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THE RELATIONSHIP AMONG PROSTAGLANDIN E_2, LEUKOTRIENE B_4, CREATINE KINASE, LACTIC ACID AND DELAYED-ONSET MUSCLE SORENESS

by

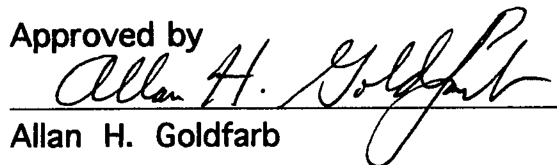
Brian Trevor Boyer

A Dissertation Submitted to
the Faculty of The Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Greensboro

1995

Approved by



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BOYER, BRIAN TREVOR, Ph.D. The Relationship Among Prostaglandin E_2, Leukotriene B_4, Creatine Kinase, Lactic Acid and Delayed-Onset Muscle Soreness. (1995)
Directed by Dr. Allan H. Goldfarb. 216 pp.

The purpose of this study was to examine the relationship among plasma levels of prostaglandin E_2 (PGE_2), leukotriene B_4 (LTB4), creatine kinase (CK), lactic acid (LA), and delayed-onset muscle soreness (DOMS) after an acute weight lifting bout involving eccentric contractions in order to determine if PGE_2 and/or LTB_4 contribute to DOMS. Fourteen college males participated in this study. Nine subjects were randomly assigned to a group which performed a weight lifting bout involving the major muscle groups of the body. Five subjects served as non-exercising controls. Two weeks prior to the weight lifting session both groups were tested for their one-repetition maximum (1RM) on the exercises used in the workout. Two weeks after 1RM testing, subjects in the treatment group performed three sets of each exercise at an intensity of 70% of their 1RM to volitional failure. Venous blood samples and ratings of perceived muscle soreness were obtained before the workout, immediately after the workout, and every 24 hours after the workout for five days. Venous blood samples and ratings of perceived muscle soreness were obtained for the control group every 24 hours for six days.

A MANOVA and t-tests determined that there were no significant changes in any of variables from resting values in the

control group over the 120-hour sampling period. After the workout DOMS was significantly elevated immediately after the workout, peaked 24 hours after the workout, and returned to baseline by 120 hours. Plasma CK was significantly elevated after the workout, peaked 96 hours after the workout (1307.3 $\pm$ 617.4 IU/L), and remained elevated thereafter. Plasma LA was elevated immediately after exercise (10.7 $\pm$ 1.6 mM) and returned to baseline (1.3 $\pm$ mM) by 24 hours. Plasma PGE_2 and LTB_4 remained at baseline levels after exercise (51.4 $\pm$ 15.8 pg/ml & 15.3 $\pm$ 3.4 pg/ml, respectively). These results suggest that plasma levels of PGE_2 and LTB_4 are not associated with DOMS resulting from a weight lifting bout involving eccentric contractions.

APPROVAL PAGE

This dissertation has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Dissertation Advisor ______________________

Committee members ______________________

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11-8-95
Date of Acceptance by Committee

11-8-95
Date of Final Oral Examination

ACKNOWLEDGEMENTS

The author wishes to thank the following individuals for their contribution to the completion of his doctoral study:

Dr. Allan Goldfarb for his guidance and patience throughout my doctoral studies. His concern as a friend helped us get through the tough times we encountered.

Dr. Tom Martinek for his encouragement and help in data interpretation.

Dr. Don Morgan for his willingness to help whenever I encountered problems and his thoughtful and insightful advice concerning my dissertation.

Sharon Maynor for her assistance with the creatine kinase and lactate assay.

Thanasis Jamurtas for his help in the laboratory and encouragement.

The American College of Sports Medicine Foundation for providing funding for my dissertation research.

Dr. Donald Herr for his help and support in statistical analyses of the data. His sense of humor provided laughter when times were hard.

Mark Gailey for his help in the laboratory and with data analysis. His computer expertise contributed significantly to this project.

My friend and business partner Mike Gailey for his constant support and encouragement.

Most importantly, this work is dedicated to the three people who made this all possible: my mother, Ann Boyer, my father, Dr. Don R. Boyer, and my grandfather, Raymond Boyer.

TABLE OF CONTENTS

Page

APPROVAL PAGE....ii

ACKNOWLEDGEMENTS....iii

CHAPTER

I. THE PROBLEM....1

Introduction....1
Statement of the Problem....11
Hypotheses....11
Delimitations....13
Limitations....13
Significance of the Study....13
Definition of Terms....14
Abbreviations....15

II. REVIEW OF LITERATURE....16

Introduction....16
Theories of Delayed-Onset Muscle Soreness....16

Muscle Tissue and Connective Tissue Damage and DOMS....19

Acute Inflammation and DOMS....27
Prostaglandin E_2 and DOMS....35
Leukotriene B_4 and DOMS....56
Summary....65

III. METHODS AND PROCEDURES....67

Introduction....67

Selection of Subjects 67
Experimental Design 68

1RM Testing 70
Weight Lifting Session 71
Perceived Muscle Soreness 72

Blood Sampling 73
Chemical Determinations 74

PGE_2 Determination 74
LTB_4 Determination 78
Creatine Kinase Determination 80
Lactate Determination 81

Statistical Analyses 82

IV. RESULTS 84

Introduction 84
Treatment of Individual Data 84
Subject Characteristics 85
Evaluation of Muscle Soreness 85
Plasma Creatine Kinase Values 88
Plasma Lactate Values 92
Plasma PGE_2 Values 94
Plasma LTB_4 97
Correlations among the Variables 99

V. DISCUSSION 103

Effect of the Weight Lifting Bout on DOMS 104
Effect of the Weight Lifting Bout on CK 106
Effect of the Weight Lifting Bout on Lactic Acid 111
Effect of the Weight Lifting Bout on PGE_2 113
Effect of the Weight Lifting Bout on LTB_4 123
Correlations Among the Variables 129

VI. CONCLUSION AND RECOMMENDATIONS....133

BIBLIOGRAPHY....139

APPENDIX A. INFORMED CONSENT FORM....180

APPENDIX B. MEDICAL HISTORY QUESTIONNAIRE....184

APPENDIX C. SUBJECT INSTRUCTIONS....188

APPENDIX D. 1RM TESTING SESSION FORM....190

APPENDIX E. WEIGHT LIFTING SESSION FORM....192

APPENDIX F. PERCEIVED MUSCLE SORENESS QUESTIONNAIRE....194

APPENDIX G T-VALUES AND P-VALUES FOR T-TESTS....196

APPENDIX H. RAW DATA....208

CHAPTER I

THE PROBLEM

Introduction

Delayed onset muscle soreness (DOMS) is a tender, aching feeling in muscles that have undergone unaccustomed exercise. DOMS usually develops 24 hours after exercise, peaks 48-72 hours after exercise, and gradually diminishes in intensity until there is no more soreness or pain (Armstrong, 1984; Asmussen, 1956; Hough, 1902). The sensation of DOMS may persist 4-7 days after exercise (Ebbeling & Clarkson, 1989). Eccentric activity often results in DOMS (Byrnes et al., 1985; Clarkson, Byrnes, McCormick, Turcotte & White, 1986; Fridén, 1984) and can range in intensity from mild to severe, depending on the intensity and duration of the activity (Tiidus & Ianuzzo, 1983).

Increases in blood levels of creatine kinase (CK) have also been associated with DOMS and have been used as indicators of muscle damage (Armstrong, 1986; Byrnes et al., 1985; Clarkson, Byrnes, Gillisson & Harper, 1987; Clarkson et al., 1986; Evans et al., 1986; Manfredi et al., 1991; Maughan et al., 1989; Tiidus & Ianuzzo, 1983). The time course of changes in CK in the blood can vary, depending on the type of exercise, duration, and intensity (Hortobágyi & Denahan, 1989). Eccentric contractions appear to be particularly effective in elevating blood CK values (Ebbeling & Clarkson, 1989). Activities

such as downhill running appear to result in peak plasma levels of CK 18 to 24 hours after exercise (Byrnes et al., 1985). Peak values of CK in plasma appear to be delayed in activities involving intense, eccentric muscular activity, with peak values not occuring until 48-120 hours after exercise (Clarkson & Tremblay, 1988; Jones, Newham, Round & Tolfree, 1986; Newham, Jones & Edwards, 1986).

Although increases in CK and DOMS are both associated with unaccustomed exercise, the time course of DOMS does not coincide with the changes in blood CK levels (Ebbeling & Clarkson, 1989; Newham et al., 1986). Therefore, the elevation of blood CK levels and the generation of DOMS may be caused by different mechanisms (Ebbeling & Clarkson, 1989; Evans & Cannon, 1991).

The idea that DOMS results from an accumulation of lactic acid has been a popular explanation for DOMS within the exercise community (Ebbeling & Clarkson, 1989). This hypothesis does not seem plausible, since, eccentric contractions involve less energy expenditure than other types of contractions (Abbott, Bigland & Ritchie, 1952; Armstrong, Laughlin, Rome & Taylor, 1983; Asmussen, 1953; Bonde-Peterson, Knuttgen & Henriksson, 1972). Furthermore, Schwane, Watrous, Johnson & Armstrong (1983) found that downhill running involved significantly lower rates of oxygen consumption and resulted in lower levels of lactic acid, but produced more severe DOMS.

Presently, the mechanism of DOMS has not been identified (Armstrong, 1984; Ebbeling & Clarkson, 1989; Smith, 1992). Several

theories have been proposed to explain DOMS (Ebbeling & Clarkson, 1989). One theory which is currently being explored is that the acute inflammatory response underlies DOMS (Hikida, Staron, Hagernam, Sherman & Costill, 1983; Kuipers, Drukker, Frederik, Geurten & Kranenburg, 1983; Smith, 1991; Stauber, 1989). Similarities between DOMS and the acute inflammatory response have been observed (Armstrong, 1984; Armstrong, 1986; Armstrong, Ogilvie & Schwane, 1983; Cannon et al., 1989b; Castor, 1981; Colley, Fleck, Goode, Muller & Myers, 1983; Doherty, Downey, Worthen, Haslett & Henson, 1988; Fridén, Sjostrom & Ekblom, 1983; Janoff & Carp, 1982; Kasperek & Snider, 1985; Newham, McPhail, MIlls & Edwards, 1983; Ryan & Majno, 1977). This acute inflammatory response may produce a series of local and systemic events, including DOMS, which serve to repair exercise-induced tissue damage and protect from further injury (Evans & Cannon, 1991; Stauber, 1989; Stauber, Clarkson, Fritz & Evans, 1990).

The products of the inflammatory process which are similar in characteristics to DOMS are pain and hyperalgesia (Bennett, 1988; Ebbeling & Clarkson, 1989; Smith, 1991; Taiwo, Goetzl & Levine, 1987; Tidball, 1991). The generation of pain due to inflammation is usually associated with III and IV pain afferents (Martin, Basbaum, Kwiat, Goetzl & Levine, 1987; Mense, 1977; Mense & Schmidt, 1977). These pain afferents are slow conducting nerve fibers which respond to noxious stimuli and have a high threshold for mechanical stimulation (Mense, 1981; Mense, 1982). They are primarily

distributed in the connective tissue surrounding muscle fibers and are especially concentrated around arterioles and capillaries (Mense, 1977). A large number of pain afferents can also be found at the myotendinous junctions (Tidball, 1991). These afferent fibers respond to chemical, mechanical, and thermal stimuli (Fock & Mense, 1976; Martin et al., 1987). In addition, there are a number of inflammatory mediators which can lower the pain threshold or increase pain sensitivity resulting from activation of these pain afferents by noxious stimuli (Martin et al., 1987; Mense, 1981; Taiwo et al., 1987). These include: bradykinin, norepinephrine, and products of arachidonic acid metabolism (Madison, Whitsel, Suarez-Roca & Maixner, 1992; Martin et al., 1987; Mense, 1981; Taiwo et al., 1987).

A paucity of research exists regarding inflammatory mediators and DOMS. One group of inflammatory mediators which may be associated with the generation of DOMS are products of arachidonic metabolism. Products of arachidonic metabolism are formed by a cascade of reactions which result in the production of arachidonic acid metabolites, namely, prostanoids and leukotrienes. To initiate this cascade of reactions phospholipid membranes are acted upon by the enzyme phospholipase A_2. A schematic diagram of the conversion of arachadonic acid to prostaglandins and thromboxanes via the cyclooxygenase pathway and leukotrienes via the lipoxygenase pathway is presented in Figure 1. Two of the products of arachidonic acid metabolism-prostaglandins and leukotrienes may

be involved in the sensation of DOMS, due to their ability to increase the sensitivity of pain afferents to chemical, thermal, and mechanical stimuli (Bennett, 1988; Ford-Hutchinson & Letts, 1986; Martin et al., 1987; Mense, 1981). Recent research has indicated that increased prostaglandin synthesis and release may accompany DOMS (Bansil, 1984; Smith et al., 1993; Wells, 1991).

Eccentric contractions have been associated with the generation of DOMS (Asmussen, 1953; Clarkson et al., 1986; Fridén et al., 1983; Newham, Mills, Qugley & Edwards, 1983). Products of arachidonic acid metabolism may be associated with the generation of DOMS, since muscle fibers which are subjected to eccentric contractions may disrupt sarcolemmal and myofibrillar elements (Armstrong, 1990). This may allow phospholipase A_2 to activate the phospholipid elements of the muscle fiber (Armstrong, 1990). Eccentric contractions have been shown to result in damage to skeletal muscle fibers, as indicated by myofibrillar and sarcolemmal disturbances in animals (Armstrong et al., 1983), and humans (Evans et al., 1986; Fridén et al.,1983; Sjöström & Ekblom, 1981; Jones et al., 1986; McCully & Faulkner, 1985).

Connective tissue disruption has also been associated with DOMS (Abraham, 1977; Stauber et al., 1990; Tidball, 1991). Disruption of connective tissue associated with contractile elements may accompany muscle damage resulting from eccentric

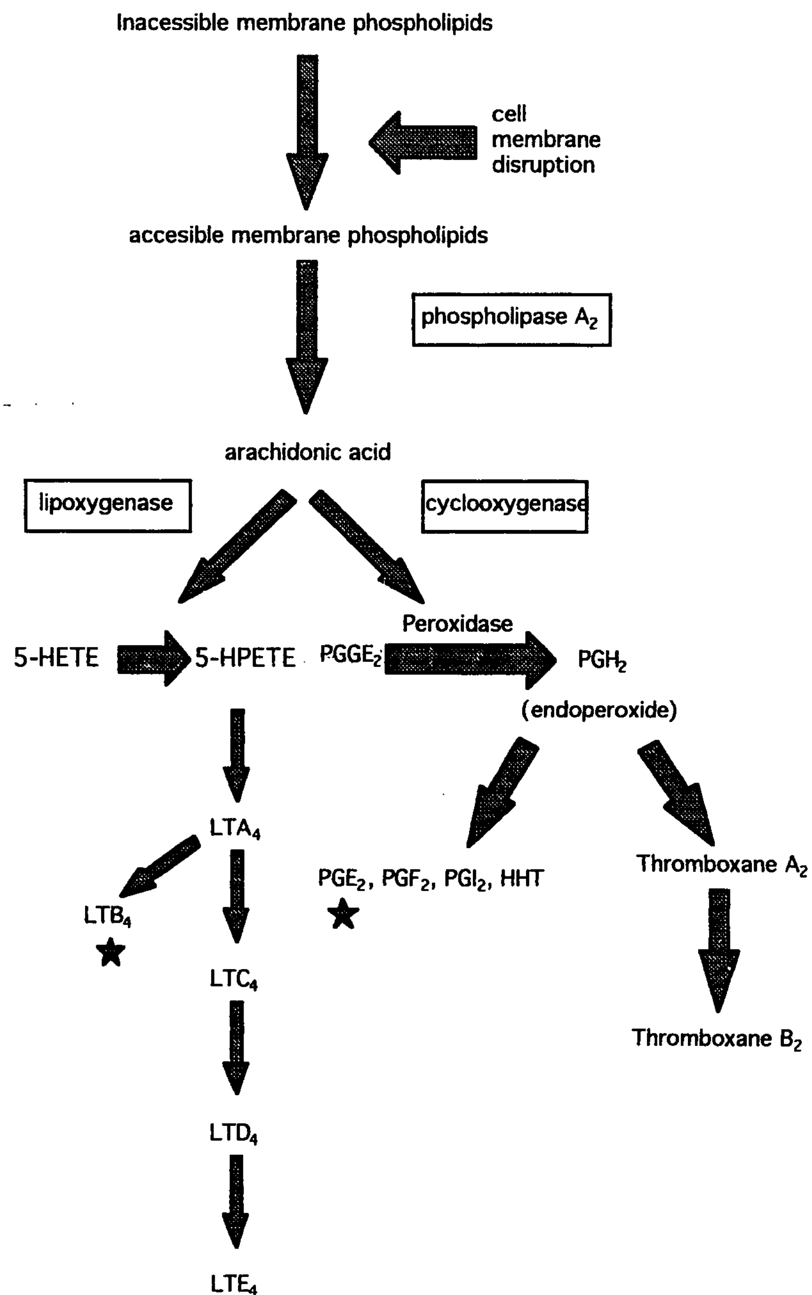

Figure 1. Conversion of arachidonic acid to leukotrienes, prostaglandins, and thromboxanes.

exercise (Fridén et al., 1983; Fridén et al., 1981; Fritz & Stauber, 1988; Stauber et al., 1990) This disruption of connective tissue could result in the migration of inflammatory cells, primarily monocytes, into the damaged area (Postlethwaite & Kang, 1976).

Armstrong has suggested that arachidonic acid metabolism during and immediately after exercise may serve as an important autogenic mechanism in muscle fiber injury (Armstrong, Warren & Warren, 1991). Therefore, arachidonic acid metabolites may play a role in the response to muscle fiber and connective tissue damage due to exercise, resulting in a number of responses, including DOMS.

Two products of arachidonic acid metabolism that are commonly associated with hyperalgesia are prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) (Ferreira, 1972; Ferreira, Moncada & Vane, 1974; Levine, Gooding, Donati, Borden & Goetzl, 1985; Madison et al., 1992; Martin et al., 1987; Rackham & Ford-Hutchinson, 1983; Soter, Lewis, Corey & Austen, 1983; Taiwo et al., 1987). These substances can be produced by virtually all inflammatory cell types, with the exception of lymphocytes (Moore, 1985). Of all the types of cells associated with the acute inflammatory response, the macrophage is considered to play a primary role in wound healing, with macrophage levels peaking 24 to 48 hours after tissue injury (Hurley, 1983; Peacock, 1983; Ryan & Majno, 1977). Additionally, the macrophage appears to be the predominant cell type at the injury site resulting from eccentric activity (Armstrong, 1984; Jones et al., 1986; Round, Jones & Cambridge, 1987; Tullson & Armstrong, 1981). Macrophages

play an important role in the production of prostaglandins during the inflammatory response (Ferraris, DeRubertis, Hudson & Wolfe, 1974; Goldyne & Stobo, 1979; Kennedy, Stobo & Goldyne, 1980; Kurland & Bockman, 1978; Morley, Bray, Jones, Nugteren & VanDorp, 1979). In addition, macrophages are also responsible for the production of leukotrienes during the acute inflammatory response (Neill, Henderson & Klebanoff, 1985; Williams, Czop & Austen, 1984). In both instances macrophage concentrations appear to peak between 24 to 48 hours. Macrophages synthesize and release leukotrienes during the inflammatory process (Neill et al., 1985; Williams et al., 1984). Therefore, release of prostaglandins and leukotrienes may exhibit a time course similar to DOMS. This suggests a possible relationship between these arachidonic acid metabolites and DOMS.

There are several other cell types involved in acute inflammation and the wound healing process which are capable of producing leukotrienes and prostaglandins (Lefer, 1985; Moore, 1985). Fibroblasts infiltrate areas of tissue injury and are involved in deposition of collagen and other substances associated with connective tissue (Dayer, Roelke & Krane, 1981; Koun, Halushka & LeRoy, 1980). Infiltration by fibroblasts has been found in rat muscle tissue following downhill running, a predominately eccentric activity (Armstrong et al., 1983; Tullson & Armstrong, 1981).

Infiltration of injured tissue by neutrophils occurs early in the inflammatory process, with a life span of only one to two days (Bainton, 1988). A similar neutrophil response has also been

observed with exercise, with increases in circulating neutrophils occuring during (Steel, Evans & Smith, 1974) and for several hours after exercise (Cannon et al., 1990; Smith, McCammon, Smith, Chamness & O'Brien, 1989). Neutrophil infiltration of muscle tissue has been observed immediately and two hours after exercise (Kuipers et al., 1983).

Mast cells are also involved in the inflammatory process (Peters et al., 1987). Eccentric exercise has been shown to result in mast cell degranulation 48 hours after exercise in association with a disruption of the extracellular matrix surrounding skeletal muscle (Stauber et al., 1990).

Although products of arachidonic acid metabolism appear to be likely candidates for playing a role in the manifestation of DOMS, currently only prostaglandins of the E series have been associated with DOMS. Bansil, et al. (1984) found a similar time course for increases in plasma PGE_1 after eccentric exercise, indicating a possible relationship between these variables.

Smith and co-workers (Smith et al., 1993) found significant increases in plasma PGE_2 48 hours after peformance of the eccentric phase of a chest press exercise which resulted in DOMS. On the other hand, Wells (1991) found that performance of the eccentric phase of a chest press exercise did not result in increases in plasma PGE_2. Instead, plasma PGE_2 levels decreased 96 hours after exercise. Based on current research, the relationship between DOMS and PGE_2 has not been established.

The possibility exists that products of arachidonic acid metabolism other than PGE_2 are involved in DOMS. Leukotriene B_4 is the leukotriene most associated with the production of hyperalgesia (Levine, Lau, Kwiat & Goetzl, 1984; Martin, 1990; Martin, Basbaum, Goetzl & Levine, 1988; Rackham & Ford-Hutchinson, 1983), and therefore, may be involved in the generation of DOMS. The relationship between DOMS and LTB_4 has not been investigated.

However, a wide range of inflammatory mediators are capable of synthesizing and releasing LTB_4. Muscle fiber or connective tissue damage caused by eccentric exercise may result in increased synthesis and release of LTB_4.

PGE_2 and LTB_4 may play a role in the generation of DOMS by sensitizing type III and type IV pain afferents associated with areas of tissue damage to noxious stimuli. Under these conditions the pain receptors may be more susceptible to mechanical or chemical stimuli than which would occur normally (Davies, Bailey & Goldenberg, 1984; Juan, 1978; Levine et al., 1984; Martin, 1990; Martin et al., 1988; Mense, 1981; Taiwo et al., 1987). Chemical substances associated with the inflammatory process involving connective tissue and muscle tissue degeneration and repair may then stimulate these pain afferents, resulting in the sensation of pain (Fock & Mense, 1976; Mense, 1981; Stauber, 1989; Stauber et al., 1990; Taiwo et al., 1987). DOMS is usually experienced during contraction or palpatation of the affected muscle (Armstrong, 1984). It has been suggested by Smith (Smith, 1991) that a low

level of edema may be associated with DOMS. Therefore, during muscular contraction small increases in pressure may occur which might provide a mechanical stimulus for sensitized pain receptors. Hence, in addition to chemical stimulation, III and IV pain afferents may be stimulated by mechanical input when sensitized by PGE_2 and LTB_4. Thus, it can be proposed that DOMS results from sensitization of pain receptors by either PGE_2, LTB_4, or both arachidonic acid metabolites which are stimulated by chemical and mechanical stimuli.

Statement of the Problem

The purpose of this study is to examine the relationship of plasma levels of PGE_2, LTB_4, CK, lactic acid, and DOMS over 120-hours after an acute weight lifting bout involving eccentric contractions in order to determine if PGE_2 and/or LTB_4 are contributing factors in the process of DOMS. The response of plasma lactic acid to the weight lifting bout will be examined in order to estblish that the weight lifting bout elicits responses which are typical of heavy resistance exercise protocols. The plasma CK response to the weight lifting bout will be examined in order to establish that the weight lifting bout provides the plasma CK response which is typically associated with exercise which results in DOMS.

Hypotheses

An acute weight lifting bout to exhaustion which involves all the major muscle groups of the body will cause delayed onset muscle soreness. The resulting soreness should also be accompanied

by increases in plasma creatine kinase values. Increases in plasma lactic acid should also be seen immediately after the weight lifting bout. Plasma lactic acid should return to baseline values by 24 hours after exercise.

It has been suggested that increased levels of certain inflammatory mediators may play a role in the generation of DOMS. Therefore, similar increases in the inflammatory mediators PGE_2 and LTB_4 and DOMS over time may indicate a relationship among these variables. The following hypotheses will be tested in this study:

1. The acute weight lifting bout will result in the manifestation of DOMS with a time course similar to that which has been documented in the literature.

2. The acute weight lifting bout will result in an increase in plasma lactic acid values immediately after exercise, and will return to resting values by 24 hours after exercise.

3. The acute weight lifting bout will result in elevated plasma creatine kinase levels which will peak 48-120 hours after the acute weight lifting bout.

4. The acute weight lifting bout will result in increases in plasma levels of PGE_2 which will exhibit a time course similar to that of DOMS over the 120-hour time period.

5. The acute weight lifting bout will result in increases in plasma levels of LTB_4 which will exhibit a time course similar to that of DOMS over the 120-hour time period.

6. Plasma levels of PGE_2 and DOMS will be significantly correlated before and immediately after the weight lifting bout, as well as 24 hours, 48 hours, 72 hours, 96 hours, and 120 hours after the weight lifting bout.

7. Plasma levels of LTB_4 and DOMS will be significantly correlated before and immediately after the weight lifting bout, as well as 24 hours, 48 hours, 72 hours, 96 hours, and 120 hours after the weight lifting bout.

Delimitations

1. The subjects will be sedentary college-aged males who will be instructed to refrain from exercise prior to and during the study.

2. The subjects will be instructed to fast for four hours prior to the collection of blood samples.

Limitations

1. It must be assumed that each subject is attempting to perform maximally during the weight lifting sessions.

2. Muscle soreness will be assessed by having each subject rate muscle soreness on a subjective scale.

Significance of the Study

The results of this investigation will help determine if plasma PGE_2, plasma LTB_4, are related to the generation of DOMS following an intense weight lifting bout. This will help determine if PGE_2 and LTB_4 are contributing factors in the process of DOMS resulting from exercise which is associated with muscle damage.

Plasma levels of PGE_2 associated with exercise have shown a great deal of variability in the current literature. Furthermore, plasma levels of LTB_4 in association with exercise have not been established. Therefore, this study provides further information which will help establish an accurate range of values for plasma LTB_4 and PGE_2 associated with exercise.

Definition of Terms

1. Delayed onset muscle soreness (DOMS)- the dull, aching pain which is accompanied by muscular tenderness and stiffness. DOMS usually develops 24-48 hours after exercise and gradually increases in severity, usually peaking 24-72 hours after exercise. DOMS is usually associated with eccentric muscle contractions.

2. Creatine Kinase- the enzyme in muscle responsible for the formation of ATP from the reaction of ADP and creatine phosphate. The release of CK into the blood is associated with alterations in the muscle cell membrane.

3. Prostaglandin E_2 (PGE_2)-an unsaturated lipid made from fatty acid precursors which belongs to the E series of prostanoids. PGE_2 acts locally as a tissue hormone and has a wide variety of actions including: vasodilation of capillaries, increases in vascular permeability, sensitization of afferent pain receptors, and mediation of immune functions.

4. Leukotriene B_4 (LTB_4)-a member of the leukotriene family formed via the lipoxygenase pathway from arachidonic acid which

induces leukocyte accumulation, affects vascular permeability and modulates pain responses.

5. Eccentric contraction-a contraction in which the muscle lengthens while developing tension against an external resistance which exceeds the force generated by the muscle.

6. Concentric contraction-a contraction in which the muscle shortens as it develops the tension necessary to overcome an external resistance.

7. Repetition- The number of consecutive times a particular movement or exercise is performed.

8. Set-the number of groups of repetitions of a particular movement or exercise.

9. One repetition maximum (1RM)-the most resistance which can be overcome in a particular exercise for one repetition.

Abbreviations

CK: creatine kinase

DOMS: delayed-onset muscle soreness

IL-1: interleukin-1

LTB_4: leukotriene B_4

MTJ: myotendinous junction

NSAIDS: non-steroidal anti-inflammatory drugs

PGE_2: prostaglandin E_2

CHAPTER II

REVIEW OF LITERATURE

Introduction

The purpose of this study was to examine the time course relationship of PGE_2, LTB_4, and DOMS resulting from an intense weight lifting bout. The literature review will be organized under the following headings: Theories of Delayed-Onset Muscle Soreness, Muscle Tissue and Connective Tissue Damage and DOMS, Inflammation and DOMS, Prostaglandin E_2 and DOMS, Leukotriene B_4 and DOMS, and Summary.

