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TUMOR NECROSIS FACTOR, INTERLEUKIN-1 AND TISSUE OXYGEN LEVELS IN MYOFASCIAL PAIN AND FIBROMYALGIA PATIENTS

BY

SHARLA J. KING

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of MASTER OF SCIENCE.

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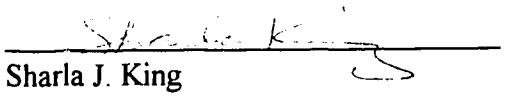

Sharla J. King
Box 101
Lloydminster, SK
S9V 0X9

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UNIVERSITY OF ALBERTA

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The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled TUMOR NECROSIS FACTOR, INTERLEUKIN 1 AND TISSUE OXYGENATION LEVELS IN MYOFASCIAL PAIN AND FIBROMYALGIA submitted by SHARLA J. KING in partial fulfilment of the requirements for the degree of MASTER OF SCIENCE.

Dr. Brian Fisher
Supervisor

Dr. Robert Burnham
Committee member

Dr. Gordon Bell
Committee member

Dr. Sharon Warren
Committee member

August 15, 1995

DEDICATION

This thesis is dedicated to my parents, who have always instilled in me the importance of an education and have provided every opportunity for me to obtain one. My brother, for keeping me partially sane through my graduate years . And finally to my sister, who unbeknownst to her, has always been a constant source of strength and encouragement to help me overcome any obstacles.

Abstract

Objectives: First, to compare cytokines Tumor Necrosis Factor (TNF-α) and Interleukin-1 (IL-1β) levels and tissue oxygen levels between Fibromyalgia (FS), Myofascial Pain Syndrome (MPS) and controls to support or refute the theory of the cause of pain originating from the periphery. Secondly, to determine if any differences exist between FS and MPS subjects on the previously mentioned items.

Methods: Ten patients fulfilling the criteria for FS, as outlined by the American College of Rheumatology (ACR), ten patients fulfilling the criteria for MPS (Travell and Simons, 1983) and ten healthy controls were the subject groups. The trigger or tender points in the upper trapezius muscle were identified and the tissue oximeter (RunMan device) was placed on the mark to record tissue oxygen levels. The subjects held that same arm as the oximeter was placed in 90 degrees shoulder abduction for 5 minutes (min) with 0 weight (kg), 3 min with 1 kg and 2 min with 2 kg, with 4 min rest intervals between each contraction. Blood was drawn at baseline before the contractions and then at 0, 15, 30 and 60 min post contractions. The tissue oximeter readings were recorded for the entire exercise protocol and for five min. after completion of the protocol.

Results: The tissue oximeter measures the deoxygenated blood and the levels showed no significant differences between all three groups. The FS and MPS subjects did not have significantly higher TNF-α levels as compared to the controls. The IL-1β had too many non-detectable values to analyze statistically.

Conclusions: The lack of differences between the pain and control groups does not concur with the theory of pain having a peripheral origin. The origin of MPS and FS pain does not appear to be related to cytokine induced soft tissue sensitization or hypoxia.

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I would like to thank first my advisor and mentor, Brian Fisher, who saw in me the ability to achieve something greater than I ever thought possible. Words could never express the gratitude I feel towards the guidance and friendship he has provided.

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CHAPTER ONE

Introduction

Myofascial Pain Syndrome (MPS) and Fibromyalgia (FS) are two common, yet complex chronic muscle pain syndromes. Prevalence studies report the occurrence of Primary Fibromyalgia in rheumatologic and general practice settings to be approximately 5% of all patients (Prescott et al., 1993). A study from Norway (Forseth and Gran, 1993) reported the prevalence of Fibromyalgia in women between the ages of 20-49 years to be 10.5%. These figures did not include people who did not seek medical treatment. Musculoskeletal disorders rank first among registered occupational diseases in Denmark (Andersen and Gaardboe, 1993), and 10% of newly admitted patients into a rheumatology clinic have been diagnosed with fibromyalgia (Reilly and Littlejohn, 1992). People from all occupations and backgrounds can be afflicted with one or both of these conditions (Andersen and Gaardboe, 1993; Rosen, 1993). The fact that there is no cure places this population in a continual cycle of rehabilitation and treatment using health care dollars. Although most commonly seen in an outpatient setting, soft tissue pain syndromes also contribute to the pain, stiffness, weakness and disability level of patients with conditions like rheumatoid arthritis, endocrine abnormalities and musculoskeletal polytrauma. A better understanding of the etiology of Myofascial Pain and Fibromyalgia and the identification of an objective measure of disease activity would greatly assist in establishing diagnostic criteria, appropriate treatment, assessing treatment efficacy and exploring preventative strategies.

According to Travell and Simons (1983), Myofascial Pain Syndrome (MPS) is characterized by chronic muscular pain localized in a taut band of skeletal muscle. Present in

this taut band is a hyperirritable locus called a trigger point (TrP). This TrP can be either active or latent. An active TrP causes the patient pain and a latent TrP may cause a restricted range of motion and weakness, but is clinically silent with respect to pain. Palpation of the TrP will refer pain to another area. The severity of the referred pain is related to the degree of irritability of the TrP and not to the size of the muscle where the TrP is located. The irritability of the active TrP varies from day to day. Snapping palpation of the TrP will elicit a local twitch response and digital pressure on an active TrP will elicit a "jump sign". Few epidemiological studies exist on the gender and age distribution of the Myofascial Pain Syndrome, although it has been documented that women are more often afflicted than men and the prevalence of the TrP has been found to increase between the ages of 30 to 60 years. (Campbell, 1989; Cooper et al., 1986; Fricton et al., 1985).

Fibromyalgia (FS) is a nonarticular rheumatic condition which differs from Myofascial Pain Syndrome in that it produces generalized widespread musculoskeletal pain and tenderness. It is characterized by poorly defined, diffuse pain, usually in the neck, shoulders, lower back and lower limbs (Wolfe et al., 1990). Also present are highly sensitive tender points (TP) in more than three areas of the body (Scudds and McCain, 1988). The patients are almost all women, the average age being 53 years (Greenfield, 1992). A group of researchers (Pellegrino et al., 1989) proposed that FS is an inherited condition. Their evaluation of 50 relatives from 17 FS patients led them to believe that FS may occur through an autosomal dominant gene, which appears in several generations. They went on to explain that the variability in onset and severity was due to different genetic, environmental and behavioural factors. More research is required to determine if the cause of FS is related to environmental or physiological factors.

The cause of the continual pain for both conditions has not been substantiated and presently only theories exist. Past clinical analysis has focused on the effect of ischemia and static contractions on muscle, but no significant lab findings have resulted. The new non-invasive methods of measuring soft tissue oxygenation (near infrared spectroscopy) have not been applied to these patients. No extensive research has been done with respect to cytokines and the role they may play in the Myofascial Pain Syndrome and Fibromyalgia.

Purpose

This study was designed to determine possible factors contributing to MPS and FS, which would contribute support to theories regarding the source of the pain, being caused by either a central or peripheral mechanism.

The specific aims were:

1) to measure levels of TNF-α and IL-1β pre-isometric contraction and post-isometric contraction.
2) to quantitate oxygen levels in trigger points or tender points in the trapezius muscle during intervals of isometric contractions and rest.
3) to compare laboratory and oximeter results from MPS and FS subjects to those of healthy controls.

Definitions

Trigger Point - A point of hyperirritability in a tissue that is locally tender on compression and can give rise to referred pain and tenderness. (Travell and Simons, 1983).

Taut Band - A group of palpable muscle fibers associated with a myofascial TrP (Travell and Simons, 1983).

Local Twitch Response - Contraction of a group of muscle fibers containing a TrP, usually a taut band, in response to stimulation. (Travell and Simons, 1983).

Tender Point - Anatomical sites of excessive tenderness on palpation. Found at characteristic locations, and characteristic of Primary Fibromyalgia. (Wolfe et al, 1990).

Ischemia - Inadequate blood flow to maintain normal function.

Hypoxia - Inadequate amount of oxygen available at tissue level for cellular respiration

Delimitations

The study was delimited to:

1) female subjects with either MPS or FS in the trapezius muscle and healthy controls between the ages of 30-60 years.

2) analysis of blood samples by ELISA assay kits.

Limitations

The study was limited by:

1) accuracy of the kits to detect cytokine levels in high and low ranges.

2) the accuracy of the calibration of the tissue oximeter (RunMan Device, NIR device).

Research Hypothesis

It is believed that the cause or explanation for the diffuse and local chronic muscle pain experienced by FS and MPS patients is multifaceted. With this belief in mind, studying one factor as the single cause can be limiting and misleading. It has been shown that the cytokines, TNF-α and IL-1β, are activated by means of muscle microtrauma or trauma that commences a destructive process against the muscle. In MPS and FS patients, the muscle microtrauma may not create muscle necrosis, but rather induce structural and biochemical changes in the muscle and its components, thereby disrupting its normal pain free function. Another possible factor causing the chronic pain is the development of a hypoxic environment, leading to short periods of ischemia, followed by reperfusion. This ischemic period may be very short, resulting from static contractions, such as can occur in certain occupations (e.g.. typist, dental hygienist, sewing machine operator, etc.) (Andersen and Gaardboe, 1993). These two factors, cytokines and ischemic injury, may act in concert with one another to produce chronic soft tissue pain as is experienced in MPS and FS.

If TNF-α, IL-1β and muscle oxygen levels are no different in FS and MPS sufferers, as compared to normal controls, then support would be given to the cause of pain originating from peripheral mechanisms other than ischemia or cytokine activation or from central mechanisms.

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CHAPTER TWO

REVIEW OF THE LITERATURE

I. MYOFASCIAL PAIN AND FIBROMYALGIA SYNDROMES: A REVIEW

In order to understand the present mystery surrounding the cause and amplification of pain in FS and MPS, a review of past research relating to the pathology and etiology has been undertaken. Myofascial Pain Syndrome (MPS) is believed to be induced either by an acute or a chronic overload stress on the muscle (Hurri et al., 1991; Fricton et al., 1985; Travell and Simons, 1983). As described by Travell and Simons (1983), and supported by Simons (1988), Fricton et al. (1985) and Thompson (1990), local tissue damage in a muscle due to a strain, results in pathophysiological changes, in both normal and Myofascial Pain Syndrome populations. Travell and Simons (1983) state that the muscle remains in a prolonged state of contraction to protect the injured area creating an ischemic environment causing further pain.

Andersen and Gaardboe (1993) studied the occurrence of neck and upper limb disorders in sewing machine operators, as well as the exposure-response relationship between the clinical syndromes and the number of years as a sewing machine operator. In addition to examining the occurance of pain, this research evaluated the reliability of the clinical exam and the correlation between complaints of pain and palpatory findings. The subjects were divided into three groups based on years of employment as an operator; 0-7 years (21 subjects), 8-15 years (25), > 15 years (36): the control group contained 25 age-matched normal subjects. The authors did find a significant positive correlation between the number of years as a sewing machine operator and neck and shoulder syndromes. In this study, the syndromes were not

categorized as fibromyalgia or MPS, but rather cervicobrachial fibromyalgia, rotator cuff syndrome or cervical syndrome, with definitions for each syndrome provided for in the appendix to their report. A patient was considered to have cervicobrachial fibromyalgia if tenderness was found in the muscles of the upper limb (infraspinatus, supraspinatus, pectoralis major and trapezius), and the lower limb (vastus medialis and gluteus medius), as well as in the cervicobrachial region. The Cervicobrachial fibromyalgia was the most frequently diagnosed condition, which the authors considered to be a localized form of MPS. Regarding the reproducibility of data generated by the two examiners, kappa values were between 0.56 and 0.78. The reliability between the subjects' complaints and examiners' findings resulted in a sensitivity of 0.85 (examination was sensitive enough to pick up the conditions) and specificity (examination was specific enough to identify which condition) of 0.83 (chronic neck complaints and cervical syndrome and/or MPS in the neck); and a sensitivity of 0.94 and specificity of 0.77 (chronic shoulder complaints, rotator cuff syndrome and/or MPS in the shoulder). All four of the foregoing values are high, indicating that the examiners were reliable in identifying patients' pain and defining the nature of their syndrome.

The pathogenesis of Fibromyalgia (FS) is still not completely understood (Thompson, 1990; Bengtsson et al., 1986). Several non-musculoskeletal symptoms co-exist including anxiety and stress and non-restorative sleep (Yunus et al., 1988; Bengtsson et al., 1986). There are at least two theories related to this condition. One theory states that stress-induced muscle tension leads to hypoxia in the muscle (Lund et al., 1986). A study by Greenfield, Fitzcharles and Esdaile (1992) reported that 29 out of the 127 fibromyalgia patients (23%) were able to identifiy a specific event, usually traumatic, prior to the onset of their symptoms.

Another, more increasingly popular theory is the hypothesis of an aberrant central pain mechanism resulting from a neurohormonal dysfunction. These two theories, the peripheral vs central mechanisms are believed to be related (Yunus, 1994), with the central, neuroendocrine dysfunction playing a more important role.

Questions regarding the diagnosis of Myofascial Pain and Primary Fibromyalgia were addressed in a study by Wolfe et al. (1992) suggesting that the criteria to distinguish Primary Fibromyalgia from the Myofascial Pain Syndrome may not be mutually exclusive. When the definition of a trigger point (TrP) was changed to exclude a taut band and a twitch response, and was redefined as the presence of pain on palpation, the Primary Fibromyalgia patients with TrP increased from 17.2% to 38.0% and the Myofascial Pain Syndrome patients with TrP increased from 17.3% to 23.4%. The foregoing becomes significant when diagnosing and treating Primary Fibromyalgia and the Myofascial Pain Syndrome. If a taut band and a twitch response are not necessary to define a TrP, then are the two conditions so very distinct? The question also arises, whether TrPs in general are essential for a diagnosis of Myofascial Pain Syndrome because fewer than 25% of Myofascial Pain Syndrome patients had TrPs on clinical examination.

Research in the past has attempted to explain the constant, agonizing pain experienced by MPS patients. Although extensive work has been done, no conclusive evidence has been put forward regarding the cause of the pain,or the reason for its continuation. Presently only theories and hypotheses remain.

