hours, respectively. Males had a significantly greater ($p < 0.05$) increase in IL-6 than females, with the greatest increase in both genders occurring from pre- to immediately post-race. IL-6 in males increased from 0.7 ± 0.05 to 56.9 ± 45.6 pg/ml and increased in females from 0.8 ± 0.7 to 27.0 ± 13.0 pg/ml. There was no effect for gender on CRP, with all subjects having a similar increase in CRP from pre- to 4 hours post-race. CRP concentrations increased from 0.5 ± 0.8 to 4.6 ± 1.6 mg/l in men and 1.3 ± 1.9 to 2.7 ± 2.3 mg/l in women, showing a prominent acute phase response within the first few hours following exercise. The study also measured CK levels following the race to determine the extent of muscle damage. Results showed that the inflammatory response was not

linked to changes in CK activity, which is consistent with other studies showing a lack of relationship between muscle damage and the acute phase repsonse.[34, 59, 70]

The relationship between gastro-intestinal complaints, cytokine release, and the acute-phase response was studied in 1 female and 29 male triathletes following the Ironman distance triathlon in Embrun, France.[34] The event consisted of a 3800 m swim, 185 km cycle ride, and a 42.2 km run. Blood samples were taken on the day prior to the race, immediately after the race, and 1, 2, and 15-20 hours after the race. IL-6 was increased 27-fold immediately following the race, and then decreased slowly thereafter, although still staying greater than pre-race levels up to 2 hours following the race. IL-6 returned to pre-race levels 16 hours after the race. CRP concentration was significantly elevated 2 hours after the race and reached an average of 30.2 ± 3.0 μg/ml 16-hours after the race. There was a significant correlation between the highest IL-6 and CRP concentrations ($r = 0.442$, $p = 0.016$), however, there was no correlation found between CK and changes in CRP and IL-6. Using information provided by the athletes regarding gastrointestinal complaints, it was found that CRP was associated with intestinal cramps ($r = 0.397$, $p < 0.05$) and diarrhea ($r = 0.511$, $p < 0.05$) and IL-6 was associated with vomiting ($r = 0.268$, $p < 0.05$) and diarrhea ($r = 0.504$, $p < 0.05$) following the race. These results led the authors to conclude that endotoxemia, and potentially other exercise-induced processes such as muscle damage, may be responsible for increased cytokine acute-phase protein release following a long-distance triathlon.

Lechtermann et al. studied the inflammatory response to a marathon and 3 separate treadmill running bouts performed at different intensities and grades.[39]

Seventeen male runners of different training status performed a marathon run. Thirteen male and female subjects performed three treadmill bouts: 80% of VO_{2max}, 60% of VO_{2max}, and a downhill grade of negative 12% at 80% of VO_{2max}. No information regarding time of treadmill runs or blood sampling was provided. The only results provided for this study was that CRP levels were maximal the day after the marathon run.

Prolonged, vigorous endurance exercise has consistently shown an acute phase response following exercise. Elevations in CRP were found immediately following exercise,[70] and within the first 24 hours following exercise.[8, 10, 34, 39, 44, 70] The inflammatory response to these types of events was also extremely prominent immediately following activity.[10, 34, 44]

Risk for Myocardial Infarction with Physical Activity

The American Heart Association recommends increasing physical activity as one method for reducing heart attack risk.[20] Although the absolute risk for sudden cardiac death or a cardiac event associated with physical activity is low, evidence is available showing an increased risk for acute coronary syndromes with physical activity and heavy physical exertion.[83] Data from the Physician's Health Study was used to determine the risk of sudden death during, and within, 30 minutes of performing light or vigorous physical exertion.[1] Subjects included 21,481 male physicians between the ages of 40 and 84, who were initially free from cardiovascular disease. Over the 12-year follow-up, 122 sudden deaths occurred that were attributable to cardiac causes. Information regarding activity during time of death was obtained from medical records or next of kin, and was

available for 80 percent of the men. Of all cardiac deaths, 13.9 percent occurred during vigorous exertion and 4.9 percent occurred within 30 minutes after vigorous exertion. Compared to any other time point surrounding the death, the relative risk for sudden death occurring within 1-hour of vigorous exertion was 16.9 ($p < 0.001$, 95% CI 10.5 to 27.0).

Willich et al. investigated the risk of myocardial infarction (MI) occurring with strenuous physical exertion.[82] Information was gathered on 1914 hospital patients who were admitted with a primary diagnosis of acute MI. Patient interviews included questions regarding medical history, physical activity, unusual life events, and location and circumstances of the MI. Age and sex matched controls ($n = 532$) were asked the same interview questions as the MI patients, but were told to answer as if they had experienced chest pain at a specific time provided by the interviewer over the past 24 hours. The specific times given to the control were distributed in a circadian pattern identical to the times of MI onset of the MI patients. All physical activity was measured and reported in terms of metabolic equivalents (MET). Compared to the control group, the relative risk of a MI for those engaging in strenuous activity ($\geq$ 6 MET) was 1.9 (95% CI 1.1 to 3.5). After adjusting for factors known to influence the risk of MI or factors that differed between case and control subjects (hypertension, hyperlipidemia, diabetes, smoking, previous MI, angina pectoris, use of cardiac drugs, current employment, age, sex, and time of awakening), an independent relative risk of 2.1 (95% CI 1.1 to 3.6) still existed.

Although the number of people suffering from a myocardial infarction following exercise is low, the small excess risk can be detrimental for those who may already be suffering from coronary artery disease. With an increased risk of a cardiac event being shown with vigorous exercise, recommending moderate intensity activity may be the safest in terms of exercise prescription. However, establishing the exact cause of MI occurring with vigorous exercise may also help in decreasing the risk associated with this intensity of exercise. Therefore, since the risk for MI is greatest during and within the hours directly following vigorous activity, establishing what occurs with exercise that leads to the occlusion of coronary arteries during this time frame is needed.