Theories of Delayed-Onset Muscle Soreness

Muscle soreness can result from strenuous or unaccustomed exercise. Muscle soreness can occur during or immediately after exercise, as well as 24-72 hours after exercise. These two types of soreness have been classified as temporary and delayed muscle soreness, respectively (Talag, 1973). Temporary muscle soreness can occur during exercise and persist for several hours after exercise. It is thought that this type of soreness results from the accumulation of metabolic end-products which affect local pain afferents and contribute to tissue edema (Asmussen, 1956; Brendstrup, 1962; Hough, 1902).

The sensation of pain associated with delayed-onset muscle soreness usually starts 24 hours after exercise, peaking 24-48 hours after exercise, and may persist for several days (Armstrong, 1984; Ebbeling & Clarkson, 1989; Fridén, 1984). DOMS has been primarily associated with eccentric contractions (Byrnes, 1985; Byrnes et al., 1985; Clarkson et al., 1987; Clarkson et al., 1986; Clarkson & Tremblay, 1988; Cote, 1988; Davies & Barnes, 1972; Ebbeling & Clarkson, 1989; Newham, Jones & Clarkson, 1987; Newham et al., 1986; Newham et al., 1983). The cause of DOMS has not yet been determined. Three primary factors have been suggested as causal agents of DOMS (Armstrong, 1984; Ebbeling & Clarkson, 1989; McArdle, Katch & Katch, 1991). These factors include: 1) torn muscle tissue or connective tissue resulting from high contractile tension; 2) accumulation of metabolic waste products from muscle contraction; 3) muscle spasms produced by altered neural activation resulting from increases in contractile tension.

The idea that muscle spasms promoted DOMS was originaly proposed by Travell, Rinzler & Herman (1942). This theory of soreness suggests that muscle pain resulting from increased contractile activity causes or promotes a positive feedback cycle which leads to tonic muscular spasm (DeVries, 1980). This spasm may then cause further pain through the production of local ischemia (DeVries, 1980). In support of this theory, DeVries and co-workers have reported increases in electromyographic (EMG) activity in sore

muscles (Cobb, DeVries, Urban, Luekens & Bagg, 1975; DeVries, 1960; DeVries, 1966; DeVries, 1968).

In contrast, McGlynn, Laughlin & Rowe (1979) reported increases in EMG activity in muscle, but the magnititude of these increases were not related to the perception of soreness. In addition, other researchers have not observed increases in EMG activity in sore muscles (Abraham, 1977; Newham et al., 1983).

The accumulation of metabolic metabolites, primarily lactic acid, have been suggested to cause DOMS. DOMS is primarily associated with eccentric contractions (Clarkson et al., 1986; Talag, 1973), which have a lower metabolic cost than concentric contractions at the same power output (Armstrong et al., 1983; Bonde-Peterson et al., 1972). Therefore, eccentric contractions should result in a lesser accumulation of lactic acid than concentric contractions at the same power output.

Schwane et al. (1983) examined the relationship between blood lactic acid levels and DOMS following downhill and level running in humans. The downhill running resulted in DOMS which was not accompanied by significant increases in plasma lactic acid. Conversly, subjects running only on a level surface demonstrated significant increases in plasma lactic acid without experiencing DOMS.

Kuipers et al. (1983) reported that rats running on a treadmill at a low intensity demonstrated indications of muscle damage without an elevation in plasma lactic acid values. The findings of

Kuipers et al. further support the contention that DOMS does not result from an accumulation of lactic acid.

Muscle Tissue and Connective Tissue Damage and DOMS

The idea that a disruption in the myofibrillar elements is responsible for DOMS was first proposed by Hough in 1902 (Hough, 1902). Subsequently, the theory that DOMS results from muscle tissue and/or connective damage has gained considerable support (Armstrong, 1984; Brooks & Fahey, 1985; Ebbeling & Clarkson, 1989). As previously noted, DOMS is primarily associated with eccentric contractions. These eccentric contractions have been shown to result in considerable damage to muscle fibers in both animal (Armstrong et al., 1983; Kuipers et al., 1983; McCully & Faulkner, 1985; Ogilvie, Armstrong, Baird & Bottoms, 1988) and human studies (Fridén, 1984; Fridén et al., 1983; Fridén et al., 1981; Jones et al., 1986; Manfredi et al., 1991; Newham et al., 1983; O'Reilly et al., 1987). In rodents, disruption of myofibrillar banding patterns and sarcolemmal disruption, as well as fiber degeneration has been demonstrated immediately after eccentric contractions (Armstrong et al., 1983; McCully & Faulkner, 1985). At 24 hours after eccentric contraction, increases in the size of necrotic lesions in muscle fibers were observed (Armstrong et al., 1983; McCully & Faulkner, 1985). These necrotic lesions appeared to peak in size at 48 hours (Armstrong et al., 1983; McCully & Faulkner, 1985). Infiltration by monocytes, macrophages, and fibroblasts were also noted at 24 hours by Armstrong et al. (1983).

Similar types of muscle fiber damage have also been reported in humans. Myofibrillar disruption, which includes focal damage, disruption and streaming of the Z-band, and distribution of Z-line material througout the fiber has been observed in muscle biopsies taken immediately after eccentric exercise (Fridén et al., 1983; Manfredi et al., 1991; Newham et al., 1983; O'Reilly et al., 1987). Disruption of the sarcoplasmic reticulum, as well as evidence of mitochondrial damage has also been reported in severly damaged fibers immediately after eccentric exercise (Manfredi et al., 1991). This damage appeared to become more extensive over the next 2-3 days, with increases in size of the focal areas of muscle damage and increased Z-band disruption (Fridén et al., 1983; Fridén et al., 1981; Newham et al., 1983). Some researchers have indicated that this type of muscle damage can take approximately 10 days to repair (Newham, 1988). O'Reilly et al. (1987) and Manfredi et al. (1991) reported the presence of muscle fiber damage in muscle biopsies 10 days after eccentric exercise. Although it appears that this muscle fiber damage is related to the generation of DOMS, the mechanism by which this muscle damage contributes to DOMS is not understood (Armstrong, 1984; Newham, 1988).

It has been demonstrated that eccentric contractions resulting in DOMS are also responsible for increases in plasma CK values (Byrnes et al., 1985; Clarkson et al., 1986; Clarkson & Tremblay, 1988; Maughan et al., 1989; Newham et al., 1986). Hence, increases in plasma values of CK have been used as an indirect indicator of

muscle damage (Armstrong, 1984; Evans et al., 1986; Schwane, Johnson, Vandenakker & Armstrong, 1983). It has been established that the magnitude and time course for increases in plasma CK depends on the type of exercise performed, as well as the intensity and duration of the exercise (Ebbeling & Clarkson, 1989; Tiidus & Ianuzzo, 1983). Byrnes et al. (1985) and Schwane et al. (1983) reported significant increases in plasma CK approximately six hours after exercise, with plasma CK levels peaking around 24 hours after exercise.

Other types of eccentric activities have resulted in peak increases in plasma CK which have occurred later than 24 hours after exercise. Newham et al. (1986) reported peak levels of plasma CK in subjects 4-7 days after downhill walking on a treadmill inclined at 13°. Similar results were obtained by Evans et al. (1986) using subjects who exercised on a cycle ergometer designed for eccentric leg exercise. Plasma CK values were elevated three hours after exercise and peaked 3-5 days later. Clarkson & Tremblay, (1988) had subjects perform 70 repetitions using eccentric exercises involving the forearm flexors. This exercise protocol resulted in significant increases in plasma CK levels which persisted five days after exercise.

The time course of CK increases in plasma has also been investigated using a regimen of high-intensity weight lifting contractions. Paul, DeLany, Snook, Seifert & Kirby (1989) examined the effect of a high-intensity weight lifting bout on serum and

urinary markers of skeletal muscle damage in trained and untrained weight lifters. Subjects performed three sets of repetitions to fatigue using 70-80% of their 1RM on the bench press, shoulder press, latissiumus pulldown, arm curl, leg press and leg curl. All of the exercises were performed on Universal Gym Equipment. One minute of rest was provided between sets, and two minutes of rest were utilized between exercises. Significantly elevated levels of serum CK were observed 12 hours after exercise, with higher values obtained after 24 hours. Serum CK values were not obtained after 24 hours by the investigators.

In order to examine the relationship between indicators of muscle damage over a longer period of time than that which was used by Paul et al. (1989), Boyer, Lewis & Goldfarb (1991) examined the effect of a high-intensity weight lifting bout on DOMS, plasma CK, and plasma malondialdehyde over a 72-hour time period. Subjects performed three sets of repetitions to volitional exhaustion on the following free weight exercises: bench press, triceps pushdowns, military press, barbell curl, and reverse-grip curl. The exercises were performed at 70% of the subject's 1RM. The subjects were allowed to rest two minutes between each set of each exercise. The investigators reported that despite a trend toward increasing CK values 24 hours after exercise, significant increases in plasma CK were not observed until 72 hours after exercise. Unlike plasma CK values, muscle soreness was

significantly increased from baseline values 24 and 48 hours after exercise, with muscle soreness peaking 48 hours after exercise.

Connective tissue damage has also been purported to play a role in the generation of DOMS. The pain associated with DOMS is usually experienced in the areas around the musculotendinous junctions (Asmussen, 1956; Komi & Buskirk, 1972; Komi & Rusko, 1974; Newham et al., 1983). The manifestation of pain in areas where connective tissue is most abundant led Asmussen (1956) to hypothesize that DOMS was caused by over-stretching of the series elastic components of muscle tissue. However, Newham (1988) has suggested that the localisation of pain may be dependent on the intensity, duration, and type of eccentric contraction performed.

Abraham (1977) concluded that exercise-induced damage to connective tissue elements associated with muscle was responsible for soreness. Abraham found an increased hydroxyproline/creatinine ratio in urine collected througout the day subjects experienced peak soreness. Since hydroxyproline is a unique breakdown product of connective tissue (Kivirikko, 1970), this suggests connective tissue breakdown occurs concomitantly with peak soreness.

Work by Stauber et al. (1990) has also suggested that connective tissue disruption is associated with eccentric muscle action. Stauber et al. found chondroitin 6-sulfate proteoglycan localization in the endomysial area around muscle fibers 48 hours after 70 maximal eccentric contractions of the elbow flexors. Proteoglycans are important components of the extracellular matrix

associated with connective tissue, and, hence, their degradation serve as indicators of extracellular matrix and connective tissue disruption (Stauber et al., 1990). Similar findings were reported by Fritz & Stauber (1988) in rat muscles subjected to forced lengthening. Histological disruption of the proteoglycan complex was evident in damaged muscle fibers by 24 hours.

Direct evidence that connective tissue disruption occurs as a result of mechanical stress has not been documented. Therefore, studies examining connective tissue disruption have been limited to examination of products of connective tissue and proteoglycan breakdown (Abraham, 1977; Fritz & Stauber, 1988; Stauber, 1989; Stauber et al., 1990). Because the time course of DOMS and muscle fiber damage resulting from eccentric exercise are not comparable, Stauber and co-workers have suggested that connective tissue and extracellular matrix may be associated with DOMS, since it appears that the time course of this disruption more closely resemble that of DOMS (Fritz & Stauber, 1988; Stauber, 1989; Stauber et al., 1990).

As previously described, the myotendinous junction (MTJ) is an area which muscle soreness is usually experienced. The MTJs are interfaces between tendons and muscles and are sites of force transmission resulting from contraction of contractile elements (Tidball, 1991). The structure of MTJ is complex and appears to consist of myofibirils which terminate into a dense material which is attached to the cell membrane via structural proteins (Tidball, 1991). The muscle cell is associated with the extracellular matrix

via structural proteins. Components of the extracelluar matrix involved in the MTJ include proteoglycans and a wide variety of other structural molecules.

There appears to be an association between both muscle and connective tissue damage at the MTJ and DOMS. MTJs are thought to be primary sites of lesions associated with muscle fiber tears (Garrett & Tidball, 1988). Tidball (1991) has suggested that damage to MTJ may be involved in the generation of DOMS. Eccentric loading resulting in incomplete tears has been shown to result in edema and inflammation at the MTJ from rats, indicating a possible underlying mechanism for DOMS (Almekinders & Gilbert, 1986). The time course of morphological changes resulting from partial tears at the MTJ also appears to be similar to that of DOMS. Initial insults at the MTJ are followed by an inflammatory response for the next 1-4 days (Almekinders & Gilbert, 1986; Garrett & Tidball, 1988), with muscle repair occuring at four days following injury (Almekinders & Gilbert, 1986). Thus, repair of damage at MTJs seems to follow a time course similar to the disappearance of DOMS.

Although it is widely believed that tissue damage is associated with DOMS, the mechanism by which this damage results in the generation of DOMS is presently not known. One theory which has been suggested is that muscle edema is responsible for producing DOMS (Fridén, Sfakianos & Hargens, 1986; Howell, Chila, Ford, David & Gates, 1985; McArdle et al., 1991). Fridén (1984) suggested that as a result of myofibrillar damage, degraded protein

compounds and protein-bound ions are released (Fridén, 1984; Salminen & Vihko, 1983). This would effect an increase in osmotic pressure, causing fluid to build up. This subsequent increase in fluid pressure could then activiate nocioceptors located in areas where connective tissue and the contractile components meet (Mense & Schmidt, 1974), resulting in soreness (Fridén, Sfakianos, Hargens & Akeson, 1988). Fridén et al. (1988) examined intramuscular pressure and morphological changes which occur after eccentric exercise and concluded that muscle fiber swelling following eccentric exercise was associated with DOMS. Eccentric contractions involving the anterior tibialis muscle resulted in increases in size of type II muscle fibers after exercise in some subjects. In addition, this increase in size was significantly correlated with the length of time needed to return to resting pressure. The eccentrically stressed muscles exhibited increased water content as compared to resting values. No muscle fiber necrosis or significant signs of inflammation were observed in eccentrically stressed muscle tissue.

Other studies have been undertaken to establish if there is a relationship between DOMS and edema. Bobbert, Hollander & Huijing (1986) found increases in limb volume relative to controls 48 and 72 hours after eccentric calf exercise. Fridén et al. (1986) found fluid pressure in the anterior tibial compartment of the leg increased 48 hours after exercise, when DOMS usually peaks.

In contrast, Talag (Talag, 1973) failed to find a significant correlation between limb volume and DOMS following eccentric contractions of the forearm flexors. Furthermore, Newham (1988) found no significant increases in intramuscular pressure of the elbow flexor compartment after eccentric contraction. Newham hypothesized these results may have been obtained because the compartment around the elbow flexors is more distensible than the tibialis anterior compartment, which has been shown to demonstrate increases in intramuscular pressure after eccentric contractions (Fridén et al., 1986). Based on these studies it appears that the research regarding the relationship between DOMS and edema is equivocal and further research is necessary.

Another theory explaining the generation of DOMS from tissue damage resulting from eccentric loading is that acute inflammation underlies DOMS (Brooks & Fahey, 1985; Evans & Cannon, 1991; Smith, 1991; Smith, 1992; Stauber, 1989). The association between DOMS and acute inflammation will be examined in the following discussion.

Acute Inflammation and DOMS

The inflammatory response is a series of events which represents the body's ability to defend against infection and promote the healing of tissue damage. This inflammatory response serves to provide plasma and cellular infiltrates to extravascular tissue, as well as play a role in the clearance and repair of damaged tissues (Evans & Cannon, 1991; Sell, 1987). Inflammation initiated by

trauma or tissue necrosis can be characterized by the following phases (Sell, 1987): 1) immediate vasoconstriction followed by vasodilation resulting in increased blood flow to the damaged area and, subsequently, edema, 2) infiltration of neutrophils into damaged tissue, 3) tissue infiltration by mononuclear cells (lymphocytes,macrophages), 4) clearing and repair of damaged tissue or fibroblastic cell proliferation when there is significant tissue loss. The classic signs of inflammation include: redness, swelling, calor, pain, and loss of function. Because physiological changes associated with DOMS are similar to some of the classic signs of inflammation, the two phenomena have been linked (Brendstrup, 1962; Smith, 1991).

Because the acute inflammatory response results in a series of events which have been observed following eccentrically-induced muscle contraction and connective tissue damage, some researchers have associated DOMS with the acute inflammatory response (Armstrong, 1984; Armstrong et al., 1983; Brooks & Fahey, 1985; Hikida et al., 1983; Kuipers, Drukker, Frederiks, P.Geurten & Kranenburg, 1983). A number of studies involving both animals and humans have associated an acute inflammatory response with muscle fiber and connective tissue damage. Armstrong et al. (1983) examined muscles following downhill walking (eccentric contractions) in the rat. The size of the necrotic lesions in muscle fibers appeared to peak at 48 hours, which is similar to the peak soreness for DOMS. In addition, the investigators found increases in

mononuclear cells in the interstitium of the muscles and in some of the muscle fibers by 24 hours after exercise, and remained at this level 48 hours after exercise. However, neutrophils were rarely found in muscle tissues at any time. This finding led the investigators to conclude that the inflammatory response observed in this situation was not respresentative of inflammation in the classical sense.

Findings similar to those reported by Armstrong et al. (1983) were reported by Faulkner, Jones & Round (1989) in mice muscle fibers following forced lengthening. The muscle fibers demonstrated infiltration of muscle fibers by mononuclear cells. On the other hand, Kuipers et al. (1983) found neutrophil infiltration in the soleus muscles from rats which ran for up to two hours uphill, which involved lengthening of the soleus muscle.

Studies involving humans have also suggested a link between inflammation and muscle damage associated with DOMS. Smith et al. (1989) reported significant increases in neutrophils after eccentric exercise (downhill running). Increases in neutrophils were also observed after concentric exercise (uphill running). However, neutrophil levels after eccentric exercise were significantly higher than those observed after concentric exercise. Cannon et al. (1990) demonstrated similar findings, with circulating levels of neutrophils significantly higher than resting values thirty-six hours after eccentric exercise (downhill running).

The appearance of macrophages in areas where necrotic lesions have been observed after eccentric exercise has been documented in human studies 24 to 48 hours after exercise (Round et al., 1987), which reflects a time course similar to that of DOMS. However, other human studies have indicated that although mononuclear cell infiltration does occur, this infiltration was not observed until after DOMS had been considerably reduced or disappeared (Jones et al., 1986; Manfredi et al., 1991; O'Reilly et al., 1987).

One of the cytokines involved in the acute phase reaction which has been associated with muscle tissue damage from eccentric muscle contraction is interleukin-1 (IL-1). IL-1 can be released from blood monocytes (Dinarello et al., 1987) and macrophages at the site of tissue injury (Dinarello, 1988). IL-1 is also associated with increased sensitivity to pain (Ferreira, Lorenzette, Bristow & Poole, 19). Cannon et al. (1989b) found increased levels of IL-1β in human muscle tissue up to 5 days after eccentric exercise. Cannon et al. (1991) conducted another study to determine the influence of damaging exercise on cytokine production and muscle tissue breakdown and reported significant increases in endotoxin-induced secretion of IL-1β in cells obtained from subjects exercising eccentrically 24 hours after exercise. Evans et al. (1986) found increased plasma levels of IL-1 three hours after eccentric exercise. It appears from these studies that IL-1 levels increase following eccentric activity.

Connective tissue damage has also been associated with the acute inflammatory response (Castor, 1981; Postlethwaite & Kang, 1976), as well as DOMS (Armstrong, 1984; Armstrong et al., 1983; Fridén, 1984; Stauber, 1989). Armstrong et al. (1983) noted active fibroblasts were present in the interstitium of the soleus of rats following eccentric exercise. Since these cells are involved in synthesis and release of substances associated with connective tissue it was proposed that the exercise may have stimulated these cells for repair processes.

Stauber et al. (1990) suggested that disruption of connective tissue initiates the inflammatory response, since mast cell granules were found 48 hours after eccentric exercise. Furthermore, Stauber et al. hypothesized that DOMS was caused from an inflammatory response to extracelluar matrix disruption. Further study is necessary to determine the association between connective tissue disruption, the acute inflammatory response, and muscle soreness.

Research also exists which concludes that muscle and connective tissue damage does not result in the acute inflammatory response, thereby, rejecting the hypothesis that acute inflammation underlies DOMS.

As previously described, work by Jones et al. (1986) indicated that although mononuclear cell infiltration was observed in damaged human muscle tissue, the time course of this infiltration was much slower than the time course of DOMS. Fridén et al. (1983) and Fridén et al. (1981) found no mononuclear cell infiltration two to three

days after eccentric muscle contraction in humans despite DOMS occuring during this time.

Schwane et al. (1983) examined the effect of eccentric exercise (downhill running) on peripheral white blood cell (WBC) count, an indicator of the activation of the acute inflammatory response, on seven male subjects. No significant increases in peripheral WBC count were observed after the exercise. Similar results were obtained by Bobbert et al. (1986) with humans utilizing eccentric exercise, and Janssen, Kuipers, Verstappen & Costill (1983), who eccentrically exercised rats. It should be noted that WBC is a very indirect measure for inflammation.

Based on the research presented dealing with DOMS and acute inflammation the relationship between these variables appears equivocal. However, the discrepancies in the literature may be attributed to several factors. The size of the tissue sample taken from muscle in morphological studies is extremely small compared to the overall size of the muscle. In addition, muscle biopsies are taken from the belly of the muscle. Therefore, it is possible that the muscle biopsy missed the site of muscle damage, due to its' small size (Manfredi et al., 1991; O'Reilly et al., 1987). Additionally, there is the possibiltiy that the site of the injury is in another area besides the belly of the muscle, such as the MTF (Tidball, 1991). Hence, a muscle biopsy might miss the necrotic lesion sites. Moreover, Armstrong, (1984) has indicated that the muscle biopsy could easily miss lesions sites within the muscle.

The discrepancies between studies involving WBCs and plasma neutrophil counts may be a result of different intensities and duration of exercise utilized.

As previously described, similarities between DOMS and various aspects of the acute inflammatory response have resulted in studies which examined the relationship between tissue damage, swelling, and tissue infiltration by cellular components. Another important aspect of both DOMS and the inflammatory response is pain (Armstrong, 1984; Ebbeling & Clarkson, 1989; Fridén, 1984; Ryan & Majno, 1977). The generation of muscle pain results from the activation of myelinated type III and unmyelinated type IV afferent fibers (Berberich, Hoheisel & Mense, 1988; Franz & Mense, 1975; Goodman, 1983; Iggo, 1961; Kumazawa & Mizumura, 1978; Mense, 1977; Paintal, 1960). These pain afferents are activated by noxious stimuli (Kniffki, Schomburg & Steffens, 1981; Martin et al., 1987; Mense, 1977; Moncada, Ferreira & Vane, 1978), mechanical (Martin et al., 1987; Mense & Meyer, 1985), as well as chemical stimuli (Boivie & Perl, 1975; Martin et al., 1987). These pain afferents have polymodal nerve endings located in the sheaths surrounding muscle fibers, tendons and, througout skeletal muscle fibers (Armstrong, 1984; Mense & Meyer, 1985; Mense & Schmidt, 1977). Type III and IV nerve fibers which are classified as cutaneous receptors have been extensively studied. Group III and IV afferent fibers innervating skeletal muscle have been less well studied (Mense & Meyer, 1985). However, it appears that skeletal muscle pain is mediated by group

III and IV afferents similarily to cutaneous areas (Kniffki et al., 1981; Mense, 1982; Mense & Meyer, 1985). It has not been definitively established that these nerve fibers are responsible for the generation of DOMS (Armstrong, 1984; Byrnes & Clarkson, 1986; Smith, 1991).

Chemical substances which can activate these nerve afferents include: bradykinin, 5-hydroxytryptamine, histamine, and potassium (Fock & Mense, 1976; Mense, 1982). In addition to the substances which directly activate these pain afferents, there are substances which modulate the activity of these nerve endings. Products of arachadonic acid metabolism-particularly prostaglandins and leukotrienes and 5-hydroxytryptamine can sensitize these receptors to noxious stimuli by reducing the threshold of activation (Juan, 1978; Martin et al., 1987; Mense, 1981). Histamine, 5-hydroxytryptamine, bradykinin, and products of arachidonic acid metabolism are mediators in the inflammatory process (Sharma & Mohsin, 1990). Therefore, these substances are possible candidates for the production of DOMS via the inflammatory response. Products of arachidonic acid metabolism and bradykinin have been demonstrated to be potent mediators of inflammation and pain (Bennett, 1988; Juan, 1978; Mense, 1981; Rackham & Ford-Hutchinson, 1983; Sharma & Mohsin, 1990). Currently, the role which bradykinin might play in producing DOMS has not been investigated. Lack of appropriate procedures in measuring

bradykinin have made determination of its role unfeasable at this time.

Several studies have suggested that arachidonic acid metabolites, namely prostaglandin E, may be associated with DOMS (Bansil, 1984; Wells, 1991; Smith et al., 1993). Two products of arachidonic acid metabolism, prostaglandins and leukotrienes are mediators of a great number of immune responses. These two inflammatory mediators are important components in the generation of pain resulting from tissue trauma (Bennett, 1988; Juan, 1978; Larsen & Henson, 1983; Levine et al., 1984; Levine, Lam, Taiwo, Donatoni & Goetzl, 1986). PGE_2 and LTB_4, a prostaglandin and leukotriene respectively, are particularly important primary mediators of immune function (Ninemann, 1988). Although LTB_4 has not been associated with DOMS in the exercise literature, its role as a primary mediator of inflammation and pain in conjuction with PGE_2 suggests that LTB_4 may be involved in DOMS. The following discussion will examine the literature regarding prostaglandin E_2, leukotriene B_4, and DOMS.

Prostaglandin E_2 and DOMS

Prostaglandins are unsaturated lipids which are composed of 20 carbon atoms attached to a carboxyl group. A cyclopentane ring is attached at carbons 8-12. Prostaglandins and thromboxanes belong to a family of related lipid compounds called prostanoids. Thromboxanes are non-prostaglandin compounds which are derived from the same precursors as prostaglandins. The term prostaglandin

was first suggested by vonEuler in 1934 for the spasmogen isolated from the prostate gland of humans and sheep (vonEuler, 1934). In 1960, Bergström and Sjövall identified two separate classes of prostaglandins-PGE and PGF (Bergström & Sjövall, 1960a; Bergström & Sjövall, 1960b). Another class of prostaglandins was identified by Lee and co-workers in the kidney medulla of the rabbit (Lee, 1967). This class of prostaglandins was first referred to as medullin, but was subsequently classified as PGA_2. In addition to these classes of prostaglandins, PGB, PGC, PGD, PGH, and PGI have also been isolated. The various series of prostaglandins are distinguished from each other by alterations in the cyclopentane ring and substitutions in the aliphatic side chains. These differences result in the varying biological properties which are expressed through the different classes of prostaglandins. Within each class of prostaglandins differences in the number of double bonds in the aliphatic side chains are indicated by a subscript number. Of the different numbers of aliphatic side chains, the PG_2's are the most frequently occuring species.

The most common synthesis of prostaglandins involves formation from arachidonic acid in response to a stimuli. When arachidonic acid is released from membranes via phospholipase A_2, the enzyme cyclooxygenase acts to form the cyclic endoperoxide PGG_2. This reaction has been shown to be inhibited by aspirin, indomethacin, and other non-steroidal anti-inflammatory drugs (Lee,

1967). PGG_2 is then converted to PGH_2. PGH_2 can then be converted to PGE_2, PGD_2, and $PGF_{2\alpha}$.

Once synthesized, prostaglandins are released locally and serve as mediators of a wide variety of biological actions. Although prostaglandins act locally, they can be released into the venous circulation, where they are metabolized in the lungs. Prostaglandins are rapidly degraded within the lungs (Oates et al., 1980). PGE and PGF can be metabolized in a single passage through the lungs.