The following is a review of the research on FS and MPS in three major areas concerning the peripheral theory: muscle biopsies, electromyographic results and tissue

oxygenation. A review of the theories concerning the central mechanisms will follow.

A. PERIPHERAL THEORIES

MUSCLE BIOPSIES

In 1984, Kalyan-Raman and colleagues examined the muscle pathology of tender points in twelve FS patients using light and electron microscopy (EM) and histochemistry to determine if any objective changes existed. Light microscopy revealed scattered hyalinized muscle fibers in five of the twelve patients; scattered split fibers in five subjects; increased central nuclei in two; and there was an absence of inflammatory cells. In nine of the twelve patients histochemical findings were abnormal. Type II fiber atrophy was observed in seven patients and type I fibers had a significantly 'moth eaten' appearance in five patients. Extensive segmental necrosis of myofibrils was found when examined with EM, along with deposition of glycogen in mitochondria in all twelve patients. The sarcolemmal membrane had papillary projections in several places in eleven of the twelve patients and glycogen accumulated with deposits of mitochondria, particularly in the area of the papilllary projections. Narrowing of the I band in two of eleven patients, suggested that a hypercontraction of the muscle was the cause of the papillary projections. However, no narrowing of the I band was found in nine other cases, thus negating the previous explanation for the papillary projections. In ten of the twelve cases, mitochondria in the areas of myofibril lysis showed alterations in shape (elongated or severly distorted), size, orientation and distribution. The mitochondria occasionally were located perpendicular instead of parallel to the myofibrils. Z line changes (zig zagging or smearing) were seen in two of the twelve

patients. The EM findings were nonspecific and can be seen in a variety of other muscle diseases (muscular dystrophy, collagen vascular disease). Papillary projections are seen in polymyositits and neurogenic atrophy. The authors concluded that the findings overall were nonspecific for FS; however, they did indicate significant pathological alterations in the FS muscle biopsies.

Bengtsson et al. (1986c) compared seventy-seven muscle biopsies from fifty-seven FS patients were compared to seventeen biopsies from nine healthy controls (). The biopsies were taken from various sites from each subject (anterior tibialis, vastus lateralis or medius, deltoid, brachioradialis) with the majority (forty-one) taken from the upper part of the trapezius muscle. Thirty-one of the forty-one trapezius biopsies were taken from tigger or tender points. The TrP/TP were defined as a localized area of intense pain on muscle compression, often with a radiation of pain. The control biopsies came from the upper medial trapezius (ten) and the brachioradialis (seven).

The capillary density did not differ significantly, in nine controls and ten FS patients. Muscle fiber degeneration, regeneration or splitting was found only in occasional fibers. Discrete groups of lymphocytes were evident in only nine biopsies. The most obvious change was the presence of 'moth-eaten' fibers and ragged red fibers in type I muscle fibers; however, trapezius muscle from controls also showed moth-eaten fibers (i.e. $11.9 \pm 7.6\%$ [mean and SD] of type I fibers in FS had moth-eaten appearance, and $9.2 \pm 5.9\%$ in controls had a moth-eaten appearance). The authors felt the moth-eaten appearance could have been due to hypoxia, but this was only a speculation.The ragged red and moth-eaten fibers were not specific for FS. They noted the moth-eaten appearance could be due to overuse, and not a

sign of disease. These results did not agree with Kalyan-Raman et al.(1984), who discovered selective atrophy in type II muscle fibers in patients with FS, as well as pathological alterations. Overall, Bengtsson and colleagues (1986c) concluded that the diagnosis of FS should still be based on clinical features, not on morphological changes.

Studies of muscle biopsies in FS and MPS have not revealed a consistent or specific muscle defect. Local muscle changes have been observed, including a reduction in high energy phosphate compounds, scattered red-ragged fibers and local changes in oxygen tension. It has been hypothesized that these changes are the result of micro muscle trauma (MMT) (Bennett, 1992). MMT studies have shown a defect in the sarcolemmal membrane leading to an influx of Ca^{++} ions and contraction of the involved fibers. This possibly is the cause of the palpable band. When the ATP-dependent Ca^{++} pumps attempt to correct the influx of Ca^{++}, the sarcolemmal stores of high energy phosphates compounds become depleted.

Soderlund, Hultman and Bengtsson (1992) analyzed ATP and PCr in whole muscle samples, as well as in separated and characterized single muscle fibers from eight FS patients. They did not find significant differences between FS patients and healthy subjects. The researchers did note that the number of subjects and the number of single muscle fibers was very small. The foregoing may pose a problem when inferring results, because only a limited number of fibers may be affected.

In a study of muscle pain, Drewes et al. (1992) took fifty biopsies from the quadriceps muscle of twenty females with FS. These biopsies were subjected to blind comparison with fifteen biopsies from ten normal controls, matched for age and sex. Their results showed no moth-eaten or ragged red fibers, and no evidence of an inflammatory myopathy. Abnormal

findings included empty sleeves of basement membrane, many lipofuscin bodies and other degenerative changes in the FS patients, but not in the controls. The researchers concluded that the abnormal changes were non-specific and could be related to either metabolic disorders or to increased muscle tension. It was not noted if the biopsies came from TrP or a specified area of the quadriceps muscle. The degenerative changes could be due to a lack of activity, as compared to controls.

Lindman and colleagues (1992) obtained muscle biopsies from tender points in the trapezius muscle of patients with work-related myalgia or FS. These biopsies were compared to biopsies from the same muscle region from healthy controls. The total volume density of muscle mitochondria and of capillaries were quantitated using electron microscopy and morphometry. The results showed significantly higher mitochondrial volume density in patients with work-related myalgia. Deranged endothelial cells in capillaries were frequent in the FS patients. The researchers concluded that these observations may be associated with a disturbed microcirculation or localized hypoxia/ischemia, which may reflect the pathophysiology of the two disorders. The higher volume of mitochondria may be an adaptive response to reduced blood flow, hypoxia/ischemia, or to overuse, whereas the deranged capillary endothelium may result from, or be the cause of, localized hypoxia/ischemia.

CLINICAL LABORATORY TESTS

Bengtsson et al. (1986a) compared clinical symptoms (i.e. stiffness in morning, difficulty falling asleep, often feeling cold, etc.) and routine lab test results from fifty-five FS

patients to thirty rheumatoid arthritis (RA) patients. In ten of the FS patients an ischemic forearm exercise test was done to study muscle metabolism. Pre- and post-exercise lactate levels in the venous blood were measured and found to rise normally in both groups. An EMG examination performed in twenty-nine patients on seventy-five muscles (trapezius, 17; deltoid, 11; biceps brachii, 12; other muscles of the upper extremity, 12; tibialis anterior, 14; other muscles of the lower extremity, 9), resulted in normal tests or borderline results in 65 of the muscles. Statistical analysis was done using the Chi square test when comparing the differences between clinical symptoms, in percentages, between the FS and RA patients. Muscle contraction data were expressed as means and standard deviations and was evaluated with the unpaired Student's t-test.

The laboratory tests [erythrocyte sedimentation rate, peripheral blood count, and determinations in serum of sodium, potassium, creatinine, alanine-aminotransferase (ALAT), aspartate-aminotransferase(ASAT), creatine kinase, thyroxine, serum triiodothyronine, T-3 uptake, thyroid stimulation hormone, rheumatoid factor; antinuclear antibodies (ANA) and antibodies against smooth muscle (SMA)], were all normal, although low titres of IgG, IgM, ANA, SMA were found in nineteen of the FS patients, but these were not regarded as significant. Results from the maximal voluntary contraction were significantly lower in the nine FS patients than in the healthy control group (32.1 ± 3.5 units vs. 42.0 ± 2.1 units). The small number of subjects tested for maximal grip strength may account for this level of significance. The authors found that the FS patients had a more pronounced feeling of illness than the RA patients and were just as handicapped by their symptoms as were the RA patients, even though the FS patients did not have the joint destruction that is present in RA patients.

The researchers concluded that these results lend support to the hypothesis that the FS pain is nociceptive and of muscular origin, caused by a disturbed microcirculation and depletion of energy stores in muscle fibers, resulting in pain and fatigue. Again, the foregoing conclusion is speculative.

Bengtsson, Henriksson and Larsson (1986b) analyzed the energy metabolism from biopsies of tender points in the trapezius muscle of FS patients and compared them to nontender point sites from FS muscles and to healthy controls. The subjects were broken into three groups: group one had their trapezius muscle biopsied; group two had their tibialis anterior muscle biopsied; and group three were the healthy controls who had their trapezius muscle biopsied. The samples were analyzed for levels of ATP, adenosine diphosphate (ADP), AMP , PC, creatine, lactate, pyruvate and glycogen. The results demonstrated a decrease in the levels of ATP, ADP and PC, and an increase in the levels of AMP and creatine in the painful muscles of the FS patients. No significant changes were found in the nontender point muscles on the FS patients as compared to the healthy controls. The authors concluded that changes of high-energy phosphate levels are evident in muscles with pain and trigger points. It may be misleading to make that conclusion, since the comparison between trigger point muscles and nontrigger point muscles was made on two different sets of FS patients. The study could have been more accurate by making a comparison between muscle groups on the same patients. One plausible explanation or partial explanation for their findings, was the presence of hypoxia in the painful muscle.

Another method for the examination of muscle in FS patients was used by Yunus et al. (1989). Mulitphase skeletal scintigraphy was employed to determine if synovitis or other soft

tissue or bony changes existed to explain the pathophysiology of the condition and possibly to assist in the diagnosis of FS. Sixteen FS patients were analyzed, fifteen of whom were women. Scintigraphy uses a large field of view (LFOV) gamma camera to view synovial tissue or tender point locations (as in this study). An abnormal reading may result from factors such as increased blood flow, edema, calcium deposition or increased osteoblastic activity. Hypoxia has been suggested as a possible cause of FS pain, but the negative results reported in this study failed to provide evidence for this mechanism. The authors did comment that the techniques used may not have been sensitive enough to pick up a diminished blood flow. The results were negative (no abnormal reading) in fourteen of the sixteen FS patients; therefore no analysis of normal controls was required. However, the researchers did conclude that in FS there is an absence of synovitis and other soft tissue or bony abnormalities as measured by multiphase skeletal scintigraphy.

A study by Simms et al. (1992) examined thirteen female FS patients and thirteen female sedentary controls with similar levels of aerobic capacity. Using $_{31}$P-NMR spectroscopy, all subjects had their upper trapezius and tibialis anterior muscles analyzed at rest, during a nine minute muscle-fatiguing exercise, at 50% of maximum voluntary contraction, and during recovery. The results showed no significant differences in muscle energy metabolism between the two groups; therefore no support for defects in muscle energy metabolism could be established.

A similar study (Wigers, Aasly, Timm, Rinck, 1992) used $_{31}$P-NMR spectroscopy on the dorsal calf muscle of twelve patients with FS at rest, submaximal exercise and recovery. The results showed no metabolic deficiencies in the muscle, as compared to eighteen healthy

controls.

ELECTROMYOGRAPHIC STUDIES

Fricton et al. (1985) examined the TrP in the upper trapezius muscle of MPS patients using electromyographic (EMG) recordings and compared the results to the contralateral, painfree muscle. There were 16 subjects (10 females and 6 males), all volunteers from the TMJ and Craniofacial Pain Clinic of the Department of Oral and Maxillofacial Surgery at the University of Minnesota School of Dentistry. The probes from the electrodes were placed within 1 cm of the TrP at a depth of 2 cm. A snapping palpation was performed within 5 cm of the needle to elicit the local twitch response and to receive an EMG recording. The snapping palpation was performed 4 times to ensure reproducibility and minimize variability. The probe was then moved to the contralateral muscle and the procedure was repeated. The results demonstrated a significantly higher motor unit activity upon the snapping palpation in the TrP muscle as compared to the normal muscle.

Durette et al. (1991) evaluated the TP, TrP and palpable muscle bands at rest and during a voluntary contraction in four FS and twenty-one focal MPS patients, using a needle electrode (EMG). The results showed at both rest and during muscle contraction, no abnormal potentials from any location, or patient group. The researchers did use poorly defined subject groups. Their criteria to define FS came from the Textbook of Rheumatology, a reputable source, although Wolfe et al. redefined the criteria for FS in 1990, which is now the base employed by the American College of Rheumatology for defining FS. The number of subjects for each group was skewed and very low in the FS group. Also, their review of the literature

was outdated. References were taken from the early 1940's and 1960's. Since then at least one study has been published on FS and MPS subjects exclusively (Bengtsson et al., 1986a). Another defect in the study was that no comparison was made to normal subjects. The evidence did suggest, however, that TrP/TP are electrically silent.

Elert et al. (1991) studied the muscle performance (using EMG) and fiber type composition in females with FS, work-related myalgia and healthy volunteers. The subjects were required to perform 100 repetitive shoulder flexions using an isokinetic dynamometer while the surface EMG recorded the amplitudes. In all the FS patients, there was an inability to relax the muscle between contractions. The work-related myalgia subjects were also unable to relax the myalgic trapezius.

Oberg et al. (1992) examined 11 female subjects with unilateral work-related myalgia of the trapezius muscle and their response to increasing static loads. The probes from the EMG were placed over the upper part of the trapezius muscle, half-way between the spinous process of C7 and the acromion. The subjects held one arm at a time elevated and in 90° abduction. The first interval was with no weight for 5 minutes. The second interval was with a 1 kg weight for 3 minutes and the final interval was for two minutes with a 2 kg weight. All but one patient were able to complete the five minute interval, and only four went on to the higher weights. The reason the subjects cited for not wanting to continue was due to the pain involved in sustaining the contraction. The signal from the EMG was analyzed every 0.5 seconds. The mean power frequency (MPF) and the root mean square (rms) were calculated and a regression analysis was done on the ten second means at each load. The results demonstrated an increase in rms and a decrease in MPF with increasing time and load, demonstrating the classic signs of

muscle fatigue. Unexpectedly, these results demonstrated greater fatigue in the unaffected side than in the affected side in these patients. The authors concluded that there is a difference between myalgic and healthy muscle, but one single factor may not be the cause. Instead, a multitude of factors may be involved.