Triggering of an Acute Coronary Syndrome

Coronary plaque disruption is the primary mechanism by which atherosclerosis results in an acute coronary syndrome.[21] Over 70% of all sudden deaths occurring with exercise in people over the age of 35 years are attributed to the occlusion of coronary arteries by platelet-rich thrombi.[15, 42] The main cause of plaque disruption is inflammation.[41] Activated inflammatory cells secrete proteinases that break down the extracellular matrix. Although this process occurs for normal turnover of cellular tissue, an imbalance in regulating this process can lead to pathological tissue destruction. For example, breaking down the structural molecules of the extracellular matrix can lead to weakening of the fibrous cap, making it more prone to rupture. The plaque disruption causes platelet aggregation and thrombosis, resulting in unstable angina, acute myocardial infarction, or sudden death. The actual plaque disruption is in reality an

asymptomatic event, with the events following the plaque disruption, including thrombosis and platelet aggregation, resulting in the clinical event. Studies have revealed that 9% of normal healthy persons and 22% of individuals with diabetes or hypertension have asymptomatic disrupted plaques, showing that this potentially dangerous event may occur more frequently than is recorded.[14]

An increase in circulating CRP levels above an individual's normal concentration may be one of the triggers of acute myocardial infarction, with higher circulating levels of CRP resulting in a destabilization of plaque. Recent evidence supports the idea that CRP is involved in the process of plaque rupture by inducing endothelial cell dysfunction.[77] This process includes stimulating the production of matrix metalloproteinase-1, inhibiting nitric oxide production, and inducing the upregulation of chemokines and adhesion molecules at the site of plaque formation.[58, 77]

To determine if CRP may play a role in triggering acute coronary events, studies have compared CRP levels following different acute conditions.[7, 72, 85] Burke et al. investigated the relationship between CRP and fatal coronary artery disease using autopsy information from patients who died of sudden coronary death.[7] Deaths were classified as plaque rupture, plaque erosion, stable plaque, or control cases (unnatural sudden death or non-cardiac death not related to elevated CRP). CRP was significantly higher in deaths with plaque rupture ($p < 0.0001$), plaque erosion ($p = 0.005$), and stable plaque ($p = 0.0003$) compared to controls. There was a significant association between the degree of plaque burden (total amount of luminal narrowing in measured arterial beds) and CRP ($p = 0.03$).

To determine whether CRP was associated with an increased risk for plaque rupture or only atherosclerotic burden, Yip et al. measured CRP in patients following an acute myocardial infarction (AMI).[85] Their methodology was based on information gathered by Tomoda and Aoki, who provided evidence that CRP measured within 6 hours of an AMI was representative of inflammatory activity prior to the AMI and not inflammation as a result of myocardial damage.[73] Therefore, knowing that serum CRP levels taken within 6 hours after the onset of an AMI offers information regarding inflammatory activity at the time of plaque rupture,[73] this study compared CRP measured within and after 6 hours of onset of AMI symptoms. One hundred fifty-one patients had blood samples taken within 6 hours after the onset of the AMI. Fifty-one patients had blood samples taken greater than 6 hours, but less then 12 hours, following the onset of an AMI. Additionally, 30 subjects who underwent a percutaneous coronary intervention (PCI) following angina were used as coronary artery disease controls and 30 age- and gender-matched volunteers were used as healthy controls. CRP was significantly higher in patients with a measurement within 6 hours after AMI (2.7 ± 2.3 mg/l) compared to patients with angina (1.4 ± 0.7 mg/l) and healthy controls (1.0 ± 0.6 mg/l). In patients with measurements within 6 hours, there were significantly higher levels of CRP at baseline in women, those with hypertension, and those without previous MI ($p = 0.04$). The CRP levels were significantly higher in the 51 patients with measurements after 6 hours (14.1 ± 16.5 mg/l) compared to the 106 patients with measurements within 6 hours (2.7 ± 2.3 mg/l). This study concluded that the higher levels of CRP in patients with measurements greater then 6 hours reflected myocardial damage and the increased CRP

in patients measured within 6 hours reflected the baseline CRP levels, or that at the onset of the AMI. They also concluded that these two separate timeframes can show the impact of CRP on atherosclerotic lesions as well as the response to an AMI. They conclude that their results support that of Tomoda and Aoki,[73] that a spike in CRP may be a prerequisite for plaque rupture.

Tokac et al. concluded that CRP was directly involved in the triggering of an acute coronary event.[72] The study included 15 patients with stable angina pectoris (SAP), 16 patients with unstable angina pectoris (UAP), and 16 patients who had undergone percutanious transluminal coronary angioplasty (PTCA). Blood samples were taken in SAP patients 1 day after hospitalization and in UAP patients within 6 hours after onset of pain and 12 hours following the first sample. Samples were taken from the PTCA patients before the procedure and 2 and 14 hours after the procedure. Fifty-three of the 55 patients also underwent coronary angiography for determination of significant coronary artery disease. CRP increased significantly in the UAP and PTCA groups. UAP patients increased from 10.9 $\pm$ 7.2 mg/dl within 6 hours of pain onset to 18.8 $\pm$ 14.9 mg/dl at 12 hours after pain onset. PTCA patients had significantly higher CRP levels 14 hours after their procedure (24.5 $\pm$ 23.8 mg/dl) compared to 2 hours after their procedure (12.4 $\pm$ 6.4 mg/dl). Both UAP and PTCA patients had significantly higher CRP levels at 6 hours after onset of pain and 2 hours after surgery, respectively, compared to CRP levels in SAP patients after hospitalization (7.1 $\pm$ 5.6 mg/dl). The authors concluded that the higher CRP levels in the UAP group compared to the SAP group, and the continual

rise in CRP levels, showed that the increased inflammatory activity caused earlier plaque rupture.

Both mechanistic and clinical studies have provided evidence that CRP may be a culprit in triggering an acute coronary event. Although the exact levels of CRP that may cause plaque rupture and a resulting coronary event are unknown, an inflammatory response that causes a quick release of CRP in high concentration may result in plaque rupture. With coronary plaque rupture being the primary cause of MI associated with exercise, one could assume that an acute phase reaction in response to exercise may cause a spike in CRP, leading to plaque rupture.

Conclusion

Physical activity is recommended in the treatment and prevention of cardiovascular disease and is used as rehabilitation for those recovering from cardiac complications. There is evidence however that vigorous physical activity increases the risk for an acute coronary syndromes. The disrupting of plaque formations by CRP may be one trigger for acute coronary syndromes. During an inflammatory response, IL-6 stimulates an acute phase reaction, resulting in the release of CRP from the liver. The inflammatory response to exercise, which has been shown to result in the production of IL-6, may stimulate a resulting acute phase response. Research available on the acute phase response to exercise has reported varying results due to inconsistencies in methodology. Studies investigating the inflammatory response to exercise more consistent with physical activity recommendations have failed to examine the time period

directly following exercise, and instead has looked at subsequent days. These studies have found an inflammatory response, but not necessarily a resulting acute phase response. Because of a potential lag time in stimulation of CRP release and then the shorter half life of this protein, the time frames for sampling may have missed any acute phase response that did occur. Research that has looked at the time period directly following exercise has been performed on athletes competing in endurance events. Although these studies have found an inflammatory and acute phase response following exercise, the nature of the activity is more vigorous then most individuals would undertake. Since the risk for death with exercise is greatest during and within the first hour following activity, the acute phase response during this time period must be established to determine whether this may play a role in triggering acute coronary syndromes that occur with exercise. Since an inflammatory response has been found with moderate-intensity activity, it should be established whether both moderate and vigorous activity may put an individual at an increased risk for a coronary event.