Prostaglandins have been implicated in numerous processes such as water excretion, renal blood flow and sodium excretion, reproduction, platelet function, digestion, hormone secretion, and carbohydrate and fat metabolism. The relationship between prostaglandins and DOMS is based on the role that prostaglandins play in the immune response and acute inflammation. Prostanoids are found at the site of tissue inflammation. There are several sources of these prostanoids associated with inflammation. The skin, smooth muscle, and blood vessels associated with the site of inflammation have the ability to synthesize prostanoids. As the inflammatory response progresses, prostaglandin synthesis and release can occur from leukocytes, monocytes, and macrophages (Ferraris et al., 1974; Goldyne & Stobo, 1979; Kurland & Bockman, 1978; Morley et al., 1979; Zurier & Sayadoff, 1975). Macrophages are a major source of prostaglandin secretion and release (Ferraris et al., 1974; Goldyne & Stobo, 1979; Kurland & Bockman, 1978; Morley et al., 1979), and are also affected by prostaglandins

(Ninemann, 1988). Monocytes were shown to be the primary source of prostaglandins in blood, particularly PGE (Bankhurst, Hastain, Goodwin & Peake, 1981). Macrophages which produce prostaglandin E function to suppress the immune response by induction of suppressor T cells, interaction with lymphocytes (demonstrated in a culture medium), and mediation of T-cell supressor factors (Humes et al., 1977). Prostaglandin E production inhibits both lymphocyte activity and subsequent secretion of PGE (Bonta & Parnham, 1982). Furthermore, macrophage production of PGE_2 appears to be regulated by T lymphocytes (Goodwin, Kaszubowski & Williams, 1979; Goodwin, Wiik, Lewis & Williams, 1979).

The breakdown of connective tissue matricies associated with tissue injury and inflammation may be mediated by the production of PGE_2. Dayer, Trentham & Krane (1982) reported that mononuclear cells from both normal subjects and subjects with rhuematoid arthritis responded to the presence of collagen with release of PGE_2. Furthermore, the release of substances such as collagen have been suggested as a possible mediator of the immunological response associated with rheumatiod arthiritis (Dayer, Robinson & Krane, 1977; Dayer, Russell & Krane, 1977; Deuppens, Rodriguez & Goodwin, 1981; Goodwin, Ceuppens & Rodriguez, 1983; Ninemann, 1988). Since collagen release has been associated with connective tissue damage and the generation of DOMS from exercise (Abraham, 1977; Armstrong, 1984; Stauber, 1989; Stauber et al., 1990; Stauber,

Fritz, Vogelbach & Dahlmann, 1988), a relationship between mononuclear cell production of PGE_2 and DOMS is plausible.

Prostaglandin E production occurs early on in the inflammatory process. This is due to the important role that neutrophils play in production and secretion of prostaglandins (Zurier & Sayadoff, 1975). Secretion and function of histamine, an immunological mediator of pain (Bennett, 1988), is potentiated by the presence of E series prostaglandins (Sondergaard & Greaves, 1971).

The link between PGE_2 and the generation of DOMS has been suggested because of the important role which PGE_2 plays in the production of hyperalgesia (Larsen & Henson, 1983). Nociocepters located in muscle are capable of exhibiting a decrease in threshold of activation and response to stimuli which are usually not capable of producing excitability (Campbell, Meyer & LaMotte, 1979; Fitzgerald, 1979; Fitzgerald & Lynn, 1977; Lynn, 1979). This decrease in threshold when compounds such as PGE_2 are present has been termed hyperalgesia (LaMotte, Thalhammer & Robinson, 1982; LaMotte, Thalhammer & Robinson, 1983) or sensitization (Bessou & Perl, 1969; Habgood, 1950). This state of hyperalgesia can result in increased activation of type III and IV pain afferents by stimuli which may not normally activate these pain afferents. In this state of hyperalgesia these pain receptors are more likely to respond to heat, cold, pressure, and chemical substances than is the case in the absence of these sensitizing agents (Campbell et al., 1979; Croze, Duclaux & Kenshalo, 1976; Fitzgerald, 1979; Fitzgerald & Lynn,

1977; Handwerker, 1975; Lynn, 1979). Eicosanoid products of arachidonic acid metabolism, particularly prostaglandin E_2, have been shown to produce this hyperalgesia (Ferreira, 1972; Ferreira et al., 1974; Juan, 1978; Juhlin & Michaelsson, 1969; Mense, 1981; Staszewska-Barczak, Ferreira & Vane, 1976) . It has been documented that prostaglandin E_2 hyperalgesia is involved in the sensation of peripheral pain (Ferreira, 1972; Ferreira, Nakamura & Castro, 1978; Handwerker, 1975; Mense, 1981; Mense, 1982). Activation of the inflammatory response results in the production of chemical substances such as bradykinin, 5-hydroxytryptamine (serotonin), and histamine, which directly activate type III and IV nocioceptors, resulting in pain (Bennett, 1988; Franz & Mense, 1975; Juan & Lembeck, 1974; Juan & Lembeck, 1976; Mense, 1977; Mense, 1981; Mense, 1982). Furthermore, production and secretion of these inflammatory mediators, particularly bradykinin, further stimulate prostaglandin E_2 production (Burch, Connor & Axelrod, 1988; Juan & Lembeck, 1976; Lembeck, Popper & Juan, 1976; Ninemann, 1988).

As previously described, muscle injury associated with DOMS often involves an inflammatory component. This inflammatory response may result in the release of prostaglandin E_2 and algesic substances, such as histamine and bradykinin (Bankhurst et al., 1981; Ferraris et al., 1974; Goldyne & Stobo, 1979; Juan & Lembeck, 1976; Kennedy et al., 1980; Kurland & Bockman, 1978; Lembeck et al., 1976; Mense, 1981; Morley et al., 1979; Smith, 1991; Zurier & Sayadoff, 1975). This has led to the hypothesis that PGE_2 may play

an important role in the sensation of DOMS (Armstrong, 1984; Smith, 1991). Prostaglandins may be released during the post-exercise period and sensitize type III and IV nocioceptors. This enhanced sensitivity could result in activation of these pain afferents by chemicals associated with the inflammatory process activated by post-exercise muscle damage, producing pain. Tissue edema has also been associated with this tissue damage (Fridén et al., 1986; Newham, 1988). This edema may result in increases in intramuscular pressure in non-compliant compartments and increases in intramuscular pressure during contraction in compliant compartments. Nocioceptors which respond to mechanical stimulation may not normally discharge under these circumstances (Martin et al., 1987; Mense, 1982; Smith, 1991). However, the presence of PGE_2 may result in these nocioceptors discharging with these conditions, thereby, producing pain. If these conditions do exist during the time period after exercise resulting in muscle damage, it is plausable that PGE_2 sensitization accompanied by increased concentrations of inflammatory mediators and mechanical distortion are responsible for DOMS.

The idea that PGE_2 may play a role in DOMS resulting from exercise appears plausible based on current research regarding exercise and prostaglandins, particularly PGE_2. Much of the literature regarding prostaglandins and exercise pertains to renal prostaglandin synthesis (Lijnen, Fagard, Staessen & Amery, 1982; Lijnen, Staessen, Fagard & Amery, 1990; Nowak & Wennmalm, 1978;

Zambraski, Dodelson, Guidotti & Harnett, 1986; Zambraski & Dunn, 1980). During exercise (Kotchen et al., 1971) plasma renin levels increase and this increase is thought to be related to renal prostaglandin release (Kotchen et al., 1971). Although all tissues are capable of synthesizing and releasing prostaglandins, the kidney has the greatest capacity for synthesis and release of prostaglandins (Dunn & Hood, 1977). The results of these studies are summarized in Table 1. Collectively, these studies suggest that acute exercise stimulates renal PGE_2 release.

Other researchers have examined the effect of aerobic exercise on PGE_2 release and have reported conflicting results. Several studies have indicated that plasma PGE_2 concentrations increase with aerobic exercise (Demers, Harrison, Halbert & Santen, 1981; Nowak & Wennmalm, 1978). Although plasma PGE_2 levels were not reported, Pedersen et al. (Pedersen, 1991) indicated that increases in PGE_2 production by circulating neutrophils occurred during and two hours after exercise. The results of these studies are summarized in Table 1. It is possible that any differences in plasma PGE_2 concentrations observed in these studies may be due to the mode, intensity, and duration of exercise used.

Table 1

Exercise-Induced Changes in PGE_2 Concentration in Various Tissues

Investi-gators	Date	Exercise Mode	Subjects	Tissue	$[PGE_2]$ at Rest	$[PGE_2]$ during Exercise	$[PGE_2]$ -Post Exercise
Demers etal.	1981	42.2 K run	male & female	plasma	1147 ±453 pg/ml	NA	5 min. after 1674±237 pg/ml
Lijnen et al.	1982	bicycle ergometer	hyper-tensive males & females	plasma	@80 pg/ml	@60 pg/ml	NA
Lijnen et al.	1991	bicycle ergometer	men	plasma	42.3 (14.1-112.8) pg/ml	45.8 (21.1-84.6) pg/ml	NA
Nowak & Wennmalm	1978	bicycle ergometer	men	femoral plasma	19 ± 5 pg/ml	40 ± 9 pg/ml*	NA

Smith et al.	1993	Eccentric bench press	male & female	plasma	326±137 pg/ml	NA	24 hrs after 2071±261 pg/ml*
Zambraski et al.	1986	treadmill running	females	urine	111 ± 23 pg/min.	45 ± 23 pg/min.*	88 ± 40 pg/min.
Zambraski et al.	1980	treadmill running	dogs	renal plasma	49-313 pg/ml	80-800 pg/ml	657 pg/ml

Note: *Indicates significant difference from pre-exercise values at the $p < 0.05$ level; NA = not available.

Although the aforementioned studies indicate that PGE_2 production increases with exercise, they do not address the question of whether PGE_2 synthesis and secretion is associated with DOMS for several reasons. First, these studies primarily attempted to examine the role which prostaglandins play in processes other than DOMS, particularly renal processes. Therefore, the presence of DOMS in these studies was not investigated, and hence, the relationship between increases in DOMS and PGE_2 production was not examined.

Secondly, increases in PGE_2 concentrations in the venous circulation are most likely due to overflow from tissues where local metabolism is unable to keep up with local synthesis and secretion of PGE_2 (Lee & Katayama, 1985). This overflow into the circulation is rapidly metabolized by a single passage through the lungs. Thus, prostaglandin concentrations in the circulation should not remain elevated once tissue production decreases and overflow into the circulation diminishes. If the increase in plasma PGE_2 results from processes occuring during exercise rather than from the delayed effects of exercise-induced muscle damage and subsequent inflammatory processes, PGE_2 concentrations in the plasma should return to normal shortly after exercise. This would suggest that the increases in plasma PGE_2 demonstrated in these studies are not necessarily related to DOMS. However, the sensitization of nocioceptors can remain even after PGE_2 levels have returned to normal (Ferreira et al., 1978,Fitzgerald & Lynn 1977 ; Martin et al., 1987). This heightened sensitization has only been shown to last for

up to several hours (Ferreira et al., 1978; Fitzgerald & Lynn, 1977; Martin et al., 1987). Since DOMS is usually not experienced until 24 after exercise (Armstrong, 1984; Ebbeling & Clarkson, 1989), this release of PGE_2 during exercise is probably not related to DOMS.

In addition to studies examining changes in PGE_2 concentrations resulting from primarily aerobic activity, research exists which examined the relationship between PGE_2, DOMS and muscular activity which results in muscle damage and repair. This research is represented by several areas of study. The three areas which will be discussed in this review include: 1) the relationship between PGE_2 synthesis and muscle growth and repair, 2) the relationship between DOMS and PGE_2 after muscular activity, and 3) the effects of non-steroidal anti-inflammatory drugs (NSAIDS) which inhibit synthesis of prostaglandins on DOMS.

It has been established that prostaglandins are regulators of protein turnover in skeletal muscle (Baracos, Greenberg & Goldberg, 1986; Rodemann & Goldberg, 1982; Turinsky, 1986) In particular, it has been demonstrated that PGE_2 alters protein degradation (Turinsky, 1986). Research indicates that mechanical forces which are applied to skeletal muscle affect changes in protein synthesis and degradation via increased release of arachidonic acid and increased prostaglandin synthesis (Smith, Palmer & Reeds, 1983). This has been demonstrated both in vitro (Smith et al., 1983) and in vivo (McMillan, Reeds, Lobley & Palmer, 1987; Templeton, Padalino & Moss, 1986). Vandenburgh, Hatfaludy, Sohar & Shansky (1990)

investigated the relationship between protein turnover resulting from intermittent mechanical stimulation of avian skeletal muscle cells in vitro for 48 hours. They found increases in PGE_2 and $PGF_{2\alpha}$ efflux from these muscle cells. Efflux rates of PGE_2 and $PGF_{2\alpha}$ increased dramatically during the first five hours of stimulation. However, PGE_2 efflux rates returned to control levels by 24 hours after mechanical stimulation, while PGF_{2a} efflux rates continued to be elevated for at least 48 hours. Since mechanical stress is related to generation of DOMS, it is possible that this stretch-induced increase in PGE_2 efflux from skeletal muscle plays a role in muscle soreness. However, it is not known if this stretched-induced increase in skeletal muscle PGE_2 efflux is associated with increased production of PGE_2 resulting from tissue injury (Vandenburgh et al., 1990).

Although the research involving stretch-induced increases in PGE_2 efflux only hint at a relationship between PGE_2 and DOMS, studies exist which have investigated the relationship between DOMS and PGE_2. These studies have examined the time course relationship between prostaglandins and DOMS and have yielded conflicting results (Bansil, 1984; Smith et al., 1993; Wells, 1991). The results of these studies are summarized in Table 1 and Table 2.

In order to investigate the relationship between prostaglandins E, $F_{2\alpha}$ and DOMS, Bansil examined the time course of changes in plasma PGE_1, $PGF_{2\alpha}$, and DOMS in 22 young, male subjects after the performance of three sets of 10 repetitions of the barbell

squat at an intensity of 67.5% of the subjects' one repetition maximum (1 RM). Blood samples were taken immediately before, after, and every 12 hours after the squats for a period of 72 hours. Bansil found significant increases in PGE_1 immediately after exercise. PGE_1 levels were found to peak 36 hours after exercise. $PGF_{2\alpha}$ plasma levels were reported to follow a time course similar to that of PGE_1. DOMS was present 24 hours after exercise and peaked at 48 hours after exercise. Based on this data Bansil concluded that the onset of muscle soreness was related to increases in plasma PGE_1. Bansil also suggested that the delay in the onset of muscle soreness was due to the inhibitory effects of $PGF_{2\alpha}$ on PGE_1. In a continuation of this work, Bansil examined the effects of aspirin, an inhibitor of prostaglandin production, on PGE_1, $PGF_{2\alpha}$, and range of motion (ROM). The results of this experiment revealed that aspirin ingestion resulted in no changes in plasma prostaglandin levels over time. ROM was found to be decreased in both the aspirin group and the group not using aspirin. However, the magnitude of the loss in ROM was lower in the group ingesting aspirin than the ROM decrements observed in the group not ingesting aspirin. Based on these results, Bansil concluded that the degree of muscle soreness experienced by the aspirin group was less than that of the placebo group, further suggesting a relationship between prostaglandins and DOMS. However, since actual muscle soreness was not evaluated in the study involving aspirin, this conclusion may not be valid.

There is another problem associated with the study by Bansil (1984). In this study plasma PGE_1 values were measured, rather than PGE_2. Although PGE_1 is associated with the production of pain, the ability of PGE_2 to sensitize nocioceptors, resulting in hyperalgesia is better documented in the literature (Ferreira et al., 1978; Fitzgerald & Lynn, 1977; Juan, 1978; Juan & Lembeck, 1974; Martin et al., 1987; Mense, 1981). Additionally, PGE_2 is the prostaglandin in the PGE series which is usually associated with the inflammatory response (Lee & Katayama, 1985; Ninemann, 1988). Therefore, conclusions regarding the relationship of DOMS and prostaglandins based on the work of Bansil are incomplete until the relationship between plasma PGE_2 and DOMS has been examined.

Smith and co-workers (Smith et al., 1993) examined the time course relationship between DOMS and plasma PGE_2 after the eccentric phase of the chest press on the Universal® chest press. Plasma PGE_2 values were significantly elevated above resting values from 24 to 48 hours after exercise, concurrent with peak levels of DOMS. Both plasma PGE_2 and DOMS returned to baseline values by 72 hours. Based on the work of Smith et al., it appears that there is an association between the manifestation of DOMS and plasma PGE_2.

In an another study examiining the relationship between PGE_2 and DOMS, Wells (1991) sought to determine if indomethacin, an inhibitor of prostaglandin synthesis, had an effect on DOMS and increases in plasma PGE_2, interleukin-1β, and creatine kinase. Twenty-one untrained males were randomly assigned to one of two

groups. One group received a placebo and the other group received 75 mg of Indocin (indomethacin). Each group performed four sets of 12 eccentric repetitions of the Cybex® chest press at 100% of their concentric 1RM. Plasma PGE_2 was assessed pre-exercise, six, 12, 24, 48, 72, 96, and 120 hours post-exercise. Muscle soreness was evaluated at the same times except for the six-hour time period. The results revealed no significant treatment effects for the Indocin on DOMS or plasma PGE_2. Both groups exhibited significant increases in plasma PGE_2 and DOMS. Plasma PGE_2 levels were not significantly different from pre-exercise levels until 96 hours after exercise, when PGE_2 values were significantly lower than pre-exercise values. DOMS was significantly elevated 24 hours after exercise, and peaked at 48 hours post-exercise. The results of this study appear to suggest that PGE_2 is not related to DOMS. However, the results of this study must be viewed with some caution, since Indocin, an inhibitor of prostaglandin synthesis, was not effective in decreasing plasma PGE_2 levels.

Much of the research investigating the relationship between PGE_2 and DOMS have involved non-steroidal anti-inflammatory drugs (NSAIDS) (Almekinders & Gilbert, 1986; Donnelly, Maughan & Whiting, 1990; Donnelly, McCormick, Maughan, Whiting & Clarkson, 1988; Francis & Hoobler, 1987; Hasson et al., 1993; Kuipers, Keizer, Verstappen & Costill, 1985). The results of these studies are summarized in Table 2. NSAIDS inhibit the action of cyclooxygenase, an enzyme which is responsible for converting arachidonic acid to

prostaglandins and thromboxanes. These studies hypothesized that PGE_2 was involved in the inflammatory response resulting from exercise-induced muscle damage and the generation of DOMS. Hence, if PGE_2 production was inhibited, then muscle damage and DOMS should be reduced. The results of these studies have yielded conflicting conclusions. Work by Salminen & Kihlström (1987) has indicated that the administration of the prostaglandin inhibitor indomethacin before and during exercise was effective in reducing levels of enzymatic indicators of necrotic lesions in mouse skeletal mouse. However, indomethacin treatment after exercise had only a slight effect on these markers. A study by Almekinders & Gilbert (1986) examining the effect of NSAIDS on muscle healing and the inflammatory process after muscle strain in rats yielded similar conclusions. Rats which had been given the NSAIDS demonstrated a delay in the inflammatory response and muscle regeneration, as compared with controls. Based on these studies it appears that prostaglandins have an influence on the changes in skeletal muscle involving the inflammatory process which are associated with the generation of DOMS.

The ability of NSAIDS to decrease DOMS has been examined by several investigators. NSAIDS are thought to block production of prostaglandins by inhibiting the metabolism of arachidonic acid by the enzyme cyclooxygenase. This reduction of prostaglandins could lead to decreased sensitization of pain afferents to noxious stimuli, thereby, reducing the sensation of DOMS. However, the research

regarding the efficacy of NSAIDS to reduce DOMS is not conclusive. Hasson et al. (1993), Francis & Hoobler (1987) and Macintyre & McKenzie (1985) reported decreases in DOMS with the use of NSAIDS. On the other hand, other investigators have reported that NSAIDS were not effective in reducing DOMS (Donnelly et al., 1990; Donnelly et al., 1988; Kuipers et al., 1985). The results of these studies are summarized in Table 2.

There are several explanations for the conflicting results obtained from these studies. Of particular importance is the fact that prostaglandin levels were not assesed in these studies. Therefore, it is not known if the NSAIDS were actually effective in decreasing prostaglandin production. The previously discussed study by Wells (1991) illustrates this point. Wells found that indomethacin was not effective in decreasing DOMS. However, indomethacin was not efficacious in decreasing prostaglandin levels. The possibility exists that if the indomethacin was effective in decreasing prostaglandins, then DOMS may have been reduced.

Table 2

Effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) on DOMS and PGE

Investigator	Exercise Mode	[PGE] before exercise w/out NSAIDS	[PGE] post-exercise w/out NSAIDS	Effect of NSAIDS on DOMS	[PGE] w/ NSAIDS
Bansil (1984)	squat	377.25[a]	604.37*[a] 24 hours post-exercise	NA	suppresed PGE_1
Donnelly et al. (1990)	downhill running	NA	NA	no effect on DOMS	NA
Donnelly et al. (1988)	downhill running	NA	NA	no effect on DOMS	NA
Francis & Hobbler (1984)	eccentric elbow flexion	NA	NA	reduction in DOMS	NA

Hasson et al. (1993)	bench stepping	NA	NA	reduction in DOMS	NA
Kuipers et al. (1985)	eccentric bicycle ergometer	NA	NA	no change in DOMS	NA
Macintyre & McKenzie (1995)	eccentric leg dynamometer	NA	NA	Reduction in DOMS	NA
Wells (1991)	eccentric bench press	1073.62[b]	461.37 ± 319.96*[b]	no change in DOMS	no effect

Note: PGE levels are in pg/ml; *indicates significant difference from pre-exercise values. [a]Plasma PGE_1 value. [b]Plasma PGE_2 value.

There may be other reasons for the inability of NSAIDS to reduce DOMS or pain. The possibility exists that a prostaglandin inhibitor may shift metabolism of arachidonic acid to the lipoxygenase pathway, resulting in the increased production of leukotrienes, which also cause sensitization of group III and IV pain afferents (Bennett, 1988). Hence, in some cases the sensation of DOMS may be modulated by leukotrienes when the production of prostaglandins is blocked by NSAIDS.

Finally, the time at which the NSAIDS are ingested may have an effect on reduction of DOMS. Since the sensitization of pain afferents by prostaglandins may last for several hours (Ferreira et al., 1978; Fitzgerald & Lynn, 1977; Martin et al., 1987), blocking prostaglandin synthesis some time after the hyperalgesia has been established would be ineffective in reducing DOMS. This hypothesis was proposed by Hasson et al. (1993) to explain the ability of ibuprofen to decrease muscle soreness reported in their investigation. Hasson et al. contended that most studies examining the effectiveness of NSAIDS to reduce muscle soreness did not utilize NSAIDS early enough to prevent the hyperalgesic response produced by prostaglandins. They speculated that the NSAIDS must be given prior to the exercise in order to inhibit prostaglandin production which would result in prolonged hyperalgesia. However, Macintyre & McKenzie (1985) demonstrated a decrease in sensation of DOMS resulting from eccentric leg exercise on an isokinetic dynamometer from 0 to 168 hours post-exercise when Anaprox DS®,

a NSAID, was ingested twice daily begining on the first day post-exercise and stopping at the end of the seventh day post-exercise. Since there was no measure of inflammatory mediators, it can only be hypothesized that the NSAID reduced inflammation due to muscle damage, subsequently reducing DOMS.

Based on the aforementioned studies examining the effectiveness of NSAIDS on reducing exercise-induced DOMS, it has not been established if prostaglandin inhibition by NSAIDS is effective in reducing DOMS. Furthermore, it appears that other factors involved in the inflammatory process as well as the timing of the dosages of NSAIDS may play a crucial role in the generation of DOMS.

Leukotriene B_4 and DOMS

Leukotrienes are a group of chemical mediators derived from the conversion of arachidonic acid by the calcium-dependent enzyme 5-lipoxygenase. The term leukotriene was used by Borgeat & Samuelsson (1979) to describe a family of compounds which contain three conjugated double bonds and a peptide chain containing one, two, or three amino acid residues with a sulphur linkage at carbon five. There are several different naturally-occurring leukotrienes which are alphabetically designated in the order which they were discovered. Currently, leukotrienes of the A, B, C, D, and E series have been identified in biological tissues. Leukotrienes are normally abbreviated LTA_4, LTB_4, LTC_4, etc., with the subscript indicating the presence of four double bonds in the molecule. It was established by

Radmark, Malmsten, Samuelsson, Clark & Corey (1980) that hydroperoxyeicosatetraenoic acid (5-HPETE) is formed from arachidonic acid and then converted to LTA_4. LTA_4 can then be metabolized to either LTB_4 or LTC_4.

Leukotrienes C_4, D_4, and E_4 are associated with the slow-reacting substance of anaphylaxis, and are potent bronchoconstrictive mediators (Kikawa et al., 1992). Leukotriene B_4 has been associated with leukocyte accumulation and function (Bray, Cunningham, Ford-Hutchinson & Smith, 1981a; Ford-Hutchinson, 1985; Ford-Hutchinson, Bray, Doig, Shipley & Smith, 1980), changes in vascular permeability (Bray, Cunningham, Ford-Hutchinson & Smith, 1981b; Wedmore & Williams, 1981), and hyperalgesia (Levine et al., 1985; Levine et al., 1986; Madison et al., 1992; Martin, 1990; Martin et al., 1988; Martin et al., 1987; Rackham & Ford-Hutchinson, 1983; Soter et al., 1983).

Numerous cellular and immune functions are affected by LTB_4, making LTB_4 a potent mediator of physiological responses (Ford-Hutchinson & Letts, 1986; Ninemann, 1988). Since both LTB_4 and PGE_2 produce hyperalgesia in primary afferent nocioceptors, it is possible that both PGE_2 and LTB_4 play a role in the generation of DOMS. Although the relationship between PGE_2 and DOMS has received preliminary investigation, the role that LTB_4 may have with DOMS has not been studied. However, existing research regarding leukotrienes, particularly LTB_4, suggest a relationship between LTB_4 and DOMS. Since research does not exist dealing exculsively with

LTB_4 and DOMS, the relationship between DOMS and LTB_4 will be discussed based on the following topics: leukotrienes and pain, studies involving DOMS and NSAIDS, leukotrienes and the acute inflammatory response, and studies examining cell membrane permeability and creatine kinase (CK) release.

As previously described, products of arachidonic acid metabolism are potent inducers of hyperalgesia in group III and IV receptors. *Unlike PGE_2, the mechanism by which hyperalgesia is* produced by LTB_4 is dependent on the presence of polymorphonuclear leukocytes (PMNLs) (Levine et al., 1984; Wedmore & Williams, 1981). PMNLs exposed to LTB_4 secrete15-lipoxygenase products (Ford-Hutchinson & Letts, 1986). These substances have been shown to elicit hyperalgesia in rats (Levine et al., 1985). LTB_4 has been found to induce hyperalgesia in animals (Levine et al., 1985; Levine et al., 1986,Levine, 1985 #841; Rackham & Ford-Hutchinson, 1983).

Furthermore, Martin et al. (1987) concluded that there was a correlation between the percentage of afferent fibers sensitized by PGE_2 and LTB_4 in cutaneous high-threshold C- and A-Delta mechanonociceptors in the skin of rat hindlimbs. PGE_2 and LTB_4 sensitized 73% of C-polymodal, 60% of C-mechano-heat, 42% of C-mechano-cold nonciceptors and 70% of A-delta high-threshold mechanonociceptors. The authors found that in a majority of fibers tested that application of one agent, such as PGE_2, which produced a decrease in threshold was followed by a further threshold decrease upon application of the second agent, such as LTB_4. Furthermore, a

fiber which was unresponsive to one type of eicosanoid was also unresponsive to a second eicosanoid agent. This led Martin and associates to conclude that a parallel response was found in afferent nocicieptors upon exposure to either PGE_2 or LTB_4. This decrease in the threshold of activiation of mechanoreceptors has also been demonstrated in other studies (Martin, 1990; Martin et al., 1988). Hyperalgesia produced by LTB_4 has also been reported in humans in cutaneous afferents in the skin (Bisgaard & Kristensen, 1985; Soter et al., 1983). LTB_4 was shown to sensitize A-delta fibers in dental pulp (Madison et al., 1992). This sensitization was found to persist for at least 20 minutes after removal of LTB_4.

The pain associated with chronic inflammation has been linked with LTB_4. Quinn and Bazan (1990) reported that subjects experiencing inflamed, dysfunctional temporal mandibular joint syndrome exhibited increased levels of PGE_2 (160-1,520 pg/mL) and LTB_4 (95 to 1,600 pg/mL) also demonstrated high scores on the acute synovitis index. This led the authors to conclude that there is a correlation between the presence of metabolites of arachidonic acic metabolism and temporalmandibular joint synovitis. Although no control samples were taken from normal temporamandibular joints, the investigators assumed that PGE_2 and LTB_4 would not be present in normal joints.