A study by Hubbard and Berkoff (1993) investigated the needle EMG activity in active TrPs and adjacent nontender muscle fibers of the same muscle. Twenty-nine patients with chronic tension-type headaches with pericranial muscle tenderness, who were admitted to the Neurologic Centre for Headache and Pain, were subjects for the study. The subjects had mild to moderate daily fluctuating bilateral frontal and occipital pain and normal neurologic examinations, except for the presence of TrPs. Twenty-five patients met the American College of Rheumatology criteria for FS. Eight normal subjects with no history of significant head, neck or back pain, but with latent TrP were also examined. Eighty percent of the subjects were women. The results demonstrated that spontaneous EMG activity could be recorded from the TrPs of all normals and patients, but that the activity ceased when the needle was moved as little as 1mm. From the non-TrPs, no spontaneous activity was recorded. In all subjects the needle activity corresponded to the report of pain, with referral of pain up into the cervical, occipital or temporal areas. The TrP mean EMG amplitudes for the normal subjects were significantly lower than for the fibromyalgia patients. The researchers concluded that the EMG activity was restricted to a very small area located within the TrP and the adjacent muscle fibers were not affected. Their hypothesis was that sympathetically stimulated intrafusal contraction causes an involuntary low-grade, but symptomatic muscle tension. Prolonged or chronic spindle tension becomes painful by distending, distorting or chemically

sensitizing the spindle capsule.

Another study by Svebak, Anjia and Karstad (1993) using EMG, tested the hypothesis that increased levels of muscle tension are present in fibromyalgia, causing algogenic substances to accumulate in the muscle due to the increased metabolic activity.
The subjects were ten female fibromyalgia patients and ten matched healthy controls. The electrodes from the EMG machine were placed on the left forearm flexor carpi radialis area and the upper section of the right trapezius area. Each subject was required to operate a joystick to control the position of a car on a video screen. EMG activity was taken from the passive forearm flexor and trapezius 30 seconds pre- and post-test (baseline periods), and five successive 30 second periods during the perceptual-motor task. Results demonstrated that both groups had significantly increased trapezius muscle activity with the onset of the task in relation to the pre/post-test levels, but no significant differences existed between the groups. The passive forearm flexors did show an increase in EMG activity, but it was not significant within or between groups. These results did not support the hypothesis that fibromyalgia patients experience higher levels of muscle tension as compared to normals. Due to these results, the researchers concluded that the biological substrate for fibromyalgia is located in the afferent and central nervous systems for motor control, rather than in the efferent pathways to electromyographic regulation. They went on to explain that enduring hypoxia is one condition that can cause hypersensitivity in the pain pathways. Their hypothesis lends support to the assumption of hypersensitive pain pathways in FS due to hypoxia.

In summary, the current research has been inconclusive. Three studies (Durette et al., 1991; Oberg et al., 1992; Sveback et al., 1993), all found results contradictory to the theory

of hyperactivity in the painful muscle. Fricton et al. (1985) did report a higher level of motor unit activity in affected, as compared to contralateral muscles in FS patients, but no healthy matched controls were studied. Hubbard and Berkoff (1993) found the mean amplitude to be higher in FS than the controls. Elert et al. (1992) made the most conclusive finding to date, namely that the inability to relax a muscle after a contraction. He hypothesized that this could initiate and sustain muscle pain. The reason for these discordant results is unclear. The authors agree that no single factor is involved, but that a multitude of interactions occur. Research using EMG analysis in conjunction with another technique in research on FS may be beneficial, to expand upon the current methodological limitations.

MUSCLE OXYGENATION/HYPOXIA

Lund et al. (1986) investigated oxygen levels in the trapezius and brachioradialis muscles of FS patients and healthy controls, by using the Mehrdraht Dortmund Oberflache (MDO) oxygen electrode. Statistically significant abnormal oxygenation in the trapezius and brachioradialis muscles of the FS patients was demonstrated, as compared to the control group. The foregoing finding supports the theory that the painful muscle may be in a hypoxic state for reasons unknown.

Bruckle et al. (1992) measured the tissue oxygen pressure (tissue-pO_2) using polarographic needle probes in the erector spinae muscle of ten healthy controls, ten Fibromyalgia patients and ten low back pain patients. The total mean tissue-pO_2 in both patient groups was significantly higher than in the controls and the Fibromyalgia patients had higher levels than the low back pain patients. No areas of hypoxia were found in the muscle.

The researchers report that the elevated tissue-pO_2 in the Fibromyaglia muscles could be explained by an increase in local blood flow or by a disturbance in oxygen-utilization by muscle cells.

A study (Sietsema, et al., 1993) on the oxygen uptake during exercise in fourteen patients with FS, as compared to controls, used cycle ergometry to examine the VO_2 response to graded exercise. The subjects performed one maximal test and then two submaximal tests. One submaximal test was at 80% of anaerobic threshold (AT) and the other was at the half way point of AT. Seven of the patients did not meet the criteria for maximal effort, three of whom stated that they stopped due to fear of increased pain the following day. The peak VO_2 values for the patients were not significantly different from the controls. No significant differences between groups arose with the AT, $\Delta VO_2/\Delta WR$ or the mean response time (MRT) for VO_2 for the low or high work rate tests. The visual analogue scores were all higher for the patient group. From these results, the authors concluded that the hypothesis of generalized muscle ischemia leading to FS was not supported.

This conclusion may seem difficult to support, if one examines other possible disturbances in oxygen supply to the cell. Erdmann et al. (1992) stated that other pathophysiological conditions can interfere with the oxygen consumption balance that are independent of disturbances in oxygen uptake and transport. These conditions alter the tissue's environment, thereby disrupting the oxygenation of that tissue. This may relate to FS or MPS patients by causing a disturbance in PO_2, which by present means of analysis, has not been detectable.

B. CENTRAL MECHANISMS

Yunus (1992) proposed a model explaining the pathophysiology of FS as an aberrant central pain mechanism with peripheral modulation. The important aspect of this model are the central mechanisms beginning with neurohormonal dysfunction, leading to aberrant central pain mechanisms. He proposed that there is a dysfunction of the neurotransmitters or other neurohormonal modulators of pain. Either a deficiency of inhibitory neurotransmitters (eg, serotonin, norepinephrine, GABA and somatostatin) or an overactivity of excitatory neurotransmitters (eg, Substance P). This neurohormonal dysfunction may be genetically determined and triggered by non-specific stress, such as physical trauma, mental stress or viral infection.

Scudds et al. (1989) confirmed a previous report (Carette et al., 1986) of the effectiveness of an anti-depressant drug, amitriptyline, on the pain, tender point sensitivity and general improvement in generalized pain responsiveness in FS patients. Although the authors did not state in their conclusion the real importance of this finding, their results do support the theory of an aberration in the central pain mechanism. This drug augments neurotransmission in norepinephrine and sertonin neurons by blocking reuptake of the neurotransmitter from the synaptic cleft back into the presynaptic terminal. Amitryptline and other tricyclic antidepressants markedly depress rapid eye movement sleep by increasing stage IV sleep and decreasing the number of nocturnal awakenings (Julien, 1988). Disturbed sleep at stage IV has been found in FS patients.

Vaeroy et al. (1988) discovered elevated levels of Substance P in the CFS of FS patients, which would lead to hyperactivity of the nociceptors, thereby decreasing the pain

threshold. Hamaty et al (1989) studied the clinical effect of five months of cyclobenzaprine versus a placebo on seven FS patients. Weekly measurements of endorphin, prostaglandin E (PGE) and catecholamines (epinephrine, norepinephrine and dopamine) were taken. No reduction in pain severity occurred, but sleep was found to be significantly more refreshing while the patients were on the medication. They found an elevation in plasma dopamine and PGE, while norepinephrine was normal to high and epinephrine levels were continually low to normal. The conclusion drawn was a possible failure of the CNS to modulate pain. One should be cautious with these results due to the small sample size.

In 1992 a group of researchers (Russell et al.) measured the levels of biogenic amine metabolites (5-hydroxyindole acetic acid [h-HIAA], a product of serotonin metabolism; 3-methoxy-4 hydroxyphenethylene glycol [MHPG] from norepinephrine and homovanillic acid [HVA] from dopamine), collected from the CSF by lumbar puncture in FS and non-FS patients. Significantly lower MHPG and HVA levels were discovered in the FS group than in the non-FS group, while the 5-HIAA approached signifigance. These results suggest a metabolic defect at the neuroregulatory level.

van Denderen et al. (1992) examined the influence of exhaustive exercise on biochemical indices between FS and controls. They observed lower norepinephrine, epinephrine and cortisol values in FS patients than in healthy controls. Lower heart rates in the FS group were also discovered indicating a possible reduction in sympathetic activity. The decreased cortisol levels could also be indicative of an altered hypothalmic - pituitary - adrenal axis.

The pathophysiology of FS and MPS may result from an abnormal hypothalmic -

pituitary - adrenal axis (HPA). There are reports of a loss of diurnal variation in serum cortisol, growth hormone and prolactin levels and a hyperprolactinemic response to thyrotropin releasing hormone (TRH). Serotonin, a modulater of the release of prolactin, was hypothesized to be deficient in FS patients, thus eliciting a connection. Sleep physiology is also related to the HPA axis, since growth hormone is released during stage IV sleep, which has been reportedly disrupted in FS patients (Moldofsky, 1989), possibly indicating a link.
With a lack of sleep, due to serotonin deficiency, pain and fatigue may worsen. This may lead to depression or anxiety, which only accentuates the pain. These factors all lead back to the dysfunction of pain modulation.

The role that peripheral mechanisms play in the pathophysiology of FS may be minor in comparison to the central mechanisms. Yunus (1992) believes that physical trauma may initiate or aggrevate FS in patients who are neurohormonally susceptible to this condition. This theory may lend support to the suggestion by some investigators that MPS may lead to FS. The development of CNS plasticity may also arise. This phenonemom exists when chronic pain perpetuates the aberrant central pain mechanism in a vicious cycle. Thus trauma may lead to muscle deconditioning, not vice versa, leading to decreased isometric and isokinetic muscle strength, muscle hypoxia and decreased high energy phosphates.

II. CYTOKINES

Cytokines are released locally from macrophages or lymphocytes, in response to bacteria, viruses or inflammation, for the purpose of amplifying the immune response and

stimulating the production of growth factors. The released products act to either stimulate repair or damage tissue. (Wong and Goeddel, 1989; Oppenheim, 1990). One such cytokine is tumor necrosis factor (TNF). In inflammation, TNF-α activates neutrophils and induces degranulation and phagocytosis and the generation of oxygen free radicals. Following their migration into a tissue, neutrophils release free radicals and degradative enzymes (lysosomal hydrolases and elastase) (Cannon et al. 1990). The degradative enzymes that neutrophils release may contribute to muscle catabolism. In a study by Tracey et al. (1988), it was demonstrated that recombinant human TNFα infused into rats could induce an inflammatory reaction. The role that neutrophils play in skeletal muscle has been related to an ischemia-reperfusion type of injury. Ischemia and subsequent reperfusion in muscle results in reduced function, increased histological evidence of cellular damage, and an increase in cytoplasmic enzymes (Cannon et al., 1990). An increase in the neutrophil content has also been observed during reperfusion.

Rotto et al. (1989) discovered in cat gastrocnemius muscle that, after a static contraction, the levels of arachidonic acid become elevated as compared to the contralateral resting muscle and to resting ischemic muscle. Prostaglandins, products released in response to a variety of physiological and pathological stimuli (Samuelsson et al., 1978), are metabolites of arachidonic acid which are produced by mononuclear phagocytes (Male et al., 1988). Inhibition of prostaglandin production with a non-steroidal anti-inflammatory drug after trauma to rat muscle resulted in a decrease in the acute catabolic loss of skeletal muscle protein over a period of three days (Fisher, Baracos and Reid, 1991). TNFα and Il-1 both have been found to provoke prostaglandin synthesis (Male et al., 1988). The sequence of events after damaging

exercise or injury may commence with the local disruption of sarcomeres due to physical overload or to oxidative stress. The resulting tissue damage signals activate the complement system that in turn induces monocytes to become reactive (Cannon et al., 1991). TNFα can also stimulate the growth of fibroblasts, and induces them to produce Interleukin-1 (IL-1). TNFα and IL-1 have been shown to share many similar biological activities (Wong and Goeddel, 1989). IL-1 also increases muscle proteolysis when infused in vivo (Wong and Goeddel, 1989).

TNFα has been shown to increase muscle proteolysis when infused into rats (Flores et al, 1989; Charters and Grimble, 1989; Goodman, 1991). Whether cytokines (Il-1 and TNFα) have a direct or indirect effect on muscle proteolysis has not been established, but the foregoing studies do demonstrate that cytokines (IL-1 and TNFα) are involved in muscle protein breakdown. These cytokines could be the cause of the chronic pain experienced in MPS and in FS. Some muscle biopsies have shown muscle cell degeneration and ragged fibers (Elert et al, 1992; Lindman et al, 1991; Yunus et al, 1988), thereby supporting the theory that MPS/FS muscle protein is in a catabolic state, possibly due to increased levels of cytokines (IL-1/TNFα).

The cytokine, Interleukin-2, was found elevated in eight of sixteen Fibromyalgia patients (Peter and Wallace, 1988), suggesting some link between Fibromyalgia and this cytokine. A study by Wallace et al. (1990) analyzed cytokines in Primary Fibromyalgia as compared to controls and found no significant difference between the two groups. This study did not match for age or gender, and blood collection was done at rest, not after muscle exertion.

No literature can be found regarding cytokine analysis in MPS. The research literature regarding MPS provides data on muscle biopsies (Lindman et al., 1991a; Lindman et al., 1991b; Jacobsen et al., 1991), EMG (Oberg et al., 1992; Fricton et al, 1985) and TrP analysis, all results being inconclusive . No biochemical analysis for TNFα in MPS patients has been reported. Research regarding cytokines and MPS and FS has been limited.