CHAPTER 3

METHODS

Subjects

Ten healthy, non-smoking, recreationally trained male cyclists, between the ages of 18 and 40 were recruited for this study. Subjects were volunteers from the University of Tennessee and surrounding community. Written informed consent, approved by the University of Tennessee Institutional Review Board, was obtained prior to testing (Appendix A). Subjects were included if they participated in vigorous cycle exercise at least 4 days per week for greater than 30 minutes per day. A health history questionnaire was completed (Appendix B). Height was measured using a stadiometer. Weight and body composition were assessed by air displacement plethysmography using the Bod Pod system (LMI, Inc., Concord, CA).

Maximal Oxygen Consumption

Subjects performed an incremental graded exercise test on a Lode Excalibur Sport electronically braked cycle ergometer (Groningen, NL). Subjects were asked to choose a self-selected cadence between 60 and 80 rpm. The test began with a 2-minute warm-up at 50 watts. After two minutes the work rate was increased 25 watts per minute until volitional fatigue. Respiratory gas exchange analysis was done using the TrueMax 2400 computerized metabolic system (ParvoMedics, Salt Lake City, UT). Before each test, O_2 and CO_2 analyzers were calibrated using gases of known concentrations, and the flow meter was calibrated using a 3-L syringe. Heart rate was monitored using a Polar Heart

Rate Monitor (Polar Electro Inc., Lake Success, NY), and was recorded every minute. The test was considered maximal if two of the following criteria had been satisfied: 1) a respiratory exchange ratio (RER) $\geq$ 1.15, 2) heart rate within 15 beats per minute of age predicted HR_{max} (220-age), and 3) leveling off in VO_2 despite an increase in work rate (<150 $ml \cdot min^{-1}$ increase between stages).

Moderate and Vigorous Cycling Bouts

Subjects performed a moderate and vigorous exercise bout on two different occasions separated by 1-2 weeks. All testing began between 6am and 9am and subjects started both testing days at the same time. Subjects were asked to refrain from all exercise and alcohol consumption for 48 hours prior to testing. When subjects arrived at the laboratory a venous catheter was placed into the forearm. The catheter was kept patent with a sterile saline drip. After resting for 15 minutes, a baseline (B) blood sample was taken.

VO_2 was monitored during exercise using the TrueMax 2400 metabolic system. The moderate exercise bout was performed at 50% of VO_{2max} and the vigorous exercise was performed at 80% of VO_{2max}. The subjects performed a 5-minute warm-up on the cycle ergometer, during which time the work rate was gradually increased to a level eliciting the pre-determined moderate or vigorous VO_2. Subjects chose a comfortable pedal speed between 60 and 80 rpm to maintain throughout the exercise bout. After the 5-minute warm-up, the subject continued to cycle at the same work load for 40 minutes. The average VO_2 for each session was calculated by averaging the VO_2 values at each

minute over the 40-minute period. Blood samples were taken 30 minutes into the cycle bout (30) and 0 (0), 15 (+15), 30 (+30), 45 (+45), 60 (+60), 90 (+90), 120 (+120), 180 (+180), and 240 minutes (+240) post-exercise.

Blood Samples

A 5 ml blood sample was obtained from a forearm vein during each sampling period for determination of CRP and IL-6. Blood samples were collected into a serum separator tube. Samples were centrifuged for 10 minutes and serum was removed and frozen for subsequent analysis.

All blood samples were stored and analyzed at the end of all testing at The University of Tennessee Medical Center DynaCare Laboratories. Samples were kept at -80°C and returned to room temperature prior to running the analyses. Procedures for running the hs-CRP (Immulite 2000 High Sensitivity CRP, DPC) and IL-6 (Immulite 2000 IL-6 EIA, DPC) assays were performed according to the manufacturer's guidelines. All samples were run in duplicate.

Statistical Analysis

All statistical analyses were performed using SPSS Version 13.0 (SPSS Inc., Chicago, IL). A two-way repeated measures ANOVA (time x exercise intensity) was used to compare the inflammatory response at different time-points following exercise. A Pearson's Product Moment Correlation was used to see if there was a relationship between CRP and IL-6 response following each exercise bout.

CHAPTER 4

RESULTS

Ten male participants completed both cycling bouts. Participant characteristics are presented in Table 1. Average VO_{2max} for participants was 50.6 $\pm$ 7.1 ml/kg/min. The average percentage of VO_{2max} maintained by participants for the moderate exercise bout (52.7 $\pm$ 1.6 percent) was significantly lower ($p < 0.001$) than the average percent of VO_{2max} maintained for the vigorous exercise bout (76.8 $\pm$ 5.0 percent).

There were no differences in baseline CRP and IL-6 values for participants between the moderate and vigorous exercise days and between the first and second testing days, regardless of intensity. CRP and IL-6 levels during and following exercise are presented in Table 2. Compared to baseline levels, CRP was significantly higher during, immediately following, and 15-minutes after the completion of the moderate exercise bout ($p < 0.05$) (Fig. 1). CRP was significantly higher during and immediately following vigorous exercise compared to baseline levels ($p < 0.05$) (Fig. 1). There was an increase in IL-6 following moderate and vigorous exercise compared to baseline levels (Fig. 2). IL-6 was increased during and for 1 hour following vigorous exercise, with the highest level being measured 15-minutes post-exercise. IL-6 was increased 15 minutes following moderate exercise, but the increase was not as large as the increase following vigorous exercise for this same time point ($p = 0.001$).