Based on these studies it has been theorized that LTB_4 is effective in sensitizing afferent nociceptors. Furthermore, a decrease in the mechanical threshold for excitation for nociceptors

can persist for several hours following exposure to LTB_4 (Martin et al., 1987). If LTB_4 plays an important role in inflammatory pain, such as the pain associated with DOMS, the presence of LTB_4 after exercise resulting in muscle damage and activation of the inflammatory response needs to be documented. Although studies do not exist which directly address the relationship between LTB_4 and the process of muscle damage and repair, it has been demonstrated that LTB_4 plays a fundamental role in many aspects of the acute inflammatory response (Ninemann, 1988).

The monocyte and macrophage are inflammatory mediators which are important components of the inflammatory response accompanying tissue damage resulting from exercise (Armstrong, 1984; Armstrong et al., 1983; Smith, 1991). Therefore, it has been suggested that these inflammatory mediators may play a role in the generation of DOMS, since they are a major source of PGE_2 (Ferraris et al., 1974; Humes et al., 1977; Kurland & Bockman, 1978; Morley et al., 1979). Macrophages are also a source of 5-lipoxygenase products such as LTB_4 (Bonta & Parnham, 1982; Williams et al., 1984). It has been suggested that the release of both leukotrienes and prostaglandins by macrophages represents a feed-back system which controls macrophage-lymphocyte interaction (Bonta & Parnham, 1982). PGE_2 production leads to inhibition of lymphocyte responses and PGE_2 production by macrophages (Bonta & Parnham, 1982). On the other hand, leukotrienes appear to stimulate

leukocyte activity (Bonta & Parnham, 1982) and promote release of PGE_2 by macrophages (Feuerstein, Foegh & Ramwell, 1981).

Neutrophils are also involved in the acute inflammatory process and may migrate to areas of injury following tissue damage resulting from exercise. Neutrophils are capable of synthesis of LTB_4 (Borgeat & Samuelsson, 1979). In addition, LTB_4 seems to promote infiltration of neutrophils during the inflammatory process (Smith, Ford-Hutchinson & Bray, 1980; Zurier & Sayadoff, 1975). Although neutrophils are capable of synthesizing prostaglandins, the metabolism of arachidonic acid promoted by neutrophils yields primarily LTB_4 (Borgeat & Samuelsson, 1979; Ninemann, 1988). LTB_4 promotes leukocyte accumulation (Smith et al., 1980; Soter et al., 1983), adherence to the vascular endothelium (Bray et al., 1981a), formation of superoxide anions (Mogbel, Sass-Kuhn, Goetzl & Kay, 1983), and enhanced release of lysosomal enzymes (Nagy, Lee, Goetzyl, Pickett & Kay, 1982). Because of these potent chemotactic and chemokinetic activities, LTB_4 may be involved in the process of muscle and connective tissue injury and repair which occurs after exercise-induced tissue damage, suggesting that LTB_4 may be involved in the generation of DOMS.

Other inflammatory mediators besides neutrophils, monocytes, and macrophages are capable of synthesizing and secreting LTB_4. Mast cells are inflammatory mediators which are found in many tissues including the lungs, intensines, skin, and connective tissue (Peters et al., 1987). Increases in the number of mast cells is often

associated with painful inflammatory disorders of the joints, such as rheumatoid arthritis (Godfrey, Hardi, Engber & Granziana, 1984). Mast cells are capable of synthesizing and secreting both histamine and products of arachidonic acid metabolism, primarily LTB_4 and LTC_4 (Peters et al., 1987). Elevated levels of LTB_4 have been reported in the synovial fluid of patients with rheumatoid arthritis (Klickstein, Shapleigh & Goetzl, 1980), suggesting a possible relationship between mast cell production of LTB_4 and generation of inflammation related to joint pain.

In addition to the suggested relationship between painful inflammatory disorders of the joints and mast cells which exists in the literature, researchers have reported a possible relationship between mast cell activity and DOMS. Stauber et al. (1990) examined the effects of eccentric activity on the extracellular matrix and connective tissue elements associated with a contracting muscle. They reported degranulation of mast cells in the extracelluar matrix and connective tisssue 24 hours after exercise. Furthermore, the authors hypothesized that products secreted by mast cells, such as histamine, may play a role in DOMS which was experienced by the subjects. This study suggests that DOMS may be influenced by the secretion of chemical substances secreted by mast cells. The possibility exists that the degranulation of mast cells which Stauber et al. observed may have resulted in production of mast cells which sensitized pain afferents

to mechanical and chemical stimuli, resulting in the sensation of DOMS.

Another body of research involving NSAIDS and DOMS indirectly implicates leukotrienes and DOMS. As previously described, conflicting results were obtained regarding the efficacy of NSAIDS in reducing DOMS. It is possible that the NSAIDS may have been effective in blocking sensitization of nociceptors by prostaglandins. This inhibition of prostaglandin synthesis occurs by NSAIDS blocking the cyclooxygenation of arachidonic acid. However, the NSAIDS used in these studies (Almekinders & Gilbert, 1986; Donnelly et al., 1990; Donnelly et al., 1988; Francis & Hoobler, 1987; Hasson et al., 1993; Kuipers et al., 1985) do not block the lipoxygenase pathway of arachidonic acid metabolism. This could cause a diversion of arachidonic acid metabolism products into the lipoxygenase pathway, resulting in increased levels of algesic compounds such as LTB_4. Increased levels of LTB_4 could promote sensitization of nociceptors which is equally effective as PGE_2 (Martin et al., 1987), resulting in no diminuation of DOMS by NSAIDS.

Research examining the role lipoxygenase enzymes have in promoting the release of intracellular enzymes from damaged skeletal muscle also suggests the presence of compounds such as LTB_4. Jackson, Wagenmakers & Edwards (1987) examined which products of arachidonic acid metabolism were important in the release of intracelluar enzymes from damaged skeletal muscle in vitro using inhibitors of cyclo-oxygenase and lipoxygenase enzymes.

They found that the cyclo-oxygenase inhibitor suppressed prostaglandin efflux, but not creatine kinase release from the damaged muscle. However, use of a lipoxygenase inhibitor was found to significantly reduce creatine kinase efflux from the damaged muscle.

Since exercise-induced muscle damage can also result in efflux of creatine kinase into the blood and DOMS, the presence of products of lipoxygenase products such as LTB_4 after exercise which promotes muscle damage and DOMS is possible. The inability of cyclo-oxygenase inhibitors to prevent CK release from muscle has been documented in studies involving exercise resulting in DOMS (Hasson et al., 1993). Furthermore, Donnelly et al. (1990) reported increases in plasma CK in subjects using ibuprofen, a cyclo-oxygenase inhibitor following downhill running.

The role of the lipoxygenase pathway in muscle damage has been examined by Barsacchi, Manni, Pelosi, Camici & Ursini (1986). Barsacchi and collegues compared the formation of peroxide radicals by chemiluminescence from the surface of an isolated, perfused rat heart following the addition of hydroperoxides and glutathione-depleting agents with and without the presence of aspirin. It was found that aspirin produced a higher steady state concentration of hydroperoxy radicals than without the presence of aspirin. The authors concluded that this increase in hydroperoxy radicals was do to a shift in arachidonic acid metabolim to the lipoxygenase pathway. This shift in metabolism indicates that leukotrienes may

contribute to damage resulting from oxidative stress (Lefer, 1985). This study supports the hypothesis that oxidative stress may contribute to muscle damage and the accompanying muscle soreness (Armstrong et al., 1991; Maughan et al., 1989; Sjödin, Westing & Apple, 1990). Based on the aforementioned studies, it appears that the products of arachidonic acid metabolim may play a role in exercise-induced muscle damage and DOMS.

Summary

Unaccustomed exercise and exercise involving eccentric contractions have been shown to result in muscle damage, as indicated by morphological changes, elevation of intracellular enzymes in the blood, decreases in the ability to generate muscular force, and DOMS. DOMS is usually experienced 24 hours after exercise, peaking at 48 hours, and gradually diminishing in intensity several days thereafter. Currently the underlying mechanism behind the generation of DOMS resulting from this muscle damage is unknown. However, it has been theorized that the cascade of reactions involved in the acute inflammatory response is triggered by muscle injury resulting from this exercise. Although there are a wide range of chemicals associated with the inflammatory response and the generation of pain, two inflammatory mediators which appear to mediate DOMS are PGE_2 and LTB_4. These products of arachidonic acid metabolism are capable of sensitizing type III and IV pain afferents which are located in skeletal muscle and in the connective tissue elements associated with skeletal muscle. It has

been suggested that these inflammatory mediators are secreted by components of the immune system, such as macrophages and mast cells during the process of muscle breakdown and repair associated with the acute inflammatory response. Increases in secretion of PGE_2 and LTB_4 result in sensitization of type III and IV pain afferents. Therefore, these pain afferents may be stimulated by chemical and mechanical stimulation which might not normally promote the sensation of pain. Furthermore, some edema may be associated with exercise-induced muscle damage, thereby, causing small increases in intramuscular pressure. A combination of these factors may result in the production of DOMS.

The research regarding the role which PGE_2 and LTB_4 play in DOMS is currently incomplete. Three studies have examined the relationship of DOMS and prostaglandins of the E series. One study reported a similar time course relationship between plasma PGE_1 and DOMS, while another reported a decrease in plasma PGE_2 96 hours after exercise. The relationship between LTB_4 and DOMS has not yet been addressed. Therefore, this study will help to elucidate if there is a relationship between PGE_2, LTB_4 and DOMS.

CHAPTER III

METHODS AND PROCEDURES

Introduction

The purpose of this study was to examine the time course relationship of plamsa levels of PGE_2, LTB_4, and DOMS over 120-hours resulting from an acute weight lifting bout involving eccentric contractions. This chapter will describe the methods which were utilized in this study under the following headings: Selection of Subjects, Experimental Design, Chemical Analyses, Statistical Analyses.

Selection of Subjects

Fifteen healthy male volunteers, eighteen to thirty-two years of age from the University of North Carolina, Greensboro were solicited for this study. Only male subjects under the age of 35 years were used in this study to provide for a more homogeneous subject group, since gender and age differences may exist regarding exercise-induced muscle damage and DOMS (Hortobágyi & Denahan, 1989; Manfredi et al., 1991). Thus, this study reflects the response of plasma PGE_2, plasma LTB_4, and CK to exercise which generates DOMS in males under the age of 35. Subjects were recruited by word of mouth and flyers and announcements distributed throughout the University of North Carolina, Greensboro campus. Subjects solicited

were sedentary and had not engaged in resistance training for at least two months prior to the study. The subjects were asked to refrain from novel physical activity or exercise while participating in the study. Each subject was provided with a verbal and written explanation of the procedures, risks associated with the study, and right to terminate particpation in the study in accordance with the University of North Carolina, Greensboro Human Subjects Review Committee. The subjects provided a statement of informed consent prior to participating in the study (Appendix A).

Each volunteer completed a medical history questionnaire prior to participation in the study (Appendix B). Any volunteers who had any illnesses which have an inflammatory component or pain syndrome which might be exacerbated by DOMS were excluded from the study. Any individual who was being treated with medication which can alter inflammatory responses was excluded from the study. Any individual who provided postive responses to either questions #17 and #18 were excluded from the study. In addition, subjects were asked to refrain from taking medications which can alter the inflammatory response while participating in this study. Each subject was provided with an instruction sheet for subjects, which described what they should do in preparation for testing and the investigator's telephone number (Appendix C).

Experimental Design

Eleven subjects were randomly selected to perform the weight lifting bout designed to elicit DOMS and five subjects were

randomly selected to serve as controls. Other studies examining the effects of resistance exercise on muscle soreness and muscle damage have not utilized a control group (Ebbeling & Clarkson, 1989; Smith, 1993). Since resting plasma values of plasma PGE_2 and LTB_4 seem to be quite variable (Drey, 1975; Granström & Kindahl, 1990; Sinzinger, 1985), a control group was included to help discern if any changes in the variables in the treatment group were merely attributable to daily variation. However, due to the difficulty in obtaining subjects fulfilling all the criteria to participate in the study only five subjects were randomly assigned to the control group. Furthermore, decreasing the number of subjects in the treatment group to provide for an equal number of subjects in each group would result in a decreased ability to detect significant changes in the variables as a result of the weight lifting bout (D. Herr, personal communication, November 9, 1995).

Control subjects were tested for their one repetition maximum (1RM), but did not perform the weight lifting session. The controls were instructed to remain sedentary throughout the remainder of the study. The treatment subjects performed a 1RM testing session which was followed by the weight lifting bout at least two weeks later. Subjects in the treatment group were instructed to refrain from any other physical activity during the testing period. Venous blood samples and perceived muscle soreness ratings were obtained prior to, immediately after, and 24, 48, 72, 96, and 120 hours after exercise. The controls reported to the

laboratory at least two weeks after their 1RM testing session. Venous blood samples and perceived muscle soreness ratings were obtained from the controls every 24 hours for seven days using the same protocol which was used for the treatment group. Subjects in both groups were instructed to report to the laboratory in a fasted condition prior to the blood draw. All testing sessions, evaluation of muscle soreness and blood draws occurred between 7 a.m.-9 a.m.

1RM Testing

In order to determine each subject's 70% of 1RM capacities for the weight lifting session, each subject's 1RM was determined on the following exercises: bench press, triceps pushdowns, military press, biceps curls, leg press, and wide grip pulldowns. All of the exercises were performed on Universal® Gym Equipment (Irvine, CA, USA). The weight lifting sessions, blood drawing, and evaluation of muscle soreness were performed in the University of North Carolina, Greensboro, Exercise Physiology Laboratory.

The subjects were tested for their 1RM following a protocol described by Fleck & Kraemer (1988) and Pauletto (1991). Prior to attempting a maximal effort on each exercise, the subjects performed an adequate warm-up. This warm-up consisted of the subject performing ten repetitions with a resistance which could be performed with extreme ease. Following this set, the subjects performed subsequent warm-up sets of 2-5 repetitions with increases in intensity of 10-20 pounds per set. When the subject felt that the warm-up repetitions were becoming difficult, the

subject attempted a single repetition with a resistance approximately 10-20 pounds more than his previous warm-up repetition(s). Upon completition of this single attempt the subject attempted to perform a single repetition with a small increase in resistance. If the subject was unable to perform a single repetition at a selected weight he was allowed two more attempts to successfully complete the lift. If the subject was unsuccessful after his third attempt the last successful lift was considered his 1RM on that particular exercise.

Each subject was allowed an adequate rest period of approximately 3-5 minutes between maximal attempts. Strict adherence to proper performance techniques was observed during testing. Any lift which was not performed using proper techniques was not considered a valid 1RM attempt.

Weight Lifting Session

At least two weeks after determination of each subjects' 1RM, the eleven exercising subjects performed an acute weight lifting session. Each subject began by performing one set of ten repetitions at 40% of 1RM on both the bench press and leg press. Since these exercises utilize a large number of muscle groups, this provided an adequate warm-up for all of the subsequent exercises. After this set was performed each subject did a second warm-up set of 5 repetitions at 50% of 1RM.

Following the two warm-up sets subjects in the treatment group started the weight lifting session. The subjects lifted in the

same order as was used in the 1RM testing session. Each subject performed three sets with a resistance of 70% of each subject's 1RM. Each set was performed until volitional exhaustion or until the subject was unable to properly perform the exercise. Two minutes of rest was provided between each set.

Perceived Muscle Soreness

Prior to the lifting session subjects were asked to evaluate their overall muscle soreness on a scale of 0 to 10 with one being normal and ten being very, very, sore on a muscle soreness rating sheet (Appendix F). The subjects circled the number which they felt best represented their muscle soreness at that time, based on the descriptors of soreness accompanying the soreness scale. This muscle soreness rating scale is a modified version of the scale used by Clarkson (Byrnes & Clarkson, 1986; Clarkson et al., 1987; Clarkson et al., 1986). In addition, subjects were asked what muscle groups were particularly sore on a chart of the body which was positioned underneath the muscle soreness scale. Extensive evaluation of muscle soreness in different areas of the body will not be utilized in this study. Work by Wells (Wells, 1991) has indicated that that one overall rating may be used to report soreness as accurately as an average soreness rating of different areas of the body. Ratings of muscle soreness for the lifting group were obtained prior to lifting, immediately after the lifting bout, 24, 48,72, 96, and 120 hours after the lifting bout. The ratings of muscle soreness for the control group were obtained every 24 hours for six days.

Ratings of perceived muscle soreness were obtained before blood sampling for both groups.

Blood Sampling

After obtaining muscle soreness ratings from the subjects, the subjects were instructed to sit quietly for 10 minutes. After this period of time, 20 ml blood samples were taken from an antecubital forearm vein with one venapuncture. Blood samples (2) were drawn into 10 ml Vacutainer® tubes containing 0.10 microliters of 15% ethylenediaminetetraactic acid (EDTA) solution and 0.18 mg of acetylsalicylicacid (ASA) dissolved in a 80% ethanol solution. The ASA served to inhibit in vitro production of prostaglandins. The blood in the Vacutainer® tubes was centrifuged at 3000 rpm for 10 minutes at 4°C. After centrifugation 500 microliter aliquots of plasma were pipetted into polypropylene sample tubes and frozen at -80°C for four-six months until analyzed. Sinzinger (1985) has indicated that frozen plasma samples which had been used over a nine-month period demonstrated a variability of $\pm$ 7%, with no significant increase in PGE_2. The effect of four-six months of storage on the concentration of LTB_4 in plasma has not been documented, although it can be hypothesized that the effects of storage may be the same as seen with PGE_2 concentrations in plasma.

Chemical Determinations

PGE_2 Determination

PGE_2 concentration in the plasma sample was determined using the Prostaglandin E_2-Monoclonal Enzyme Immunoassay (EIA) Kit from Cayman Chemical Company (Ann Arbor, MI). Prior to analysis, the PGE_2 was extracted from the plasma samples using a modified version of the PGE_2 extraction method described by Vandenburgh et al. (Vandenburgh et al., 1990). Five hundred microliters of each plasma sample were placed in 10 ml polypropylene test tubes and acidified to a pH of 3.5-4.0 with 6N HCL. A C_{18} Sep-Pack solid phase extraction cartridge (Waters Division, Millipore, Milford, MA) was washed with 5 ml of pure ethanol and then 5 ml of ultra-pure water. The plasma sample was then passed through the cartridge, followed by 2.5 ml of ultra-pure water. This was followed by 2.5 ml of 15% ethanol and 2.5 ml of HPLC grade hexane. The PGE_2 was eluted off the cartridge with 3 ml of methyl formate into a 7 ml glass scintillation vial.

To determine recovery percentages, a known amount of PGE_2, two identical aliquots of PGE_2 standard and two identical plasma samples were used. One of the PGE_2 aliquots was added to one of the plasma samples. The sample + standard aliquot, standard-only aliquot, and sample- only aliqout were processed in the same manner as the other samples.

The collection vials were placed in a test tube rack and the methyl formate was evaporated to dryness under a stream of

nitrogen using a S/P® Brand mini-Vap® Six-Port Concentrator/Evaporator (Baxter Diagnostics, Inc., Charlotte, NC).

The EIA was performed according to the instructions accompaning the PGE_2 kit. This assay utilizes a specific amount of PGE_2-acetylcholinesterase conjugate which competes for a small amount of PGE_2 monoclonal antibody in a reaction well. Thus, the amount of PGE_2-acetylcholinesterase which binds to the PGE_2 monoclonal antibody is inversely proportional to the concentration of PGE_2 in the sample well. Each well in the kit is coated with goat anti-mouse antibody. The antibody-PGE_2 complex binds to the goat anti-mouse antibody in the wells. Any unbound reagents are removed from the wells by rinsing with a wash solution. Ellman's reagent is added to each of the wells. Ellman's reagent contains a substrate to acetylcholinesterase. The subsequent enzymatic reaction results in the appearance of a yellow color which absorbs from 405-420 nm. Thus, the intensity of the yellow color is proportional to the amount of PGE_2-acetylcholinesterase conjugate, which is inversely proportional to the concentration of PGE_2 in the sample well.

The EIA buffer solution and wash buffer solutions were prepared by adding 500 ml of ultra-pure water to the packets provided with the kit. These buffers were then stored at 4°C. The lyophilized prostaglandin E_2 standard, PGE_2 acetylcholinesterase conjugate (tracer), and PGE_2 monoclonal antibody were reconstituted according to the kit instructions and stored at 4°C. One ml of EIA buffer was added to the residue in the vials and vortexed.

The concentrations of the standards were prepared by labeling eight polypropylene test tubes #1-#8. Nine-hundred microliters of EIA buffer were aliquoted to tube #1 and 500 microliters were aliquoted to tubes #2-#8. One-hundred microliters of PGE_2 standard (10 ng/ml) was added to tube #1 and vortexed. The standard was then serially diluted by adding 500 microliters from tube #1 and adding to tube #2, vortexing. This process was repeated for tubes #3-8.

After preparation of the standards, the 96 well plate was removed from the plate packet and the wells were rinsed once with wash buffer. The plate was inverted and blotted on tissue wipes. Any wash buffer remaining in the wells was removed by pipetting. Before adding any of the reagent to the plate wells a plate format was determined. Each plate contained two blanks, two non-specific binding wells (NSB), two maximum binding wells (B_0), one total activity well, and eight standard concentrations in duplicate. The remaining wells contained samples, each assayed in duplicate. This plate format was recorded on a template sheet provided with the kit.

Upon completion of the template, one-hundred microliters of EIA buffer was added to each NSB wells. Fifty microliters of EIA buffer was added to the B_0 wells. Starting with the lowest concentration of PGE_2 standard (#8), 50 microliters were added to each of the lowest two standard wells. This process continued until all the standards were aliquoted.

Fifty microliters of sample were then added to the appropriate wells. Each sample was assayed in duplicate. Fifty microliters of PGE_2 tracer was added to each well, except for the total activity and the blank wells. Finally, fifty microliters of PGE_2 antibody was added to each well, except for the total activity, NSB, and the blank wells. The plate was then covered with plastic film and incubated for 18 hours at room temperature.

Prior to developing the plate, one vial of Ellman's Reagent was reconstituted with 20 ml of ultra-pure water in an amber bottle and stored in the dark. The plate wells were then emptied and rinsed five times with wash buffer. After the final rinse with wash buffer, the plate was inverted and gently blotted on tissue wipes. Any remaining wash buffer was removed by pipette. Two-hundred microliters of Ellman's reagent was added to each well and five microliters of the acetylcholinesterase tracer was added to the total activity well. The plate was then covered with plastic film and placed on an orbital shaker in the dark. The plate was allowed to develop for 90 minutes.

After development, the bottom of the plate was wiped with a tissue to remove smudges and dirt. The plastic film was carefully removed from the plate and the plate was read in a 340 ATTC plate reader (SLT LabInstruments®, Salzburg) at 405 nm.

A recovery ranging from 64-78% was obtained from this procedure. This recovery is not as high as those reported by Smith et al. (1993), 80-90%, Dray, Charbonnel & Maclouf (1975), >90%, or

Powell (1980), 98%. On the other hand, both Nowak & Wennmalm (1978), and Zijlstra & Vincent (1984) reported a 73% recovery of PGE_2 from plasma. Furthermore, Cayman Chemical Company reports that utilization of this type of extraction method and EIA usually results in a recovery percentage of 40-75% (J. McDonnell, personal communication, August 11, 1995).

LTB_4 Determination

Determination of the LTB_4 values in the plasma samples was performed using the Leukotriene B_4 Kit by Cayman Chemical Company (Ann Arbor, MI). This kit is an EIA in which LTB_4 competes with a specific amount of LTB_4 acetylcholinesterase conjugate (tracer) for a small amount of rabbit antiserum in a reaction well. As previously described in the PGE_2 assay, the amount of bound tracer is inversely proportion to the concentration of free LTB_4 in the well. The antiserum-LTB_4 complex binds to the mouse monoclonal antibody which coats the reaction wells. After addition of these reagents to the wells they are allowed to incubate. After incubation, the wells are washed to remove any unbound reagents and Ellman's reagent is added. As previously described, this reagent contains the substrate for acetylcholinesterase. The intensity of the color resulting from the activity of acetylcholinesterase is measured spectrophotometrically at 405-420 nm and is proportional to the amount of LTB_4 which is bound to a well. The amount of LTB_4 bound to a well is inversely proportional to the concentration of free LTB_4 in a well.

Before performance of the assay, the LTB_4 was extracted from the samples using the extraction procedure outlined by the LTB_4 EIA kit. Either 500 or 1000 microliters of each sample was pipetted into 2 ml polypropylene test tubes. Two milliliters of ethanol was added to each tube and vortexed. Eight milliliters of 0.1 M phosphate buffer (pH 4.0) was added and vortexed. A C_{18} Sep-Pack solid phase extraction cartridge (Waters Division, Millipore, Milford, MA) was washed with 5 ml of pure ethanol and then 5 ml of ultra-pure water. Each sample was then passed through the cartridge and rinsed with 5 ml of ultra-pure water, followed by 5 ml of HPLC grade hexane. The LTB_4 was eluted with 3 ml of ethyl acetate into a 7 ml glass scintillation vial. The ethyl acetate in the vials was then evaporated in the manner previously described.

To determine recovery percentages, a known amount of LTB_4, two identical aliquots of LTB_4 standard and two identical plasma samples were used. One of the LTB_4 aliquots was added to one of the identical plasma samples. The sample + standard aliquot, standard-only aliquot, and sample- only aliqout were processed in the same manner as the other samples.

The LTB_4 assay was performed according to the instructions accompanying the kit, which are identical to the procedures described for the PGE_2 EIA. A recovery ranging from 91-94% was obtained from this procedure. This is higher than the 70% recovery for LTB_4 reported by Zijlstra & Vincent (1984). According to the manufacturer's of the LTB_4 EIA kit (Cayman Chemical Company, Ann

Arbor), recoveries of 90-100% are possible with this type of extraction and assay procedure (P. Balthazour, personal communication, August 11, 1995)

Creatine Kinase Determination

Plasma levels of creatine kinase were determined using the Paramax® (Baxter Diagnostics, Inc., Charlotte, NC) automated analyzer. Paramax® Creatine Kinase Reagent (#B6105-4) was used for the analysis. This reagent formulation is based on Rosalki's modifications of the Oliver procedure (Baxter Diagnostics, 1992). This procedure involves a series of coupled reactions. Initially creatine phosphate + ADP → creatine + ATP via the action of CK. This reaction is followed by ATP + glucose → ADP + glucose-6-phosphate (G-6-P) via the action of hexokinase. Finally glucose-6-phosphatase serves as a catalyst for the reaction G-6-P + $NADP^+$ → 6-phosphogluconate + NADPH. The amount of creatine kinase activity is proportional to the rate of reduction of $NADP^+$ and is measured bichromatically at 340/405nm.

Prior to CK analysis the Paramax® analyzer was calibrated for the creatine kinase assay according to the Paramax® Operating Manual (Baxter Diagnostics, 1991). The Paramax® CK reagent tablets were removed from their package and allowed to reach room temperature. The CK tablet reagent dispenser was then placed into the reagent carousel. Dade Monitrol® I & II Quality Control material was measured in the analyzer to monitor assay reliability. The samples were then poured into Paramax® sample tubes and labeled

with a barcode. The samples were then placed in the analyzer carousel and the RUN button was pressed. The sample values were reported via a printout. Any sample values which were outside of the measurement range were diluted with Paramax® Dilutant (#B6110-3A) and re-assayed.

Lactate Determination

Lactic acid levels of the plasma samples were determined using the Paramax® (Baxter Diagnostics, Inc., Charlotte, NC) automated analyzer. Paramax® Lactate Reagent (B6106-12) was used for lactate analysis. This reagent contains the reactants for the reduction of NAD^+ to NADH with lactate in the presence of lactate dehydrogenase to NADH + 2-p-iodophenyl-3-p-nitrophenyl-5-phenyl-2H-tetrazolium chloride → NAD^+ + formazan via the action of the diaphorase. The formazan is then measured bichromaticaly at 550/630 nm.

Prior to lactate measurement the Paramax® analyzer was calibrated according to the Paramax® Operating Manual (Baxter Diagnostics, 1991) using Paramax® Comprehensive Calibrators I & II for plasma (#B6108-1 and #B6108-2). The Paramax® Reagents were allowed to reach room temperature then removed from their container and placed in the reagent carousel. Dade Monitrol® I & II Quality Control material was evaluated by the analyzer to monitor assay reliability. The samples were then poured into Paramax® sample tubes and labeled with a barcode. The samples were then placed in the analyzer carousel and the RUN button was pressed. The

sample values were reported via a printout. Any sample values which were outside of the measurement range were diluted with Paramax® Dilutant (#B6110-3A) and re-assayed.