III. TISSUE OXYGENATION

One commonly believed cause of MPS and FS is a static contraction, usually of the muscles of the shoulder girdle, such as is experienced in some occupational settings or daily activities. As outlined by Bennett (1989), the sympathetic cholinergic system induces arterioles of skeletal muscle to vasodilate upon the initiation of exercise. Factors preventing or impeding this vasodilation are hypoxia, low pH, lactate, adenosine compounds, potassium, phosphate ions and prostaglandins. These factors are all produced locally and some or all may be relevant in the etiopathology of MPS and FS. A sustained contraction may cause a disruption in the blood flow, hence lower oxygen distribution to the muscle, which may eventually elicit pain. (Bennett, 1989) The trigger/tender points or areas of pain referral, could be deficient in oxygen, due to a focal disturbance in the microcirculation, resulting from a static contraction.

The reasons for a review of the pathophysiology of ischemia-reperfusion skeletal muscle injury are twofold. First, one possible explanation for the chronic pain is a hypoxic environment; secondly, cytokines, TNFα and IL-1β, are implicated in skeletal muscle necrosis following reperfusion. The hypoxia rationale has been outlined in a previous section; therefore, the

following section will briefly review ischemia-reperfusion injury only.

Ischemia/Reperfusion

Ischemia or hypoxia is complex and involves many factors. What is considered normal will vary from person to person, i.e., a marathon runner vs an infirm person. There are also many different types of hypoxia. *Tissue hypoxia* is a deficiency of oxygen at the tissue level, resulting from a deficit in either the delivery or a defect in the utilization of oxygen. Two types of tissue hypoxia are hypoxic hypoxia and ischemic hypoxia. If produced by an abnormally low arterial partial pressure of oxygen it is termed *hypoxic hypoxia. Ischemic hypoxia* results when the nutritive perfusion of the tissue is reduced below the point where increased extraction of the oxygen from the blood can compensate for the reduced delivery. The tissue becomes hypoxic as a result of ischemic perfusion. Ischemic hypoxia can occur from reduced perfusion pressure, increased vascular resistance or both, even in tissue with normal arterial oxygen content and partial pressure. Hypoxic hypoxia and ischemic hypoxia are examples of inadequate oxygen delivery to the tissue.

Much of the severity of hypoxia depends upon the demands of the tissue. A tissue using minimal amounts of oxygen can survive with a minimum oxygen delivery system, whereas an active or hypermetabolic tissue requires an increased supply of oxygen. If the demands are high enough, even a fully functioning oxygen delivery system can falter. If the oxygen supply and utilization do not meet the metabolic demands of the tissue for cell survival, absolute hypoxia and tissue damage occur. The tolerance of skeletal muscle to ischemia is significantly reduced when the metabolic rate is increased by exercise or direct electrical stimulation (Messina and Faulkner, 1990)

A major determinant of ischemia is perfusion pressure, the pressure gradient across a particular tissue from the local artery to the local vein. Regional blood flow is another factor regulating ischemia. Finally, a decreased tissue activity level or an energy failure may directly contribute to local biochemical degradative processes in ischemic tissue, or in a remote tissue from plasma borne components of tissue injury. One example of this could be the breakdown products of nucleotide metabolism being released into the blood. Ischemia and hypoxia also impede ATP resynthesis, resulting in toxic levels of end products, further damaging the tissue.

Another factor involved in the reaction of skeletal muscle to ischemia is the muscle fiber type. Jennische and Hansson (1986), as cited in Messina and Faulkner (1990), demonstrated in the extensor digitorum longus muscle in rats, that the fast-glycolytic fibers sustained greater injury than did the slow-oxidative fibers after 5 to 15 hours of reperfusion. The fast-oxidative glycolytic fibers showed an intermediate level of injury. Similarly, Petrasek et al. (1994) found greater muscle necrosis in fast twitch fibers than in slow twitch fibers, in rabbits exposed to five hours of ischemia .

Differences in fiber type susceptibility to hypoxia become important when looking at the muscles of the shoulder girdle, which are composed mainly of slow oxidative or slow twitch fibers. A greater duration of ischemia may be tolerated with less injury, but over time this injury may be cumulative and injury or damage that was initially undetectable could produce pain.

Petrasek et al. (1994) also found that more damage was sustained by muscle tissue that was located proximally rather than distally. They felt that this was due to the slower cooling of proximal areas close to the torso than occurs in more distal areas, which cool more quickly. These

results identify tissue temperature as a factor in muscle necrosis due to ischemia.

Muscular Changes Due to Ischemia

Post- ischemia, gross changes in the appearance of skeletal muscle are difficult to observe and histologic changes may not be detectable, even after a delay, (Messina and Faulkner, 1990). Factors involved in the extent of skeletal muscle necrosis due to ischemia are: duration of ischemia, metabolic rate, and the type and duration of reperfusion. Messina and Faulkner (1990) reported that a short duration of ischemia (up to 1 hour) does not result in any long or short term ultrastructural damage. After 2 hrs. of ischemia, mitochondria swell and there is a decrease in the amount of glycogen within the muscle fibres, intramuscular nerves and nerve endings of motor end plates. A few leukocytes may also be seen along the muscle fibers. Irreversible histologic changes occur after prolonged ischemia (4-6 hours). The Z line disappears, the cell membrane disrupts and the muscle mitochondria become swollen and vacuolated. After 6 hours of ischemia, changes include partial disruption and disappearance of the plasma membrane and profound structural changes affecting mitochondria, the sarcoplasmic reticulum and sarcomeres.

Reperfusion

Skeletal muscle does have the ability to regenerate after ischemic injury; therefore revascularization of the tissue is possible (Messina and Faulkner, 1990). If the muscle is successfully revascularized, the incoming blood flow will bring with it macrophages and neutrophils, which phagocytose cellular debris. Following the phagocytosis of necrotic debris, the muscle begins to regenerate, creating new sarcomeres and muscle fibres.

However, regeneration will not occur if blood flow has been reduced from normal to ischemic levels, known as "no reflow". Strock and Majno (1969) found that during reperfusion of ischemic skeletal muscle in the rat hindlimb, many areas experienced this "no reflow" phenomenon. Using the electron microscope, endothelial cell injury was discovered in the form of swelling of mitochondria and the endoplasmic reticulum, dilatation of the perinuclear cisterna and condensation of nuclear chromatin. This study was one of the first to discover microvascular injury after reperfusion of ischemic skeletal muscle.

Microvascular injury is characterized by a patchy loss of perfusion throughout the microcirculation and changes in capiliary permeability, which result in tissue edema. This "no-flow" phenomenon is a failure to restore microvascular perfusion fully during the reperfusion of ischemic tissue (Messina and Faulkner, 1990). Four mechanisms have been identified to explain this phenomenon: 1) thrombosis of the microcirculation; 2) endothelial cell swelling; 3) extravascular compression of the microcirculation by interstitial edema or hemorrhage, and 4) leukocyte obstruction of the capillaries (Messina and Faulkner, 1990). Of the four mechanisms, the obstruction of the capillary by leukocytes has been implicated as the major cause (Strock and Majno, 1969 and Engler et al., 1986).

Zamboni et al. (1993) studied in vivo, the microscopic, morphologic changes or events that occurred in the microcirculation of rats during reperfusion from ischemia. Within five minutes of reperfusion, there was a significant increase in the number of sticky and adherent leukocytes (neutrophils) to the endothelium in postcapillary venules, as compared to controls. Two hours after reperfusion the endothelial walls had become ill-defined because of marginating and extravasating leukocytes. This excessive adherence was discovered to actually destroy sections of

the capillary endothelium. It was also discovered in this study that following reactive vasodilation, arteriolar vasoconstriction ensued, but only in the arterioles close to venules. This would lead one to believe that the local micro-environment, including leukocyte adherence, is partially responsible for the arteriolar response. The authors hypothesized that a platelet reaction occurs within the neutrophil damaged venule resulting in a release and interstitial diffusion of thromboxane or other vasoactive substances causing vasocontriction in the adjacent arterioles. The latter, in turn results in the "no-reflow" phenomenum in the arterioles supplying the site of muscle injury.

A study by Labbe et al. (1987) determined that ischemic intervals of three, four and five hours respectively result in 2.0, 30.3 and 90.1 % muscle necrosis after forty-eight hours of reperfusion. Lesser degrees of necrosis were found after four, six and eight hours of ischemia (i.e., 98, 59 and 23% of total muscle areas remained normal) (Blebea et al. 1987). Neither of these studies determined whether the muscle necrosis resulted predominatly from endothelial cell swelling or from an adherence of leukocytes to the vascular wall.

A few researchers took a different approach in their ischemia-reperfusion studies by questioning the extent of nerve damage and the relationship of the latter to muscle impairment. Rocko et al. (1986) found that contractility induced by nerve stimulation was absent after three hours of ischemia followed by two hours of reperfusion.

Chervu et al. (1989) found in rabbits that after one hour of complete ischemia, muscle and nerve stimulation elicited no response, but after two hours of reperfusion, both responses improved significantly. This restoration of function was better than after three hours of ischemia. Recovery was nearly complete after a two- hour reperfusion period in the one hour ischemic group, yet not in the three hour group. Nerve recovery in the group experiencing three hours of

ischemia after two hours of reperfusion was significantly less than in the group exposed to one hour. The authors suggested that the use of nerve stimulation to assess muscle function after ischemia and reperfusion may lead to inaccurate or erroneous conclusions. Peripheral nerve function may be more sensitive to ischemia than skeletal muscle. Thus the muscular contraction deficit may be due to nerve dysfunction rather than to skeletal muscle damage.

Partial vs Complete Ischemia

Partial or incomplete ischemia may cause more irreversible damage than complete ischemia (D'Alecy and Zelenock, 1990), due to a sustained low level trickling of degradative compounds from the damaged tissue.

Roberts et al. (1985) examined the effects of partial vs complete ischemia in dog skeletal muscle by analyzing ATP, creatine phosphate and lactic acid contents, as well as transmembrane potentials. These investigators found that within three hours of reperfusion in both partially and completely ischemic muscles, the blood flow returned to a level that was sufficient to support normal muscle cell function. The tissue lactate levels returned to normal during the recovery period from partial ischemia. Complete ischemia resulted in a better cellular recovery than parital ischemia and seemed unrelated to blood flow, because the ATP and creatine phosphate levels returned to normal. A depolarization of the membrane was evident in the paritally ischemic muscle probably due to a dysfunction of Na^+-K^+ ATPase, or to a change in the ion permeabilities of the sarcolemmal membrane. They also felt that the damage to the membrane could have been due to the production of free radicals or other biologically active substances.

Seyama (1993) compared differences in skeletal muscle injury in rats, and the effect of free

radical scavengers after complete and incomplete ischemia. The amount of muscle damage was greater in the rats that had experienced complete ischemia than in those that had experienced incomplete ischemia. Seyama (1993) concluded that post-ischemic tissue injury consists of at least two major components: ischemic injury due to hypoxia and reperfusion injury mediated by oxygen- derived free radicals. This study reported that ischemic damage plays a major role in complete or severe ischemia-reperfusion injury, while reperfusion injury plays an important role in incomplete or mild ischemia-reperfusion injury. This study also provides a hypothesis first put forward by Hoshimo et al. (1988) regarding the mechanisms involved in producing tissue injury. There are two extremes of ischemia, namely, a short period where the post-ischemic injury is not measurable and therefore assessed as "no injury", and a long period leading to irreversible tissue damage assessed as "beyond treatment". In the middle is a "treatment window", which is dominated by the reperfusion component with little contribution from the ischemic component. It is within this window that free radical ablation therapy can assist in decreasing free radical tissue injury, since the free radical scavengers are only effective against the reperfusion component. Seyama (1993) also concluded that the pathophysiology of an ischemia-reperfusion injury varies in direct relation to the severity of ischemia, thereby stressing the importance of determining the respective contributions of ischemia and reperfusion to tissue damage in order to determine the most appropriate treatment.

To date, no clear understanding exists concerning the complete mechanism of reperfusion injury in skeletal muscle. Research is lacking with respect to very short intervals (seconds to minutes) of ischemia as opposed to more prolonged periods of time. In relation to MPS or FS patients, if ischemia over a short period cannot be readily detected, it may still be disrupting

normal metabolic events, or at least contributing to their dysfunction. Hence the unexplained and undetectable basis for the chronic pain. Future studies should be directed to this aspect of ischemia-reperfusion injury in MPS and FS patients .

Calcium and Ischemia

Calcium is another factor involved in tissue injury from ischemia. Damaged tissue accumulates calcium (Bonventre et al., 1990) and it even has been proposed that calcium is the primary mediator of cell injury associated with ischemia. An increase in the concentration of calcium may activate the calcium-dependent proteases and phospholipases leading to proteolysis and membrane disruption. (Fantone, 1990) Elevated calcium concentrations can adversely affect mitochondrial ATP production, and may further contribute to ATP depletion. The interfibrillar mitochondria have a greater capacity for calcium accumulation. Calcium also structurally alters cell integrity and in contractile cells it leads to hypercontraction and tetany.

As reported in D'Alecy and Zelenock (1990) Ca^{2+} concentration increased two to three-fold after ten minutes of global ischemia, but the foregoing was not associated with damaging injury because the sarcolemma remained intact, and Ca^{2+} levels returned to normal upon reperfusion. However, pH levels, becoming more acidic with ischemia due to lactate accumulation, rapidly returned to normal during reperfusion, resulting in increased intracellular pH levels, which in turn activated and enhanced phospholipase A_2. Such changes could lead to further alterations in membrane structure, secondary to enhanced Ca^{2+} permeability, resulting in additional phospholipase A_2 activity.

Roberts et al. (1985) outlined the effects of calcium on perfused cardiac muscle. A

"calcium paradox" exists inasmuch as when calcium is introduced after having been depleted, there is resulting cellular damage. The authors suggested that a similar situation occurs in skeletal muscle, when calcium or oxygen is depleted during ischemia and then is reintroduced during reperfusion cellular damage results.

Tumor Necrosis Factor and Other Metabolites

Arachidonic acid (AA) is part of the cyclooxygenase pathway, which produces prostaglandins, a mediator of pain. It is of interest that as little as two minutes of ischemia could increase AA levels in muscle.