Table 1. Baseline characteristics of participants (n = 10)

Measure	Mean ± SD
Age (y)	30.3 ± 5.7
Height (cm)	181.1 ± 5.2
Body mass (kg)	82.8 ± 5.9
Body fat (%)	14.6 ± 9.6
VO_{2max} (ml/kg/min)	50.6 ± 7.1

Table 2. Comparison of CRP and IL-6 before, during, and after a bout of moderate and vigorous exercise (Mean ± SE)

Measure	Before	During	Immediately post-	15 min post-	30 min post-	45 min post-	1 h post-	1.5 h post-	2 h post-	3 h post-	4 h post-
CRP (mg/l)											
Moderate	0.51 ± 0.26	0.57 ± 0.27*	0.58 ± 0.28*	0.56 ± 0.26*	0.48 ± 0.23	0.52 ± 0.24	0.53 ± 0.26	0.49 ± 0.23	0.48 ± 0.20	0.51 ± 0.22	0.52 ± 0.21
Vigorous	0.68 ± 0.22	0.77 ± 0.24*	0.77 ± 0.25*	0.69 ± 0.22	0.66 ± 0.19	0.66 ± 0.21	0.61 ± 0.19	0.61 ± 0.20	0.57 ± 0.17	0.58 ± 0.17	0.55 ± 0.17
IL-6 (pg/ml)											
Moderate	2.86 ± 0.57	2.92 ± 0.53	3.17 ± 0.51	3.23 ± 0.49*	3.31 ± 0.58	3.3 ± 0.59	3.1 ± 0.55	2.85 ± 0.56	2.89 ± 0.56	2.93 ± 0.44	2.72 ± 0.41
Vigorous	2.69 ± 0.42	3.5 ± 0.42*	4.59 ± 0.48*	4.76 ± 0.53*†	4.66 ± 0.58*	3.83 ± 0.59*	3.59 ± 0.59*	3.06 ± 0.57	3.39 ± 0.64	2.69 ± 0.41	2.9 ± 0.43

* significantly different than before exercise ($p < 0.05$)

† change from before exercise significantly different between vigorous and moderate exercise ($p < 0.001$)

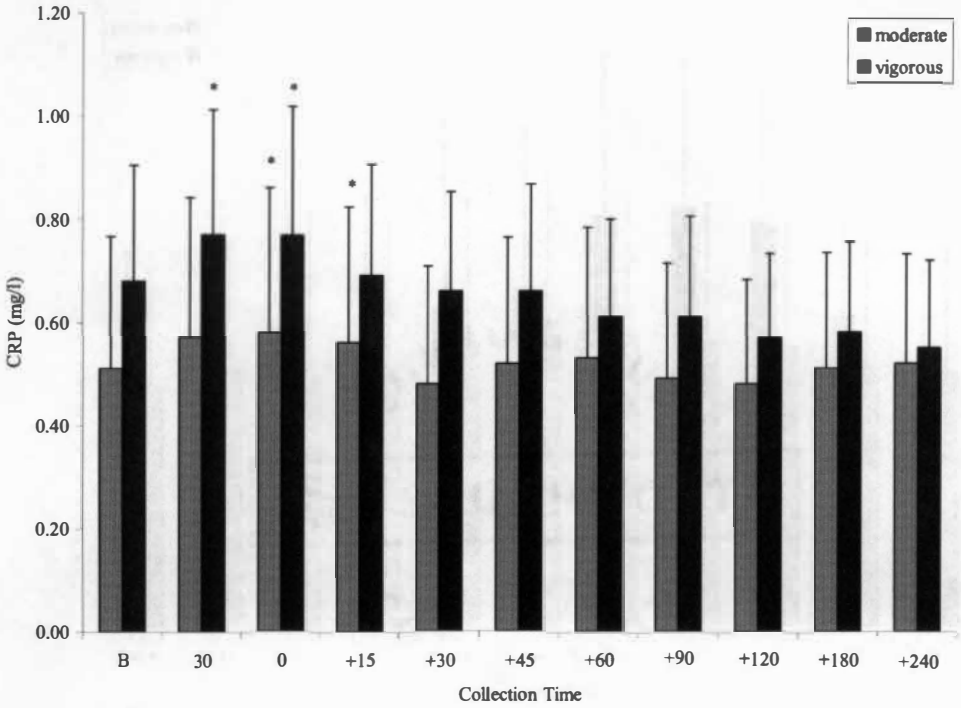

Figure 1. CRP levels following moderate and vigorous exercise (Mean ± SE)

* significantly different from baseline

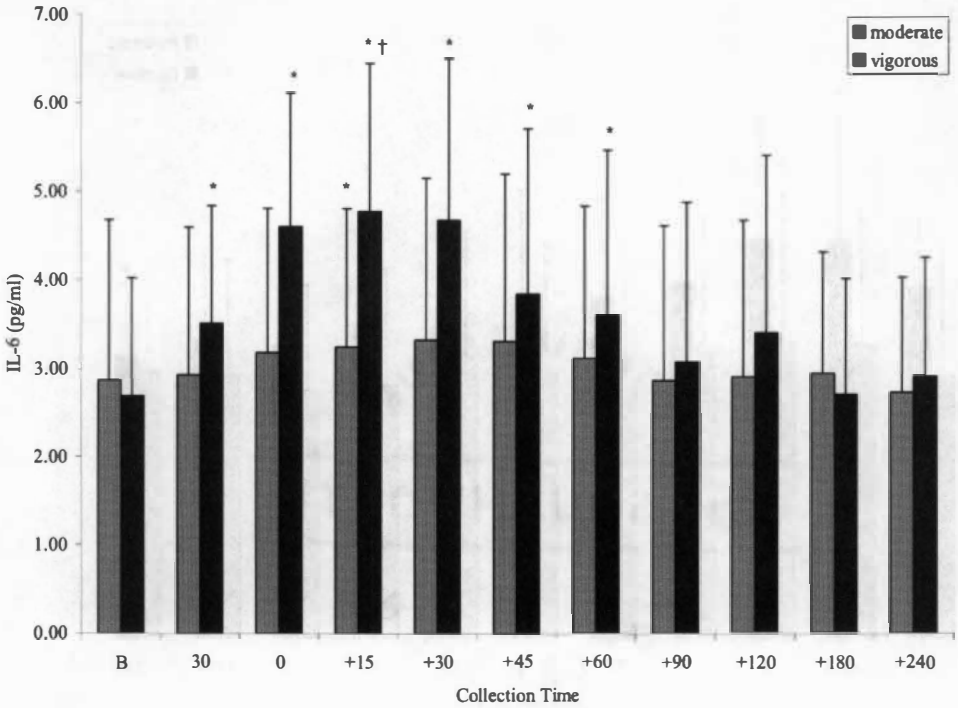

Figure 2. IL-6 levels following moderate and vigorous exercise (Mean ± SE)

* significantly different than before exercise ($p < 0.05$)

† change from before exercise significantly different between vigorous and moderate exercise ($p < 0.001$)

Individual CRP responses to moderate and vigorous exercise are shown in Figures 3 and 4, respectively. Individual IL-6 responses to moderate and vigorous exercise are shown in Figures 5 and 6, respectively.

The differences from baseline in IL-6 and CRP were calculated to determine if there was an association between the increases found in these markers. There was a significant association during vigorous exercise between the increase in IL-6 during exercise and the increase in CRP immediately following exercise ($p = 0.003$, $r = 0.826$).