Statistical Analyses

The effect of the weight lifting bout on LTB_4, PGE_2, CK, DOMS and lactate values were determined using a multi-variate analysis of variance (MANOVA). A MANOVA was performed on each variable in the study for the treatment group. There were not enough subjects in the control group to utilize the MANOVA model (n=5) The MANOVA evaluated each variable as a vector and tested the hypothesis that the mean change in a variable from the mean resting value at each time period was zero (μ=0). Wilk's lambda was used to determine significant F-values. A significant F-value for a MANOVA indicated a significant change in a variable over the 120-hour time period.

In addition to the MANOVA, a ANOVA was performed on the CK data since CK values demonstrate a great deal of inter- and intra-subject variability (Ebbeling & Clarkson, 1989; Maughan et al., 1989; Evans, et al., 1986). Furthermore, the number of subjects in this study was small (n=14). Thus, a MANOVA performed on the treatment group and a 2x6 ANOVA involving the treatment and control groups provided for a more accurate assesement of CK activity in these groups.

Paired t-tests were used to determine if specific values were significantly different from resting values for a particular variable over time in the treatment group. Significant differences between

two values at adjacent time periods for a each variable were also determined using paired t-tests for the treatment group. This procedure illustrates differences between values for a variable at two successive time periods. This procedure also determined if exercise values differed from the resting values.

Since a MANOVA was not suitable for analysis of the control group data, changes in control group variables over time were assesed using paired t-tests. Differences between initial resting values and values at other time periods for each variable were examined. In addition, differences between values for a variable at two succesive time periods were also examined.

Differences between the control group and treatment group for each variable over time were determined using the t-test for two group means.

Pearson correlation coefficients were determined for every pair of variables at each time period for both the control and workout groups in order to assess relationships between the variables at specific time periods. The level of significance was set at the 0.05 level for all analyses.

CHAPTER IV

RESULTS

Introduction

The results of this study are presented in the following sequence: treatment of individual data, subject characteristics, evaluation of muscle soreness, plasma creatine kinase values, plasma lactate values, plasma PGE_2 values, plasma LTB_4 values, and correlation analysis among the variables.

Treatment of Individual Data

Sixteen male college students (19-32 years old) participated in the study. Eleven subjects were assigned to the weightlifting group and five subjects were assigned to the control group. One subject in the weightlifting group took NSAIDS during the course of the study, and was subsequently removed from the study. A second subject in the weight lifting group exhibited plasma CK and PGE_2 values which may have indicated the presence of a clinical condition. This subject was removed from the mean treatment group analysis. However, the data associated with this subject is presented with the correlations among the variables due to the parallel time courses exhibited by these inflated values.

Subject Characteristics

Analysis of the subject characteristics by the t-test procedure revealed no significant differences between the two subject group's age, height, and weight. The mean values of these variables are presented in Table 3.

Table 3

Subject Characteristics

Group	N	Age (years)	Weight (kg)	Height (cm)
Treatment	9	25.0 ± 1.4	75.9 ± 5.0	180.9 ± 3.0
Control	5	23.2 ± 1.4	77.4 ± 3.6	176.8± 2.6

Note. The values represent means ± Standard error of the mean (S.E.M.)

Evaluation of Muscle Soreness

The control group reported a mean initial soreness rating of 0.2 ± 0.2, and did not show significant changes in perceived muscle soreness over the 120-hour time period from initial values (Figure 2), or between successive time periods (Figure 3). Furthermore, there was no significant differences between mean soreness ratings for the control and treatment groups at rest.

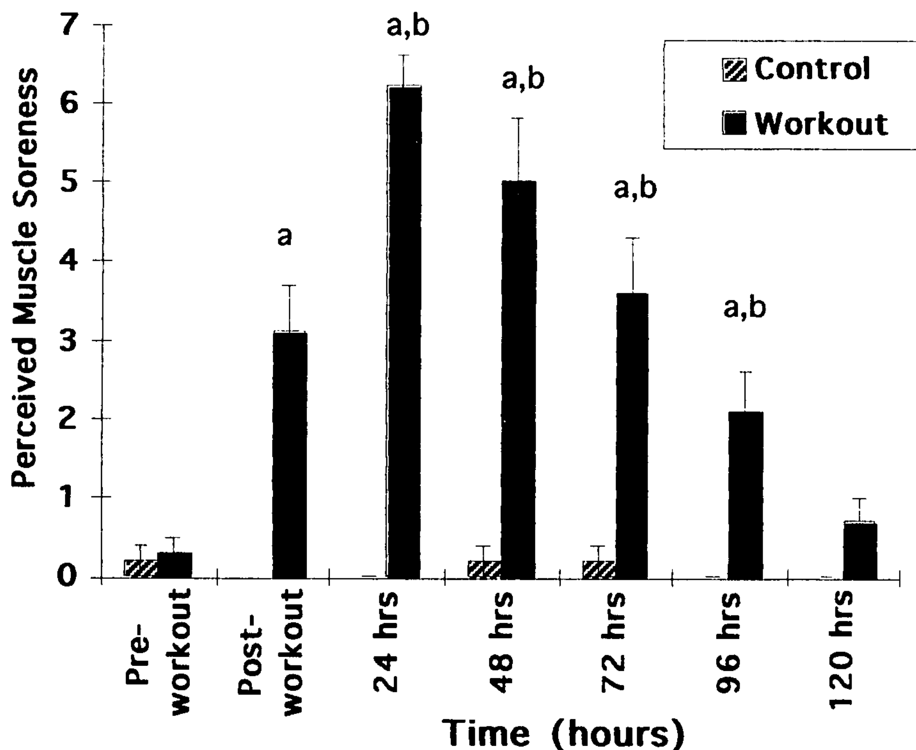

Figure 2. Mean perceived muscle soreness ratings (± S.E.M.) for pre-workout and post-workout time periods in the control and treatment groups. [a]Significant difference from resting mean at the $p < 0.05$ level. [b]Significant difference between treatment and control group means at the $p < 0.05$ level.

Subjects in the treatment group indicated that their muscle soreness was occurred primarily in the area of the chest, shoulders, triceps, and quadriceps. A MANOVA indicated a significant main effect for muscle soreness (Table 3) in the treatment group. Paired t-tests revealed that perceived muscle soreness was significantly elevated above resting values post-workout (3.1 ± 0.6), 24 hours (6.2 ± 0.4), 48 hours (5.0 ± 0.8), 72 hours (3.6 ± 0.7), and 96 hours (2.1 ± 0.3) after the workout (Figure 2). Paired t-test analyses between

succesive time periods in the treatment group revealed significant increases in muscle soreness from mean pre-workout muscle soreness ratings up to 24 hours after exercise (Figure 3). Significant decreases in soreness ratings occurred from 24 hours after exercise to 120 hours after exercise (Figure 3). The data show that peak muscle soreness occurred at 24 hours for the treatment group.

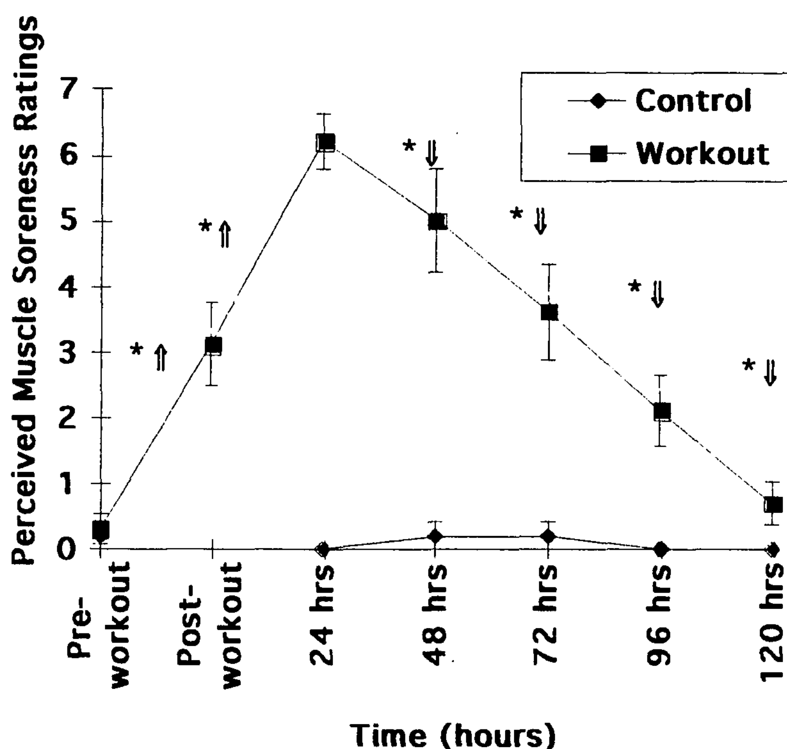

Figure 3. Time course changes in perceived muscle soreness ratings for the treatment and control groups. Values are mean (± S.E.M.).
*⇑Significant increase from previous mean at the p < 0.05 level.
*⇓Significant decrease from previous mean at the p < 0.05 level.

Table 4

MANOVA tests for Changes in each Variable Over Time in Treatment Group

Variable	Wilks' Lambda	df	F	p
DOMS	0.017	5	45.27	0.0013
Lactate	0.058	5	12.90	0.014
CK	0.32	5	1.65	0.32
PGE_2	0.00	5	3.095	0.26
LTB_4	0.077	5	9.52	0.02

A comparison of the perceived muscle soreness values at each time period between the workout and control groups (Figure 2) revealed significant differences between groups at 24 hours (6.2 ± 0.4 vs. 0.0 ± 0.0) , 48 hours (5.0 ± 0.8 vs. 0.2 ± 0.2), 72 hours (3.6 ± 0.7 vs. 0.2 ± 0.2), and 96 hours ($2.1 + 0.5$ vs. 0.0 ± 0.0). The F-values and their respective p-values for the t-tests which were performed on the muscle soreness ratings data are presented in Appendix G.

Plasma Creatine Kinase Values

T-tests revealed no significant increase in mean CK values from mean resting values in the control group (Figure 4). In addition, no significant changes in succesive mean control group values over the 120-hour time period were obtained (Figure 5). Furthermore, no significant differences were found between mean resting CK values for the control and treatment groups (Figure 4).

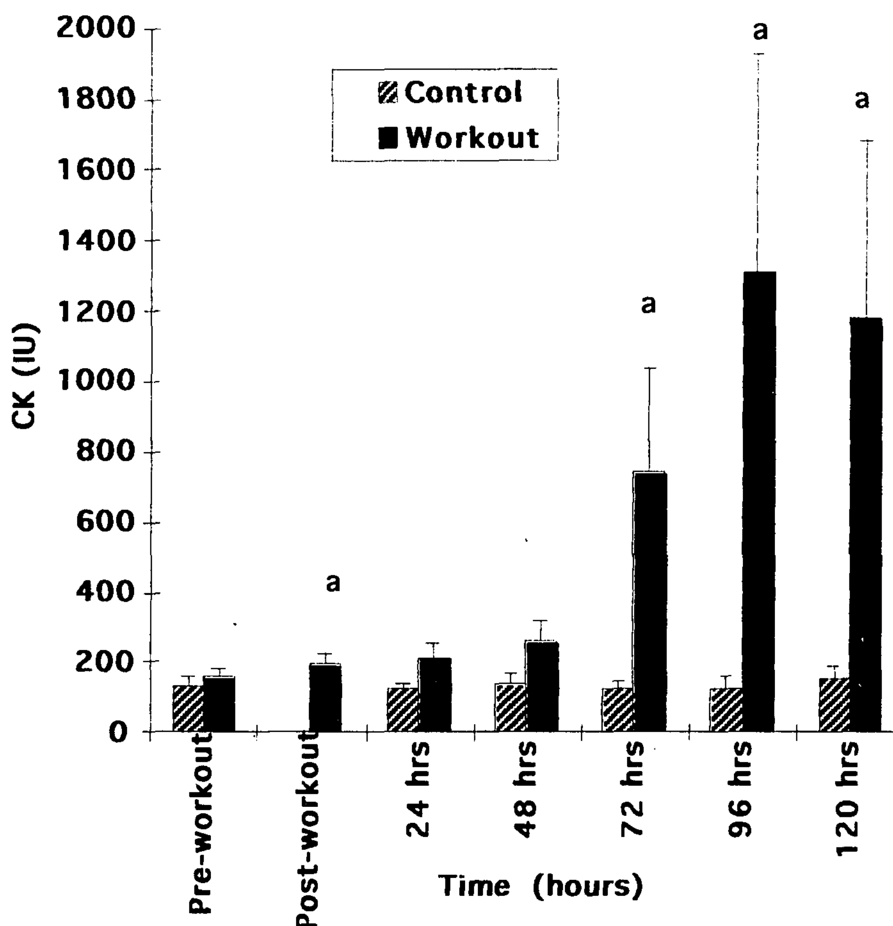

Figure 4. Mean plasma CK values (± S.E.M.) for pre-workout and post-workout time periods in the control and treatment groups. [a]Significant difference from resting mean at the $p < 0.05$ level.

A MANOVA indicated that there was not a significant change in CK values over the measured time period for the treatment group (Table 4). However, paired t-tests used to illustrate differences between specific time periods produced significant differences in this group. Increases in CK from resting values (54.9 ± 25.4 IU/L) were found at the post-workout period (189.7 ± 29.4 IU/L), 72 hours

after exercise (737.4 ± 297.8 IU/L), 96 hours after exercise (1307.3 ± 617.4 IU/L) and 120 hours after exercise (1178.4 + 502.4 IU/L).

Significant differences between successive time periods were also found in the treatment group (Figure 5). There was a significant increase in CK values from 48 hours to 72 hours (254.1 ± 58.4 IU/L to 737.4 ± 297.8 IU/L) and from 72 hours to 96 hours (737.4 ± 297.8 IU/L to 1307.4 ± 617.4 IU/L). The results indicate that plasma CK values peaked at 96 hours after the workout and remained significantly elevated above resting values at 120-hours after the workout.

The 2x6 ANOVA performed on the control and treatment group indicated a significant main effect for groups, indicating a significant difference between the plasma CK levels of the two groups (Table 5) Conversely, a comparison of the plasma CK values at each time period between the workout and control groups demonstrated no significant differences (Figure 4). However, differences between the control group and treatment group from 24 hours to 120-hours approached significance. The F-values and their respective p-values for the t-tests which were performed on the CK data are presented in Appendix G.

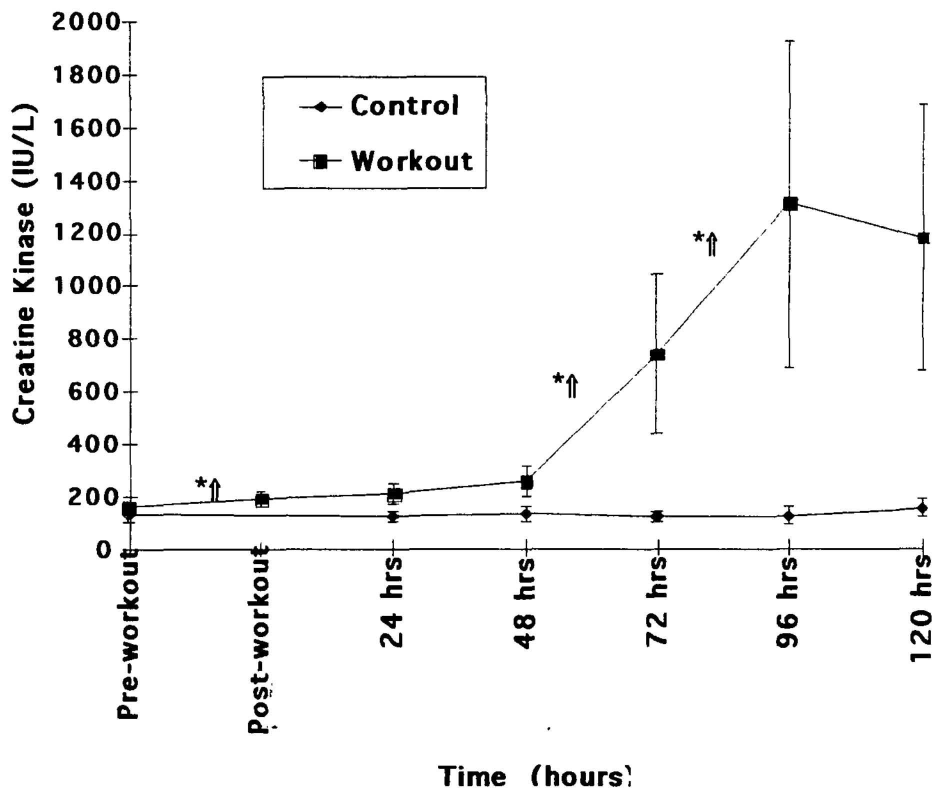

Figure 5. Time course changes in plasma CK for the treatment and control groups. Values are mean (± S.E.M.). *⇑Significant increase from previous mean at the $p < 0.05$ level.

Table 5

Analysis of variance for CK (group x time)

Source	df	Variance Estimate	F-ratio	p-value
Group (G)	1	5023429.7	6.89	0.010*
Time (T)	5	1533182.4	2.10	0.074
G x T	5	834366.7	1.14	0.34
Residual	72	729069.7		
Total	83	835592.7		

Note. *$p < .05$.

Plasma Lactate Values

There were no significant changes in mean plasma lactate values over the time period in the control group (Figure 6). No significant difference was found between mean resting lactate values for the control and treatment groups. (Figure 6 and Figure 7).

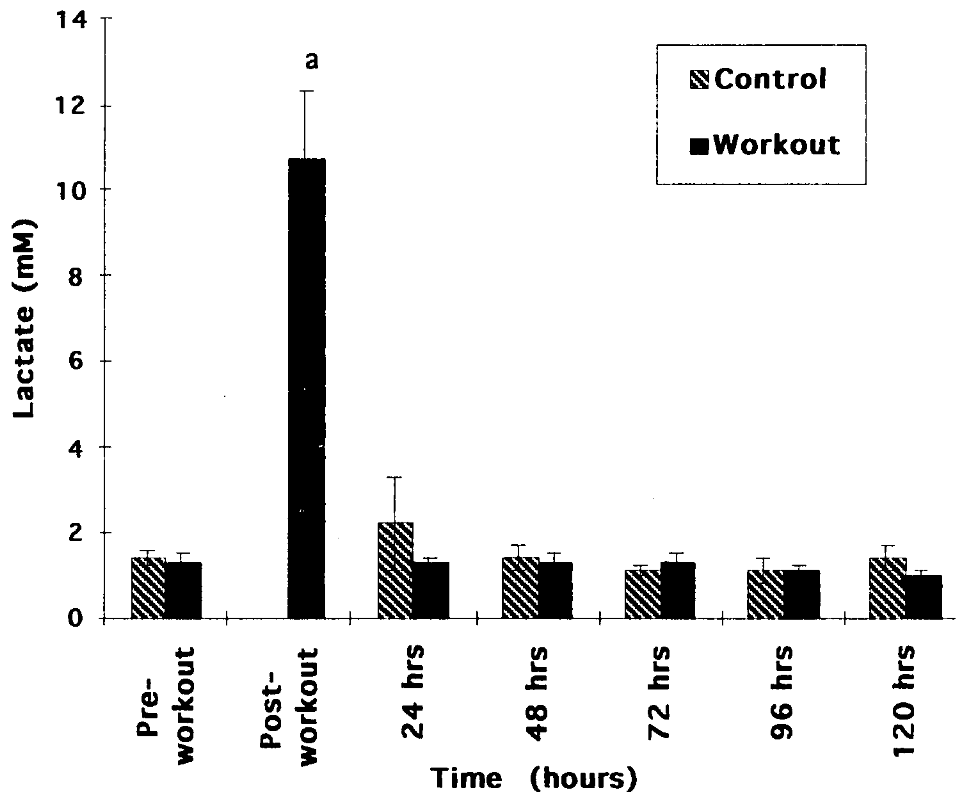

Figure 6. Mean plasma lactate values (± S.E.M.) for pre-workout and post workout time periods in the control and treatment groups. [a]Significant difference from resting mean at the $p < 0.05$ level.

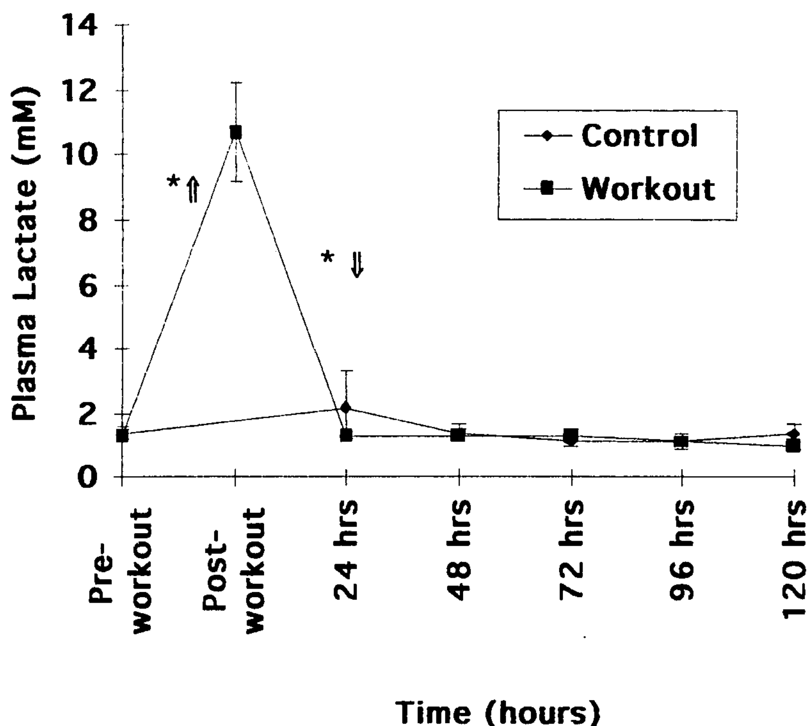

Figure 7. Time course changes in plasma lactate for the treatment and control groups. Values are mean (± S.E.M.) *⇑Significant increase from previous mean at the $p < 0.05$ level. *⇓Significant decrease from previous mean at the $p < 0.05$ level.

A MANOVA indicated that there were was a significant change in lactate values over the 120-hour time period in the treatment group (Table 4). T-tests revealed a significant increase in mean plasma lactate values immediately after exercise from mean resting values (1.3 ± 0.2 mM to 10.7 ± 1.6 mM; Figure 6). Mean lactate values significantly decreased 24 hours after exercise (10.7 mM ± 1.6 to 1.3 + 0.1 mM), and were not significantly different from resting values thereafter (Figure 7).

There were no significant differences between mean lactate values of the control and treatment groups pre-workout, and 24, 48, 72, 96, 120 hours post-workout. (Figure 6). The F-values and their respective p-values for the t-tests which were performed on the lactate data are presented in Appendix G.

Plasma PGE_2 Values

No significant differences were found between mean plasma PGE_2 values at rest and mean plasma PGE_2 values at each of the other time periods in the control group (Figure 8). In addition, there was no significant difference between mean plasma PGE_2 values for the control group and treatment group at rest (Figure 8). Paired t-tests examining differences between successive time periods (Figure 9) revealed a significant decrease in plasma PGE_2 values from 24 hours to 48 hours (71.9 $\pm$ 10.0 pg/ml to 50.3 $\pm$ 10.2 pg/ml) in the control group.

A MANOVA indicated that there were no significant changes in mean plasma PGE_2 values from mean resting values (60.6 $\pm$ 14.8 pg/ml) over the 120-hour time period in the treatment group (Table 4). Furthermore, paired t-tests indicated no significant differences between PGE_2 values after exercise and resting values (Figure 8).

However, the paired t-test analysis for differences between successive time periods (Figure 9) indicated a significant increase in mean plasma PGE_2 values from 72 hours to 96 hours (59.9 $\pm$ 10.2 pg/ml to 81.7 $\pm$ 12.3 pg/ml) in the treatment group. No statistical difference was found between treatment and control group means at

comparable time periods. The F-values and their respective p-values for the t-tests performed on the PGE_2 values are presented in Appendix G.

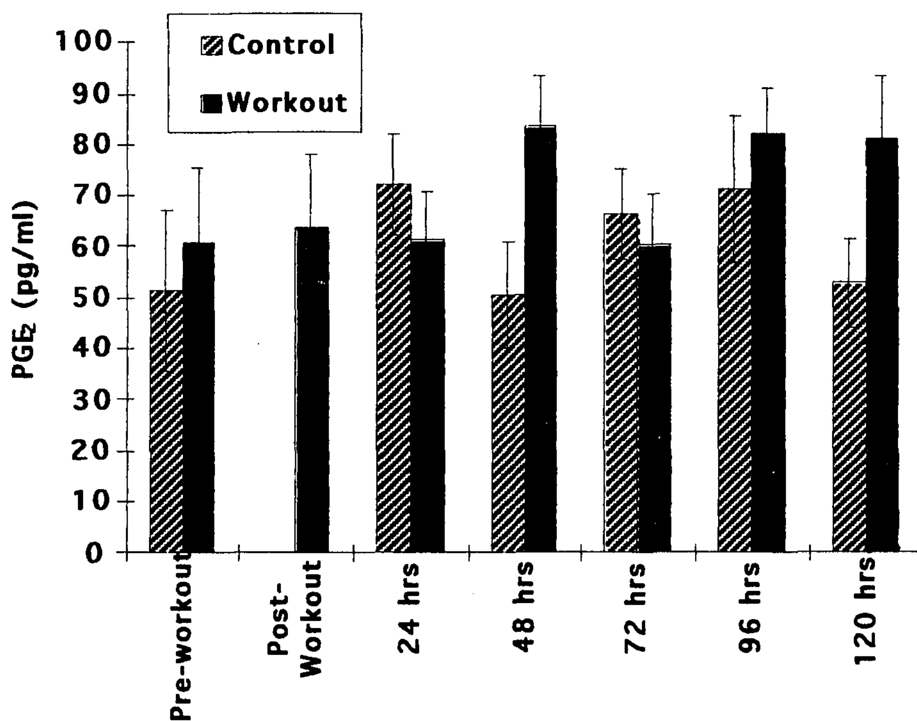

Figure 8. Mean plasma PGE_2 values (± S.E.M.) for pre-workout and post-workout time periods in the control and treatment groups.

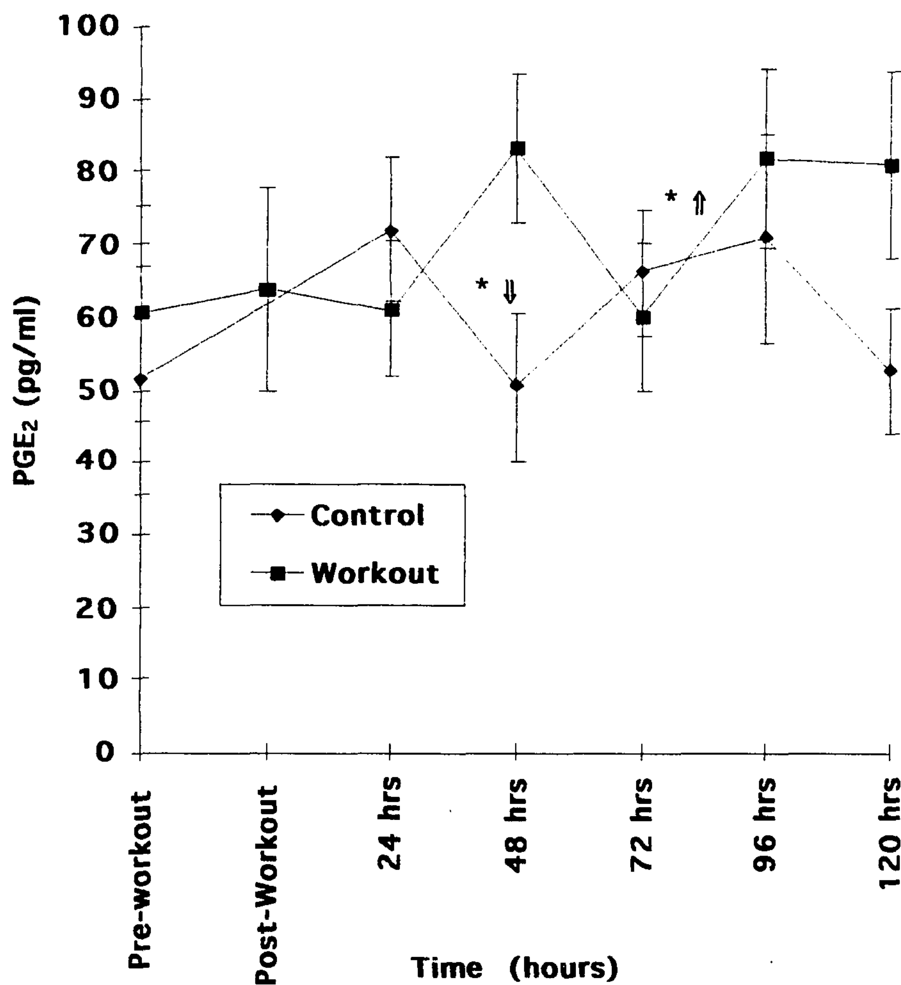

Figure 9. Time course changes in plasma PGE_2 values for the treatment and control groups. Values are mean (± S.E.M.).
*⇑Significant increase from previous mean at the $p < 0.05$ level.
*⇓Significant decrese from previous mean at the $p < 0.05$ level

Plasma LTB_4 values

No significant differences between mean resting plasma LTB_4 values and mean plasma LTB_4 values at the other time periods were found in the control group (Figure 10). Furthermore, no significant differences were found for plasma LTB_4 values at successive time periods in this group (Figure 11). No significant differences between the control group and treatment group mean resting plasma LTB_4 values were found (Figure 10).