Rotto et al. (1989) investigated AA levels in the gastrocnemius muscle of cats after a static contraction. The cats were assigned to one of three groups. Group 1 (n=12), provided a comparison of AA levels between the freely perfused resting gastrocnemius muscle and the freely perfused, statically contracted contralateral gastrocnemius muscle (60 second contraction). In group 2 cats, both hindlimbs were rendered ischemic (n=12). Group 3 cats provided a comparison of AA levels in one resting gastrocnemius muscle freely perfused, and the contralateral resting muscle that was rendered ischemic for two minutes (n=18). Indomethacin was administered to each cat 20-30 minutes before any tissue sampling . Indomethacin, inhibits the cyclooxygenase pathway; therefore the conversion of AA to prostaglandins and thromboxanes was slowed, so that the detection of AA was facilitated.

The authers reported that the levels of AA were higher in the statically contracting muscle than in the contralateral resting muscle. Eleven out of the 12 cats demonstrated higher AA levels by 8.4 ± 2.9 nmol/g wet wt in the statically contracted ischemic muscle than in the contralateral

resting ischemic muscle (P<.01). In 14 out of 18 cats higher levels of AA were discovered in the ischemic resting gastrocnemius muscle than in the freely perfused resting muscle (P<.02) (4.6 ± 2.4 nmol/g wet wt). This finding demonstrates that an ischemic muscle contains increased levels of AA.

Ascer et al. (1992) found lower TNFα levels during reperfusion of the gracilis muscle in twelve canines. This result was unexpected, because in previous work increased levels of IL-1β were found in the same animal model. They attributed this difference to the short circulating half-life (six minutes) of TNFα, and to the fact that TNFα production is regulated by prostaglandin derivatives. The decreased TNFα level could have resulted from arachidonic acid production and accumulation.

Seekamp et al. (1993) demonstrated in the hind limb of rats that ischemia/reperfusion injury can significantly increase the plasma levels of TNF-α, IL-1 and IL-6. The rats underwent four hours of ischemia followed by four hours of reperfusion, at which time blood samples were drawn at varying time points. Four hours of ischemia did not produce detectable levels of TNF-α, but after four hours of reperfusion the levels increased within 60 minutes and reached a maximum level of 22.7 ± 2.7 units/ml at 120 minutes. At the end of four hours, the TNF-α levels, which had been significantly elevated, were beginning to decline. IL-1 only increased slightly, after four hours of ischemia. It was during the reperfusion period that IL-1 increased dramatically and reached a peak of 1,075.3±183.2 pg/ml at 120 minutes above control levels of 89.7 to 103.4 pg/ml.

TNFα activates neutrophils, which are known to accumulate and adhere to endothelial vessel walls during reperfusion, leading to ischemia-reperfusion injury (Jerome et al., 1994). The

neutrophils are sources of oxidants (free radicals) that are believed to recruit granulocytes to the post-ischemic tissue and appear to be involved in TNF-α mediated injury. TNF-α mediates increases in vascular permeability through neutrophil dependent and independent mechanisms (Seekamp et al., 1993). Seekamp et al. (1993) detected significant increases in the plasma levels of TNF-α, IL-1β and IL-6 in the hindlimb of rats after four hours each of ischemia and reperfusion, which peaked at two hours reperfusion. Significant increases were also noted in skeletal muscle vascular permeability after reperfusion, which was believed to be due to actions of TNFα and

IL-1β, because treatment of rats with antibody to IL-1β decreased vascular permeability by 24.7%. These authors noted that due to the rapid clearance of TNFα, it could be produced to act locally, with no detectable changes in its level in the plasma.

The results reported by Ascer et al.(1992) and Seekamp et al. (1993) appear to be contradictory and may be explained by the complex interactions of metabolic and immunologic pathways that produce cytokines.

Conclusion

The role of ischemia-reperfusion injury with respect to FS and MPS is undetermined. If the muscle is constantly contracted, thereby creating an ischemic micro-enviroment, even if only briefly, and then the tissue is reperfused, the cascade of events that occurs metabolically with ischemic-reperfusion injury may occur in the affected muscles of the FS and MPS patients. This chain of events, at the cellular level, may be initiated by an extended isometric contraction, leading to neutrophil margination and adherence to the capillary endothelium. TNFα and IL-1β

may contribute to the damage by increasing the permeability of capillary walls. An accompanying excess of calcium may cause muscle fibers to hypercontract and result in tetany; hence the trigger or tender points found in FS and MPS patients. As yet, no quantitative data exist to support this theory.

Finally, the etiology and pathogenesis of the chronic muscle pain experienced by patients with MPS and FS remain a mystery. Previous research has not provided any firm conclusions as to the cause of the pain. Cytokines and ischemia are two relatively recent research avenues to be followed in relation to these conditions. Moreover, more than one factor may be responsible for the severe focal muscle pain, which is such a prominent clinical feature of these syndromes.

IV. NEAR INFRARED SPECROSCOPY (NIR)

To measure tissue oxygenation non-invasively in skeletal muscle, a device called the near-infrared spectometer (NIR) has been used. The principle behind this device is the interaction of light with hemoglobin in red cells in the tissue. A wavelength of light has varying transmission characteristics through tissue. The NIR is composed of 75-W tungsten iodine lamp, providing a light source filtered at 760 and 800/850 nm by the use of a 60-Hz rotating wheel. This allows the lamp bulb to give brief flashes of light every second at a power of less than 1 W (Mancini et al., 1991). A probe emits the light through fiber optic bundles into a tissue sample (muscle), the light scatters randomly with some eventually being reflected back to photodetectors. The depth of penetration of the photons from the optic bundles, is approximately 2-3 cm in a diffusion-like pattern, rather than in a linear pattern, with an average pathlength of 5-10 cm. Absorption of the light in the internal tissue is dependant upon

the physiological characteristics of the tissue, particularly the oxygenation of hemoglobin (Sevick et al., 1991). To assess changes in hemoglobin oxygenation, the difference in absorption at the selected wavelengths, (760nm-800nm) is monitored. Absorption at 760nm represents the amount of deoxyhemoglobin, and at 800nm represents the total hemoglobin (oxygenated and deoxygenated) (Chance et al., 1992). 800nm is considered to be the isosbestic point (a point between oxyhemoglobin and deoxyhemoglobin), eliminating the need to correct for interferring signals.

Limitations

Unfortunately, photons of light can only travel a very short distance, decreasing the instruments validity if deep penetration is needed. Therefore, only superficial muscle tissue can be measured. The NIR does not measure absolute levels; it only represents trends in muscle oxygenation due to the fact that the acutal photon pathlength can only be estimated. Since no absolute values are ascertained, an assumption that the initial hemoglobin saturation levels are normal must be made. For analysis, arbitrary values can be used to provide some basis for comparison. The difference of the two received wavelengths represents the hemoglobin deoxygenation, essentially the differences between the two detected wavelengths.

Calibration must be done for each subject and presently, the RunMan is a very sensitive instrument; calibration can take up to one-half hour. Calibration must also be done while the subject is very relaxed and motionless, or else a baseline readout will not be possible, and the results will be incorrect. In very young subjects, for example, accurate calibration may not be possible.

Placement of the probes is crucial. The probes cannot be placed over tendons, non-exercised muscle or bone, in order to achieve an accurate reading. Bone has little effect on light transport, even though it has a similar index of refraction to that of tissue in the NIR range (NIR Inc.Handbook, 1991).

Skin pigmentation has not been found to be a limitation (Chance et al., 1988), although the thickness of the skin may be a factor. Wilson et al., (1989) found that the NIR signal did not change during exercise in two of their obese heart failure patients, who were respectively 121% and 164% above ideal body weight, because the light was unable to pass through the adipose tissue to reach the muscle; therefore no measurement occurred. Their other subjects were not considered to be obese (under 121% of ideal body weight), and in these subjects the NIR signal changed with exercise.

Reliability

Smith et al. (1990) used dual wavelength reflectance spectrometers to assess brain and quadriceps oxygenation in patients undergoing an operation for the insertion of an automatic internal cardioverting defibrillator for the treatment of hypotension and nonfibrillatory tachyarthythmias. Results demonstrated that the changes which occurred in hemoglobin saturation in the brain correlated well with changes in mean arterial blood pressure and the electroencephalogram (EEG).

A study by Mancini et al. (1991) examined whether respiratory muscle deoxygenation occurs during exercise in patients with heart failure and in age-matched controls, using NIR spectroscopy on the serratus anterior muscle. The wavelength selected was between 760nm

and 800nm. In normal controls after submaximal bicycle exercise, the NIR showed almost no change in the difference between light absorption at 760nm and 800nm wavelengths; at peak exercise, only a small change was observed. In the heart failure patients, a progressive increase in the difference between light absorption at 760nm and 800nm was observed, which was consistent with an increasing quantity of deoxygenated hemoglobin in the muscle.

DeBlasi et al. (1991) studied the oxygenation of the brachioradialis muscle during forearm ischemia and venous outflow restriction in fifteen healthy volunteers using a fast scanning spectrophotometer (Model 6500, NIR Systems). Similar oxygen patterns were established at rest in the brachioradialis muscle, as compared to a forehead spectrum. At forearm occlusion, a rapid decrease in oxygenation occurred, which after four minutes plateaued until the inflated cuff was released. This was followed by a slow recovery to normal values. These results coincided with those in other reports (Hampson and Piantadosi, 1990). Occlusion of the venous outflow was discovered to mainly affect the blood volume, leading to a slowing of the capillary flow and an increase in deoxyhemoglobin in veins, but the oxygen extractability by muscle was not effected.

Validity

When a new instrument is introduced claiming to measure or evaluate a parameter, its validity must be examined. Seiyama et al. (1988) used the NIR to analyze blood oxygenation in rat skeletal muscle. To test the validity of their technique, direct measurements of oxygen saturation (SO_2) of arterial and venous bloods were compared with the calculated saturation. The researchers found the calculated SO_2 values to be very close to the values directly

measured, although no exact data were given.

Hampson and Piantadosi (1988) investigated changes in skeletal muscle oxygenation caused by ischemia, using the NIR spectrometer. The results from the first protocol showed that during the first four-five minutes of ischemia, the oxygen stores were depleted, as demonstrated by the decrease in the NIR signal. During the recovery period, the signal rapidly returned to baseline, with no measurement remaining significantly different from baseline after four minutes of recovery. No significant changes occurred in any of the NIR signals. The deoxygenated hemoglobin and myoglobin signals increased for approximately three minutes after inflating the cuff and rapidly returned to baseline after the cuff was removed. No significant changes occurred in the oxygenated hemoglobin and myoglobin signals. This study demonstrated that the NIR spectrometer is sensitive to sudden forearm ischemia and reperfusion.

Wilson et al. (1989) evaluated NIR spectroscopy as a means of assessing oxygen delivery to skeletal muscle in working dog gracilis muscle, and subsequently in patients with heart failure, as well as in normal controls. A close linear relationship was found between the NIR absorption (between 760-800nm) and venous hemoglobin oxygen saturation, with a correlation coeffecient of -0.97 ± 0.01. As the NIR absorption of light increased, the venous hemoglobin oxygen saturation increased. In normal controls, the results showed a slight increase in hemoglobin-myoglobin oxygenation at the initial load, followed by a progressive decrease of $27\% \pm 5\%$ at maximal exercise.

Heart failure patients exhibited progressive reductions in hemoglobin-myoglobin oxygenation that were significantly greater than the normal controls. At maximal exercise, the

patients reached levels of 26%±4%, comparable to normals, but at a reduced work load (normals 140W±9; patients 60W±8). At peak exercise in normals it was found that the desaturation level plateaued, which was consistent with maximal oxygen extraction. A repeat of the exercise testing two-three weeks later in five patients demonstrated comparable results to their initial levels.

Another study by Hampson and Piantadosi (1990) examined the sensitivity of the NIR signal in detecting oxygen differences in feline brain and skeletal muscle during respiratory acid-base imbalances, hypercapnia and hypocapnia. Comparing their present results to results obtained either by differential spectrophotometry in the visible wavelength range or other invasive techniques, they found the NIR was able to detect the same changes, rendering it sensitive to the respiratory imbalances noted above. Using the NIR, it was discovered that during acute CO_2 inhalation, the flow of oxygen increased to the brain and decreased to muscle, due to vasoconstriction in skeletal muscle and a direct relaxing effect of CO_2 on cerebrovascular smooth muscle mediated by changes in the extracellular fluid pH.

Chance et al. (1992) used a muscle tissue spectrophotometer on the quadricep muscles of elite rowers and cyclists to document the trend of deoxygenation during heavy exercise. The same results were seen with the cycle and rowing ergometer, namely increased in oygenation as the power ouput increased to 360 W, where even the addition of a cuff to induce complete ischemia caused a $<2\%$ increase in the deoxygenation signal.

Sahlin (1992) used a near infrared spectroscopy device (RunMan device) to measure the oxygen availability during prolonged arterial occlusion and static contraction in the human vastus lateralis muscle. These results were compared to muscle biopsy assays for NADH

content. The results using the cuff were in agreement with previous results demonstrating a decline in oxygen saturation with an increase to normal pre-contraction values, after occlusion ended. The static contraction results showed a rapid decrease in oxygenation during the contraction, and a rapid increase in saturation when the cuff was deflated. During arterial occlusion, NADH results showed that NADH increased rapidly, and more than doubled after five minutes, while the lactate and lactate pyruvate remained unchanged. Changes mainly occurred within mitochondria and provided an index of available cellular oxygen .

The level of NADH after static contraction increased rapidly, and after five seconds of the contraction was more than twice the value at rest. The authors suggested that oxygen stores were deplcted after five seconds; therefore the NADH did not increase further when the contraction continued to the point of exhaustion. After four minutes of recovery, NADH was still above its precontraction level, even though after one minute of recovery, the major part of the increase had reverted. The foregoing indicates that factors other than oxygen availability may influence mitochondrial redox levels.