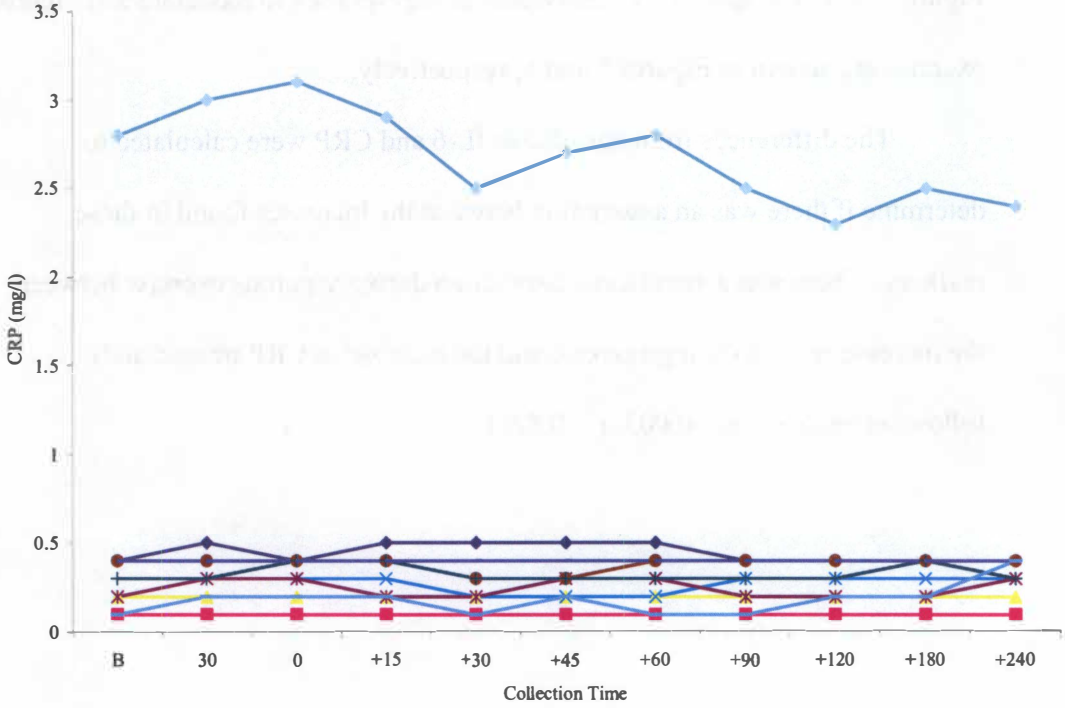

Figure 3. Individual CRP responses to moderate exercise

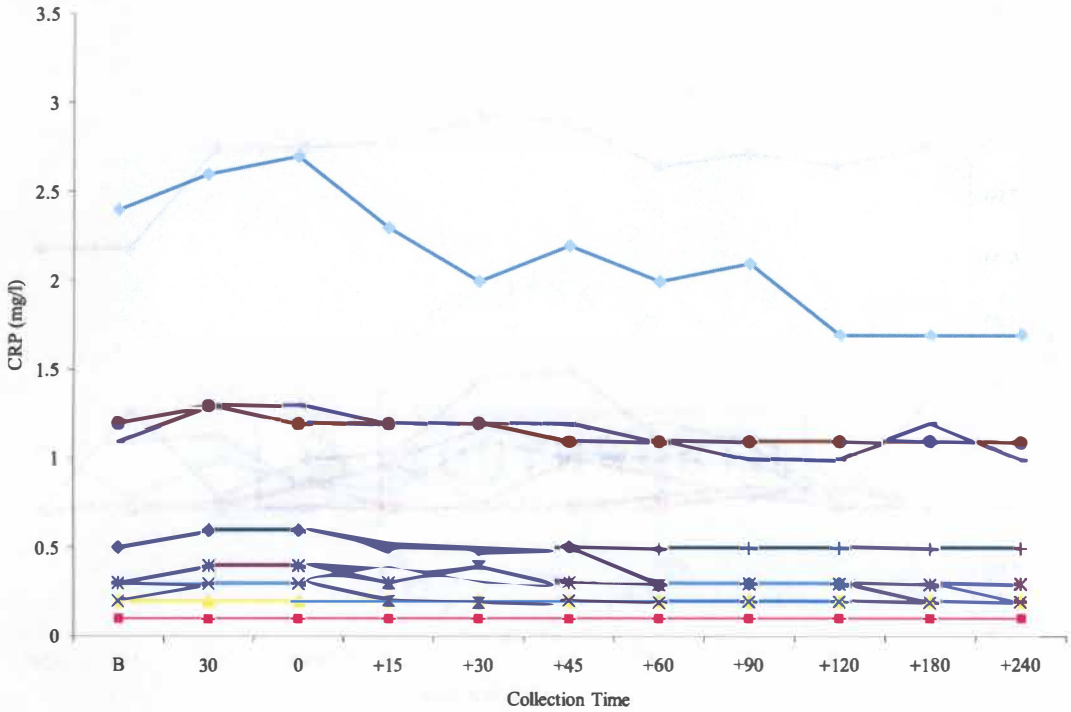

Figure 4. Individual CRP responses to vigorous exercise

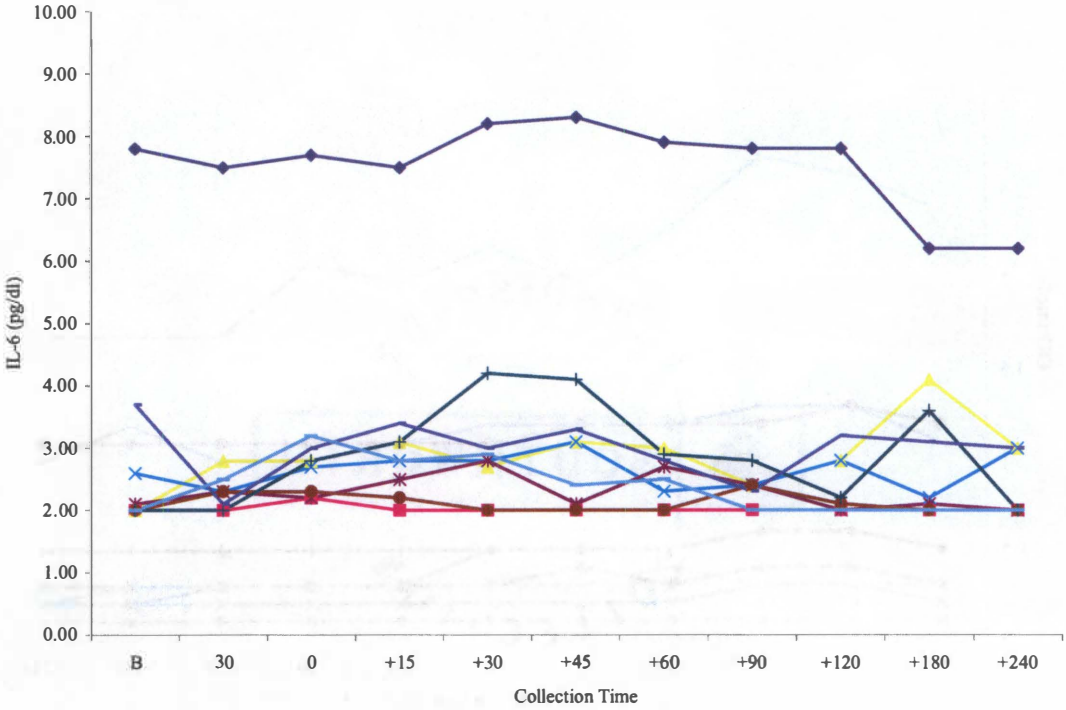

Figure 5. Individual IL-6 responses to moderate exercise

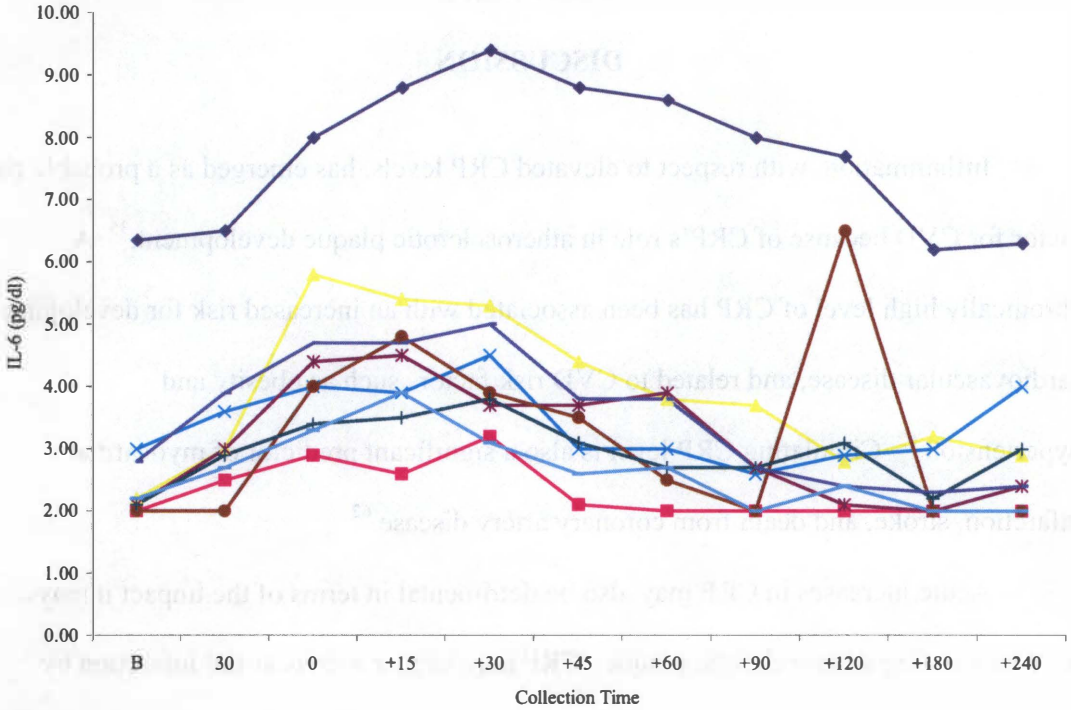

Figure 6. Individual IL-6 responses to vigorous exercise

CHAPTER 5

DISCUSSION

Inflammation, with respect to elevated CRP levels, has emerged as a probable risk factor for CVD because of CRP's role in atherosclerotic plaque development.[35] A chronically high level of CRP has been associated with an increased risk for developing cardiovascular disease, and related to CVD risk factors such as obesity and hypertension.[62] Circulating CRP level is also a significant predictor of myocardial infarction, stroke, and death from coronary artery disease.[62]

Acute increases in CRP may also be detrimental in terms of the impact it may have on existing atherosclerotic plaque. CRP may trigger a myocardial infarction by disrupting the caps of fibrous plaque.[18, 69] This cap breakdown could then ultimately lead to vessel occlusion and a resulting cardiac event. Therefore, establishing the types of events or conditions that could lead to acute elevations in CRP may help lower the risk of suffering from an acute coronary syndrome.

The purpose of this study was to establish if acute bouts of moderate and vigorous aerobic exercise result in an acute phase reaction during the time period when risk for MI associated with exercise is greatest. When determining the optimal exercise prescription for general and special populations, the degree of risk associated with the activity must be taken into account. If vigorous exercise provides a greater inflammatory challenge, the risks must be weighed when prescribing exercise.

Studies investigating the acute phase response to acute exercise have been inconsistent in methodology. More specifically, the time frame for measurement has