The MANOVA indicated that there were significant changes in mean plasma LTB_4 values over the 120-hour time period in the workout group (Table 4). However, paired t-tests did not reveal any significant differences between mean resting plasma LTB_4 values (15.3 ± 3.4 pg/ml) and mean plasma LTB_4 values at the other time periods (Figure 10). Furthermore, there were no significant differences between successive time periods after exercise (Figure 11). No significant differences were found in plasma LTB_4 values between the control and treatment groups at comparable time periods (Figure 10). F-values and their respective p-values for the t-tests performed on the LTB_4 data are presented in Appendix G.

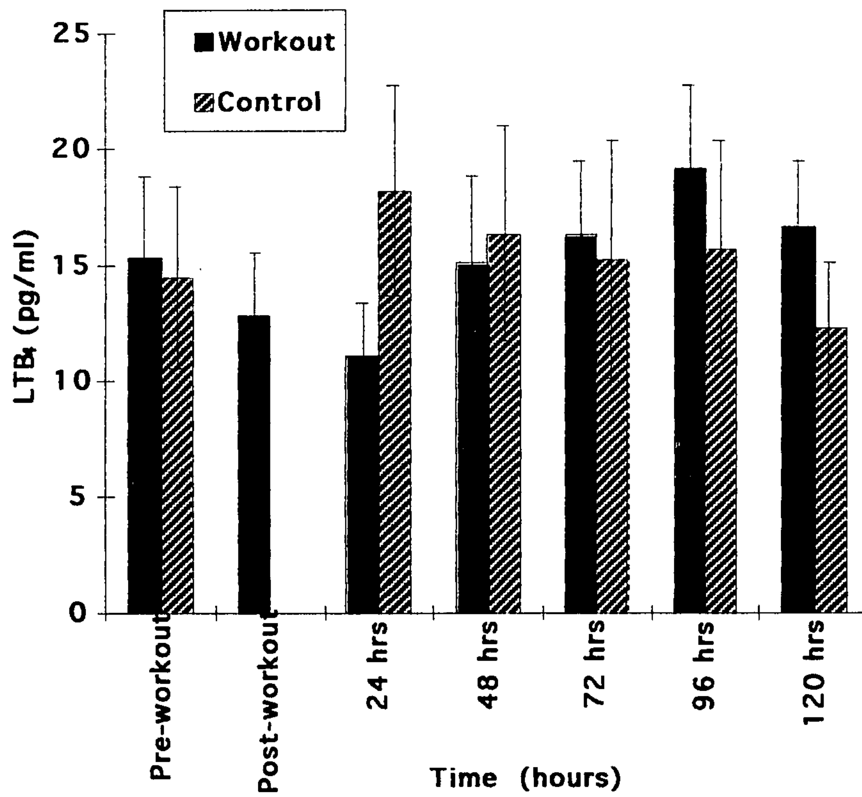

Figure 10. Mean plasma LTB_4 values (± S.E.M.) for pre-workout and post-workout time periods in the control and treatment groups.

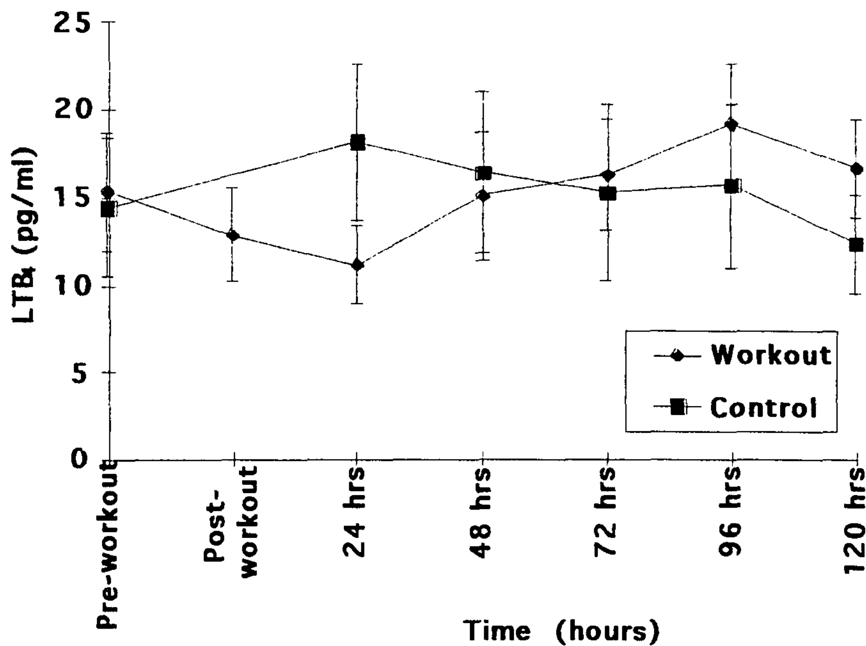

Figure 11. Time course changes in plasma LTB_4 values for the treatment and control groups. Values are mean (± S.E.M.)

Correlations among the Variables

A correlational analysis among the variables was performed to assess relationships between changes in the variables from resting values. Significant Pearson correlation coefficients for the workout group are presented in Table 6. There were no significant Pearson correlation coefficients among changes in the variables from resting values in the control group.

One subject in the treatment group (subject #8) was not included in the mean statistical analyses due to CK values which were of the magnitude to indicate the presence of a pathological condition (Clarkson & Ebbeling, 1989). Furthermore, subject #8's

PGE_2 resting and post-workout values were much higher than the values obtained from the treatment group. Subject #8's CK and PGE_2 values are compared to the treatment group's mean CK and PGE_2 values in Table 7. Subject #8's perceived muscle soreness ratings and the treatment group's mean perceived muscle soreness ratings are compared in Table 8.

Table 6

Significant Pearson Correlation Coefficients for Changes Over Time in Variables-Workout Group

	Change Score					
Variable	Post-Pre	24 hr-Pre	48 hr-Pre	72 hr-Pre	96 hr-Pre	120 hr-Pre
DOMS	- -	- -	- -	- -	- -	- -
CK	LA (0.92)	LA (-0.78)	- -	LA (-0.77)	- -	- -
LA	CK (0.92)	CK (-0.78)	- -	CK (-0.77)	- -	- -
	- -	- -	- -	LTB_4 (0.75)	- -	- -
LTB_4	- -	- -	- -	LA (0.75)	- -	- -
PGE_2	- -	- -	- -	- -	- -	- -

Note: Change scores represent pre-workout values subtracted from value obtained for a particular time period. The level of significance for coefficients is $p < 0.05$.

Table 7

Comparison of Plasma CK and PGE_2 Values for Subject #8 and Treatment Group

Variable	Pre-workout	Post-workout	24 hours	48 hours	72 hours	96 hours	120 hours
CK #8	385 vs.	499 vs	4,234 vs.	15,318 vs. 2	32,928 vs.	67,692 vs.	38,712 vs.
T.G. CK	54.9 ± 25.4	189.7 ± 29.4	208.8 ± 38.6	254.1 ± 58.4	737.4± 297.8	1307.± 617.4	1178.± 502.4
PGE_2 #8	176 vs.	100 vs.	106 vs.	120 vs.	140 vs.	486 vs.	52 vs.
T.G. PGE_2	60.6 ± 14.8	63.7 ± 14.0	60.9 ± 9.3	83.1 ± 10.2	59.9 ± 10.2	81.7 ± 12.3	80.8 ± 12.9

Note: T. G. = treatment group. CK values are reported in IU, and PGE_2 values are reported in pg/ml. The first value represent that of subject #8 and the second value represents the mean value and the S.E.M from the treatment group.

Table 8

Comparison of Percieved Muscle Soreness Ratings for Subject #8 and Treatment Group

Subject	Pre-workout	Post-workout	24 hours	48 hours	72 hours	96 hours	120 hours
Subject #8	0.0	2.0	5.0	5.0	5.0	2.0	1.0
T. G.	0.3 ± 0.2	3.1 ± 1.8	6.2 ± 1.2	5.0 ± 0.8	3.6 ± 0.7	2.1 ± 0.5	0.7 ± 0.3

Note: T. G. = treatment group. Treatment group values are mean (± S.E.M).

CHAPTER V

DISCUSSION

Novel physical activities, exercise with a strong eccentric component, and activites at a high level of intensity or duration have been shown to elicit DOMS (Armstrong, 1984; Byrnes & Clarkson, 1986; Cleak & Eston, 1992; Newham, 1988; Tiidus & Ianuzzo, 1983). The specific mechanisms which elicits DOMS is currently not known. It has been suggested that DOMS may be caused by an inflammatory process resulting from muscle and connective tissue damage (Smith, 1991). Inflammatory mediators, including PGE_2 and LTB_4, are associated with hyperalgesia and pain (Ferreira et al., 1974; Madison et al., 1992; Martin et al., 1987; Taiwo et al., 1987). This study examined the relationship between changes in plasma levels of PGE_2, LTB_4, and the time course of DOMS after an acute weight lifting bout in order to determine if these inflammatory mediators may play a role in the generation of DOMS.

Changes in plasma levels of CK and lactic acid were examined in this study in order to determine if the these blood markers exhibited changes typically documented in the literature after exercise resulting in DOMS. Thus, these measurements served to indicate whether a normal response to this type of exercise was elicited.

Effect of the Weight Lifting Bout on DOMS

It was hypothesized that the acute weight lifting bout would result in the manifestation of DOMS with a time course similar to that which has been documented in the literature. In the present study the weight lifting bout resulted in perceived muscle soreness ratings which increased significantly from the pre-workout mean value (0.3 ± 0.7) to a peak mean value of 6.2 ± 0.4 at 24 hours. Mean muscle soreness ratings demonstrated significant decreases at 48 hours (5.0 ± 2.2), 72 hours (3.6 ± 2.1), 96 hours (2.1 ± 1.5), and 120 hours (0.7 ± 0.9). Except for the mean muscle soreness rating at 120 hours, these mean values were significantly higher than pre-workout values.

DOMS is usually characterized in the exercise literature as the feeling of pain or tenderness in muscles which usually begins 6-24 hours after exercise, peaks 24 to 48 hours after exercise, and gradually subsides over 5-10 days after exercise until the soreness is gone (Armstrong, 1984; Clarkson et al., 1986; Ebbeling & Clarkson, 1989; Miles & Clarkson, 1994; Newham, 1988). There is a rapid adaptation to exercise which causes DOMS. A muscle which has been used in a prior exercise bout involving eccentric contractions will demonstrate a dimunition in DOMS (Byrnes et al., 1985; Donnelly, Clarkson & Maughan, 1992). This preventitive effect has been observed up to six weeks after the initial exercise bout (Byrnes et al., 1985). However, it appears that the initial “protective” exercise bout must be separated by the subsequent exercise bout by

a time period greater than 48 hours in order for this protective response to be manifested (Smith et al., 1994). The subjects participating in the present study were all individuals who were currently sedentary and had not engaged in resistance training for at least eight weeks in order to eliminate any protective effect from a previous weight lifting bout. The time course of the perceived muscle soreness ratings followed the time course for perceived muscle soreness characterized in the literature. Therefore, the hypothesis that the acute weight lifting bout would result in the manifestation of DOMS with a time course similar to that which has been documented in the literature was accepted.

As previously described, DOMS usually is not manifested until several hours after exercise (Ebbeling & Clarkson, 1989; Fridén, 1984; Miles & Clarkson, 1994; Smith et al., 1994). In the current study, the weight lifting bout resulted in a significant perceived muscle soreness rating immediately after exercise compared to baseline values. This perception of soreness may not be DOMS, but the sensation of soreness associated with fatiguing exercise which may persist for a short period of time after exercise (Fridén, 1984; Miles & Clarkson, 1994) This type of soreness or discomfort is thought to be the result of activation of pain receptors by compounds associated with metabolism in contracting muscle, such as lactic acid (Fridén, 1984; Miles & Clarkson, 1994; Talag, 1973). In the present study, the weight lifting bout resulted in elevated plasma levels of lactic acid. This suggests that the soreness

experienced immediately after the weight lifting session may have resulted from the accumulation of metabolic products of muscular contractions, and was not DOMS.

Effect of the Weight Lifting Bout on CK

Resting plasma CK values for the workout group (154.9 $\pm$ 25.4 IU) and control group (129.6 $\pm$ 24.2 IU) were within the normal range of 50-200 IU/L for males (Tietz, 1995), and similar to resting values in males reported by other researchers (Clarkson, Litchfield, Graves, Kirwan & Byrnes, 1985; Clarkson & Tremblay, 1988; Paul et al., 1989)

Typically, exercise involving a strong eccentric component is associated with the manifestation of DOMS and the appearance of CK in the circulation (Appell, Soares & Duarte, 1992; Armstrong, 1986; Ebbeling & Clarkson, 1989). Exercise such as downhill running (Byrnes et al., 1985; Cannon, Fiatarone, Fielding & Evans, 1994; Maughan et al., 1989; Schwane et al., 1983), and some forms of eccentric exercise isolating a specific muscle group (Clarkson et al., 1987) have resulted in increased plasma CK within hours after exercise, which peak 18- 24 hours later (Byrnes et al., 1985; Cannon et al., 1994; Maughan et al., 1989; Schwane et al., 1983). However, it appears that exercise involving a repeated eccentric component at a high intensity elicits a delayed increase in plasma CK which may not occur until 48 hours after exercise and not reach peak levels until three to seven days after exercise (Clarkson & Tremblay, 1988;

Donnelly et al., 1992; Evans et al., 1986; Manfredi et al., 1991; Newham et al., 1986; Saxton & Donnelly, 1995; Smith et al., 1994).

The MANOVA performed on the CK data indicated that there were no significant changes in plasma CK over the time period after exercise. On the other hand, t-tests indicated that plasma CK levels were significantly elevated immediately after exercise, with plasma CK levels peaking at 1307.3 ± 617.4 IU/L 96- hours after exercise. Plasma CK levels continued to be significantly elevated 120 hours after exercise (1178 ± 502.4 IU/L). Interpretation of the plasma CK results is complicated further by the lack of significant differences between control group values and treatment group values at each time period. However, the conclusion that significant increases in plasma CK occurred as a result of the weight lifting bout appears to be valid for several reasons. Although there were no significant differences found between the control group and workout group at any time period at the $p < 0.05$ level, at 24, 48, 72, 96, and 120 hours post-exercise the p values approached the $p < 0.05$ level of significance. This is particularly important since the control group (n=5) and workout group (n=9) were small. The interpretation of the p values as either significant or not significant should be done within the context of sample size, with p values slightly larger than the pre-determined level of significance indicating a possible significant effect when small sample sizes are analyzed (Ludwig, 1995).

Another factor which may have contributed to the statistical results is the large inter-subject variability in plasma CK values in both the workout and control groups. Moreover, it appeared that the subjects in the workout group could be divided into two groups; one group which exhibited only small changes in plasma CK and a second group which demonstrated larger changes in plasma CK over the 12-hour time period. Four of the subjects in the workout group demonstrated either small increases (less than 50%) or small decreases in plasma CK, while the remaining five subjects demonstrated peak plasma CK values at least 200% above resting values. This phenomena has been observed by other investigators examining exercise and plasma CK levels (Clarkson et al., 1986; Maughan et al., 1989; Newham, Jones & Edwards, 1983). Maughan et al. (1989) described these two groups as low CK responders and high CK responders. Maughan et al. observed that although there were no significant differences between the subjects in the high CK responders and low CK responders in terms of subject characteristics, the two groups demonstrated similar response patterns for plasma lactate dehydrogenase, thiobarbituric acid reactive substances, and aspartate aminotransferase. In the present study there were no predictors of high and low CK response for the workout group members. The identification of high CK responders and low CK responders after exercise confounds the interepretation of plasma CK values.

The results of the present study seem to support the hypothesis that the weight lifting bout will result in increases in plasma CK values which will peak 48-120 hours after exercise. Furthermore, the CK response in the present study resulting from the workout bout was comparable to those reported by other investigators. Newham et al. (1986) examined the effect of downhill (primarily eccentric) and uphill (primarily concentric) walking on plasma CK values. Newham et al. found that subjects walking downhill demonstrated plasma CK values ranging from 70-15,000 IU/L which peaked four-seven days after the exercise bout. Donnelly et al. (1992) reported peak CK values around 6000-7000 IU/L 4-5 days after exercise consisting of 70 maximal contractions of the flexor and extensor muscles of the arm. Smith et al. (1984) reported peak serum CK values of 3500 IU/L 3-4 days after exercise involving the eccentric phase of the Universal® chest press. Clarkson & Tremblay (1988) reported that after exercise involving eccentric contraction of the forearm flexors, serum CK values peaked around 2300 IU/L 4-5 days after exercise. Saxton and Donnelly (1995) found serum CK to peak at 1553 $\pm$ 615 IU/L 96 hours after a regimen of eccentric exercise using the flexors of the forearm.

Although much of the research concerning the effects of exercise on CK levels in the blood involves eccentric contraction of a specific muscle group or a single movement or exercise, research exists which has examined the CK response after a multi-exercise resistance protocol. In a previous study by Boyer, Lewis & Goldfarb,

(1991), the effects of a weight lifting bout on serum creatine kinase, lipid peroxidation, and DOMS were examined using a protocol identical to the weight lifting protocol used in the present study, except for the type of resistance equipment used. In the former study, free weights were used, while the present study utilized Universal Centurion® exercise equipment. However, the exercises used in both protocols were comparable, and, furthermore, the lower body muscle groups were exercised on the Universal Centurion® leg press in both protocols. In the earlier study plasma CK values did not demonstrate significant increases over baseline values until 72 hours after exercise. Even though ratings of perceived muscle soreness were similar in both studies, peak plasma CK values resulting from the workout bout in the present study (1307.3 $\pm$ 617.4 IU/L) were 249% higher than in the earlier study (374.4 $\pm$ 130.7 IU/L).

Paul et al. (1989) examined the effects of a high-intensity weight lifting bout on serum and urinary markers of skeletal muscle damage using a protocol similar to the protocol used in the present study. Subjects inexperienced with weight training performed a weight lifting bout involving six exercises on Universal® resistance equipment. The subjects performed three sets on each exercise at an intensity of 70-80% of their 1RM until volitional exhaustion. The researchers found significant increases in serum CK values 12 and 24 hours after exercise, with peak values observed at 24 hours

(@620 IU/L). Serum CK values were not determined 24 hours after exercise.

Boone et al. (1990), observed that plasma CK was significantly elevated above pre-exercise values immediately post-exercise and 24 hours after exercise following a weight lifting session consisting of free-weight squats with a variety of intensities and repetitions in experienced weight lifters. However, these elevated levels were still within the range for normal resting values (Tietz, 1995).

Effect of the Weight Lifting Bout on Lactic Acid

In the present study, the weight lifting bout resulted in an elevation in plasma lactate (10.7 $\pm$ 1.6 mM) immediately after exercise and returned to baseline values by 24 hours. Therefore, the hypothesis that the acute weight lifting bout would result in an increase in plasma lactic acid values immediately after exercise, and return to resting values by 24 hours after exercise was accepted.

Both the weight lifting group and control group exhibited mean resting plasma lactate values which fell into the normal resting range for plasma lactate values of 0.3-2.4 mM (Häkkinen & Pakarinen, 1993; Kraemer et al., 1993; McMillan et al., 1993; Tietz, 1995). Similar changes in plasma and whole blood lactate values immediately after resistance exercise have been reported by other investigators. Rozenek et al. (1990) examined the metabolic responses resulting from an exercise bout in athletes using anabolic

steroid and athletes not using steroids. The researchers found that immediately after performing 5 sets of 10 repetitions in the squat that in athletes not using anabolic steroids, mean plasma lactate values were 12.1 $\pm$ 1.4 mM. Plasma lactate values continued to be elevated 30 minutes after exercise. Plasma lactate values were not measured after this time period.

In another study by Rozenek and co-workers (Rozenek, Rosenau, Rosenau & Stone, 1993), subjects performed five sets of 10 repetitions in the bench press at 70% of their 1RM. Blood lactate levels were measured after each set. At the end of the fifth exercise (comparable to a post-exercise value) blood lactate was approximately 7 mM. Blood lactate levels were not determined after this time period.

Craig & Kang (1994) used a squat workout to determine the role of hGH in exercise-induced muscle hypertrophy. In this study mean plasma lactate levels immediately after exercise in the group performing a squat at 75% of their 1RM were 11.59 mM. Subjects using an intensity of 90% of their 1RM demonstrated mean plasma lactate values of 12.61 mM. Using a similar squat protocol Häkkinen & Pakarinen (1993) reported post-workout blood lactate values of 15.0 $\pm$ 4.0 mM.

In a study examining hormonal responses to resistance exercise, Kraemer et al. (1990) had one of the treatment groups perform a weight lifting workout on Universal® resistance equipment with a protocol similar to the exercise protocol used in

the present study. The researchers reported mean post-workout blood lactate levels in the 8-10 mM range.

The elevated post-exercise lactate levels reported in the present study and other studies involving resistance exercise are usually associated with high intensity exercise (Gollnick, Byly & Hodgson, 1986; Karlsson & Jacobs, 1982; Rozenek et al., 1993). These studies indicate that high-intensity resistance protocols consisting of a high number of repetitions (10 or more repetitions) per set with short rest periods between sets seem to elicit higher blood lactate levels than high-intensity resistance protocols with a lower number of repetitions (5 or more repetitions) per set and longer rest periods (Kraemer et al., 1993; Kraemer et al., 1990). High-intensity resistance training protocols involving a high number of repetitions may also elicit higher levels of DOMS than lower repetition protocols, due to the greater number of eccentric contractions performed (Clarkson & Tremblay, 1988; Tiidus & Ianuzzo, 1983). The return of plasma lactate to resting levels fairly quickly after exercise is typical (Gladden, 1989).

Effect of the Weight Lifting Bout on PGE_2

Since some investigators have suggested that DOMS may be the result of an inflammatory process resulting from exercise-induced muscle damage, it has been suggested that PGE_2 may play a role in DOMS (Smith, 1991). Smith suggested that increases in synthesis of PGE_2 results in sensitization of pain afferents and an increase in plasma levels of PGE_2 In the area of cancer research and treatment

plasma prostaglandin levels have been used as a diagnostic tool as a measure of tumor malignancy and cancer progress (Chiamoff, Malachi & Halbrecht, 1985; Matejka, Gisinger, Porteder, Watzek & Sinzinger, 1983; Nell, Porteder, Matejka & Sinzinger, 1989; Petit & Kort, 1988), since prostaglandins (including PGE_2) serve as mediators in carcinogenesis (Bockman, 1983; Honn, Bockman & Marnett, 1981) and exhibit elevated levels in tissues with malignent tumors (Karmali, 1980).

Likewise, it could be argued that if exercise-induced muscle damage which results in DOMS causes increases in PGE_2 synthesis in the affected muscle tissue, then this increase will be reflected in elevated plasma PGE_2 levels. Several studies have examined the effect of exercise on plasma PGE_2 levels. Most of these studies have suggested that exercise causes increases in plasma PGE_2 (Demers et al., 1981; Lijnen et al., 1990; Nowak & Wennmalm, 1978; Zambraski & Dunn, 1980). However, these increases were observed in plasma samples taken either during exercise or immediately after exercise. It is likely that these increases in plasma PGE_2 levels are associated with the the role which PGE_2 plays in the cardiovascular and renal processes associated with exercise (Lee & Katayama, 1985; Lijnen et al., 1982; Lijnen et al., 1990; Zambraski et al., 1986). Thus, elevated PGE_2 levels within this context do not seem to be related to DOMS.

Work by Vandenburgh et al. (1990) indicated that mechanical stimulation of avian skeletal muscle resulted in increased PGE_2

synthesis accompanied by muscle damage. It could be hypothesized that a similar response may occur in skeletal muscle which has been damaged through exercise. However, the increases in PGE_2 efflux reported by Vandenburgh et al. returned to control levels by 24 hours. Therefore, it seems that this PGE_2 response is not associated with the generation of DOMS, since the time course of PGE_2 efflux is much shorter than that of DOMS.

Cannon et al. (1991) examined mononuclear cells from blood samples obtained from subjects running downhill on a treadmill. PGE_2 secretion by plasma mononuclear cells was significantly increased 1-2 days after exercise (3-4 ng/ml) in subjects ingesting a placebo. However, a treatment group ingesting 800 IU of vitamin E daily for 48 days prior to exercise did not exhibit increases in secretion of PGE_2 by the mononuclear cells. The authors attributed this lack of statistical significance to a large amount of variablity in secretion levels, and indicate that in this group mononuclear cells increased PGE_2 secretion approximately 260%. The placebo group exhibited significant PGE_2, and secretion returned to normal five days after exercise. These findings may suggests a similar time course for PGE_2 production and the generation of DOMS. However, production of PGE_2 by monocytes in the circulation may not be indicative of PGE_2 secretion by polymorphonuclear cells and leukocytes in areas of muscle damage.

Based on the aforementioned discussion, Smith's hypothesis that a relationship between DOMS and PGE_2 may be indicated by

elevated plasma levels of PGE_2 is tenable. In order to determine if plasma PGE_2 levels increase in association with DOMS, normal resting levels of PGE_2 must be established. A great deal of variation in resting plasma PGE_2 values has been reported by investigators. Mean resting PGE_2 values in the current study were 51.4 ± 15.8 pg/ml for the control group and 60.6 pg/ml $\pm$ 14.8 pg/ml for the treatment group. Several studies have reported resting PGE_2 lower than those found in the present study. Dray et al., (1975), found resting plasma PGE_2 values to fall in the 3-12 pg/ml range. Using gas chromatography negative-ion chemical ionization mass spectrometry, Schweer, Kammer & Seyberth (1985) reported plasma PGE_2 values in the 2-12 pg/ml range in healthy males.

Similarly, Petit & Kort (1988), reported mean resting plasma PGE_2 levels of 19.3 ± 3.0 pg/ml. Nowak & Wennmalm (1978) found mean resting plasma PGE_2 values to range from 15 ± 4 to 28 ± 6 pg/ml, depending on whether arterial, subclavian, hepatic, renal and femoral venous plasma were analyzed. Lijnen and co-workers (Lijnen et al., 1982; Lijnen et al., 1990) have reported mean resting plasma PGE_2 values of 40-60 pg/ml, which are similar to the values reported in the present study. Similar resting values of 48.5 pg/ml were reported by Rauramaa et al. (1984)

Resting plasma PGE_2 values have been reported in the literature which are higher than those reported in the present study. Smith et al. (1993) reported mean resting plasma PGE_2 values of 326 $\pm$ 137 pg/ml. Resting plasma PGE_2 values as high as 1100 pg/ml

have been reported in the literature (Demers et al., 1981; Wells, 1991).

The wide variation in resting plasma PGE_2 values may be due to differences in obtaining samples, handling of samples, PGE_2 extraction methodology, and specificity of the assay for PGE_2 (Dray et al., 1975; Nell et al., 1989; Peskar, 1985; Petit & Kort, 1988; Pradelles, Grassi & Maclouf, 1985). In addition, there seems to be daily variations in plasma PGE_2 values for an individual (Petit & Kort, 1988; Sinzinger, 1985) The time of day which the blood sample is taken may also influence plasma PGE_2 levels (Dray et al., 1975). In vitro production of PGE_2 can be influenced by factors such as venous occlusion, diameter of needle used for sampling, the presence of a anticoagulant in sampling tube, processing temperature, and presence of a cyclooxygenase inhibitor in the sampling tube (Kuzuya, Matsuda, Hoshida, Yamagishi & Tada, 1985; Nell et al., 1989; Sinzinger, Reiter & Peskar, 1985). It has been suggested that elevated eicosanoid values may be the result of sample artifact and measurement of PGE_2 analogs and metabolites (Dray et al., 1975; Granström & Kindahl, 1990; Kuzuya et al., 1985; Sinzinger, 1985; Stehle, 1982) It appears that resting plasma PGE_2 values at the lower end of the spectrum reflect less in vitro production of PGE_2 (Simmet, Peskar & Peskar, 1985).

In the present study it was hypothesized that a high-intensity weight lifting bout would result in DOMS which was accompanied by increases in plasma PGE_2. However, the weight lifting bout did not

appear to have any effect on plasma PGE_2 values in subjects in the treatment group. Analysis of the control group data revealed a significant decrease in plasma PGE_2 values from 24 to 48 hours post-exercise. However, plasma PGE_2 levels seem to exhibit a great deal of daily fluctuation. Since this decrease represents the only significant change found in the plasma PGE_2 analysis, it appears that this difference may merely represent a daily fluctuation in plasma PGE_2. Therefore, the hypothesis that the weight lifting bout would result in increases in plasma PGE_2 which followed a time course similar to that exhibited by DOMS was not supported by the results, indicating that plasma PGE_2 does not contribute to DOMS.

These findings are in opposition to those reported by several investigators examining the relationship between prostaglandins of the E series and DOMS. Bansil (1984) examined the effect of performing three sets of ten repetitions on the squat exercise at 67.5% of 1RM on plasma PGE_1. Six females and three males between the ages of 20 to 30 were used in the study, and were not engaged in weight training. Bansil found the workout bout resulted in significantly increased plasma PGE_1 values at 24 hours (604.4 pg/ml) from resting levels (377.25 pg/ml). Bansil also found that the maximal decrease in range of motion at the knee joint occured at 24 hours, and perceived muscle soreness ratings were also elevated at this time. Although both PGE_1 and PGE_2 are both associated with hyperalgesia (Ferreira, 1972; Juhlin & Michaelsson, 1969), PGE_2 is the prostaglandin most closely associated with increased

sensitization of pain afferents and arthritic conditions in the pain literature (Bennett, 1988; Bertin et al., 1994; Martin et al., 1987; Mense, 1981; Srivastava & Mustafa, 1992). The effects of PGE_2 and PGE_1 are very similar. However, PGE_1 is more potent in increasing levels of cAMP in human synovial cells in culture than PGE_2 (Zurier, 1990). PGE_1 inhibits aggregation of human platelets in culture, while PGE_2 does not (Zurier, 1990). The plasma PGE_1 values which Bansil reported are much higher than the plasma PGE_1 values reported by other investigators (Dray et al., 1975; Zurier, 1990). These higher plasma PGE_1 values may due to sampling technique, extraction methodology, and/or interfering substances, as previously described.

Furthermore, PGE_1 has potent vasoactive effects on penile vessels. Since levels of PGE_1 are usually very low in blood (Schrör, 1995), the elevated levels reported by Bansel could result in frequent spontaneous erections in the subjects (Mantovani, Colombo, Edoardo & Austoni, 1995; Porst, 1995; Schrör, 1995)

A study by Wells (1991) sought to determine if therapeutic doses of indomethacin, a cyclooxygenase inhibitor, would reduce DOMS and the increases in plasma PGE_2 which are hypothesized to accompany DOMS. Twenty-one untrained male subjects performed a weight lifing bout using the eccentric phase of the Universal® chest press. Subjects ingested either a placebo or indomethicin (a cyclooxygenase inhibitor), beginning 36 hours prior to the exercise and through 72 hours post-exercise. Similar increases in DOMS and

CK were found in both groups. Plasma PGE_2 was significantly lower than resting values 96 hours after exercise (1073.62 pg/ml vs. 461.37 $\pm$ 319.96 pg/ml). At 120 hours PGE_2 returned to baseline values. The decrease in plasma PGE_2 levels at 96 hours may merely reflect the large inter- and intra-subject variability demonstrated in the PGE_2 values reported in this study.

In addition, there was no significant difference between the plasma PGE_2 values of the group taking the placebo and the group taking indomethacin. Indomethacin should block the production of PGE_2, thereby preventing plasma levels of PGE_2 from increasing. Since this did not occur in this study, the reliability of the plasma PGE_2 values reported by Wells are questionable. Furthermore, the plasma PGE_2 values reported in this study, particularly the mean resting values, are of a magnitude which are outside the range reported for normal plasma PGE_2 values in the literature. This seems to indicate that in vitro PGE_2 synthesis occured in the samples or that intefering substances may have artificially elevated PGE_2 values obtained by the radioimmunoassay.

In contrast to the present study, Smith et al. (1993) found significant increases in plasma PGE_2 values concomitant with increases in muscle soreness after exercise consisting of the eccentric phase of the Universal® chest press. Plasma PGE_2 values peaked at 24 hours post-exercise (2071 $\pm$ 319 pg/ml), and returned to resting levels by 72 hours post-exercise (326 $\pm$ 137 pg/ml). Likewise, DOMS peaked at 24 hours and remained elevated until 72

hours after exercise. Based on these findings, the investigators concluded that PGE_2 may be a contributing factor to DOMS.

Although the magnitude and time course of DOMS reported by Smith et al. and the present study are similar, the values obtained for plasma PGE_2 are very different. Smith and co-workers obtained a mean resting plasma PGE_2 value of 326 ± 137 pg/ml, which is substantially higher than the mean resting value of 60.6 ± 14.8 pg/ml obtained in the present study. This mean resting plasma PGE_2 value is much higher than levels reported in a majority of the studies examining plasma PGE_2 levels in humans (Dray et al., 1975; Lijnen et al., 1990; Nowak & Wennmalm, 1978; Rauramaa et al., 1984). Furthermore, the changes in plasma levels of PGE_2 obtained by Smith et al. are of a magnitude which are not reflected by a majority of studies examining changes in plasma PGE_2 after exercise or some other modulating factor.

Only one study examining the relationship between plasma PGE_2 values and exercise seems to corroborate the findings by Smith and co-workers. Demers et al. (1981) found plasma PGE_2 values to be elevated from resting levels (1147 ± 453 pg/ml to 1674 ± 237 pg/ml) after a 42.4 kilometer run in males and females.
Although the values reported by Demers et al. (1981) and Smith et al. (1993) are similar, Demers et al. found PGE_2 values to be elevated immediately after exercise, while Smith and co-workers did not find increases in plasma PGE_2 until 24 hours after exercise. These findings may suggest that the elevation in plasma PGE_2 reported in

these two studies may represent artificial increases in PGE_2 due to methodological considerations. Granström & Kindahl (1990) suggest that very high levels of eicosanoids need to be validated by mass spectrometry or suppression of the response by a specific inhibitor before these values can be classified as real increases.

Several factors may have contributed to the difference in the plasma PGE_2 response reported in the present study and the study by Smith et al. (1993). One possible cause for the difference in plasma PGE_2 values is the use of different PGE_2 extraction techniques in the two studies. In the present study, the samples were passed through a solid phase extraction cartridge, while the samples obtained by Smith et al. were analyzed using an extraction method which appears to not utilize solid phase extraction cartridges (Pennington, 1988). Vandenburgh et al. (1990) suggest that the use of C_{18} cartridges is essential for proper extraction of prostanoids when indomethacin is used as a cyclooxygenae inhibitor in sample tubes.

Another difference between the two studies which may have led to differing results may be related to the type of exercise modality used. In the present study, a typical weight training workout was used which utilized the major muscle groups of the body. On the other hand, Smith et al. (1993) used an eccentric protocol which stressed the chest, shoulders, and arms. Work by Nowak & Wennmalm (1978) suggests that plasma PGE_2 values can vary, depending on what blood vessel they are taken from. The eccentric contractions used by Smith et al. to elicit DOMS

overloaded areas which included the muscles of the upper arm and forearm. The samples were obtained from the antecubital veins of the forearm. Since the samples were obtained from an area which was exercised intensely, it is possible that PGE_2 values obtained from this area might be higher than those obtained from blood sampled from the forearm after eccentric exercise which did not specifically target this area. However, Sinzinger (1985) indicates the sampling site is not a factor in PGE_2 levels in plasma. Even if this was a contributing factor to the the differences in plasma PGE_2 values obtained in the two studies, the magnitude of the difference suggests other causitive factors. Based on the sensitivity of plasma PGE_2 values to blood sampling techniques, storage and handling of samples, extraction methodology, and assay sensitivity (Dray et al., 1975; Granström & Kindahl, 1990; Kinoshita et al., 1985; Kuzuya et al., 1985; Nell et al., 1989; Petit & Kort, 1988; Powell, 1980; Pradelles et al., 1985; Sinzinger, 1985), it is possible that the differences in plasma PGE_2 values obtained in these two studies may be due to differences in the techniques used to isolate and measure plasma PGE_2 levels.

Effect of the Weight Lifting Bout on LTB_4

Leukotriene B_4 is an arachidonic acid metabolite which plays a major role in tissue edema and swelling, microvascular permeability, and migration of polymorphonuclear cells and monocytes to injured tissue (Barsacchi et al., 1986; Cambria, Anderson, Dikdan, Lysz & II, 1991; Hedqvist, Lindbom, Palmerz &

Raud, 1994; Hedqvist, Raud, Palmertz, Kumlin & Dahlén, 1990; Lefer, 1985). Evans (Evans, 1992; Evans & Cannon, 1991), Cannon et al. (1991), and Stauber et al. (1990) suggest that exercise-induced muscle damage stimulates an inflammatory response which is similar to the acute phase response of inflammation. This response has been to shown to result in migration of polymorphonuclear cells and monocytes into the affected tissue (Armstrong et al., 1983; Faulkner et al., 1989; Fielding et al., 1993; Jones et al., 1986; O'Reilly et al., 1987; Stauber et al., 1990), increases in endothelial and microvascular permeability (Armstrong et al., 1983; Cannon et al., 1994; Stauber et al., 1990), and increased levels of cytokines, such as IL-1 and TNF-α, which promote changes in protein metabolism and other metabolic events (Cannon et al., 1991; Dinarello, 1988; Nawabi, Block, Chakrabarti & Buse, 1990). This process may be responsible for the efflux of CK (Armstrong et al., 1983; Cannon et al., 1994; Evans et al., 1986; Virtanen, Viitasalo, Vuori, Väänänen & Takala, 1993) and increases in connective tissue and muscle markers(Stauber et al., 1990; Virtanen et al., 1993), increases in intramuscular pressure (Crenshaw, Thornell & Fridén, 1994; Fridén et al., 1988), and possibly DOMS (Armstrong, 1984; Evans & Cannon, 1991; Smith, 1991; Stauber et al., 1990).

Based on the previous discussion, it appears that LTB_4 is a prime candidate for playing a role in changes in vascular permeability, diapedis and migration of leukocytes (Ford-Hutchinson & Letts, 1986; Hedqvist et al., 1994; Hedqvist et al., 1990) and the

generation of DOMS (Bennett, 1988; Bertin et al., 1994; Levine et al., 1986; Madison et al., 1992; Martin et al., 1987; Taiwo et al., 1987). Therefore, it was hypothesized that LTB_4 may play a role in the generation of DOMS. This should lead to increases in plasma levels of LTB_4 which are associated with the time course changes of DOMS.

Plasma levels of LTB_4 have been used to determine the role that this leukotriene has in inflammatory conditions, such as arthritis and asthma. Thus, baseline or resting levels of plasma LTB_4 have been established in the literature. However, the range of values reported in the literature is quite large. At the upper end of the spectrum are the results reported by Ibe, Kurantstin-Mills, Raf & Lessin (1994) in a study to determine the role of leukotrienes in the inflammatory process in sickle-cell anemia. Ibe et al. (1994) reported mean resting plasma LTB_4 values of 8.95 ± 0.26 ng/ml.

Much lower plasma LTB_4 values were found by Nieminen et al. (1991), examining the effects of platelet-activating factor on plasma LTB_4. They reported mean plasma LTB_4 values of 150-180 pg/ml. Similar results were reported by Nieminen, Moilanen, Koskinen, Karvonen & Tuomisto (1992) examining the effects of inhaled budesonide to inhibit the platelet-activating factor-induced increases in plasma LTB_4. Nieminen et al. (1992) reported plasma LTB_4 levels ranging from 200-800 pg/ml, slightly higher than in their previous study, in subjects inhaling a dilutent control.

In contrast to these findings, Shindo, Miyakawa & Fukumura (1993) measured changes in plasma levels of LTB_4 during bronchial

asthma. They reported mean resting levels in controls of 23.5 $\pm$ 3.77 pg/ml, and mean LTB_4 levels in asthmatic patients of 34.2 $\pm$ 3.77 pg/ml prior to their asthma attacks. During the asthma attacks mean plasma LTB_4 values were 118.0 $\pm$ 49.5 pg/ml. Unlike the other studies cited which sampled venous blood from the antecubital vein of the forearm, Shindo and Fukumura sampled arterial blood from the femoral artery. Nowak & Wennmalm (1978) reported differences in plasma PGE_2 values depending on whether arterial or venous sampling was used, Work by Sinzinger (1985) has suggested that there is no difference in eicosanoid measurement when samples are either taken from the femoral artery or an antecubital vein.

Simmet et al. (1985) has suggested that normal levels of plasma leukotrienes are in the low pg/ml range. This would seem to indicate that the values reported by Shindo et al. (1993), are more accurate in representing normal plasma LTB_4 values. This idea is also suggested by the work of Bertin et al. (1994) examining the inflammatory response mediators in human rheumatoid synovial fluid. Bertin et al. found LTB_4 levels in the synovial fluid of the knee joint of patients suffering from rhuematoid arthritis accompanied by swollen knees to be around 500 pg/ml. This may indicate that the higher values reported by Nieminen (Nieminen et al. 1992; Nieminen et al., 1991) and Ibe (Ibe et al., 1994) may not reflect normal plasma LTB_4 levels.

It is possible that sampling and handling techniques (Granström & Kindahl, 1990; Nell et al., 1989; Sinzinger, 1985), and

extraction methodology (Kinoshita et al., 1985; Kuzuya et al., 1985), may have contributed to the differences in plasma LTB_4 levels reported in the literature. Of particular importance in relation to the elevation of plasma LTB_4 levels is that blood samples collected in tubes with heparin, and to some extent sodium citrate, as an anticoagulant may demonstrate artificially elevated eicosanoid levels (Granström & Kindahl, 1990; Nell et al., 1989; Sinzinger, 1985). Heparin is associated with nonspecific intereferences in analyses associated with specific antibodies (Granström & Kindahl, 1990; Sinzinger, 1985). Thus, the differences in plasma LTB_4 values reported in the preceeding studies may be, in part, due to the use of heparin as an anticoagulant by Nieminen and co-workers (Nieminen et al., 1992; Nieminen et al., 1991), and to some extent by the use of sodium citrate by Ibe et al. (1994).

It was hypothesized that the weight lifting bout would result in increases in plasma levels of LTB_4 which will exhibit a time course similar to that of DOMS over the 120-hour time period. In the present study, resting plasma LTB_4 values were 15.3 ± 3.4 pg/ml in the treatment group and 14.4 ± 3.9 pg/ml in the control group. These values are similar to the results reported by Shindo et al.(1993). According to the MANOVA performed on the plasma LTB_4 values, there was a significant treatment effect. However, a comparison of post-exercise values with resting values and values at succesive time periods did not demonstrate any individual differences. No significant differences between values for the treatment group and

control group were found. Furthermore, there was not a great deal of inter- and intra-individual variation in plasma LTB_4. Therefore, it appears that the significant p-value generated by the MANOVA is not a result of actual changes in plasma LTB_4 values. Therefore, the hypothesis that the weight lifting bout would result in increases in plasma levels of LTB_4 which will exhibit a time course similar to that of DOMS over the 120-hour time period was rejected. Thus, it seems that plasma levels of LTB_4 are not associated with the generation of DOMS.

Currently the present study is the only research to examine the relationship between plasma levels of LTB_4 and DOMS resulting from a weight lifting bout which is associated with muscle damage. However, Cannon et al. (1991) examined the effect of damaging eccentric exercise on in vitro production of mediators of inflammation, including PGE_2 and LTB_4, by mononuclear cells in plasma from individuals supplemented with vitamin E. Cannon et al. found that PGE_2 production was significantly increased after exercise in subjects not supplemented with vitamin E. However, the LTB_4 concentrations measured in the mononuclear cell cultures were not presented by the authors because they determined that the 1-10 pg/ml concentrations were at a level that might be due to cross-reaction with the prostaglandins in the culture. Based on the results of the present study, these values might be deemed appropriate.

Correlations Among the Variables

Several significant correlations were found in the present study between change scores for the variables at a specific time period. Significant correlations were found between changes in plasma lactate and CK values from resting values immediately after exercise (r= 0.92), 24 hours (r= -0.78), and 72 hours (r= -0.77) after exercise in the treatment group. A significant correlation was also found between plasma lactate and LTB_4 (r=0.77) 72 hours after exercise. The significant correlations at 24 hours and 72 hours between elevated CK levels and lactate values which had returned to baseline values do not seem to be relevant. Additionally, the significant correlation between lactate values at baseline levels and LTB_4 at 72 hours does not appear to be pertinent.

Other researchers have examined the correlations among functional and biochemical markers of exercise-induced muscle damage. Rodenburg, Bär & Boer (1993) examined correlations between plasma CK, myoglobin, DOMS, and extension and flexion angle of the elbow after forced extension and flexion of the elbow. No significant correlations were found between any of the variables. Tiidus & Ianuzzo (1983) found a significant correlation (r=0.80) between changes in serum CPK activity and changes in the magnitude of soreness perception after exercise on a leg extension apparatus. This significant relationship was attained by finding the regression line for a plot of each group mean score for changes in serum CPK

activity and muscle soreness for nine exercise treatment groups and one control group.

The significant correlation between the post-exercise changes in plasma lactate and CK appears to be realistic. However, interpretation of the CK data is somewhat difficult. A higher post-exercise plasma lactate value might indicate that a particular subject was performing the weight lifting bout at a higher level of effort than subjects with lower plasma lactate values. However, McMillan et al. (1993) found no difference in plasma lactate values between subjects experienced with weight training and untrained subjects after a single bout of weight training exercise.

Schwane et al. (1983) found that downhill running elicited increases in plasma CK without any significant changes in lactate dehydrogenase activity. Furthermore, they reported there was not a significant correlation between LDH activity and plasma CK. Thus, the value of the significant correlation between post-exercise plasma lactate and CK is questionable. In conclusion, the correlations which were hypothesized between DOMS and PGE_2, DOMS and LTB_4, CK and PGE_2, LTB_4 and CK, and PGE_2 and LTB_4 were rejected. The hypothesis that there would not be significant correlations between lactate and DOMS, and CK and DOMS was accepted.

A relationship between plasma CK and PGE_2 values was suggested by the data from subject #8. Because this subject's CK values were at a level associated with muscular disorders (Anneslet, Strongwater & Chnittzir, 1985; Stags, 1981; Yasmineh,

Abahin, Abbashezhand & Awad, 1978), this subject's values were not included in the analyses of the treatment group means. In addition, the PGE_2 values in this subject seemed to demonstrate time course changes similar to those exhibited by plasma CK values over the 120-hour time period. Furthermore, these PGE_2 values were substantially higher than those exhibited at rest for the treatment group. PGE_2 has been shown to play a role in regulation of the inflammatory response and is an important regulator of the immune response (Roper & Phipps, 1994). Elevated PGE_2 production has been associated with a number of pathological conditions (Barsacchi et al., 1986; Bockman, 1983; Roper & Phipps, 1994; Strobl-Jäger, Widhalm & Sinzinger, 1986) Therefore, it is possible that there is a connection between the changes exhibted in these two variables.

As previously described the plasma PGE_2 changes after the workout in subject #8 were substantially higher than the mean values in the treatment group. This particular subject also had the highest post-exercise lactate value in the treatment group- 17.1 mM. Values for plasma LTB_4 were not measured in this subject, so it is not known whether plasma LTB_4 levels were elevated in this subject.

Contrary to the elevation in PGE_2, subject # 8 reported a peak muscular soreness rating of five, from 24 to 72 hours after exercise. This is in contrast to a mean peak soreness rating of 6.2 for the treatment group (Table 6). The hypothesis that increases in plasma PGE_2 levels were associated with DOMS would predict that

subject #8 would experience the most severe intensity of DOMS, since he demonstrated the highest PGE_2 values. However, other subjects reported higher muscle soreness ratings than those reported by subject #8, and subject #8's peak soreness rating was lower than the mean peak soreness rating. The DOMS and plasma PGE_2 responses of subject #8, combined with the lack of change in the mean plasma PGE_2 levels over the 120-hour post-exercise time period in the treatment group, provide an arguement that plasma PGE_2 levels are not associated with the generation DOMS.

CHAPTER VI

CONCLUSIONS AND RECOMMENDATIONS

The results of the present study indicate that plasma PGE_2 and LTB_4 values do not show increases concominant with the manifestation of DOMS after an acute weight lifting bout involving eccentric contractions. This suggests that PGE_2 and LTB_4 probably do not contribute to DOMS. However, there is a body of research which suggests that these inflammatory mediators may contribute to DOMS. Therefore, further investigation into the relationship between prostaglandins, leukotrienes, and DOMS in the process of muscle damage and repair resulting from exercise is warranted.

Due to the large variability in baseline levels of plasma PGE_2 and LTB_4 exhibited in the present study and in the eicosanoid literature, a larger sample size would enhance the ability of the study to elucidate changes in the inflammatory mediators as a result of the exercise treatment. Based on the experimental design the use of seven sampling periods requires three times as many subjects as sampling periods (D. Ludwig, personal communication, November 9, 1995) in order to maximize statistical power. Thus, 21 subjects would be an appropriate number of subjects to use in future studies with a similar paradigm. Furthermore, it may be important to investigate these parameters in an older population, since the CK response has been shown to vary, depending on age (Canon et al.,

1990).

Since arachidonate and other C_{20} fatty acids such as α-linolenate and linoleate are precursors to eicosanoids (Murray, Granner, Mayes, and Rodwell, 1990), and dietary intake of these fatty acids may influence eicosanoid synthesis. Therefore, future studies should monitor the food intake of subjects while participating in this type of investigation. This may help reduce the variability seen in studies measuring plamsa prostaglandins and leukotrienes.

In the present study subjects only rested for 10 minutes prior to blood sampling. It appears that to minimize intra- and inter-subject variability not attributable to a treatment effect, it is important to have the subjects resting for 30 minutes prior to blood sampling (Nell et al., 1989; Sinzinger, 1985). Stringent adherence to optimal processing, handling, and extraction of samples would decrease in vitro production of prostaglandins and help minimize the variability associated with measurement of eicosanoids.

Since PGE_2 and LTB_4 in the bloodstream are rapidly removed from the circulation and metabolized (Granström & Kindahl, 1990; Keppler, Jedlitschky & Leier, 1994), plasma changes in these eicosanoids may be difficult to detect. However, changes in plasma LTB_4 and PGE_2 resulting from a treatment effect may be easier to detect through the measurement of longer-lived metabolites of PGE_2 and LTB_4 which are more likely to accumulate in the circulation (Granström, Hamberg, Hansson & Kindahl, 1980; Keppler et al., 1994).

Thus, the effects of eccentric exercise on DOMS and these stable metabolites should be examined in order determine if plasma PGE_2 and LTB_4 reflect the involvement of these eicosanoids in the generation of DOMS.

Although plasma PGE_2 and LTB_4 appear to indicate there is no change in these eicosanoids after exercise-induced muscle associated with DOMS, plasma values of PGE_2 and LTB_4 may not reflect tissue levels of PGE_2 and LTB_4. For example, Evans et al. (1986) hypothesized that muscle damage resulting from eccentric exercise would result in increased plasma levels of IL-1, a cytokine which is a mediator of the acute phase response of inflammation. Their research demonstrated that plasma IL-1 levels were significantly elevated in untrained subjects 3-hours after eccentric exercise, but returned to baseline values by 24 hours. Since the onset of DOMS does not usually appear until 24 hours after exercise, increases in plasma IL-1 do not follow the same time course as the manifestation of DOMS. This indicates that plasma IL-1 was not associated with DOMS. Like PGE_2 and LTB_4, IL-1 is rapidly cleared from the circulation (Dinarello, 1988). Hence, IL-1 levels in the tissue may be elevated for a longer period of time, thereby, promoting components of the inflammatory response which may contribute to the manifestation of DOMS. Work by Cannon et al. (1989a), validated this contention by demonstrating increased levels of IL-1 five days after eccentric exercise.

Therefore, it is possible that even though plasma levels of PGE_2 and LTB_4 do not show changes immediately after and 24 hours after exercise with an eccentric component, tissue levels of these eicosanoids may be elevated. Thus, the systemic levels of these inflammatory mediators may not reflect PGE_2 and LTB_4 activity in muscle tissue after exercise which generates DOMS. Future research should examine levels of PGE_2 and LTB_4 in muscle tissue which has undergone eccentric contractions which have resulted in DOMS over a time period of at least 120 hours.

The relationship between these eicosanoids and DOMS could also be studied using the rat model. Although rats are unable to report muscle soreness, Armstrong (Armstrong, 1984; Armstrong et al., 1983) has used a rat model to document muscle damage resulting from eccentric exercise. Levels of PGE_2 and LTB_4 could be examined in terms of their role in exercise induced muscle damage and repair. This would provide information as to the possible role these inflammatory mediators play in this adaptive process. The rat model provides for a larger sample number and more experimental control than with human subjects.

Future research in this area could also utilize inhibitors of the lipoxygenase and cyclooxygenase pathways to determine if DOMS is affected by decreased levels of these compounds in muscles experiencing soreness. This technique could also be used in the rat model to determine if lower levels of PGE_2 and/or LTB_4 affect the normal morphology of muscle damage and repair.

Future studies should also examine other biochemical mediators and modulators associated with pain and the inflammatory process. Bradykinin, histamine, substance p, interleukin-1β and 5-hydroxytryptamine are several substances which may be involved in the response to mechanical forces during muscle contraction which cause muscle damage (Evans & Cannon, 1991; Fritz & Stauber, 1988; Stauber, 1989; Stauber et al., 1988). Accumulation of these substances in areas of muscle damage may either directly stimulate pain afferents or increase sensitivity of these pain afferents (Bennett, 1988; Ferreira, Lorenzetti, Bristow & Poole, 1988; Mense, 1981; Taiwo et al., 1987).

Currently it is believed that DOMS is but one component of the repair and adaptation process which occurs in skeletal muscle when it is exposed to unaccustomed mechanical forces or activities. An understanding of the mechanisms associated with the generation of DOMS will provide some insight into the role which DOMS plays in this process and the processes involved in this adaptive process. In a clinical setting, this information may provide some understanding of the mechanisms involved in the manifestiation of pain in rheumatoid arthritis and other painful pathologies. Furthermore, a more thorough understanding of this entire damage and adaptation process may provide information which can be utilized in the treatment of degenerative muscular diseases (Lewis & Haller, 1989) and regeneration of muscle fibers damaged by mechanical or chemical trauma, ischemia, and other physiological insults (Carlson

& Faulkner, 1983; White & Devor, 1993). Therefore, investigation of the mechanisms underlying exercise-induced muscle soreness have a wide range of implications and merit further intensive study.

In summary, this study investigated the relationship of plasma levels of PGE_2, LTB_4, CK, lactic acid, and DOMS over 120-hours after an acute weight lifting bout involving eccentric contractions in order to determine if PGE_2 and/or LTB_4 contribute to DOMS. This study reported no significant increases in plasma PGE_2 and LTB_4 after the workout. However, significant increases in plasma CK, a marker of muscle damage, were seen immediately after exercise, and 3-5 days after exercise. Plasma lactate was significantly elevated post-exercise, but returned to baseline values thereafter. Muscle soreness was significantly elevated above resting levels immediately after exercise, peaking at 24 hours, and finally returning to resting levels by 120 hours after exercise. Based on these results it appears that PGE_2 and LTB_4, as indicated by plasma levels of these eicosanoids, does not appear to be a factor in the generation of DOMS resulting from a weight lifting bout involving eccentric contractions.