Conclusion

The tissue oximeter has been shown to be both valid (Hampson and Piantadosi, 1988; Wilson et al., 1989; Chance et al., 1992 and Sahlin 1992), and reliable (Smith et al., 1990; Mancini et al., 1991 and DeBlasi et al., 1991) with various populations and protocols. It is still a relatively new instrument, therefore more research is needed to assess its usefulness in a clinical and research setting.

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CHAPTER THREE

MATERIALS AND METHODS

Research Design

This study was in the format of a causal-comparative study between three different subject groups.

Subjects

Subjects were females between the ages of 24-57 years. There were three groups (healthy controls, MPS and FS) of ten subjects each. The patients were recruited from a FS support group in Edmonton, Alberta, a doctor specializing in the treatment of MPS sufferers and a local pain clinic. The controls were recruited from healthy women on the University of Alberta campus, and at the University of Alberta Hospital.

The inclusion criteria for patients consisted of fulfilling the criteria outlined by Travell and Simons (1983) (Appendix A) and the criteria, as outlined by the American Rheumatology Association, for the diagnosis of Fibromyalgia (Appendix B); diagnosis of one of the conditions at least six months prior to entering the study; and, trigger or tender points in the upper trapezius muscle. Exclusion criteria consisted of: an injection of cortisone one month prior to entering the study; the use of steroidal or non-steroidal anti-inflammatory drugs, or other pain relieving medications for two days prior to testing; any musculoskeletal injury one month prior to testing, and a body mass index above 68 kg/m^2.

The control subject inclusion criteria consisted of: no chronic muscle pain; no use of

anti-inflammatory drugs one month prior to testing; and no musculoskeletal injuries one month prior to testing. Exclusion criteria for controls also included any of the inclusion criteria listed above for MPS and FS sufferers. The control subjects were age-matched as closely as possible to the patient groups.

The subjects were not randomly selected, but we did obtain subjects from a range of occupations and backgrounds so as not to limit our results to a very narrow population of patients.

Testing

The testing consisted of two appointments. The first appointment was an initial screening of each subject by a doctor "blinded" to their condition, to ensure that each subject was assigned to the appropriate group. The trigger or tender point in the trapezius muscle was identified and marked by the same doctor. At this time patients also answered the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) (Appendix C) in order to obtain a general idea of the amount of pain they experienced and to determine the extent that their disease affected their acitivities of daily living. The questionnaire was filled out before the examination, but for a few subjects it was completed after the examination. The control subjects also completed part of Section 1 and all of Section 3 of the questionniare. This was done mainly to note any differences in the Activities of Daily Living item from Section 3. Section 2 did not apply to the control subjects, since it referred to how their spouse or significant other responds to them when they are in pain. The WHYMPI assesses psychosocial variables relevant to chronic pain experiences (Kerns, Turk and Rudy, 1985; Kerns and

Jacob, 1992). It surveys the patients' beliefs and appraises their pain, the impact of the latter on their lives and the social responses of others. Parts I and II have reported internal consistencies of alphas ranging from .72-.90 and .74-.84, respectively. Part III had levels of reliability alphas ranging from .70-.86. Stability levels for Parts I, II and III have been reported at correlations of .69-.86; .62-.89 and .83-.91, respectively (Kerns and Jacob, 1992).

The second appointment was two or three days later. The subject had an indwelling catheter inserted into a vein on the dorsal surface of the hand on the same side as the trigger/tender point. The intravenous catheter was kept patent by injecting 0.1ml of dilute heparin solution (Hepalean) into the catheter. Blood was drawn from the catheter into a red top test tube (Vacutainer) and immediately allowed to clot. All blood work was done by a medical doctor. A baseline blood sample was taken. The probes from the oximeter (RunMan device) were placed on the previously marked trigger/tender point and the machine was calibrated as outlined in the RunMan Device Handbook (NIR Inc., 1991). The control subjects, who did not display trigger points, chose an arm for testing and both the catheter and oximeter were used on that arm. The subject marked a vertical line on a visual analogue scale to show the amount of pain experienced the moment before testing began. The visual analogue scale (VAS) is a 10 cm horizontal line used to rate the sensation intensity and magnitude of pain (Price et al., 1983). It has two extremes of pain at either end. One end is 'no pain' and the other is 'the worst pain' or 'pain as bad as it could be'. A measurement from the 'no pain' end to the mark is taken and that is their score. The VAS was used to describe the subjects. Downie et al. (1978) found the vertical and horizontal VAS to be a valid measure of pain intensity in patients suffering from rheumatic diseases. Jensen et al. (1986) found the VAS to have a construct

validity score of 0.89 with respect to current pain levels in patients with chronic pain. The between session reliability was found to be 0.97 in patients with low back, upper back and shoulder pain (Price et al., 1983).

The testing exercise was broken into three intervals. The first interval consisted of holding the arm with the trigger/tender point in 90 degrees shoulder abduction, for five minutes or until the pain was too great to bear. The subject then had four minutes to rest quietly. She would also mark on another VAS the amount of pain experienced just prior to the moment of release from the contraction. During the four minutes rest, a 1Kg weight was placed around the wrist. At the end of four minutes the subject would again hold the arm out in 90 degree abduction for three minutes or until the pain was too great to bear. Another four minute rest period followed, during which another vertical line on a VAS was made. A 2Kg weight was then placed around the wrist and the subject held the weight in 90 degrees abduction for a maximum of two minutes. At the completion of the two minutes, a VAS was marked and a blood sample was taken and marked as 0 minutes. The subject then sat quietly for five minutes while the oximeter recorded the five minute recovery period. Blood samples were then drawn at 15, 30 and 60 minutes after the final contraction. Once the blood samples were all drawn, the subject's participation was complete. The reason for drawing blood at various points in time was due to the uncertainty of when exactly TNFα and IL-1β would be released if activated. Recombinant TNF-α has been found to be cleared systemically in rabbits within sixty minutes of intravenous injection, indicating that this cytokine rapidly exerts its effects on the body (Dinarello et al., 1986).

After each blood sample was drawn, the blood was allowed to clot for seven minutes,

to a maximum of twelve minutes to ensure that proper clotting had occurred. The sample was centrifuged for fifteen minutes at 2000 (xg). Upon completion, the serum was extracted from the sample and placed in a blue stopped test tube, which was then cooled in ice. At the end of the testing, the blood samples were stored at -80°C until analysis could be completed on all samples simultaneously to reduce interassay variability.

Chemical Analysis

The blood was analyzed using enzyme linked immuno-assay (ELISA) (INCstar) kits from Medgenix. The TNF-α and IL-1β ELISAs were performed in duplicate on serum. The assay methods conformed to the procedures outlined in the kits. For detailed descriptions, refer to kit number 40175 for TNF-α and 40121 for IL-1β. Four different kits were utilized due to the number of samples to be analyzed. The same person did all of the analyses to decrease the variability. All samples were randomly assigned to a kit for analysis.

Duplicate samples of TNF-α and IL-1β were analyzed and read using computer assisted interpretation with a UV MAX Kinetic microplate ELISA reader . The microtiter plate was read at 450nm with a reference filter of 630nm. A standard curve was constructed to determine the sample concentrations corresponding to the optical density (OD) read on the microtiter plate. The OD was plotted on the ordinate against the standard concentrations on the abscissa using Quattro Pro's linear regression to determine sample concentration in pg/ml.The standard curve concentrations for TNFα were 0, 50,150, 500 and for IL-1β 0, 20, 45, 110.

Data Analysis

The variables examined with the oximeter were:

a) the change with exercise from baseline

b) the change between exercise and recovery.

The average of the last thirty seconds of each interval (exercise and rest) were calculated. Recovery values were subtracted from exercise values to obtain the value in a) and baseline values were subtracted from exercise values to obtain the value in b). These numbers were then analyzed using a two way ANOVA from a Statistics program (Statistica software, Texas).

The assays used linear regression to determine from the raw data and kit standards the concentration levels (pg/ml) of TNF-α and IL-1β. A two way ANOVA with repeated measures was calculated.

The results from the VAS were analyzed using a two way ANOVA with repeated meaures. A Scheffe post-hoc was done to determine where the significant differences actually arose. A significance level was not set prior to any statistical anlaysis.

Ethical Consideration

No subjects were directly contacted by the researcher, and the researcher did not know their full medical histories. The subjects participated in the project on a strictly voluntary basis and it was made very clear that no penalty would be incurred for withdrawing at any stage from the

project. The subjects were each given a code number that was used on all information sheets and documents concerning their medical conditions. The key to the code numbers and subjects was kept in a confidential file and stored in a locked drawer for safety. Copies of the "Patient Information Sheet" and "Consent Form" are provided in Appendix D and Appendix E, respectively.

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CHAPTER FOUR

RESULTS

TABLE 4.1 give the means and standard deviations of the groups with respect to age, height and weight. No significant difference was found between the three groups. Three of the MPS subjects were unable to complete the entire protocol, stopping before the full exercise period was finished. One of these subjects did not finish the full five minutes during the first contraction, yet was able to complete the remaining three and two minute contractions. All of the FS and control subjects were able to complete the exercise protocol. Three of the FS subjects stated they were more motivated to push themselves because they felt better results would be achieved if they forced themselves to complete the full time. They also expressed their anxiousness for a solution to their pain and felt this study may contribute to such a solution. The control subjects stated that they experienced an uncomfortable feeling rather than pain.

Of the three subjects who could not complete the protocol, two had higher than mean (x) MPS VAS scores and one had below mean (x) MPS VAS scores. The subject with lower than mean scores possibly indicates muscular weakness and fatigue, not pain as a factor in her contraction. The two higher than average subjects had baseline pain scores higher than average before the contractions had even begun. This suggests that these subjects may not be able to deal with their pain as effectively as others or it was a 'bad day'.

TABLE 4.1 Means and Standard Deviations for age, height (cm) and weight (kg) for the MPS, FS and Control groups.

GROUP	AGE Mean ± S.D.	HEIGHT (cm) Mean ± S.D.	WEIGHT(kg) Mean ± S.D.
MPS	42.9 ± 8.5	162.5 ± 5.4	66.6 ± 8.8
FS	38.89 ± 9.0	162.2 ± 5.6	70.9 ± 23.0
CONTROL	37.56 ± 12.3	165.6 ± 6.1	68.5 ± 21.9

S.D.: Standard Deviation

Visual Analogue Scale

The results from the VAS were significant between and within groups. A Scheffe Post Hoc test was used to examine where the differences arose. Within the control group, Trial 1 was significantly lower than Trial 4 ($p \leq 0.01$). Trial 1 from the control group was significantly lower as compared with all trials from the FS group ($p \leq 0.01$) and all but Trial 1 of the MPS group ($p \leq 0.01$). Within the FS group, Trial 1 was significantly lower than the other three trials ($p \leq 0.001$) and within the MPS group, Trial 1 was significantly lower than Trial 3 and Trial 4 ($p \leq 0.05$). Between the FS and MPS groups, the MPS group had significantly lower scores ($p \leq 0.001$) than the FS group between each trial.

TABLE 4.2 Means and Standard Deviations (cm) of the Visual Analogue Scale for all subjects.

Group	Trial 1 $\bar{x}$ ± SD	Trial 2 $\bar{x}$ ± SD	Trial 3 $\bar{x}$ ± SD	Trial 4 $\bar{x}$ ± SD
Controls	0±0	1.19±0.98	2.29±2.15	2.97±2.93
MPS	1.55±1.54	4.30±2.26	5.79±2.44	6.62±2.41
FS	3.12±2.73	6.19±2.65	7.42±2.31	8.24±1.69

$\bar{x}$: Mean
SD: Standard Deviation

West Haven Yale Multidimensional Pain Inventory

See TABLE 4.3 for means and standard deviations of the WHYMPI for all three groups. Over half of the subjects (1 MPS; 6 FS; 9 Controls) were unable to answer Section 2 dealing with how their spouse or significant other reacted to their pain. The control group was significantly different to the two pain groups on two items; Interference and Pain Severity Control. The control group differed significantly from the MPS group on one item, Support, but with the FS group, there were more differences (Affective-Distress, Activities Away from Home, Social Activities and General Actvitiy rating). Significantly lower scores were found with the MPS group when compared to the FS group for the Support item. There were no differences between any of the groups for items; Life Control, Household Activities and Outdoor Activities.

Tissue Oximeter

Readings from the oximeter were possible in seven of ten controls, eight of ten MPS and eight of ten FS subjects. Means and standard deviations are given in TABLE 4.4. For three of the control subjects, the oximeter was not working and with the MPS and FS subjects the machine would not calibrate, therefore no reading could be taken. One of the FS subjects did not display a reading on the TP, but did show values on other areas of the trapezius and even the brachioradialis muscle. A two way ANOVA did not find any significant differences with the oximeter readings between or within groups on either factor (Δ with exercise or Δ with recovery) TABLES 4.5, 4.6 and 4.7 list the available oximeter values.

TABLE 4.3 Means and standard deviations of WHYMPI for the MPS, FS and Control groups.