varied dramatically making it impossible to clarify the time course for changes in inflammatory markers during and immediately following short bouts of moderate and vigorous exercise. By waiting up to 24 hours to test for changes in CRP, these studies may have failed to see any short-term acute changes. It is also difficult to establish whether short moderate or vigorous bouts of exercise result in an acute phase response during the time when risk for a cardiac event associated with activity is greatest since many of the exercise events (i.e. extremely long, intense, or competitive events) that information is based on would not be performed by the general population.[37]

This study found that during the time period when the risk for an MI with exercise is greatest, during activity and within 1-hour after activity, CRP increased 0.07 mg/l with moderate aerobic exercise and 0.09 mg/l with vigorous aerobic exercise. This is the first study to document the time course of the increase in CRP during an acute bout of aerobic exercise. Strachan et al. found a significant increase in CRP immediately following exercise, however, the activity consisted of a competitive running event, and not exercise that would routinely be engaged in by an average person.[70] Feng et al. also found CRP to be significantly elevated on average 0.11 mg/l directly following a short maximal aerobic bout.[19] Additional studies measuring CRP following competitive endurance events did find much greater increases in CRP within 24 hours following exercise than what was found with our study.[8, 10, 34, 39, 44, 70] The CRP increase in these studies ranged from 0.3 mg/l to 34.12 mg/l. More severe muscle damage or possible injury occurring with these prolonged events and more maximal efforts may have led to a longer and much greater acute phase response compared to that found with shorter exercise bouts used in this

study. By performing multiple blood withdraws during and immediately following exercise, we were able to document an increase in CRP during the time frame closely associated with exercise-related cardiac events.