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APPENDIX A
(INFORMED CONSENT FORM)

Consent Form for Human Subjects

THE UNIVERSITY OF NORTH CAROLINA AT GREENSBORO
SCHOOL OF HEALTH, PHYSICAL EDUCATION AND RECREATION

Subject's Name: ____________________________________

Project Title: The Relationship Among Prostaglandin E_2, Leukotriene B_4, and Delayed Onset Muscle Soreness

Project Supervisor: Dr. Allan H. Goldfarb, Associate Professor

Project Coordinator: Brian Boyer, Doctoral Candidate, Department of Exercise and Sport Science

I understand that the purpose of this study is to investigate the relationship between delayed onset muscle soreness (DOMS), prostaglandin E_2, and leukotriene B_4 resulting from a weight lifting bout. Whereas this study may not directly benefit me, it may advance knowledge in the field of exercise physiology.

I understand that during the study I will report to the Human Performance Laboratory (HPRD 240), for at least seven visits. During the first visit I will perform a one-repetition maximum test on the following weight training exercises: bench press, triceps pushdowns, military press, biceps curls, leg press, and wide grip pulldowns. I understand that a one-repetition maximum test involves attempting to overcome the most resistance I can with maximal effort on these exercises. I understand that during the one-repetition maximum test I may experience some muscular discomfort and I may experience some muscle soreness after the testing procedure(24-72 hours). I understand that I will not take any medications or other action to reduce the intensity of the soreness. I understand that I will contact Brian Boyer before seeking medical treatment or if I feel I am experiencing severe muscular pain. I understand that I will contact Brian Boyer if I experience any stressful situations to which I am not normally accustomed. I understand that during this test I will be continuously supervised by the researchers in order to insure that proper weight lifting safety techniques are being utilized during testing.

I understand that I will return to the lab at least two weeks after the first testing session for the weight lifting session in a fasted state. I understand that upon entering the lab, two 10 milliliter blood samples will be taken from my antecubital vein, located in the elbow region, by venapuncture with a Vacutainer. I understand that insertion and removal of the needle may be slightly painful, but that the pain will quickly subside. I understand that there may be some bruising associated with procurement of a blood sample, as well as some risk of infection. However, I also understand that the risk of bruising will be minimized since direct pressure will be applied to the area upon removal of the needle. In addition, I understand that the risk of infection will be minimized since only sterile techniques will be used. I understand that after the blood sample has been collected that I will begin the weight lifting session. I understand that during this session I will perform the following exercises: bench press, triceps pushdowns, behind the neck press, biceps curls, leg press, and wide grip pulldowns. I understand that I will perform three sets of each exercise. Additionally, I understand that I will perform as many repetitions as possible until muscular failure using a resistance of 70% of my one-repetition maximum for each set on a particular exercise. I understand that I will be provided with adequate instruction on how to properly perform each exercise which will be utilized during the weight lifting session. In addition, I understand that I will be given a proper warm-up before attempting maximal exertion on each exercise, as well as being constantly monitored by the researchers throughout the weight lifting session. I understand that performance of the exercises during this session may result in some muscular discomfort and may provide some muscle soreness for several days after the weight lifting session. I understand that immediately after the weight lifting session another blood sample will be taken in exactly the same manner as the previous blood sample.

I understand that I will return to the laboratory every day for the next five days at approximately the same time at which I performed the weight lifting session. I understand that during these visits blood samples will be taken in exactly the same manner as the previous blood samples.

I confirm that my participation in this study is completely voluntary, and that no coercion of any kind has been used to obtain

my cooperation. I also understand that I can withdraw my consent and terminate my participation in this study at any time. I understand that all information obtained in this study will remain confidential and anonymous. I understand that a summary of the results of the study will be made available to me, per my request, after completion of this study.

I confirm that I have been informed of the procedures that will be used in this study. I understand what is required of me as a subject. I agree that any questions I have regarding this study and the procedures have been answered to my satisfaction; and, I wish to give my voluntary cooperation as a participant.

____
Signature of Subject

Phone Number ________

____

____
Address

____
Witness

Date__________________

APPENDIX B
(MEDICAL HISTORY QUESTIONNAIRE)

Subject Medical History Questionnaire

1. Has you doctor ever said you have any kind of heart trouble?
   Yes_____ No_____

2. Do you frequently have pains in your heart and/or chest or have abnormal heart beats?
   Yes_____ No_____

3. Do you often feel faint or have spells of severe dizziness?
   Yes_____ No_____

4. Has a doctor ever said that you have high blood pressure?
   Yes_____ No_____

5. Has a doctor ever indicated that you have a joint or bone problem (e.g., arthritis) that has been caused or made worse by exercise or that might be made worse with exercise?
   Yes_____ No_____

6. Are you unaccustomed to vigorous exercise?
   Yes_____ No_____

7. Do you smoke cigarettes? Yes_____ No_____

8. Has your father, mother, sister, or brother had any heart trouble or strokes before age 50?
   Yes_____ No_____

   If yes, who and what type of problem?______________________
   ____

9. Has your doctor ever indicated that your cholesterol was/is high?
   Yes_____ No______

10. Do you have diabetes? Yes_____ No_____

11. Have you ever had back pain/problems which lasted more than one week? Yes_____ No_____

If yes, briefly describe________________________________
____

12. Do you presently exercise? Yes_____ No_____

If yes, how many days per week?_____how many hours/day?___

Type of exercise?___________________________________
____

13. Are you currently taking any prescription medications?
Yes_____ No_____

If yes, please explain:_______________________________
____
____

14. Are you currently taking any over-the-counter medications?
Yes_____ No_____

If yes, please explain:_______________________________
____

15. Has your mother, father, sister, or brother ever had high cholesterol, died suddenly, or died prematurely?
Yes_____ No_____

If yes, please explain:_______________________________
____

15. Is there any good physical/mental reason not mentioned here why you should <u>not</u> follow a physical activity program even if you wanted to?

Yes_____ No_____

If yes, please explain:_______________________________
____
____

17. Are you currently taking any type of supplements? If so, please list:____

18. Have you recently been involved in any experiences which you consider to be of an unusually stressful nature? If yes, please explain:____

19. Have there been any events which have occured recently in your life which you consider to be unusual? If yes, please explain:____

APPENDIX C
(SUBJECT INSTRUCTIONS)

Instuctions For Weight Lifting Study Participants

(Please post in a prominent place)

1. If you are experiencing muscle soreness which you feel is inappropriate, immediately call me at school or at home.
2. Do not take any medications or any other action to alleviate muscle soreness.
3. If you are going to seek any type of medical treatment, please inform me prior to visiting a medical professional.
4. Do not take any type of supplements or new medications during the study.
5. If you have any questions at all regarding the study, please do not hesitate to call me.

Thank you again for your participation in this study. If you attempt to reach me at home or at school and I am unavailable, please leave a message on my answering machine at home or contact Dr. Allan Goldfarb, the faculty director of this research study.

Brian Boyer

Home phone number: 282-8141

School phone number: 334-3039

Dr. Allan Goldfarb: 334-3029

APPENDIX D
(1RM TESTING SESSION FORM)

1RM TESTING SESSION

Name__________ Date______________Subject__________

	1 RM	70% 1RM
Bench press	_______	_______
Triceps pushdowns	_______	_______
Military press	_______	_______
Biceps curls	_______	_______
Leg press	_______	_______
Wide grip pulldowns	_______	_______

APPENDIX E
(WEIGHT LIFTING SESSION FORM)

WEIGHT LIFTING SESSION

Name__________ Date_________ Subject_______

Exercise	Weight	Set1 Reps	Set 2 Reps	Set 3 Reps
Bench press	______	______	______	______
Triceps pushdown	______	______	______	______
Military press	______	______	______	______
Bicep curls	______	______	______	______
Leg press	______	______	______	______
Wide grip pulldowns	______	______	______	______

APPENDIX F

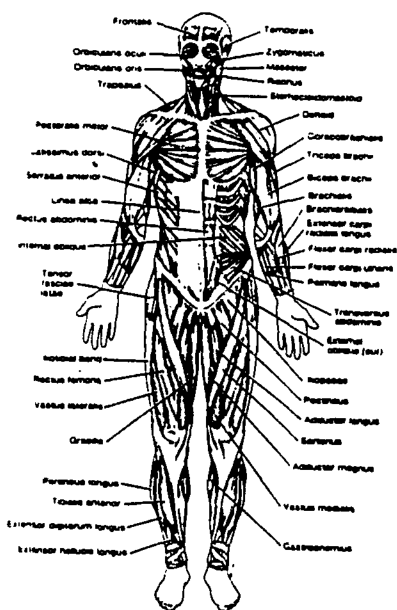
(PERCEIVED MUSCLE SORENESS QUESTIONNAIRE)

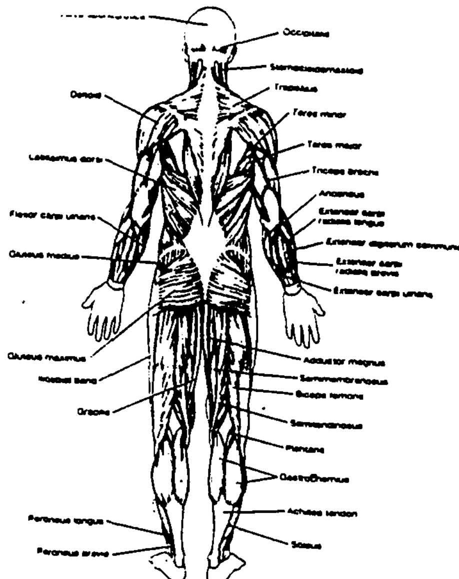
Perceived Muscle Soreness Rating Scale

0 1 2 3 4 5 6 7 8 9 10

normal mildly sore very sore very, very, sore

On the following diagram, circle the areas which seem to be the most sore.





APPENDIX G

(T-VALUES AND P-VALUES FOR T-TESTS)

Table 9

T-Test Values and p-Values for Differences in DOMS Ratings Values over 120 Hours in the Treatment Group

		pre	post	24	48	72	96	120
pre	T	- -	3.49	12.16	31.36	3.88	3.69	1.41
pre	p	- -	0.008	.0001	.0005	.0046	.0061	.1950
post	T	3.49	- -	3.9	- -	- -	- -	- -
post	p	0.008	- -	.004	- -	- -	- -	- -
24	T	12.16	3.9	- -	-2.81	- -	- -	- -
24	p	0.008	.004	- -	.023	- -	- -	- -
48	T	31.36	- -	-2.81	- -	-4.91	- -	- -
48	p	.0005	- -	.023	- -	.0012	- -	- -
72	T	3.88	- -	- -	-4.91	- -	-3.02	- -
72	p	.0046		- -	.0012	- -	.016	- -
96	T	3.69	- -	- -	- -	-3.02	- -	-3.77
96	p	.0061	- -	- -	- -	.016	- -	.005
120	T	1.41	- -	- -	- -	- -	-3.77	- -
120	p	.1950	- -		- -	- -	.005	- -

Table 10

T-Test Values and p-Values for Differences in CK Values over 120 Hours in the Treatment Group

		pre	post	24	48	72	96	120
pre	T	- -	3.83	1.67	1.54	1.95	1.96	2.16
pre	p	- -	.0025	.067	.081	.044	.043	.032
post	T	3.83		.55				
post	p	.0025		.30				
24	T	1.67	.55		.90			
24	p	.067	.30		.20			
48	T	1.54		.90		1.98		
48	p	.081		.20		.041		
72	T	1.95			1.98		1.98	
72	p	.044			.041		.042	
96	T	1.96				1.98		-0.97
96	p	.043				.042		.92
120	T	2.16					-0.97	
120	p	.032					.92	

Table 11

T-Test Values and p-Values for Differences in Lactate Values over 120 Hours in the Treatment Group

		pre	post	24	48	72	96	120
pre	T	- -	6.06	.39	.18	.18	-0.89	-2.12
pre	p	- -	.0003	.70	.86	.86	.40	.067
post	T	6.06	- -	-5.84	- -	- -	- -	- -
post	p	.0003	- -	.0004	- -	- -	- -	- -
24	T	.39	-5.84	- -	-0.13	- -	- -	- -
24	p	.70	.0004	- -	.90	- -	- -	- -
48	T	.18	- -	-0.13	- -	0.0	- -	- -
48	p	.86	- -	.90		1.0	- -	- -
72	T	.18	- -	- -	0.0	- -	-0.85	- -
72	p	.86	- -	- -	1.0	- -	.42	- -
96	T	-0.89	- -	- -	- -	-0.85	- -	-0.85
96	p	.40	- -	- -	- -	.42	- -	.42
120	T	-2.12	- -	- -	- -	- -	-0.85	- -
120	p	.067	- -	- -	- -	- -	.42	- -

Table 12

T-Test Values and p-Values for Differences in PGE_2 Values over 120 Hours in the Treatment Group

		pre	post	24	48	72	96	120
pre	T	- -	-0.04	-0.42	.84	-0.13	1.18	.76
pre	p	- -	.97	.69	.43	.90	.28	.48
post	T	-0.04	- -	-0.17	- -	- -	- -	- -
post	p	.97	- -	.87	- -	- -	- -	- -
24	T	-0.42	-0.17	- -	1.81	- -	- -	- -
24	p	.69	.87	- -	.11	- -	- -	- -
48	T	.84	- -	1.81	- -	-2.18	- -	- -
48	p	.43	- -	.11	- -	.065	- -	- -
72	T	-0.13	- -	- -	-2.18	- -	2.39	- -
72	p	.90		- -	.065	- -	.048	- -
96	T	1.18	- -	- -	- -	2.39	- -	-0.78
96	p	.28		- -	- -	.048	- -	.46
120	T	.76	- -	- -	- -	- -	-0.78	- -
120	p	.48	- -	- -	- -	- -	.46	- -

Table 13

T-Test Values and p-Values for Differences in LTB_4 Values over 120 Hours in the Treatment Group

		pre	post	24	48	72	96	120
pre	T	- -	-0.88	-1.54	-0.11	.60	1.39	.40
pre	p	- -	.40	.16	.91	.57	.20	.70
post	T	-0.88	- -	-1.55	- -	- -	- -	- -
post	p	.40	- -	.16	- -	- -	- -	- -
24	T	-1.54	-1.55	- -	1.14	- -	- -	- -
24	p	.16	.16	- -	.29	- -	- -	- -
48	T	-0.11	- -	1.14	- -	.37	- -	- -
48	p	.91	- -	.29	- -	.72	- -	- -
72	T	.60	- -	- -	.37	- -	1.28	- -
72	p	.91	- -	- -	.72	- -	.23	- -
96	T	1.39	- -	- -	- -	1.28	- -	-0.71
96	p	.20	- -	- -	- -	.23	- -	.50
120	T	.40	- -	- -	- -	- -	-0.71	- -
120	p	.70	- -	- -	- -	- -	.50	- -

Table 14

T-Test Values and p-Values for Differences in DOMS Rating Values over 120 Hours in the Control Group

		pre	post	24	48	72	96	120
pre	T	- -	- -	-1.0	0.0	0.0	-1.0	-1.0
pre	p	- -	- -	.37	1.0	1.0	.37	.37
post	T	- -	- -	- -	- -	- -	- -	- -
post	p	- -	- -	- -	- -	- -	- -	- -
24	T	-1.0	- -	- -	1.0	- -	- -	- -
24	p	.37	- -	- -	.37	- -	- -	- -
48	T	0.0	- -	1.0	- -	- -	- -	- -
48	p	1.0	- -	.37	- -	- -	- -	- -
72	T	0.0	- -	- -	- -	- -	-1.0	- -
72	p	1.0	- -	- -	- -	- -	.37	- -
96	T	-1.0	- -	- -	- -	-1.0	- -	- -
96	p	.37	- -	- -	- -	.37	- -	- -
120	T	-1.0	- -	- -	- -	- -	- -	- -
120	p	.37	- -	- -	- -	- -	- -	- -

Table 15

T-Test Values and p-Values for Differences in CK Values over 120 Hours in the Control Group

		pre	post	24	48	72	96	120
pre	T	- -	- -	-0.69	.20	-0.60	-0.40	.77
pre	p	- -	- -	.53	.85	.58	.71	.48
post	T	- -	- -	- -	- -	- -	- -	- -
post	p	- -	- -	- -	- -	- -	- -	- -
24	T	-0.69	- -	- -	.66	- -	- -	- -
24	p	.53	- -	- -	.54	- -	- -	- -
48	T	.20	- -	.66	- -	-0.75	- -	- -
48	p	.85	- -	.54	- -	.49	- -	- -
72	T	-0.60	- -	- -	-0.75	- -	.21	- -
72	p	.58	- -	- -	.49	- -	.84	- -
96	T	-0.40	- -	- -	- -	.21	- -	.79
96	p	.71	- -	- -	- -	.84	- -	.47
120	T	.77	- -	- -	- -	- -	.79	- -
120	p	.48	- -	- -	- -	- -	.47	- -

Table 16

T-Test Values and p-Values for Differences in Lactate Values over 120 Hours in the Control Group

		pre	post	24	48	72	96	120
pre	T	- -	- -	-1.11	.17	-1.73	-2.58	.16
pre	p	- -	- -	.35	.87	.16	.061	.88
post	T	- -	- -	- -	- -	- -	- -	- -
post	p	- -	- -	- -	- -	- -	- -	- -
24	T	-1.11	- -	- -	.90	- -	- -	- -
24	p	.35	- -	- -	.43	- -	- -	- -
48	T	.17	- -	.90	- -	-1.63	- -	- -
48	p	.87	- -	.43	- -	.18	- -	- -
72	T	-1.73	- -	- -	-1.63	- -	.11	- -
72	p	.16	- -	- -	.18	- -	.91	- -
96	T	-2.58	- -	- -	- -	.11	- -	1.30
96	p	.061	- -	- -	- -	.91	- -	.26
120	T	.16	- -	- -	- -	- -	1.30	- -
120	p	.88	- -	- -	- -	- -	.26	- -

Table 17

T-Test Values and p-Values for Differences in PGE_2 Values over 120 Hours in the Control Group

		pre	post	24	48	72	96	120
pre	T	- -	- -	1.62	.16	.97	- -	.74
pre	p	- -	- -	.24	.89	.51	- -	.59
post	T	- -	- -	- -	- -	- -	- -	- -
post	p	- -	- -	- -	- -	- -	- -	- -
24	T	1.62	- -	- -	-4.60	- -	- -	- -
24	p	.24	- -	- -	.044	- -	- -	- -
48	T	.16	- -	-4.60	- -	.91	- -	- -
48	p	.89	- -	.044	- -	.46	- -	- -
72	T	.97	- -	- -	.91	- -	1.17	- -
72	p	.51	- -	- -	.46	- -	.45	- -
96	T	- -	- -	- -	- -	1.17	- -	-2.05
96	p	- -	- -	- -	- -	.45	- -	.29
120	T	.74	- -	- -	- -	- -	-2.05	- -
120	p	.59	- -	- -	- -	- -	.29	- -

Table 18

T-Test Values and p-Values for Differences in LTB_4 Values over 120 Hours in the Control Group

		pre	post	24	48	72	96	120
pre	T	- -	- -	1.86	1.20	.31	.54	-0.53
pre	p	- -	- -	.13	.29	.77	.62	.62
post	T	- -	- -	- -	- -	- -	- -	- -
post	p	- -	- -	- -	- -	- -	- -	- -
24	T	1.86	- -	- -	-0.54	- -	- -	- -
24	p	.13	- -	- -	.62	- -	- -	- -
48	T	1.20	- -	-0.54	- -	-0.36	- -	- -
48	p	.29	- -	.62	- -	.74	- -	- -
72	T	.31	- -	- -	-0.36	- -	.29	- -
72	p	.77	- -	- -	.74	- -	.78	- -
96	T	.54	- -	- -	- -	.29	- -	-0.83
96	p	.62	- -	- -	- -	.78	- -	.45
120	T	-0.53	- -	- -	- -	- -	-0.83	- -
120	p	.62	- -	- -	- -	- -	.45	- -

Table 19

T-Test Values and p-Values for Differences Between Control and Treatment Groups for the Variables at Specific Time Periods

Variable		pre	post	24	48	72	96	120
DOMS	T	.38		10.50	4.45	3.34	3.29	1.46
DOMS	p	.71		.0001	.0008	.0059	.0064	.17
CK	T	.39		1.48	1.37	1.53	1.48	1.59
CK	p	.35		.082	.098	.076	.082	.069
Lactate	T	-0.49		.59	-0.34	.98	-0.01	-1.48
Lactate	p	.63		.57	.74	.35	.99	.16
PGE_2	T	.33		-0.63	1.93	-0.35	.39	1.27
PGE_2	p	.75		.54	.080	.74	.71	.23
LTB_4	T	.16		-1.58	-0.22	.18	.59	.98
LTB_4	p	.87		.14	.83	.86	.56	.34

APPENDIX H

(RAW DATA)

Raw Data for Subject #1

Height (cm)	175.3
Weight (Kg)	59.1
Age (years)	27

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	3	9	10	8	4	0
CK (IU/L)	113	131	167	125	259	474	502
LA (mM/L)	0.9	6.0	1.3	0.8	0.8	1.1	0.8
PGE_2 (pg/ml)	107.4	47.5	108.5	86.6	97.6	151.8	158.7
LTB_4 (pg/ml)	9.7	12.0	7.4	8.4	6.5	13.2	8.8

Raw Data for Subject #2

Height (cm)	167.6
Weight (Kg)	63.6
Age (years)	27

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	- -	0	0	0	0	0
CK (IU/L)	204	- -	186	244	204	247	221
LA (mM/L)	0.9	- -	1.0	0.6	0.7	0.4	0.7
PGE_2 (pg/ml)	60.2	- -	60.0	39.9	- -	- -	- -
LTB_4 (pg/ml)	20.1	- -	29.8	18.1	26.0	25.2	22.9

Raw Data for Subject #3

Height (cm)	177.8
Weight (Kg)	81.8
Age (years)	22

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	- -	0	0	0	0	0
CK (IU/L)	68	- -	94	68	102	83	91
LA (mM/L)	2.1	- -	1.9	2.0	1.4	1.9	1.4
PGE_2 (pg/ml)	73.4	- -	91.8	80.8	72.5	91.3	69.3
LTB_4 (pg/ml)	25.9	- -	28.3	31.6	29.2	28.2	10.4

Raw Data for Subject #4

Height (cm)	167.6
Weight (Kg)	52.3
Age (years)	21

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	4	5	2	2	0	0
CK (IU/L)	84	90	82	75	78	78	78
LA (mM/L)	1.2	5.7	2.1	0.9	1.4	0.7	0.8
PGE_2 (pg/ml)	72.6	9.3	31.9	27.2	31.8	50.4	74.4
LTB_4 (pg/ml)	19.4	0.2	4.4	10.2	22.4	18.2	19.0

Raw Data for Subject #5

Height (cm)	190.5
Weight (Kg)	86.4
Age (years)	28

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	6	6	3	2	1	0
CK (IU/L)	145	215	124	233	262	219	201
LA (mM/L)	1.33	16.6	1.7	0.9	1.3	1.1	1.1
PGE_2 (pg/ml)	36.5	61.2	44.2	70.5	20.5	34.3	- -
LTB_4 (pg/ml)	9.7	10.6	6.1	8.7	6.0	7.8	6.6

Raw Data for Subject #7

(data not used in mean analysis)

Height (cm)	185.4
Weight (Kg)	74.1
Age (years)	27

	Pre	Post	24	48	72	96	120
DOMS (0-10)	3	4	5	4	4	2	1
CK (IU/L)	85	135	1974	3844	11,058	19,458	20,238
LA (mM/L)	1.2	16.6	1.1	1.1	0.8	0.8	1.0
PGE_2 (pg/ml)	- -	- -	- -	- -	- -	- -	- -
LTB_4 (pg/ml)	- -	- -	- -	- -	- -	- -	- -

Raw Data for Subject #8
(data not used in mean analysis)

Height (cm)	175.3
Weight (Kg)	79.5
Age (years)	21

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	2	5	5	5	2	1
CK (IU/L)	385	499	4,234	15,318	32,928	67,692	38,712
LA (mM/L)	0.9	17.1	1.6	1.7	1.7	2.1	1.0
PGE_2 (pg/ml)	176	100	106	120	140	507	52
LTB_4 (pg/ml)	--	--	--	--	--	--	--

Raw Data for Subject #9

Height (cm)	185.4
Weight (Kg)	90.5
Age (years)	19

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	4	7	6	4	2	0
CK (IU/L)	59	109	126	287	2,420	4,826	3,814
LA (mM/L)	1.4	15.8	1.5	2.2	0.6	2.0	1.7
PGE_2 (pg/ml)	50.9	158.9	65.2	94.7	61.2	58.7	31.8
LTB_4 (pg/ml)	36.7	23.8	19.5	23.5	32.4	32.8	20.6

Raw Data for Subject #10

Height (cm)	180.3
Weight (Kg)	77.3
Age (years)	20

	Pre	Post	24	48	72	96	120
DOMS (0-10)	1	- -	0	0	0	0	0
CK (IU/L)	90	- -	99	90	96	78	84
LA (mM/L)	1.3	- -	- -	1.2	1.0	0.7	1.3
PGE_2 (pg/ml)	- -	- -	- -	41.4	48.7	50.2	42.8
LTB_4 (pg/ml)	7.4	- -	12.1	5.6	6.1	12.0	8.1

Raw Data for Subject #11

Height (cm)	185.4
Weight (Kg)	74.1
Age (years)	23

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	2	5	4	2	1	0
CK (IU/L)	147	148	82	66	83	85	87
LA (mM/L)	0.8	4.0	1.2	2.1	2.3	0.8	0.7
PGE_2 (pg/ml)	29.5	41.1	67.7	52.3	- -	64.3	67.1
LTB_4 (pg/ml)	4.4	7.6	8.6	6.1	9.8	25.4	8.2

Raw Data for Subject #13

Height (cm)	182.9
Weight (Kg)	80.0
Age (years)	21

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	- -	0	1	1	0	0
CK (IU/L)	128	- -	106	129	85	83	250
LA (mM/L)	1.8	- -	0.9	2.1	1.0	1.4	2.6
PGE_2 (pg/ml)	- -	- -	- -	- -	- -	- -	- -
LTB_4 (pg/ml)	14.2	- -	11.6	18.0	6.3	6.9	7.8

Raw Data for Subject #14

Height (cm)	178.0
Weight (Kg)	73.0
Age (years)	27

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	5	5	4	3	2	0
CK (IU/L)	264	283	275	275	544	902	1,331
LA (mM/L)	0.9	12.3	1.2	0.6	1.0	0.9	0.7
PGE_2 (pg/ml)	55.8	44.7	48.2	77.3	100.1	97.0	96.9
LTB_4 (pg/ml)	8.7	7.3	8.3	10.9	11.7	5.6	26.4

Raw Data for Subject #15

Height (cm)	190.5
Weight (Kg)	94.5
Age (years)	21

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	1	6	6	5	4	2
CK (IU/L)	216	281	311	169	187	203	247
LA (mM/L)	0.9	15.6	0.8	1.8	1.6	1.3	0.9
PGE_2 (pg/ml)	40.6	69.9	85.5	123.0	50.7	119.5	64.4
LTB_4 (pg/ml)	18.9	25.7	24.5	17.7	27.5	30.3	29.2

Raw Data for Subject #16

Height (cm)	188.0
Weight (Kg)	88.6
Age (years)	32

	Pre	Post	24	48	72	96	120
DOMS (0-10)	2	0	6	4	1	2	2
CK (IU/L)	102	124	334	499	2,113	4,222	3,680
LA (mM/L)	2.5	10.4	1.5	1.6	1.6	1.2	1.7
PGE_2 (pg/ml)	2.0	92.0	18.9	120.5	72.0	69.4	77.4
LTB_4 (pg/ml)	22.3	17.6	12.0	41.1	20.1	29.1	20.8

Raw Data for Subject #17

Height (cm)	175.3
Weight (Kg)	84.1
Age (years)	26

	Pre	Post	24	48	72	96	120
DOMS (0-10)	0	--0	0	0	0	0	0
CK (IU/L)	158	--	126	128	117	125	110
LA (mM/L)	0.9	--	0.9	1.2	1.2	1.0	1.2
PGE_2 (pg/ml)	20.7	--	63.9	39.1	77.2	--	45.0
LTB_4 (pg/ml)	4.5	--	8.8	8.4	8.4	5.8	12.2

Raw Data for Subject #18

Height (cm)	167.6
Weight (Kg)	64.5
Age (years)	27

	Pre	Post	24	48	72	96	120
DOMS (0-10)	1	3	7	6	5	4	2
CK (IU/L)	264	326	378	558	691	757	666
LA (mM/L)	1.4	10.1	0.7	0.8	1.1	0.6	0.6
PGE_2 (pg/ml)	149.9	48.8	77.8	95.4	45.5	89.6	75.6
LTB_4 (pg/ml)	8.0	10.7	9.2	8.3	9.5	9.4	9.4