GROUP	ITEM 1 $\bar{x} \pm SD$	ITEM 2 $\bar{x} \pm SD$	ITEM 3 $\bar{x} \pm SD$	ITEM 4 $\bar{x} \pm SD$	ITEM 5 $\bar{x} \pm SD$	ITEM 6 $\bar{x} \pm SD$	ITEM 7 $\bar{x} \pm SD$	ITEM 8 $\bar{x} \pm SD$	ITEM 9 $\bar{x} \pm SD$	ITEM 10 $\bar{x} \pm SD$	ITEM 11 $\bar{x} \pm SD$	ITEM 12 $\bar{x} \pm SD$	ITEM 13 $\bar{x} \pm SD$
MPS	4.0 ±1.0[a]	3.9±1.8[cd]	3.5± 1.1[a]	3.0± 1.3	3.0± 1.2	1.6 ±1.3	3.4 ± 1.5	2.2 ± 1.2	3.9 ± 1.6	0.94±1.2	2.4 ± 1.3	2.5± 1.1	2.3 ± 0.9
FS	4.2± 1.2[a]	1.1± 1.6	3.7± 1.3[a]	2.5± 1.1	4.0 ±1.2[b]	1.9 ±.66	2.5 ± 1.3	1.4 ± 1.6	3.0± 1.5	.62± .65	1.7± 1.0[b]	1.4± .65[b]	1.7± .79[b]
CONT.	.09 ± .26	0 ± 0	.04±.11	3.3± 2.0	2.0 ± 1.2	***	***	***	4.1± 1.2	1.5± 1.4	3.1± 1.3	2.7± 1.2	2.8± 1.2

ITEM 1: Interference
ITEM 2: Support
ITEM 3: Pain Severity
ITEM 4: Life Control
ITEM 5: Affective-Distress
ITEM 6: Negative Responses
ITEM 7: Solicitous Responses
ITEM 8: Distracting Responses
ITEM 9: Household
ITEM 10: Outdoor Activities
ITEM 11: Activities Away From Home
ITEM 12: Social Activities
ITEM 13: General Activities

[a]Statistically significant ($p<.05$): Control vs FS and MPS
[b]Statistically significant ($p<.05$): Control vs FS
[c]Statistically significant ($p<.05$): Control vs MPS
[d]Statistically significant ($p<.05$): FS vs MPS
***Missing data

TABLE 4.4 Group means and standard deviations for oximeter values (arbitrary units), denoting the changes with exercise and recovery.

Group	Exercise 1 $\bar{x} \pm$ SD	Exercise 2 $\bar{x} \pm$ SD	Exercise 3 $\bar{x} \pm$ SD	Recovery 1 $\bar{x} \pm$ SD	Recovery 2 $\bar{x} \pm$ SD	Recovery 3 $\bar{x} \pm$ SD
MPS	9.43± 0.37	9.36± 0.44	9.12± 0.61	9.59± 0.21	9.59± 0.21	9.39± 0.31
FS	10.01±0.39	9.88±0.50	10.26±0.65	10.11±0.19	9.96±0.41	10.19±0.68
Control	10.25±0.49	10.32±0.38	11.02±0.96	10.15±0.48	10.19±0.25	10.33±0.90

TABLE 4.5 Myofascial Pain Syndrome subjects' tissue oximeter values (arbitrary units), denoting the changes with exercise and recovery.
* No values were recorded.

MPS Subj.	Exercise 1	Exercise 2	Exercise 3	Recovery 1	Recovery 2	Recovery 3
1	8.52	8.63	8.50	8.47	8.41	8.30
2	10	10.01	9.94	9.94	9.99	9.85
3	*	*	*	*	*	*
4	10.04	10.00	9.89	9.81	9.80	9.84
5	9.94	9.99	9.99	9.97	9.98	10.01
6	7.13	6.53	5.07	8.86	8.94	7.7
7	9.84	9.89	9.85	9.77	9.76	9.70
11	10	10.06	10.05	10.06	10.1	10.15
26	*	*	*	*	*	*
31	9.97	9.79	9.7	9.81	9.7	9.58

TABLE 4.6 Fibromyalgia subjects' tissue oximeter values (arbitrary units), denoting the changes with exercise and recovery.
*No values were recorded.

FS Subj.	Exercise 1	Exercise 2	Exercise 3	Recovery 1	Recovery 2	Recovery 3
8	10.26	10.2	11	10.3	10.19	10.88
9	9.98	9.03	11.28	10.02	9.07	11.37
10	9.14	9.19	9.15	10.12	10.15	10.01
12	10.5	10.49	10.41	10.48	10.47	10.38
13	10.03	10.05	10.08	9.98	9.96	9.88
14	10.12	10.03	10.08	10.02	9.86	9.18
15	10.02	10.08	10.1	9.91	9.89	9.74
16	10.01	9.99	10	10.08	10.08	10.07
17	*	*	*	*	*	*
19	*	*	*	*	*	*

TABLE 4.7 Control subjects' tissue oximeter values (arbitrary units), denoting the changes with exercise and recovery.
* No values recorded.

Controls	Exercise 1	Exercise 2	Exercise 3	Recovery 1	Recovery 2	Recovery 3
18	10	10	10	10	10	10
20	*	*	*	*	*	*
21	*	*	*	*	*	*
22	*	*	*	*	*	*
24	11.11	10.23	11.97	11	10.02	11.82
25	9.92	9.94	12.11	9.95	10.01	9.86
27	10.12	10.6	10.56	9.81	10.4	10.47
28	10.11	10.82	10.44	9.98	10.53	9.49
29	9.87	9.84	9.8	10.05	10.01	9.99
30	9.81	9.05	9.21	9.59	9.77	9.87

TNF-α and IL-1β Levels

The serum concentrations for IL1-β and TNF-α are shown in TABLES 4.8 , 4.9 and 4.10. Normal circulating levels of IL-1 and TNF-α in humans have been found to be between 3pg/ml - 42pg/ml (Manicourt et al., 1993). A two way ANOVA with repeated measures found no significant difference between groups in concentrations of TNF-α. Due to the number of non-detectable concentrations, the IL-β could not be statistically analyzed. An ANOVA test is not possible if there are too many empty cells, as in this case.

TABLE 4.8 Myofascial Pain. TNF-α and IL-1β concentration values (pg/ml) at baseline, 0, 15, 30, 60 minutes. ND (non-detectable levels).

MPS SUBJ	TNFα Base	TNFα 0	TNFα 15	TNFα 30	TNFα 60	ILβ Base	ILβ 0	ILβ 15	ILβ 30	ILβ 60
1	4.71	3.75	1.35	ND	ND	16.3	ND	ND	ND	ND
2	ND	ND	5.43	ND	ND	ND	ND	ND	ND	ND
3	ND	4.73	ND	ND	9.23	0.51	19.8	ND	11.5	ND
4	15.3	21.8	9.54	22.57	17.1	ND	ND	ND	ND	ND
5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
7	ND	18.9	10.7	8.52	ND	ND	ND	ND	4.03	19.2
11	ND	ND	ND	ND	ND	ND	ND	96.1	ND	25.2
26	ND	ND	ND	ND	ND	ND	ND	ND	ND	6.02
31	4.73	21.1	17.5	0.47	9.23	30.6	19.3	6.14	16.8	18.5

TABLE 4.9 Fibromyalgia. TNF-α and IL-1β concentration values (pg/ml) at baseline, 0, 15, 30, 60 minutes. ND (non-detectable levels).

FS SUBJ.	TNFα Base	TNFα 0	TNFα 15	TNFα 30	TNFα 60	ILβ Base	ILβ 0	ILβ 15	ILβ 30	ILβ 60
8	ND	ND	ND	ND	0.39	ND	ND	ND	ND	ND
9	ND	ND	0.15	ND	ND	ND	ND	ND	ND	22.61
10	0.23	19.4	10.23	10.47	ND	ND	ND	ND	ND	ND
12	ND	0.47	ND	ND	ND	ND	ND	ND	ND	ND
13	ND	ND	ND	ND	ND	ND	ND	3.77	ND	1.15
14	ND	9.47	2.36	ND	ND	ND	ND	ND	ND	ND
15	2.5	3.54	7.45	7.19	ND	ND	ND	ND	ND	ND
16	25.44	12.15	12.93	21.27	17.36	ND	ND	ND	22.42	ND
17	23.9	14.3	4.23	10.47	9.27	ND	ND	1	13.98	6.88
19	46.56	35.09	49.08	25.18	25.18	13.57	ND	1.98	ND	ND

TABLE 4.10 Controls. TNF-α and IL-1β concentration values (pg/ml) at baseline, 0, 15, 30, 60 minutes. ND (non-detectable levels).

Cont.	TNFα Base	TNFα 0	TNFα 15	TNFα 30	TNFα 60	ILβ Base	ILβ 0	ILβ 15	ILβ 30	ILβ 60
18	5.67	3.99	ND	3.99	1.11	ND	ND	ND	ND	ND
20	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
21	29.65	33.73	39.97	34.69	24.38	ND	ND	5.41	ND	ND
22	4.73	22.73	15.39	17.52	ND	ND	ND	ND	ND	ND
24	8.31	4.23	5.67	1.83	7.35	14.74	2.41	6.69	7.[illegible]	6.94
25	ND	2.84	6.86	ND	8.76	ND	0.4	ND	ND	19.04
27	ND	ND	ND	ND	ND	4.18	ND	2.66	1.15	8.59
28	ND	ND	ND	ND	ND	ND	ND	0.26	ND	12.51
29	29.61	17.62	16.58	18.92	6.15	ND	3.68	1.08	3.94	ND
30	8.24	6.41	9.54	2.76	20.49	ND	ND	7.07	ND	8.37

CHAPTER FIVE

DISCUSSION

The results of the study indicated no differences in TNF-α, IL-1β and tissue oxygenation levels between women with FS, MPS and no soft tissue pain. These findings suggest cytokine-induced muscle ser[illegible]ation/catabolism [illegible]uscle hypoxia are not involved in soft tissue pain in MPS or FS. This supports the premise [illegible]tly held by many experts in the field of soft tissue pain that the source of pain for the MPS and FS patients is of a central, not peripheral origin.

Visual Analogue Scale

The results from the VAS scores showed that FS and MPS subjects experienced a greater augmentation of pain over the exercise trials than did the controls. This demonstrates either a disturbed perception of pain or an increased sensitivity to pain. Similar results were reported by Bietsema et al. (1993), who used the VAS to determine the level of subjective pain pre and post-exercise in FS patients. This group found that at all levels of exercise, the VAS scores were significantly higher in the FS subjects than that of the healthy controls.

Scudds et al. (1989) used the VAS to assess the present pain, sleep quality, anxiety and depression in FS and MPS patients. The results indicated no significant differences between the groups on the anxiety and depression scores. Unfortunately, the study did not compare their results with healthy controls. Means for present pain intensity for the FS and MPS groups were 5.91cm and 4.45cm respectively; scores that are higher than the initial scores found in the present study (FS - 3.12cm; MPS - 1.55cm). VAS values examining the pain intensity, endurability and

disturbance of the patient's symptoms between FS and MPS were reported by Wolfe et al. (1992). The FS patients have a statistically higher pain endurability score as compared to the MPS patients. Again, no comparisons were made with healthy controls. In comparison to the present research, the values were all much higher from the Wolfe et al. (1992) study. The higher values from the Scudds et al. (1989) and Wolfe et al. (1992) studies could be due to specifiying the type and quality of pain experienced instead of just stating the amount of pain, as was done in the present study. A more specific qualifier may have changed the results from the VAS scores. In conclusion, The FS and MPS groups experienced more subjective pain due to the isometric contraction, as compared to the controls. Also, the pain perception for all three groups increased from the pre-contraction levels to Trial Four. These results fit with our predictions of what would occur with the VAS.

West Haven Yale Multidimensional Pain Inventory

There were few differences between both pain groups and the control group in the present study. Two items that the control group differed from the pain groups were *Interference* and *Pain Control*. This demonstrates that the MPS and FS perceive their pain to be more of a hinderance in their lives and disrupted their daily activities. They also have the perception that they are powerless to act against it. The item, *Support*, lowest among the MPS group, could indicate that either they did not receive a lot of support from their significant other or they did not have a significant other. The latter was the most common incident. The FS group showed lower *Social Activities* scores than the MPS group. A possible explanation could be increased pain levels, therefore the FS subjects did not want or were unable to participate in social events.

Although this was not an item, the socio-economic status of the FS subjects might be lower, warranting them to stay home more. The number of differences between the control group and FS group seems plausible. An interesting result was no difference between all three groups on the *Life Control* item. Reasons for this could be either the control group having a particularly stressful week when the questionnaire was administered or the pain groups perceiving more control over their lives than they openly admit.

Since the responses for common daily activities in Section 3 are dependant upon many factors, caution is advised in interpreting these findings. For example, in the control group three of the subjects were university students, which would skew the values under questions such as how often one went to a movie or out for dinner. Some of the pain subjects were unemployed or only worked part time. The restrictions on going out socially may be due to financial reasons, not pain. Questions asking how often one worked on the car, a house repair or in the garden may be biased. If the subject lives in an apartment or does not own a car, then a low score on these items would not indicate a true problem with daily activities. The fact that all of the subjects were women may explain zeros on the previously mentioned questions (possibly an incorrect general assumption).

The means of the FS and MPS WHYMPI scores were compared to the means from a study by Kerns and Haythornthwaite (1988), who analyzed the effect of a rehabilitative program would have on depressed chronic pain patients, compared to nondepressed chronic pain patients. On all of the items, the means between the groups in the two studies were similar.

Faucett and Levine (1991) used a subscale of the WHYMPI to analyze perceptions of social support (*Solicitious Responses*) and the presence of conflict in social relationships

(*Negative Responses*) between arthritis patients and MPS patients. Their results indicated that the arthritis patients reported more family and network support was made available for them compared to the MPS patients. No differences were reported between the groups with respect to how supportive their significant other was in response to their pain. The mean scores for the MPS patients from the Faucett and Levine study (1991) were 3.34 for *Solicitious Responses* and 1.97 for *Negative Responses*. These results are again similar to results obtained from this research (*Solicitious Responses* - 3.4 and *Negative Responses* - 1.6).

The similarity in questionnaire results from the literature and this present study indicates that our subjects ' characteristics are conducive to characteristics of other MPS and FS patients. This fact is important in transferring our results from the cytokines and tissue oximeter to a greater number of MPS and FS patients.

Tissue Oxidation:

All oxygen levels remained relatively constant, but an interesting pattern was noted. It was noted that with the MPS subjects, with both exercise and recovery, the recorded values steadily decreased. The FS subjects demonstrated a drop at Exercise 2 and Recovery 2 with an increase at Exercise 3 and Recovery 3. The Controls subjects demonstrated a continual increase after each trial. Further trials with the oximeter would be necessary to make any inferences about this present data. These results do not necessarily mean that tissue hypoxia did not occurred. The use of an isometric contraction, in a protocol similar to one used by Oberg et al. (1992), was hoped to stress the muscles of the shoulder girdle in a position that commonly induces the pain, therefore effecting the oxygen levels. The protocol was possibly not stressful enough to elicit any

change. As seen in TABLES 4.5, 4.6, 4.7, no marked differences arose between subjects within the groups or between the groups.