The average amplitude change in CRP over 24-hours in healthy individuals is only 0.2 mg/l.[43] Although our study and others finding an increase in CRP within 1-hour of exercise found increases less than the average daily fluctuation in healthy individuals, the exact levels that are associated with causing a cardiac event, especially in diseased populations, are unknown. Even small changes in CRP during or immediately following exercise could be clinically significant for some individuals. Yip et al. reported that patients had an average CRP level of 2.7 + 2.3 mg/l within 6 hours of experiencing an acute myocardial infraction.[85] Individual results for our study show that no individual with a baseline level under 2.7 mg/l reached a CRP level that would be associated with a MI at any point during moderate or vigorous exercise. Therefore, the absolute CRP levels found during acute exercise in this study, in addition to the degree of change being less than normal daily fluctuation, would lead one to believe that these types of exercise bouts would not put a young healthy individual at an increased risk for a cardiac event.

Using levels of circulating CRP following exercise, however, may not be able to establish whether exercise increases risk of a cardiac event. A greater increase in CRP during or following exercise may occur locally in extrahepatic tissue, and therefore may not be detectable in circulation during or immediately following exercise. Extrahepatic tissues having the potential to locally produce CRP include peripheral mononuclear cells, coronary artery smooth muscle cells, neurons, and kidney epithelial cells.[77] Thus, local

concentrations of CRP could be increased to much higher levels than circulating CRP concentrations, making more CRP than is normally present available to act locally on endothelial cells, monocytes, macrophages, and smooth muscle cells.

In addition, although the absolute number of individuals experiencing an acute coronary syndrome during exercise is low, the consequences of this increased CRP may actually go unnoticed in some individuals. Asymptomatic coronary plaque disruption has been found in 9% of normal healthy persons and 22% of individuals with diabetes or hypertension.[14] Therefore, the potential for this acute phase response to have adverse effects on the body may go unseen.

Researchers have proposed that exercise-induced skeletal muscle damage triggers the production of IL-6 by TNF-α and IL-1β.[46, 50] IL-6 is produced to initiate an inflammatory response to repair damaged skeletal muscle, and is the principal stimulator of CRP production.[27, 48, 52] This study found an increase in IL-6 following a 40-minute bout of both moderate and vigorous exercise. Nieman et al. and Vassilakopoulos et al. both found similar increases in IL-6 following moderate and vigorous exercise bouts of similar duration.[53, 76] Our methodology, however, allows us to concluded that an acute bout of vigorous exercise results in a significantly greater inflammatory response than moderate exercise. Although markers of muscle damage were not measured, the association found between muscle damage and inflammation[4, 57] would lead us to assume that the vigorous exercise bout resulted in a higher degree of muscle damage than the moderate bout of exercise.

Previous research has found inconsistencies in the relationship between increases in CRP and IL-6 following exercise.[17, 63, 64] IL-6 is the principal stimulator of CRP production,[27] leading researchers to believe that increases in CRP would be associated with increases in IL-6 during and following exercise. The only association found in this study was between the increase in IL-6 during vigorous exercise and the increase in CRP immediately following vigorous exercise. Because of potential lag time in CRP stimulation, this staggered relationship would be expected between these two markers. With regards to the lack of association at other time points for moderate and vigorous exercise, the small and similar increases occurring within individuals for both of these markers may have made it difficult to establish any relationship. There is also the possibility that factors other than IL-6, that are yet to be established, may be responsible for stimulating CRP production during and following exercise.

This study is limited by the fact that only recreationally trained male cyclists were examined. The inflammatory and acute phase response may be different in untrained compared to trained individuals.[10, 40] Also, with females having an attenuated inflammatory response to other forms of injury and trauma compared to males,[38] the degree of the inflammatory response during and following exercise may differ between genders.[44]

To conclude, this study found that a significant acute phase response can occur during and following moderate and vigorous exercise. The degree of elevation, though statistically significant, would suggest that for young healthy cyclists, neither moderate nor vigorous bouts of exercise lasting 45 minutes in duration would greatly elevate the

risk of a cardiac event. However, it is important to define events or activities that have the potential to increase this marker for certain at-risk populations, such as those with coronary artery disease, since the exact increase in CRP that may elevate an individual's risk for an acute coronary syndrome is unknown. Although there was no difference in the acute phase response to moderate and vigorous exercise, the risk associated with activity-intensity may still differ. Moderate exercise in both healthy and coronary artery disease patients has been found to have no significant effect on platelet activity that would be involved in the events leading to a cardiac event.[79-81] Therefore, the effect that exercise has on the total series of events leading to an acute coronary syndrome may make the risk different between exercise intensities. More information is needed regarding the acute phase response during exercise in different populations including training status, disease states, and the effect of gender. It may also be important to study exercise of different durations and modalities when determining the best exercise prescription for specific populations. The increase in CRP that elevates an individual's risk for plaque disruption also needs to be established when trying to understand the risk associated with exercise.

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APPENDICES

APPENDIX A

INFORMED CONSENT FORM

Investigators: Carolyn Albright and Dixie Thompson
Address:
The University of Tennessee
Department of Exercise, Sport, and Leisure Studies
1914 Andy Holt Ave.
Knoxville, TN 37996
Telephone: (865) 974-6040

Purpose

You are invited to participate in a research study. The purpose of this study is to characterize the inflammatory response during and immediately following moderate and vigorous exercise. The inflammatory response will be determined by measuring C-reactive protein (CRP) and interleukin-6 (IL-6) levels during, and immediately following, exercise. If you give your consent, you will be asked to perform the testing described below. The first testing day will take approximately 1-hour. The second and third testing days will take approximately 6 hours. You will complete a health history questionnaire prior to participation. All testing will be performed in the Applied Physiology Laboratory in the Health, Physical Education, and Recreation (HPER) building on the University of Tennessee campus.

Testing

1. The first testing day you will arrive to the laboratory having fasted and refrained from structured exercise for 4 hours.

2. We will measure your height and weight. Your body fat will be determined using the Bod Pod. During these tests you will wear either a swimsuit or spandex cycle shorts. You will sit in the Bod Pod chamber for 2 one-minute trials while your body fat is determined. While in the chamber you will be able to breathe normally and see your surroundings.

3. You will perform a maximal oxygen consumption test (VO_{2max}) on a cycle ergometer. For this test you will breathe through a two-way breathing apparatus for respiratory gas measurement. This apparatus does not disrupt your normal breathing. You will be asked to choose a self-selected pedal speed between 60 and 80 rpm. The test will begin with a 2-minute warm-up at a very light resistance. After two minutes the resistance will then be increased the same amount each minute until you can no longer maintain your speed. Your heart rate will be monitored with a heart rate monitor. The heart rate monitor is attached to a strap that is worn around your chest, and your heart rate is transmitted to a watch.

4. You will then come in on two separate occasions having refrained from all structured exercise and alcohol consumption for 48-hours prior. The mornings that you come to the lab, you can eat whatever you are comfortable eating before doing a normal cycling ride. On one day you will perform a moderate cycle bout of exercise and on the other day you will perform a vigorous cycle bout of exercise. When you arrive, a venous catheter will be placed into your forearm. After resting for 15 minutes a baseline 5 ml blood sample will be taken. You will then be fitted again with the two-way breathing apparatus. You will perform a 5-minute warm-up on the cycle ergometer, during which the work rate will gradually be increased to a level considered moderate or vigorous. For the moderate bout you will ride at 50% of your VO_{2max} and for the vigorous bout you will ride at 80% of your VO_{2max}. You will choose a comfortable pedal speed to maintain throughout the exercise bout. After the 5-minute warm-up, you will continue to cycle at the same work rate for 40 minutes. A 5 ml blood sample will be taken 30 minutes into the cycle bout and 0, 15, 30, 45, 60, 90, 120, 180, and 240 minutes post-exercise. During the 4-hour period after cycling, you will remain in the HPER building and can perform sedentary activities such as computer work or watching a movie. You will also be provided with food during this time, or you can bring your own.

Potential Risks

The risks associated with exercising include abnormal blood pressure responses, musculo-skeletal injuries, dizziness, difficulty in breathing, and in rare cases heart attack or death. If you experience any abnormal feelings while cycling such as chest pain or severe breathlessness, stop cycling immediately. There are no known risks to the body fat test you will complete. There is a slight risk of bruising and infection when blood is withdrawn. Standard sterile procedures will be used to minimize the risk.

Benefits of Participation

From the results of your tests, you will be told your body fat percentage and VO_{2max}. These tests would typically cost $100 if you were to schedule a regular testing appointment with our laboratory.

Confidentiality

The information obtained from these tests will be treated as privileged and confidential and will consequently not be released to any person without your consent. However, the information will be used in research reports and presentations; however your name and other identity will not be disclosed. All data will be stored in a locked filing cabinet in 136 HPER. Informed consent forms will be stored for 3 years after completion of the study in HPER 340.

Contact Information

If you have questions at any time concerning the study or the procedures, or you experience adverse effects as a result of participating in this study, you should contact your physician and Carrie Albright at 974-6040. If you have questions about your rights as a participant, contact Research Compliance Services of the Office of Research at (865) 974-3466.

Right to Ask Questions and to Withdraw

You are free to decide whether or not to participate in this study and are free to withdraw from the study at any time.

Before you sign this form, please ask questions about any aspects of the study, which are unclear to you.

Consent

By signing this paper, I am indicating that I understand and agree to take part in this research study.

_____ _____

Your signature Date

_____ _____

Researcher's signature Date

APPENDIX B

HEALTH HISTORY QUESTIONNAIRE

NAME_____ DATE_____

DATE OF BIRTH_____ AGE_____

PHONE NUMBERS (HOME)_____(WORK)_____

e-mail address:_____

When is the best time to contact you?_____

Please answer the following questions. This information will only be used for research purposes and will not be made public. Please answer the following questions based on physical exercise in which you regularly engage. **This should not include daily work activities such as walking from one office to another.**

1. Do you regularly engage in exercise? Yes/No If yes, please describe.

_____

_____

2. On average, how many times per week do you engage in exercise training?

0____1____2____3____4____5____6____7____

3. On average, how many times per week do you engage in *vigorous* exercise training?

0____1____2____3____4____5____6____7____

On average, how long is each of these vigorous exercise bouts: _____

5. How long have you been exercising at this level?

Less than 6 months _____
6 – 12 months _____
1 – 2 years _____
3 or more years _____

6. Do you know of any reasons why you should not participate in physical activity:

_____

_____

MEDICAL HISTORY

Past History:
Have you ever been diagnosed with the following conditions? Please check the appropriate column.

	Yes	No	Don't Know
Rheumatic Fever	( )	( )	( )
Heart Murmur	( )	( )	( )
High Blood Pressure	( )	( )	( )
Any heart problem	( )	( )	( )
Lung Disease	( )	( )	( )
Seizures	( )	( )	( )
Irregular heart beat	( )	( )	( )
Bronchitis	( )	( )	( )
Emphysema	( )	( )	( )
Diabetes	( )	( )	( )
Asthma	( )	( )	( )
Kidney Disease	( )	( )	( )
Liver Disease	( )	( )	( )
Severe Allergies	( )	( )	( )
Orthopedic problems	( )	( )	( )
Hyper- or Hypothyroidism	( )	( )	( )
AIDS, hepatitis, or other blood-borne infectious disease	( )	( )	( )

Present Symptom Review:
Have you recently had any of the following symptoms? Please check if so.

Chest Pain	( )	Frequent Urination	( )
Shortness of Breath	( )	Blood in Urine	( )
Heart palpitations	( )	Burning sensations	( )
Leg or ankle swelling	( )	Severe headache	( )
Coughing up blood	( )	Blurred vision	( )
Low blood sugar	( )	Difficulty walking	( )
Feeling faint or dizzy	( )	Weakness in arm	( )
Leg numbness	( )	Significant emotional problem	( )

Are you taking any medications? Yes/No
If yes, please describe:_____

Do you smoke? Yes/No If yes, how many per day?_____

On average, how many alcoholic drinks do you consume per week?_____

OTHER INFORMATION
Whom should we notify in case of emergency?

Name _____

Address _____

Phone # _____

I have been given the opportunity to ask questions about any of the above items that were unclear, and I have answered all questions completely and truthfully to the best of my knowledge.

SIGNATURE_____DATE_____

VITA

Carolyn Albright was born in New Jersey to the parents of Leonard and Robyn Albright on April 14, 1979. She graduated from Lenape High School in Medford, NJ in 1997. She earned her Bachelor of Science degree in exercise science in May 2001 from James Madison University and her Master of Arts degree in exercise physiology in May 2003 from The University of Maryland, College Park. She is currently pursuing her Doctor of Philosophy Degree at the University of Tennessee in exercise physiology.

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