The results do not provide strong evidence for any abnormal activity in oxygen levels in the site of the pain or TrP/TP.

TNF-α and IL-1β Levels

The TNF-α and IL-1β detectable levels were all within normal healthy ranges and demonstrated no elevation of activity, as compared to the standards from the assay kits and previous research (Cannon et al., 1991; Dinarello et al., 1986).

Samples with non-detectable levels of TNFα and IL-1β fell below the lower limits of sensitivity provided by the commercial assay kits. The cytokines may not have been detected due to the protocol failing to trigger the events leading to their release.

The results indicate that by the means used to detect cytokines as indicators of muscle injury (elevated TNFα and IL-1β levels), no evidence of injury existed.

One point that should be discussed is the power of the tests. Power was not determined in the initial stages of planning for this study. Obviously, if the number of subjects had been greater the chance of showing an effect from the independent variables would have increased. The sample sizes were based on the purpose of the study; no prior research had been done in these areas with these particular measures, therefore it was not feasible to do the study with a large number of subjects.

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CHAPTER SIX

SUMMARY AND CONCLUSIONS

The purpose of this study was to examine the TNFα, IL-1β blood levels and tissue oxygen levels at the site of pain or TrP/TP in MPS and FS and compare these same measures to healthy controls. It was hypothesized that the MPS and FS subjects would have elevated levels of TNFα and IL-1β and altered tissue oxygen flow, indicating muscle injury and a hypoxic enviroment in the TrP/TP area. These factors could lead to the chronic pain experienced by MPS and FS subjects.

The alternate hypothesis was that if the TNFα and IL-1β blood levels were not elevated and no altered oxygen levels could be measured, then the pain most likely arises from a CNS dysfunction and not from a peripheral problem in muscle. The original hypothesis was rejected.

The following conclusions were drawn based on the results of this study:

1) MPS and FS did not have elevated TNFα and IL-1β blood levels as compared to controls.

2) MPS and FS did not have altered tissue oxygen levels in the TrP/TP as compared to controls, as measured with the tissue oximeter.

3) the origin of the pain in FS and MPS does not appear to be related to cytokine induced soft tissue sensitization/catabolism or hypoxia.

4) future research on the source of the pain should focus on central mechanisms.

APPENDICES

APPENDIX A

Diagnostic Criteria for the Myofascial Pain Syndrome

Major Criteria

1. Normal erythrocyte sedimentation rate (ESR)
2. Pain following acute or chronic muscle overload
3. Taut, palpable muscle band
4. Painful trigger point within the taut muscle band
5. Local "twitch" response and "jump" sign when trigger point palpated
6. Characteristic pattern of referred pain for that trigger point

Minor Criteria

1. Subjective muscle weakness and poor exercise endurance
2. Limited stretch range of motion of the muscle
3. Rapid symptomatic, but often temporary, pain relief with some localized therapies

Adapted from:

Scudds RA and McCain GA. The differential diagnosis of primary fibromyalgia syndrome fibrositis). Int Med. 1988; 9:83-103.

Travell JG and Simons DG. *Myofascial Pain and Dysfunction: The Trigger Point Manual.* Baltimore, MD: William and Wilkins; 1983.

APPENDIX B

Diagnostic Criteria for Primary Fibromyalgia:

1. History of widespread pain for at least 3 months
   Definition: Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

2. Pain in 11 of 18 tender point sites on digital palpation
   Definition: Pain on digital palpation, must be present in at least 11 of the following 18 tender point sites:
   Occiput: bilateral, at the suboccipital muscle insertion Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7
   Trapezius: bilateral, at the midpoint of the upper border
   Supraspinatus: bilateral, at origins, above the scapula spine near the medial border
   Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
   Lateral epicondyle: bilateral, 2 cm distal to the epicondyles
   Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
   Greater trochanter: bilateral, posterior to the trochanteric prominence
   Knee: bilateral, at the medial fat pad proximal to the joint line
   Digital palpation should be performed with an approximate force of 4 kg.
   For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender" is not to be considered "painful".

For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

Taken from:

Wolfe F, Smythe HA, Yunus MB, Bennett RM, et al. The American College of Rheumatology 1990 criteria for the classification of Fibromyalgia. Arthritis Rheumatism 1990; 33:160-72.

APPENDIX C

THE WEST HAVEN-YALE MULTIDIMENSIONAL PAIN INVENTORY

SECTION 1

In the following 20 questions, you will be asked to describe your pain and how it affects your life. Under each question is a scale to record your answer. Read each question carefully and then *circle* a number on the scale under that question to indicate how that specific question applies to you.

1. Rate the level of your pain at the present moment.

0	1	2	3	4	5	6
No pain						Very intense pain

2. In general, how much does your pain problem interfere with your day to day activities?

0	1	2	3	4	5	6
No interference						Extreme interference

3. Since the time you developed a pain problem, how much has your pain changed your ability to work?

0	1	2	3	4	5	6
No change						Extreme change

4. How much has your pain changed the amount of satisfaction or enjoyment you get from participating in social and recreational activities?

0	1	2	3	4	5	6
No change						Extreme change

5. How supportive or helpful is your spouse (significant other) to you in relation to your pain?

0	1	2	3	4	5	6
Not at all supportive						Extremely supportive

6. Rate your overall mood during the *past week.*

0	1	2	3	4	5	6
Extremely low mood						Extremely high mood

7. On the average, how severe has your pain been during the *last week?*

0 1 2 3 4 5 6
Not at all severe Extremely severe

8. How much has your pain changed your ability to participate in recreational and other social activities?
0 1 2 3 4 5 6
No change Extreme change

9. How much has your pain changed the amount of satisfaction you get from family-related activities?
0 1 2 3 4 5 6
No change Extreme change

10. How worried is your spouse (significant other) about you in relation to your pain problems?
0 1 2 3 4 5 6
Not at all worried Extremely worried

11. During the *past week* how much control do you feel that you have had over your life?
0 1 2 3 4 5 6
No control Extremely in control

12. How much *suffering* do you experience because of your pain?
0 1 2 3 4 5 6
No suffering Extreme suffering

13. How much has your pain changed your marriage and other family relationships?
0 1 2 3 4 5 6
No change Extreme change

14. How much has your pain changed the amount of satisfaction or enjoyment you get from work?
0 1 2 3 4 5 6
No change Extreme change

_____ Check here, if you are not presently working

15. How attentive is your spouse (significant other) to your pain problem?
1 2 3 4 5 6
Not at all attentive Extremely attentive

16. During the past week how much do feel that you've been able to deal with your problems?
0 1 2 3 4 5 6
Never Very often

17. How much has your pain changed your ability to do household chores?
0 1 2 3 4 5 6
No change Extreme

change

18. During the past week how irritable have you been?

0 1 2 3 4 5 6

Not at all irritable — Extremely irritable

19. How much has your pain changed your friendship with people other than your family?

0 1 2 3 4 5 6

No change — Extreme change

20. During the past week how tense or anxious have you been?

0 1 2 3 4 5 6

Not at all tense or anxious — Extremely tense or anxious

SECTION 2

In this section, we are interested in knowing how your spouse (or significant other) responds to you when he or she knows that you are in pain. On the scale listed below each question, *circle* a number to indicate *how often* your spouse (or significant other) generally responds to you in that particular way *when you are in pain*. Please answer *all* of the 14 questions.

****** Please identify the relationship between you and the person you are thinking of. _____

_____

1. Ignores me

0 1 2 3 4 5 6

Never — Very often

2. Asks me what he/she can do to help

0 1 2 3 4 5 6

Never — Very often

3. Reads to me

0 1 2 3 4 5 6

Never — Very often

4. Expresses irritation to me

0 1 2 3 4 5 6

Never — Very often

5. Takes over my jobs or duties

0 1 2 3 4 5 6

Never — Very often

6. Talks to me about something else to take my mind off the pain

0	1	2	3	4	5	6
Never						Very often

7. Expresses frustration at me

0	1	2	3	4	5	6
Never						Very often

8. Tries to get me to rest

0	1	2	3	4	5	6
Never						Very often

9. Tries to involve me in some activity

0	1	2	3	4	5	6
Never						Very often

10. Expresses anger at me

0	1	2	3	4	5	6
Never						Very often

11. Gets me some pain medication

0	1	2	3	4	5	6
Never						Very often

12. Encourages me to work on a hobby

0	1	2	3	4	5	6
Never						Very often

13. Gets me something to eat or drink

0	1	2	3	4	5	6
Never						Very often

14. Turns on the T.V. to take my mind off my pain

0	1	2	3	4	5	6
Never						Very often

SECTION 3

Listed below are 18 common daily activities. Please indicate *how often* you do each of these activities by *circling* a number on the scale listed below each activity. Please complete *all* 18 questions.

1. Wash dishes

0	1	2	3	4	5	6
Never						Very often

2. Mow the lawn

0	1	2	3	4	5	6
Never						Very often

3. Go out to eat

0 1 2 3 4 5 6
Never Very often

4. Play cards or other games
0 1 2 3 4 5 6
Never Very often

5. Go grocery shopping
0 1 2 3 4 5 6
Never Very often

6. Work in the garden
0 1 2 3 4 5 6
Never Very often

7. Go to a movie
0 1 2 3 4 5 6
Never Very often

8. Visit friends
0 1 2 3 4 5 6
Never Very often

9. Help with the house cleaning
0 1 2 3 4 5 6
Never Very often

10. Work on the car
0 1 2 3 4 5 6
Never Very often

11. Take a ride in a car
0 1 2 3 4 5 6
Never Very often

12. Visit relatives
0 1 2 3 4 5 6
Never Very often

13. Prepare a meal
0 1 2 3 4 5 6
Never Very often

14. Wash the car
0 1 2 3 4 5 6
Never Very often

15. Take a trip
0 1 2 3 4 5 6
Never Very often

16. Go to a park or beach

0 1 2 3 4 5 6
Never Very often

17. Do a load of laundry
0 1 2 3 4 5 6
Never Very often

18. Work on a needed house repair
0 1 2 3 4 5 6
Never Very often

The End

APPENDIX D

PATIENT INSTRUCTION SHEET
A STUDY ON PRIMARY FIBROMYALGIA AND MYOFASCIAL PAIN SYNDROME IN FEMALE VOLUNTEERS

You will be asked to attend two separate appointments at the Glenrose Rehabilitation Hospital or the University of Alberta. The appointments will be made at your convenience. The appointments will be two days apart.

The first appointment will be an examination to determine the location of your trigger points or tender points in the upper trapezius muscle. You will also fill out the West Haven Yale Multidisciplinary Inventory which will take 10-15 minutes. The next test day will take place two days later. The second appointment should take 1 1/2 to 2 hours.You will not be able to exercise for the two intervening days.

An indwelling catheter will be inserted into an arm vein and a blood sample will be taken at rest. The probes from the near-infrared spectrometer will be placed on the trigger point or tender point in the upper trapezius muscle. This device measures, non-invasively, the amount of oxygen in the muscle. You will then be asked to hold your arm out to the side at 90 degrees for 5 minutes. Once the five minutes has elapsed, you will have a 4 minute rest period. You will then be asked to mark on a Visual Analogue Scale the amount of pain experienced during the contraction. The next contraction will be in the same position with a 1 kg wrist weight for a duration of 3 minutes. After this contraction, you will again have a rest period of 4 minutes and will mark on the Visual Analogue Scale the amount of pain experienced during the contraction. The final contraction will be with a weight of 2 kg for two minutes in the same position. After the final contraction, you will again mark on the scale the amount of pain that you experienced. The probes will be removed. The first blood sample will be taken at this time. The subsequent samples will be withdrawn 15, 30 and 60 minutes after the final contraction. Your participation then will be complete.

You have the option to stop the contractions at any point you are too fatigued or in too much pain to continue the contractions.

APPENDIX E

CONSENT FORM
A STUDY ON PRIMARY FIBROMYALGIA AND MYOFASCIAL PAIN SYNDROMES IN FEMALE VOLUNTEERS

The diagnosis of Primary Fibromyalgia and the Myofascial Pain Syndrome is based upon the patient's own description of pain, a subjective measure and the specific criteria outlined for each syndrome. No objective or unbiased markers exist for the diagnosis of either syndrome. Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1), two substances found in the blood, are produced by the body locally in reactions to viruses, bacteria and inflammation. Both substances are associated with muscle protein breakdown. It is the researchers' feeling that these substances may be contributing to the chronic pain experienced by these patients. Another current belief in Myofascial Pain and Primary Fibromyalgia Syndromes research is that lower levels of oxygen are present in the muscle, contributing to the pain. In this study, a new instrument will be used to measure, non-invasively, oxygen tissue levels.

The purpose of this study is to analyze levels of oxygen in the muscle and TNF and IL-1 in the blood in Primary Fibromyalgia and Myofascial Pain patients to try and establish unbiased measurement criteria.

A brief medical history and examination will occur to ensure that I am an appropriate subject.

I am assured that all information will be kept **confidential**. Previous medical records will be reviewed, but will not be copied or removed for use elsewhere. The results of this study will be used in a medical publication; however, **my identity will be strictly protected.**

I will not be eligible for the study if I have any medical illness not associated with Myofascial Pain or Primary Fibromyalgia, or have experienced blunt muscle trauma in the previous month, or received an injection of cortisone in the previous month.

I understand that I must not use any non-steroidal anti-inflammatory medication, cortisone or other pain relieving medication for 48 hours before the examination day.

I am aware that an indwelling catheter will be used in this study and the risks involved include infection, bruising and catheter shear.

I have read the accompanying instruction sheet and understand that there may be some discomfort, **but I will be allowed to drop out at any time for any reason at my discretion without penalty.**

I understand that my signature means:

1. that I have read this form and the accompanying instruction sheet,
2. that I have had an opportunity to ask whatever questions I desire and these have been answered to my satisfaction,
3. that I voluntarily agree to participate in this study, and
4. that I will receive a personal copy of this consent form.

If I have further questions concerning the study, I can contact Sharla King at 439-4415 or at the University of Alberta, Dr. Brian Fisher at 492-8273.

Study Participant: Witness:

Date: Principal Investigator: