THE ACUTE EFFECTS OF TWO DIFFERENT TRAINING MODELS ON MARKERS OF INFLAMMATORY ACTIVATION AND SKELETAL MUSCLE INJURY IN PATIENTS WITH CHRONIC HEART FAILURE

by

Arlana Taylor

B.Sc. The University of British Columbia, 1990

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

The Faculty of Graduate Studies

(Human Kinetics)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2008

ABSTRACT

Over the last several decades there has been a marked increase in the prevalence of heart failure (HF). Despite advances in pharmacological therapy, patients with HF are characterized by exercise intolerance, breathlessness, fatigue and excessive neurohormonal activation associated with increased mortality. Specific abnormalities within skeletal muscle of HF patients have been identified and are believed to contribute to the observed exercise intolerance. Additionally, inflammatory activation with increased serum cytokine levels has recently been described as an important factor in the progression of HF. Although exercise training is an important therapeutic intervention in the management of HF, acute bouts of exercise may lead to increases in pro-inflammatory cytokines. Increased levels of certain pro-inflammatory cytokines (e.g., TNF-α, IL-6) have been correlated with increased severity of left ventricular dysfunction, activation of the sympathetic and renin-angiotensin systems and have been observed to mediate catabolic effects on skeletal muscle.

Recently, several alternative models of exercise training have been proposed that challenge the traditional "steady-state" model of exercise training in HF patients, including interval training. Interval training methods employ greater muscular loading and/or eccentric forces than a steady-state training method and may increase the risk of immune system activation or exercise-induced muscle injury (EIMI), leading to delayed onset muscle soreness and prolonged loss in muscle force production in the already functionally-limited HF patient. It is believed that the skeletal muscle abnormalities associated with the syndrome of HF may increase the risk of damage to skeletal muscle, (i.e., EIMI with associated inflammatory activation) especially following unaccustomed exercise training. Although interval training is currently being adopted in cardiac rehabilitation settings, little is known about the effects of interval training on EIMI and/or inflammatory markers.

The **overall objective** of this study was to evaluate the acute phase response of inflammatory and muscle injury markers in patients with HF following a single bout of either Steady State (SS) or Interval Training (IT) for a duration of 20 minutes.

Methods: Fourteen male participants with HF were matched and randomized into SS or IT for 20 minutes on a cycle ergometer: The IT involved 2 minute work:recovery phases of 90% and 40% of heart rate reserve, respectively. The SS involved continuous exercise at 65% of heart rate reserve. The total work was identical between the two groups. Biochemical markers of muscle damage and acute inflammation, concentric and eccentric isokinetic muscle torque, and subjective indicators of delayed onset muscle soreness (DOMS) and lower extremity function were evaluated at baseline, and then immediately following the training bout, and at 6, 24, and 48 hours post.

Results: There were no differences between the interval training group or the steady-state training group for markers of skeletal muscle injury or inflammatory activation. Neither group demonstrated prolonged decrements in concentric or eccentric torque, biochemical markers of inflammation or skeletal muscle injury, or in delayed onset of muscle soreness. Significance was found in both groups for the lower extremity functional scale from baseline to all time periods following the training bout.

Practical Implications: Exercise plays an essential role in the optimal treatment of patients with HF. The findings from the present study suggest that IT or SS do not result in excessive inflammatory system activation or skeletal muscle injury. These results have important implications for clinicians prescribing exercise regimes for HF

patients who may be starting back into activity after a prolonged sedentary period. Additionally, results from this study indicate that there is a need for future research looking at the actual and perceived effect of even a single bout of exercise on lower extremity function.

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGEMENTS

I want to extend a very special thank-you to my supervisor, Dr. Darren Warburton, for his enthusiasm and dedication to the field of cardiovascular research. Without Dr. Warburton's guidance, knowledge and expertise in conducting research, I would never have completed this project. His flexibility and support throughout this process has been greatly appreciated. I also want to thank my committee members, Dr. Donna MacIntyre, for her expertise in skeletal muscle injury, and her assistance and support throughout this project; Dr. Andrew Ignaszewski, for whom I hold tremendous respect, and for his valuable opinions and advice on this project and Dr. Don McKenzie, for his instruction and guidance throughout the completion of my graduate degree (and for some of the best coursework I have ever taken). Without the support of the Physiotherapy Department, the Healthy Heart Program, the Atherosclerosis Specialty Lab (ASL) and the lab at St. Paul's Hospital, this project would not have been successful. A special thanks to Dr. John Hill and Willi Yu, of the ASL, for their commitment to the project, and their advice and expertise in the analysis of the blood samples. I would also like to acknowledge the assistance and expertise of Dr. Maurice Pelsers in helping to make sense of the FABP and Myoglobin data in this study.

I am very appreciative of all the help and support of my fellow graduate students, Ben Esch, Jessica Scott, Dominic Zbogar and Steffanie Gatto. They have been invaluable in my learning and in helping to maintain my sanity and keep my vision clear in order to bring this project to completion.

I would like to acknowledge my dog Kosmo for her continual supply of Vitamin K and who was willing to spend so many hours beside me at the computer when she could have been outside.

Lastly, I want to acknowledge the assistance and support of my husband, Lars Taylor. Without his assistance in advanced computer skills and his willingness to work late in the evening so that I could meet deadlines, this paper would not be in the format it is today. I want to thank him for his patience and understanding in helping me reach my goals and to see this project through to completion (even though it made it tough to get out and play on some days!). Thank-you.

SCIENTIFIC SUMMARY

The burden of heart failure (HF) is increasing in Canada, not only as a result of the aging population, but also as a result of improved survival among patients with hypertension and coronary artery disease.[1] Prevalance rates indicate that over 400,000 Canadians are affected by HF with over 50,000 new cases diagnosed each year.[1, 2] Despite advances in pharmacological treatment of HF, there have been only modest improvements in HF outcomes on a population-wide basis over the past 25 years.[1]

The classic definition of HF is “heart failure occurs when an abnormality of cardiac function causes the heart to fail to pump blood at a rate required by the metabolizing tissues or when the heart can do so only with an elevated pressure”.[3] Maximal aerobic capacity is often reduced to less than 50% of healthy age-matched individuals, and patients often report leg muscle fatigue as their primary limiting factor on both exercise testing and training.[4, 5] Breathlessness, early muscular fatigue and exercise intolerance are hallmark symptoms of HF.[6-8] These symptoms were originally believed to be the result of central limitations in oxygen transport to the working muscles. However, it has become apparent that many indices of heart function at rest, such as left ventricular ejection fraction, correlate poorly with exercise capacity.[5, 6, 9, 10] It is, therefore, possible that non-cardiac factors may contribute to the exercise intolerance in HF patients.[11]

Specific abnormalities have been identified within the skeletal muscle of HF patients that contribute to the exercise intolerance observed and to the worsening prognosis. These peripheral abnormalities include a skeletal muscle myopathy that is

characterized by alterations in skeletal muscle ultrastructure, apoptosis (programmed cell death), a reduction in the cross-sectional area of type I and type II fibres, as well as, a shift from oxidative type I fibres to glycolytic type II fibres.[12] The peripheral abnormalities are believed to be, in part, a consequence of the compromised peripheral blood perfusion.[3, 13]

It has been demonstrated that physical deconditioning of the musculoskeletal system will lead to several changes similar to the skeletal muscle myopathic changes observed in patients with HF including: muscle weakness, muscle fibre atrophy (primarily type II fibres), decreased muscle mass and reduced oxidative enzymes.[14] Persistently high hospital readmission rates, related to disease severity, may lead to long periods of inactivity or bedrest among HF patients.[1, 5, 7, 14, 15] Additionally, patients with HF will often reduce their level of activity and adopt sedentary lifestyles as a result of the symptoms associated with the condition (e.g., breathlessness, fatigue, etc.). Physical deconditioning, with the consequent decline in function, is related to both of the previously mentioned scenarios. Activity that may be regarded as trivial to healthy individuals may be strenuous for the deconditioned patient with HF. The relatively few studies that have been carried out on this topic in patients with chronic obstructive pulmonary disease have shown that strenuous incremental cycle exercise, and even light constant cycle exercise, results in oxidative stress.[16] Skeletal muscle alterations caused by chronic inactivity, or from the syndrome of HF itself, make the remaining skeletal muscle more susceptible to damage, especially with unaccustomed activity. The ability of the muscle to recover from damage becomes severely impaired and the muscle is unable to adapt rapidly following sequential periods of exercise.[17] Exercise-induced muscle injury (EIMI) has been associated with structural damage of

the sarcomeres, protein leakage from the injured myofibres, an acute inflammatory reaction, loss of muscle force, decreased range of motion, swelling and delayed onset muscle soreness (DOMS).[18-22]

Activation of inflammatory mediators have been demonstrated after both strenuous exercise and EIMI and there is increasing evidence that inflammatory mediators play an important role in skeletal muscle wasting and fatigue in a number of clinical settings, including HF.[23, 24] Systemic inflammation may directly or indirectly have many harmful effects, for example by inducing oxidative stress.[25] Strenuous exercise, tissue damage and repetitive stimulation of skeletal muscle have been shown to increase oxidative stress in skeletal muscle.[26] Additionally, due to impaired local vasodilatory responses as a result of increased sympathetic tone, HF patients are subjected to episodic underperfusion and tissue hypoxia in exercising skeletal muscle that can also generate reactive oxygen species and activation of the inflammatory cascade.[27] There is increasing evidence to suggest that oxidative stress may play a role in the muscle fatigue that accompanies HF.[3] The larger the mismatch between maximal cardiac output and the amount of muscle mass engaged in exercise, the higher is the sympathetic activity in all parts of the body.[13] Magnusson suggests that it is possible that the sympathetic drive may become so pronounced that it could contribute to tissue damage, leading to the activation of mononuclear cells and cytokines.[13] In fact, Magnusson et al report that HF patients have overall higher arterial concentrations of noradrenalin than controls at rest and during either the one-legged or two-legged peak knee extensor exercise.[13] It remains unclear whether the activation of the inflammatory cascade is as a result of muscle damage or from sympathetic drive/oxidative stress in the exercising muscle.

Nevertheless, physical training remains an important therapeutic intervention in the management of HF and several studies on aerobic and resistance exercise training have demonstrated the beneficial effects on reversal of several peripheral pathophysiologic changes that result from HF and deconditioning.[28-40] However, despite an abundance of evidence supporting a relationship between a skeletal muscle myopathy and exercise intolerance in HF, there is a paucity of information on the optimal type of training in HF patients that will not only lead to a reversal of the skeletal muscle abnormalities and improve functional capacity, but that will not increase the patient's risk of EIMI and/or the cascade of pro-inflammatory activation.

BACKGROUND

There has been an evolution in the understanding of the pathophysiology of HF over the last several decades. Coates et al developed the “muscle hypothesis” as a mechanistic approach to define HF.[8, 41] These investigators link skeletal muscle changes and ventilatory and hemodynamic responses during exercise by means of a complex heart-muscle-lung-brain feedback interaction.[41] In this hypothesis, HF is defined by a complex interaction of cardiac dysfunction together with impaired function of the renal and respiratory systems, neurohormonal activation, imbalance within the immune system, reduced activity levels and a recognition of the pivotal role of the musculoskeletal alterations.[7]

The pathophysiological mechanisms responsible for the skeletal muscle defects in HF are poorly understood. There is objective evidence to support similarities between the changes observed with physical deconditioning and aspects of the pathophysiology of HF. However, over the course of the disease, muscles are subjected to inactivity, aging, malnutrition, altered neurohormonal status, and most likely, to repeated episodes of hypoxia.

The Cytokine Hypothesis (See Appendix 1)

Recently, the cytokine hypothesis has been put forward in which the deterioration of heart function (along with other organs, e.g., skeletal muscle) progresses because of the activation of a cascade of pro-inflammatory cytokines.[42] Elevated levels of circulating cytokines have been demonstrated in patients with HF and there is increasing evidence that inflammatory mediators play an important role in the skeletal muscle wasting and fatigue observed in HF patients.[3, 42] Interleukin-1 (IL-1),

Interleukin-6 (IL-6) and Tumor Necrosis Factor – alpha (TNF-α) have all been implicated in muscle degradation.[42, 43]

Cytokines are small biologically active molecules that regulate inflammation and are known to be secreted from several types of cells including, endothelial cells, macrophages, lymphocytes, adipocytes and myocytes.[44, 45] Previous studies indicate that cytokines in general, and specifically TNF-α, can lead to contractile dysfunction in striated muscle (skeletal and cardiac).[3, 9, 44, 45] Inflammatory cytokines can produce muscle wasting through indirect effects, i.e., anorexia, or through direct effects, e.g., promotion of apoptosis in skeletal myotubules or muscle catabolism through opposition of the trophic effects of insulin in skeletal muscle.[9, 46, 47] It has been suggested that reactive oxygen species may act as an upstream signal that activates the pro-inflammatory cascade.[3] Several triggers for oxidative stress in skeletal muscle have been identified including strenuous exercise and tissue injury, repetitive stimulation of skeletal muscle, and tissue hypoxia.[26, 27]

Tumor Necrosis Factor-alpha

Tumor Necrosis Factor- alpha acts on hepatocytes to increase acute phase protein production, induces neutrophil activation and initiates the synthesis and release of other inflammatory factors, including IL-6.[45] Tumor Necrosis Factor-alpha and interleukins can also induce expression of the inducible form of nitric oxide synthase or enhance mitochondrial generation of reactive oxygen species.[25] Excessive TNF-α can cause hyperinflammatory reactions and tissue injury and is associated with non-survival in septic patients.[45] Excessive TNF-α is also associated with left ventricular dysfunction and hypertrophy in patients with myocardial infarction.[3, 9, 45] Skeletal

muscles express TNF-α receptors and the binding of TNF-α to these receptors has a number of effects on muscle function through the adverse alteration in muscle fibres.[3, 9] For example, TNF-α has been shown to have a catabolic effect on skeletal muscle, leading to protein loss and disruption of myogenesis.[3, 45] In muscles, TNF-α overexpression causes skeletal muscle myopathy and endothelial dysfunction, leading to myocyte apoptosis and decreased skeletal muscle mass with subsequent weakness.[31] In animal models, TNF-α has been shown to decrease force of muscular contraction.[26, 48]

Interleukin 6

Interleukin 6 is a multi-functional cytokine with both pro-inflammatory and anti-inflammatory effects.[23, 45, 49, 50] Measurements of IL-6 may indirectly reflect the activities of TNF-α as the production of these two cytokines is closely linked.[51] Elevated levels of IL-6 have been related to severity of left ventricular dysfunction and to the activation of the sympathetic and renin-angiotensin systems.[23, 49, 52] Additionally, elevated IL-6 concentrations are associated with decreased New York Heart Association (NYHA) Functional Class, lowered ejection fraction and poor prognosis.[49] There are observations that IL-6 either, directly or indirectly, mediates catabolic effects on skeletal muscle and it has been suggested that it may cause a down-regulation of growth factor-mediated intracellular signaling in chronically elevated IL-6 individuals.[9, 53-56] In a recent study, Haddad et al demonstrated that relatively modest amounts of IL-6 infusion (such as the amount that might be present after exercise or with chronic low level inflammation in the elderly) into rats can directly induce skeletal muscle atrophy in otherwise healthy rats.[54] This dose of IL-6, which

was undetectable in the systemic circulation, resulted in significant muscle atrophy. Their data also indicate that IL-6 disproportionately affected the myofibrillar protein compartment, suggesting that this treatment would have significant functional effects.[54]

C-Reactive Protein

C-Reactive Protein (CRP), an acute phase protein produced exclusively in the liver, is regarded as a marker of acute inflammation as it is secreted within 6 hours of an inflammatory stimulus.[23] Data from recent investigations suggest that CRP may function to increase IL-6 secretion from endothelial cells.[57] C-Reactive Protein may serve to markedly exaggerate the actions of IL-6 at the site of the endothelium.[57] Since IL-6 is a potent stimulus for CRP expression in the liver, the increased vascular production of IL-6 may represent a positive feedback mechanism for the continued production of CRP from the liver.[57-59] Cross-sectional studies have linked low-grade elevations of TNF-α, IL-6 and CRP to increased morbidity, functional status and mortality risk in older persons.[51, 60]

Interleukin 8

Interleukin 8 (IL-8) has known pro-inflammatory properties and has been linked to an acute phase inflammatory response.[61] Interleukin 8 is produced by monocytes and macrophages, as well as by most tissues.[62] Interleukin 8 is induced by a number of stimuli, including pro-inflammatory cytokines and it acts as a chemokine on neutrophils.[62] It is believed that IL-8 is partially responsible for the mobilization of the neutrophil response following exercise.[63]

Interleukin 10

Interleukin 10 (IL-10), produced by various inflammatory cells, especially macrophages, is an important cytokine known to have anti-inflammatory properties via down-regulation of cell-mediated immune responses.[43] Interleukin 10 is a major inhibitor of pro-inflammatory cytokines and suppresses macrophage and T-cell functioning.[43] Although very little is known about the role of IL-10 in patients with HF, IL-10 has been shown to inhibit TNF-α release from blood mononuclear cells isolated from patients with HF.[43] Interleukin - 10 has been described as having protective properties in delaying disease progression, with high levels of IL-10 being associated with a significant reduction in cell death and inducible nitric oxide synthase expression.[43] It has been suggested that insufficient levels of IL-10 may be associated with a systemic inflammatory response and additional muscle damage.[45] Stumpf et al found IL-10 levels to be significantly reduced in patients with HF compared to healthy controls and patients with the most severe HF, i.e., NYHA class 3 or 4, demonstrated the lowest levels of IL-10.[43] Low levels of IL-10 have also been found to predict decreased activity and increased angina in patients with unstable angina.[45] Moderate to high levels of IL-10 may inhibit both Interleukin 1 (IL-1) and IL-6, and it may be the balance between pro-inflammatory and anti-inflammatory cytokines, versus absolute values that prevent progression of disease or disuse.[45]

Exercise-Induced Cytokine Release (See Appendix 2)

Strenuous, prolonged or exhaustive physical activity produces dramatic increases in IL-6.[45, 64, 65] There may also be increases in both TNF-α, and IL-10 following strenuous exercise; however, research to date is inconclusive.[50, 65-69] The increase

in IL-6 is the earliest and most prominent (up to 100-fold increases have been reported) cytokine to be released after strenuous exercise.[59, 65] Peak Plasma concentrations of IL-6 are known to occur immediately following, as well as during the early and late recovery periods following strenuous exercise.[64] Peake et al found plasma IL-6 increased immediately post-exercise and remained elevated 1 hour post-exercise but returned to baseline levels at 24 hours post exercise in well-trained subjects running at 10% downhill grade at 60% VO2max for 45 minutes.[63] In the study by MacIntyre et al that investigated young, healthy female subjects, it was found that IL-6 increased up to 6 hours post-exercise following an repeated eccentric exercise protocol of the quadriceps muscles.[70]

Some researchers have suggested that complex intramuscular signaling stimulates the contracting muscle to release IL-6, independent of muscle damage.[59, 68] Apart from the type of muscle contraction (i.e., eccentric > concentric), the increased IL-6 is directly related to exercise intensity, duration and muscle mass recruited.[59] A repair response from subsequent muscle damage related to the muscle contractions is believed to cause a smaller and delayed, but further increase in IL-6 production.[59] The enhanced plasma concentrations of IL-6 seen after strenuous exercise may also depend on other factors such as the release of endogenous catecholamines, tissue hypoxia and endothelial shear stress associated with increased cardiac output during exercise.[64, 71]

As a result of correlations between severity of tissue injury associated with surgical trauma, shock and sepsis, it has been inferred by other researchers that muscle damage caused by high intensity contractions may be the underlying mechanism of exercise-induced IL-6 production.[64, 70] Exercise-induced muscle injury

has been thought to be one of the primary stimuli for IL-6 production.[59] MacIntyre et al found IL-6 increased up to 6 hours post-exercise and found significant correlations between DOMS and IL-6 concentrations.[70] In the muscle injury hypothesis (see Appendix 3), the release of IL-6 may be a manifestation of an acute inflammatory response (characterized in part by cytokine release) triggered by the accumulation of cellular debris in the areas of injury or their diffusion through the damaged sarcolemma to the interstitium and plasma.[64] Eccentric exercise has also been associated with an increase in circulating neutrophils.[72] Some of the neutrophil responses are believed to be mediated by the systemic release of cytokines such as TNF-α, IL-6 and IL-8, all of which have been linked to mobilization of neutrophils after exercise.[44, 63] After acute intense exercise, neutrophils have been shown to infiltrate tissues, such as skeletal muscle, and this has been suggested to cause local inflammation by release of reactive oxygen species and chemotactic factors which attract inflammatory cells.[25, 73] Neutrophil numbers may increase three-fold immediately after prolonged exercise and continue to increase further after several hours.[73]

Several researchers have used indirect measures to assess muscle damage following exercise, including subjective rating scales of muscle soreness, maximal voluntary isometric, concentric or eccentric torque and blood protein assessment (including Creatine Kinase, Myoglobin and Myosin Heavy Chain).[19, 21, 74-80] Bruunsgaard et al found a correlation between plasma Creatine Kinase (CK) activity and IL-6 concentration after eccentric cycling which lead to the assumption that IL-6 is involved in muscle damage.[74] In another study, Peake et al found plasma IL-6 increased by 460% immediately post exercise at which time plasma myoglobin levels were at 1100% above pre-exercise values.[63] By 24 hours IL-6 had returned to

baseline while plasma myoglobin and CK remained significantly elevated above baseline. One of the criticisms of this study, however, is that neither myoglobin nor CK in itself is specific to skeletal muscle injury. Recently, however, there have been several researchers that propose the use of plasma markers of Fatty Acid Binding Proteins (FABP) as markers of tissue injury.[22, 81, 82] Fatty Acid Binding Proteins (FABP) are relatively small intracellular proteins that are abundantly produced in tissues having active fatty acid metabolism which bind long-chain fatty acids reversibly and noncovalently.[83] Heart-type FABP (H-FABP) is mainly expressed in the heart and to a lesser extent in the skeletal muscle.[81] According to these researchers, monitoring the source of H-FABP can be overcome by using the plasma ratio of myoglobin and H-FABP concentrations. This ratio in plasma reflects the ratio of the contents of both proteins in the affected tissue and can be useful in the early detection of skeletal muscle injury.[81] In cardiac muscle injury, the myoglobin/H-FABP ratio would be between 2-10 whereas in skeletal muscles, the ratio would 20-70, depending on the type of muscle.[81, 82] Sorichter et al demonstrated that after 20 minutes of downhill running (eccentric contractions) in healthy subjects, plasma H-FABP increases in a similar pattern of release and clearance from the blood to that of myoglobin.[84] Both H-FABP and myoglobin reach a significant increase at 30 minutes post-exercise and the ratio of these two markers confirmed that the source of muscle protein release was from skeletal muscle versus cardiac muscle (ratio 15).[81]

Plasma concentrations of IL-8 increases in response to exhaustive exercise comprised of both concentric and eccentric components, such as marathon running.[44, 62] Suzuki et al, in their investigation of cytokine activation following a maximal incremental exercise test to exhaustion on a treadmill, found increases in plasma levels

of IL-8.[44] These investigators state that IL-8 frequently increases immediately after brief, high intensity exercise and suggest that it is not only the duration, but also the intensity, of exercise that may be important for IL-8 release.[44] Some researchers have found no change in serum/plasma markers of IL-8 following concentric exercise alone, e.g., bicycle ergometry or rowing.[68] Akerstrom et al investigated the muscle-derived production of IL-8 following concentric exercise and concluded that there was high local expression of IL-8 but only a small, transient release of IL-8 in the plasma.[62]

Research on the effect of strenuous exercise on CRP levels is limited. Gleeson et al state that CRP increases in response to exercise that is associated with muscle damage and/or inflammation.[85] Levels of CRP have been found to increase during strenuous exercise, immediately post-exercise, 24 hours, 48 hours and at 7 days; however, results are inconsistent.[59, 85-87] Kasapis et al in their systematic review conclude that, “there is a short-term, transient increase in serum CRP after strenuous exercise, produced by an exercise-induced acute phase response mediated by the cytokine system and mainly IL-6”.[59]

There is no consensus on the effect of strenuous exercise on levels of plasma/serum IL-10. Some authors report increases in IL-10 following strenuous exercise while others report no change.[85] Although it is not clear, some studies have shown that IL-10 levels can increase up to 27-fold following strenuous exercise.[66, 69, 88-90] Activity-induced IL-10 is produced by stretching and compressing the epithelial cells, as well as in response to high levels of IL-6.[45] Kasapis et al report the relative change in IL-10 following strenuous exercise follows a similar time-course as IL-6, albeit, to a much lesser degree.[59]

Susceptibility to Exercise-Induced Muscle Injury in HF Patients

In healthy individuals, exercise-induced muscle injury (EIMI) frequently occurs after high intensity, eccentric or unaccustomed exercise leading to a profound loss of force and ultrastructural changes including: disruption of the myofilaments in the sarcomere (Z- line streaming), sarcolemmal defects, swelling of the sarcoplasmic reticulum and the mitochondria and disruption of the cytoskeleton.[91] When the exercise is unaccustomed or includes a large eccentric component, the pain and weakness may become more apparent following cessation of the activity and will likely increase in the days following. These delayed symptoms are most prominent over the first 24 to 72 hours after the causative exercise and are suggestive of muscle damage.[18] Prolonged strength loss following EIMI is considered to be one of the most valid and reliable, indirect measures of muscle damage in humans.[18] Concentric training protocols are typically associated with strength reductions of 10-30% in peak concentric torque immediately after the exercise and are generally restored within a few hours post-exercise.[18] The highest degrees of strength loss and prolonged recovery occur following high-force eccentric exercise.[18] When compared to baseline values, strength loss following high-force eccentric exercise, e.g., maximal eccentric contractions, can generate up to 50-65% loss of force-generating capacity.[18]

Age-related decrements in skeletal muscle have been documented by other researchers including greater abnormal morphology and susceptibility to injury.[92, 93] The amount of injury and recovery time in limb muscles has been found to be greater in elderly mice compared to younger mice exposed to the same loading.[94] In the young adult mice, recovery occurred within 2 weeks whereas in elderly mice, recovery was

incomplete even after 2 months.[94] An increased susceptibility to EIMI and slower regeneration are cited as reasons why aged individuals train more slowly and less effectively than younger individuals.[92, 95] Typically, HF patients are older and in a recent randomized trial looking at congestive heart failure clinics across Canada, the mean age of the patients (n= 230) was 70 years of age.[1]

One of the effects of insufficient cardiac output during exercise in patients with HF has been reported to be underperfusion of limb blood flow to the exercising muscle.[30] It is likely that the reduced blood flow to the skeletal muscle contributes to the skeletal muscle alterations observed in patients with heart failure. In a recent prospective study, Arbustini et al evaluated the presence of myopathic changes in skeletal muscle of individuals diagnosed with idiopathic dilated cardiomyopathy.[96] These investigators looked at the histomorphological, histoenzymatical and immunohistochemical characteristics of skeletal muscle and cardiac muscle and correlated changes found in skeletal muscle with those observed in the heart and with functional data.[96] One of the major findings in this study was that all of the patients showed subclinical skeletal muscle changes (which may have included myofibrillar loss and lipid droplets, fibrosis, basement membrane thickening, and/or Z-line streaming) the presence of which was unrelated to aetiology, disease duration or functional class.[96] These ultrastructural skeletal muscle changes that may occur early in the development of HF may predispose the individual to muscle damage and/or activation of the inflammatory response following unaccustomed exercise.

Because of the limited exercise capacity and symptoms associated with HF, patients typically will also reduce the amount of activity they perform when compared to the healthy population. This chronic inactivity contributes to deconditioning of the

muscle. Deconditioning or immobilization has been shown to make limb muscles weaker and more susceptible to injury.[48, 97] After immobilization, skeletal muscle is more prone to muscle injury even from the performance of what is “seemingly” trivial activity. This has been demonstrated in animal models following reloading of normal activity only (no exercise stimulus) following spaceflight.[48, 97] Activities that may be perceived as mild intensity, such as ambulation or activities of daily living, or involve eccentric muscle activity may in fact be considered strenuous in the patient with HF. The antigravity muscles of the lower extremity (i.e., the quadriceps) are at greatest risk for EIMI as they typically demonstrate the greatest atrophy.[98]

Reduced muscle mass and muscle fibre atrophy are common and may occur early in the development of HF.[11] Several investigators believe that elevated cytokine levels not only cause progression of the syndrome of HF, but also contribute to the peripheral manifestations, such as skeletal muscle wasting and reduced muscle function.[42, 99, 100] Anker et al reported that 16% of outpatients with HF were cachexic and that only 50% of the cachexic HF patients who had lost more than 7.5% of their body weight survived for 18 months[101-103] Anker defines cardiac cachexia as “nonedematous weight loss of more than 7.5% of the premorbid normal weight that occurs over a time period of more than 6 months”.[101] Vescovo et al investigated the progressive loss of skeletal muscle bulk in HF patients and determined that skeletal muscle function and bulk are not only the best predictors of exercise capacity (peak V02) but are also strong predictors of mortality in HF patients.[104] Vescovo and colleagues demonstrated that in HF patients there is an approximate 20% decline in muscle fibre cross-sectional area.[104] In aged skeletal muscle, McArdle et al found that when the cross-sectional area of skeletal muscle was reduced by 25 to 30%, it not

only made the remaining muscle fibres weaker per unit cross-sectional area but, they were also more susceptible to contraction-induced muscle damage and required a longer recovery period following the damage.[17] Under these conditions, the regenerative capacity of the muscle is severely compromised and the muscle is unable to adapt quickly to sequential bouts of exercise.[17]

For the patient with HF, it is possible that even small amounts of physical activity may cause subclinical muscle injury and lead to increases in serum cytokines, especially in the presence of an increased baseline of inflammatory markers. Further, the stress of increasing activity after periods of inactivity (e.g., sedentary, bedrest during hospital admissions, etc.) may also contribute to EIMI and/or immune system activation (synthesis of TNF-α , IL-6 and IL-10). EIMI is likely encountered in deconditioned HF patients but there is no research to date that has investigated EIMI and the relationship to inflammatory cytokines in patients with HF.

Exercise Training

Numerous aerobic and resistance training methods have been utilized in an attempt to optimize the health status and quality of life for patients with HF.[105-109] Inactivity in itself has been linked to an increase in inflammatory processes.[45] Regular physical activity has been shown to induce a counter-regulation of inflammation through the secretion of immunosuppressant mediators, such as cortisol and anti-inflammatory cytokines (e.g., IL-8, IL-10).[9, 28, 31, 33, 58, 59]

Most patients with HF are extremely deconditioned upon commencing an exercise training program and the American College of Sports Medicine recommends that HF patients initially begin exercising at low intensity (approximately 40-50% of

VO2peak or heart rate reserve) continuously or in intermittent bouts of 10 minutes for a total duration of 20-40 minutes.[110] However, early into an exercise program many deconditioned patients with HF cannot exercise for extended periods of time and therefore, an interval training method has been proposed by some researchers.[35] Myer et al propose that interval training is of particular importance in patients with HF as a means of improving peripheral muscle function and accelerating the rate of recovery of functional capacity.[35, 111] Interval training is believed to be optimal for HF patients, since it may provide a more intense stimulus for skeletal muscle adaptation without inducing greater cardiovascular stress.[35] To improve both the reduced peripheral aerobic capacity and muscle strength in HF patients, greater stimuli than that applied during conventional steady-state exercise are applied in interval training by using short bouts of work phases in repeated sequence, followed by short recovery phases. The cardiovascular response of the 30 second/60 second work/recovery interval has been compared to the response observed during steady-state training at an intensity 60-80% heart rate reserve.[112] For patients with HF, however, there has been no consideration of the effects of the higher muscular loading on risk of EIMI, or activation of the acute phase immune system response, that may accompany a high intensity or interval training program.

STATEMENT OF THE PROBLEM

Inflammatory activation with increased plasma/serum cytokine levels has recently been described as an important factor for the progression of HF.[33] Elevated levels of circulating cytokines have been demonstrated in patients with HF and are also considered to play a key role in the development of the HF-related skeletal muscle myopathy.[42] It has recently been observed that cytokines act as catabolic factors involved in the pathogenesis of peripheral muscle wasting and cardiac cachexia [33] This has important implications as skeletal muscle mass is not only an important determinant of exercise capacity (independent of central hemodynamics) but the progressive loss of skeletal muscle bulk has recently been shown to be a strong predictor of mortality in chronic HF patients.[6, 113-115]

Exercise training remains an important therapeutic intervention in the management of HF, improving exercise capacity and some of the neurohormonal abnormalities (e.g., improved ventilation,decreased lactate production and plasma catecholamines,etc.) [8, 21, 73, 88,100, 101, 147, 201] However, acute bouts of exercise can lead to increases in markers of endothelial damage, pro-inflammatory cytokines and may induce peripheral hypoxia.[3, 38] Strenuous physical activity can cause mild sub-clinical skeletal muscle injury with the potential for an excessive inflammatory reaction and immune suppression.[66] Camus et al have suggested that muscle damage, complement system activation and/or endotoxemia are some of the factors that may trigger the inflammatory response to exercise.[67] In the presence of an increased baseline of inflammatory factors, it is possible that even small amounts of physical activity can further increase plasma/serum cytokines in individuals with HF. To date, the most appropriate form of exercise training for patients with HF is not known.

Traditionally, HF patients have been trained in cardiac rehabilitation settings using low-level aerobic (steady-state) training in order to remain below a symptom threshold. Several researchers have since challenged the traditional steady state model and an interval training model and has been suggested.[13, 35, 40, 111, 116-118] Myer et al state that an interval training method is a superior method of training for HF patients as it demonstrates a greater exercise stimuli to peripheral muscle than that obtained during steady-state methods, without inducing greater left ventricular stress.[35, 117] A recent study by Wisloff et al looked at a moderate intensity vs. a high intensity exercise program and concluded that exercise intensity was an important factor for reversing left ventricular remodeling and improving aerobic capacity, endothelial dysfunction and quality of life in patients with postinfarction heart failure.[40]

There are at least 5 hypotheses with respect to the source of production for proinflammatory cytokines in patients with CHF.[119, 120] These include: i) immune activation; ii) myocardial production; iii) endotoxin absorption from the gut; iv) adrenergic stimulation; and v) tissue hypoxia. During exercise the latter two sources are considered to be important.

If both tissue injury and tissue hypoxia are potential stimuli for cytokine production and if the pro-inflammatory state is partially responsible for disease progression in HF patients, then the type of training that is prescribed for this population may carry important prognostic benefits. Given that the majority of patients with HF are severely deconditioned with muscle wasting, even low-level (unaccustomed) exercise training has the potential to induce EIMI, increased catecholamine production, endothelial shear stress, and/or tissue hypoxia that can lead to activation of the inflammatory response. There is an associated loss of function (prolonged decrements in muscle force

production, delayed onset of muscle soreness) that occurs early after EIMI, lasting for several days or weeks, that can have profound functional and prognostic implications for the already functionally-limited patient with HF. There has been no research to date that has evaluated the acute effects of various exercise training models on markers of EIMI and/or the activation of the inflammatory response in patients with HF.

The purpose of the proposed research was to compare the effect of a single bout of training using two different exercise training models (steady-state and interval training) on markers of skeletal muscle damage (decrements in maximum voluntary (peak) isokinetic concentric and/or eccentric muscle torque, myoglobin/FABP ratio and DOMS) and markers of inflammatory activation (TNF-α, IL-6, CRP, IL-8, IL-10) in HF patients. Additionally, the proposed research looked at the relationships amongst the various inflammatory and skeletal muscle injury markers at baseline.

HYPOTHESIS

An acute bout of Interval Training will lead to greater increases in markers of acute inflammation including: TNF-α, IL-6, IL-8, IL-10, CRP and markers of skeletal muscle damage, i.e., MGB:H-FABP ratio, DOMS and decreased maximum voluntary (peak) isokinetic concentric torque greater than maximum voluntary eccentric isokinetic torque, in patients with HF in comparison to an acute bout of the traditional, steady-state exercise training model.

RESEARCH METHODS

Participants

Fourteen male patients diagnosed with heart failure were recruited to complete a single bout of either a steady-state or interval training on a cycle ergometer while monitored on a 3 lead telemetry system at St. Paul's Hospital. Participants were randomized to either the steady-state or interval training group (7 per group) in this repeated measures design. All participants were sedentary, i.e., were not actively involved in a structured exercise program for at least 6 months prior to the study. All participants were over the age of 45 years, had a VO2peak less than 25 mL.kg-1.min-1 (within the previous year) and a left ventricular ejection fraction < 35%. Participant characteristics are shown in Table 1. The study protocol was approved by the Clinical Research Ethics Board of the University of British Columbia and all study participants gave their written consent to participate in this study.

General Protocol

Participants underwent 6 separate testing periods:

- **PRE** - 7 days prior to training (baseline measurements in concentric and eccentric torque, bloodwork, questionnaires).
- **TR1** - training session.
- **IMMED POST** - immediately post exercise training (concentric and eccentric torque, bloodwork, questionnaires).
- **6 HR** - **POST** - 6 hours following the training session (concentric and eccentric torque, bloodwork, questionnaires).

- **24 HR** - **POST** - 24 hours following the training session (concentric and eccentric torque, bloodwork, questionnaires).
- **48 HR** - **POST** - 48 hours following the training session (concentric and eccentric torque, bloodwork, questionnaires).

Participants were instructed to take all their medications as prescribed and to complete a food record for 3 days prior to PRE, as well as to complete a food record for the 3 days prior to the training session. Both IL6 and IL8 are affected by muscle glycogen and therefore, an analysis of diet between participants could be undertaken, if necessary, if major differences were found in these inflammatory markers.

Baseline Measures

During PRE, participants filled out a delayed onset muscle questionnaire, a lower extremity functional scale, performed concentric and eccentric torque measurements of the dominant quadriceps muscle on the KinCom IsokineticTM dynamometer and had blood samples drawn for blood work analysis of inflammatory and muscle injury markers.

Exercise Protocol

Both exercise training groups engaged in a single supervised exercise training bout on a cycle ergometer at the Healthy Heart Program at St. Paul's Hospital, Vancouver, BC at 7 days following the baseline measures. Participants were monitored with 3-lead telemetry, as well as portable heart rate monitors (Polar^{TM}) and Rating of Perceived Exertion (RPE) throughout each exercise bout. Blood pressure was taken before, during and after the exercise session. An equivalent workload was

determined for both steady-state and interval training in order that total volume of exercise was similar for each group. All individuals underwent a 5 minute warm-up and a 5 minute cool-down prior to, and following, the conditioning exercise. The duration of the conditioning portion of the exercise bout was 20 minutes.

Steady-State Group

The steady-state training group was trained as per the usual training model at the Healthy Heart Program, St. Paul's Hospital in Vancouver, B.C. i.e., 65% heart rate reserve/VO2 reserve, as well as 65% of peak watts based on the results of a recent cardiopulmonary exercise test. Additionally, previous work by our group (2005) that looked at rehabilitation in individuals with coronary artery disease used similar parameters for steady-state exercise training.[118] The duration of the conditioning exercise was based on a typical "first" exercise training session in the Healthy Heart program (i.e., 20 minutes of continuous exercise).

Interval Training Group

The interval training workloads were based on the results of the Peak $V0_2$ from a recent cardiopulmonary test and previous work done by our group that devised an interval training protocol utilizing 2 minute work phases set at 90% Heart Rate Reserve/VO_2 reserve and 2 minute recovery bouts at 40% Heart Rate Reserve/VO_2 reserve for individuals with coronary artery disease.[118] Additionally, 40% and 90% of peak watts were also used to set training workloads. The average training intensity for each participant in the interval training group was equivalent to that which would have occurred if the individual had been randomized to the steady-state training group.

Measurement of Inflammatory Activation

During PRE, IMMED POST, 6 HR - POST, 24 HR - POST and 48 HR - POST all participants underwent analysis of plasma markers of TNF-α, IL-6, CRP, IL-8, IL-10, H-type FABP and myoglobin. All blood samples were drawn into blood collection tubes from the antecubital vein (with the participant in a seated position) and then immediately immersed in a refrigerated centrifuge and centrifuged within 15 minutes of collection. Plasma levels of each cytokine (TNF-α, IL-6, IL-8, IL-10, CRP, MGB and H-FABP) was measured using a commercially available high-sensitivity ELIZA kit according to the manufacturer's instructions. The timing of the blood analysis was determined by the peak responses of the various markers of inflammation and markers of skeletal muscle injury.

Measurement of Skeletal Muscle Injury

During PRE, IMMED POST, 6 HR - POST, 24 HR - POST and 48 HR - POST participants underwent both concentric and eccentric torque measurements on the KinCom Isokinetic^{TM} dynamometer, a lower extremity functional scale questionnaire, Delayed Onset of Muscle Soreness questionnaire, and analysis of plasma markers Myoglobin, H-type FABP and the Myoglobin to H-FABP ratio. Participants were tested with their dominant leg on the KinCom Isokinetic™ dynamometer 7 days prior to the training session. This time period was chosen in order to ensure that the learning effect from the baseline testing would remain present for future testing periods. As well, to ensure adequate recovery of the quadriceps muscle group prior to the exercise intervention, the 7 day time period was chosen. Patients received verbal instructions on how to perform the contractions and were given a period of acclimatization (practice at

low effort loads only) until they were comfortable with the maneuvers. The warm-up period consisted of 3 sets of 3 submaximal concentric and eccentric isokinetic repetitions for knee extension. A relaxation period of 2-3 minutes was given prior to the test series. The testing protocol that was used was outlined by MacIntyre et al.[70] The participants performed 3 submaximal and one maximal practice simultaneous concentric and eccentric contractions, followed by four maximal voluntary test contractions with a 2-minute rest between the practice and the test contractions. Angular velocity was set at 30° per second through a range of 90° (100° - 20°) of knee flexion. The maximal voluntary concentric and eccentric torque over the knee flexion range of movement over the last three contractions was recorded as the peak concentric/eccentric muscle torque for the knee extensors.

Statistical Analysis

Differences between peak concentric and eccentric muscle torque of the knee extensors, biochemical analysis of plasma cytokine markers (TNF-α, IL-6, CRP, IL-8, IL-10, H-type FABP and myoglobin), delayed onset of muscle soreness, and lower extremity functional scale responses at baseline and after a single bout of either steady-state or interval training exercise were examined using repeated-measures analysis of variance with Tukey post hoc comparisons. The level of significance was set at priori $p < .05$. Data are presented as means ± SD at PRE, IMMED POST, 6 HR - POST, 24 HR - POST and 48 HR - POST, respectively.

Additionally, the relationship between various physiological parameters of interest and baseline levels of inflammatory and skeletal muscle injury markers were determined

by Pearson Correlation Coefficient with the level of significance set at priori $p < .05$. These relationships were evaluated in order to corroborate any significant findings.

RESULTS

An independent t-test for all patient characteristics was performed between groups. The groups were evenly matched and there was no significant difference between groups for all variables, with the exception of underlying electrical rhythm of the heart and current medications (see Table 1).

Biochemical Analysis of Cytokines and Skeletal Muscle Injury Markers

Interleukin 6 (figure 1) increased from baseline to immediately post and then returned to near baseline levels at all other time points. There was statistical significance from baseline to immediate post in both groups (steady-state and interval training group). However, there was no statistical significance in IL-6 levels between groups at any time point.

There were no significant elevations from baseline to any time point following the exercise bout with either the steady-state or interval training group for Interleukin 8 (figure 2). Interleukin 8 increases primarily in response to eccentric muscle activity and therefore, one would not expect to see increases in IL-8 given that the cycle ergometer is primarily concentric muscle contractions.[60] Thus, it may be the lack of increase in IL-8 in response to either SS or IT suggests that no skeletal muscle damage occurred following the acute training bout in either group.

There was a significant increase in IL-10 levels at 24 hours post in the IT group (figure 3). However, the individual variability in this anti-inflammatory marker was considerable between study participants and these results have not been reported in previous research.[23, 43-45, 56, 63, 140]

There were no significant elevations in TNF-α at any time point or between groups (figure 4). There were no significant changes in CRP levels from baseline to any time point for either group (figure 5). Both groups had baseline elevations in CRP levels that would be considered above normal values.

There were no significant changes in levels of H-type FABP from baseline to any time point for either group (figure 6).

There were no significant changes in levels of Myoglobin from baseline to any time point for the Steady-state training group (figure 7). There was an elevation in Myoglobin levels at 6 hours post. This change was significant with $p < .05$.

There were no significant elevations in the ratio of Myoglobin to H-FABP (figure 8). There was a non-significant increase in the ratio of Myoglobin to FABP at 6 hours post in both the SS and the IT group (range 2.19 to 49.88).

There was no significant change in the delayed onset of muscle soreness scores at any time point following the acute training session in either group (figure 9). The interval training group had a non-significant increase in DOMS in the immediate post exercise period but the actual value of the increase was minimal (i.e., less than 1 cm change).

There was a nonsignificant increase in Lower Extremity Functional Scale score from baseline to all time points in the IT group and all time points except Immediately Post for the Steady-State training group indicating improvement in function (figure 10). Statistical significance was reached from baseline to 24 HR and 48 HR POST in both groups.

Both groups saw a statistically significant decline in peak concentric torque in the time period immediately post acute training bout (figure 11). Peak concentric torque returned to slightly below, but non-significant, baseline levels at all other time periods. There was no significant difference in peak concentric torque between the Steady-State and the Interval Training group.

Both groups saw a decline in peak eccentric torque of the knee extensors in the immediate post time period that reached statistical significance (figure 12). There was no significant difference in peak eccentric torque measurements at all time periods between the groups.

Pearson Correlation Coefficients were determined for physiological variables of interest and markers of inflammation and skeletal muscle injury at baseline (see table 2). There were significant correlations ($p < .05$) for IL6 and CRP (.59) and for IL8 and CRP (.74). There was also a significant correlation between participant age and NT ProBNP (.65).

Figure 1: Interleukin 6

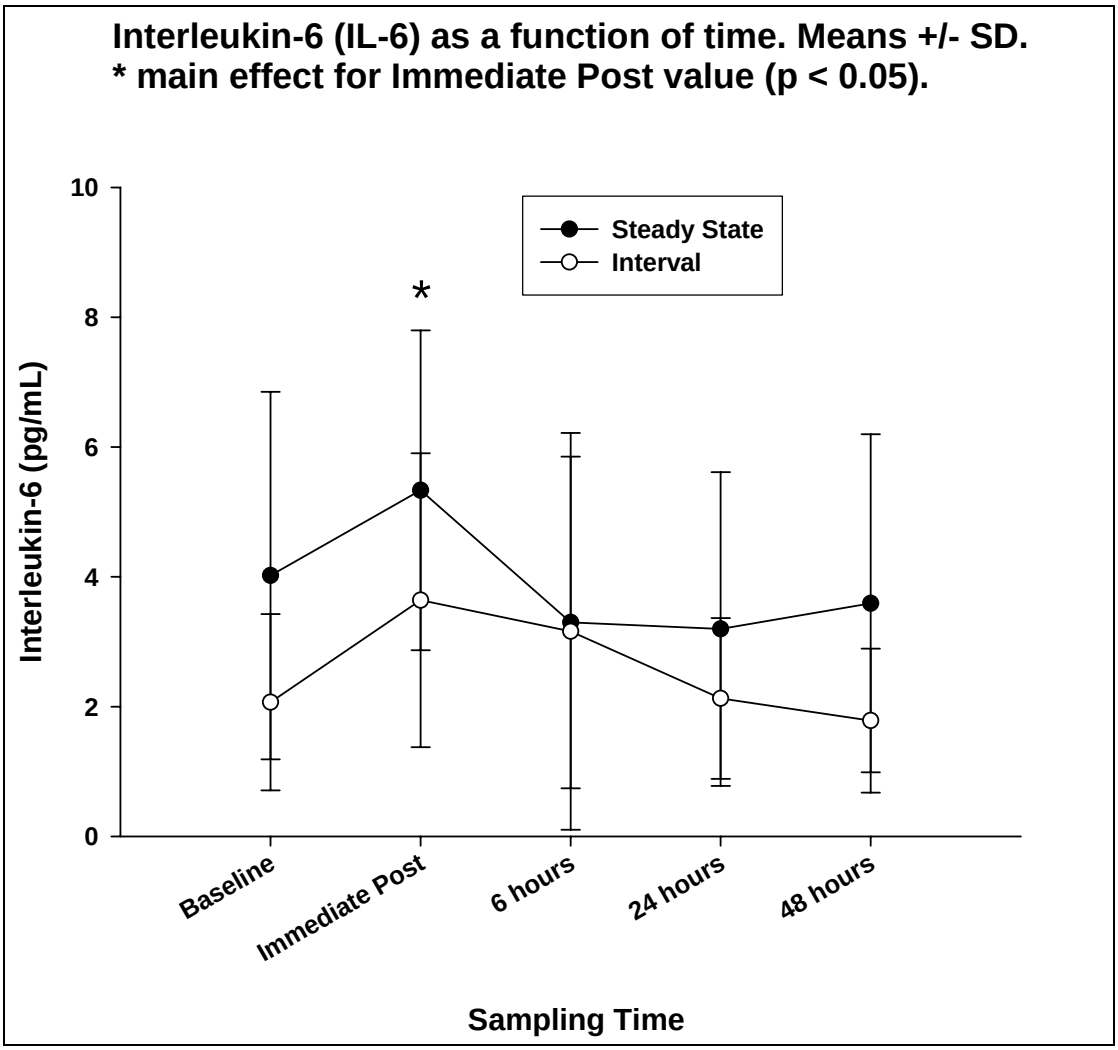


Figure 2: Interleukin 8

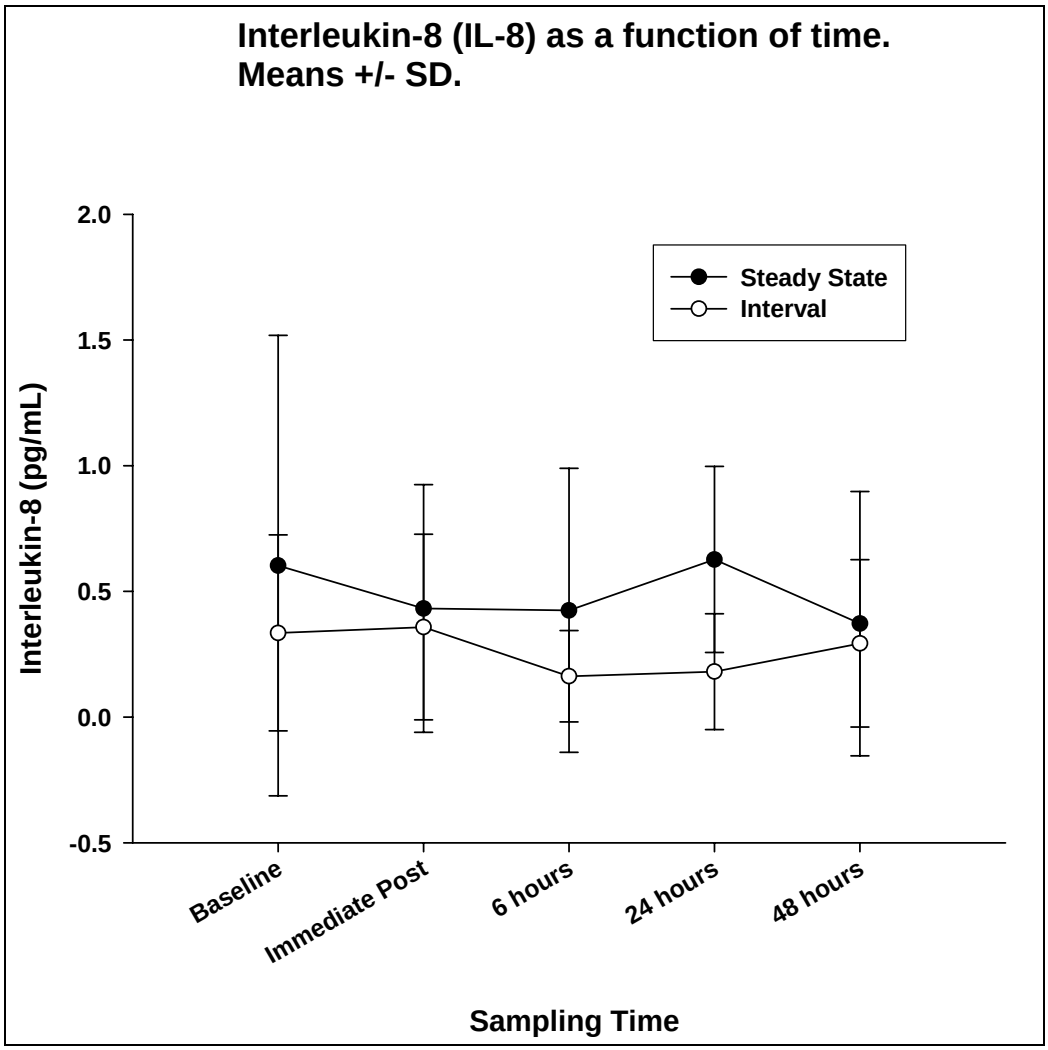


Figure 3: Interleukin 10

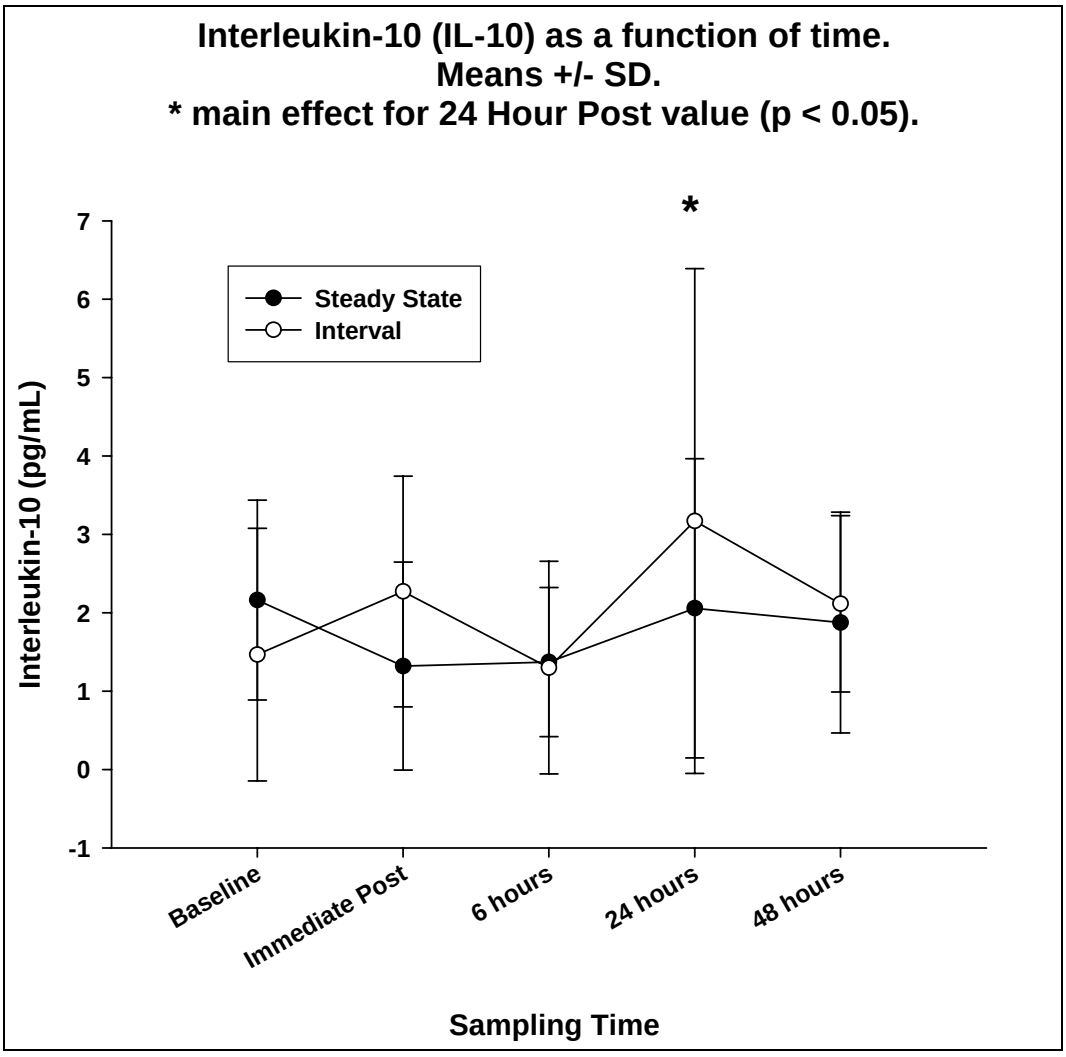


Figure 4: Tumor Necrosis Factor alpha

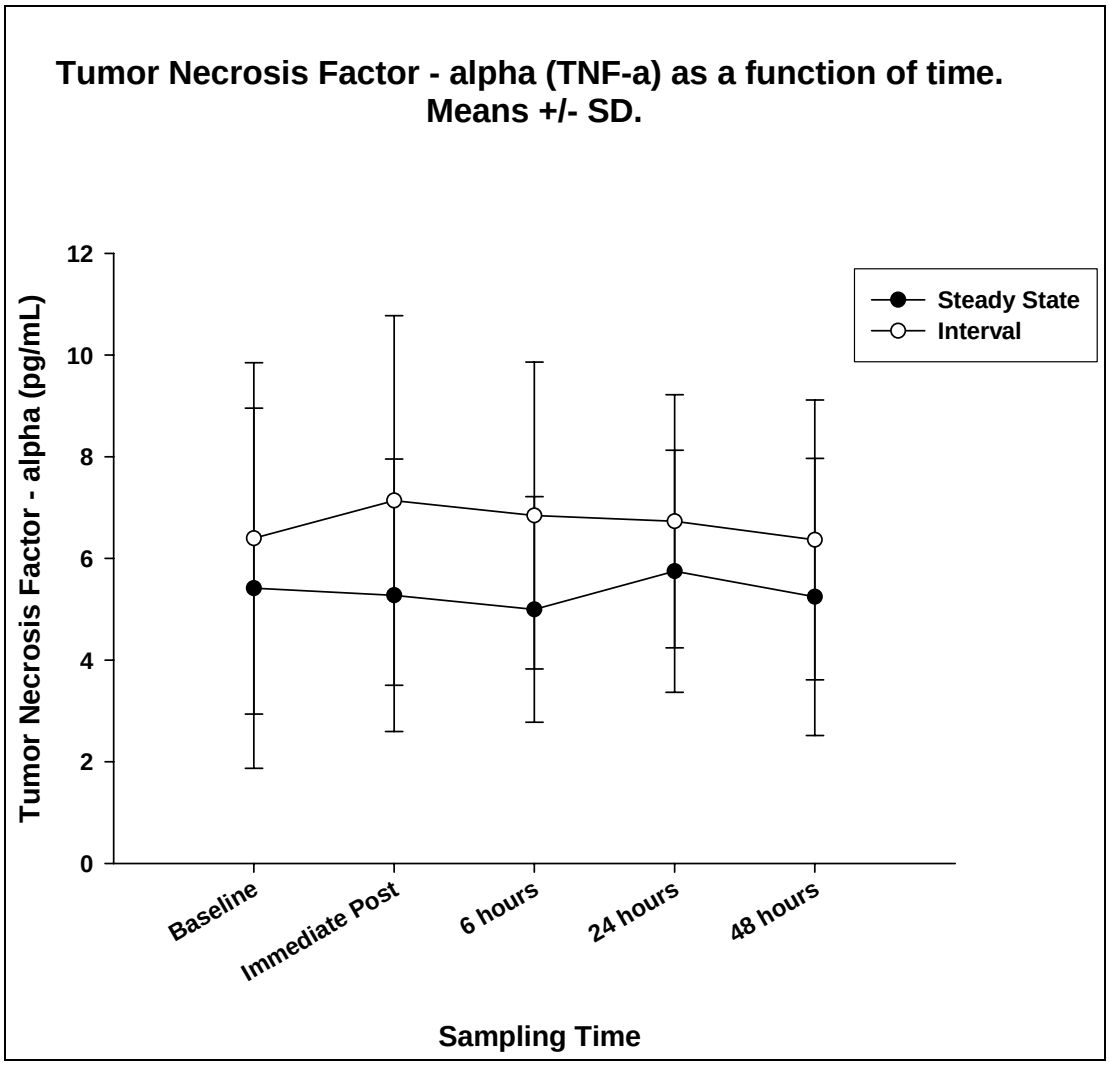


Figure 5: C-Reactive Protein

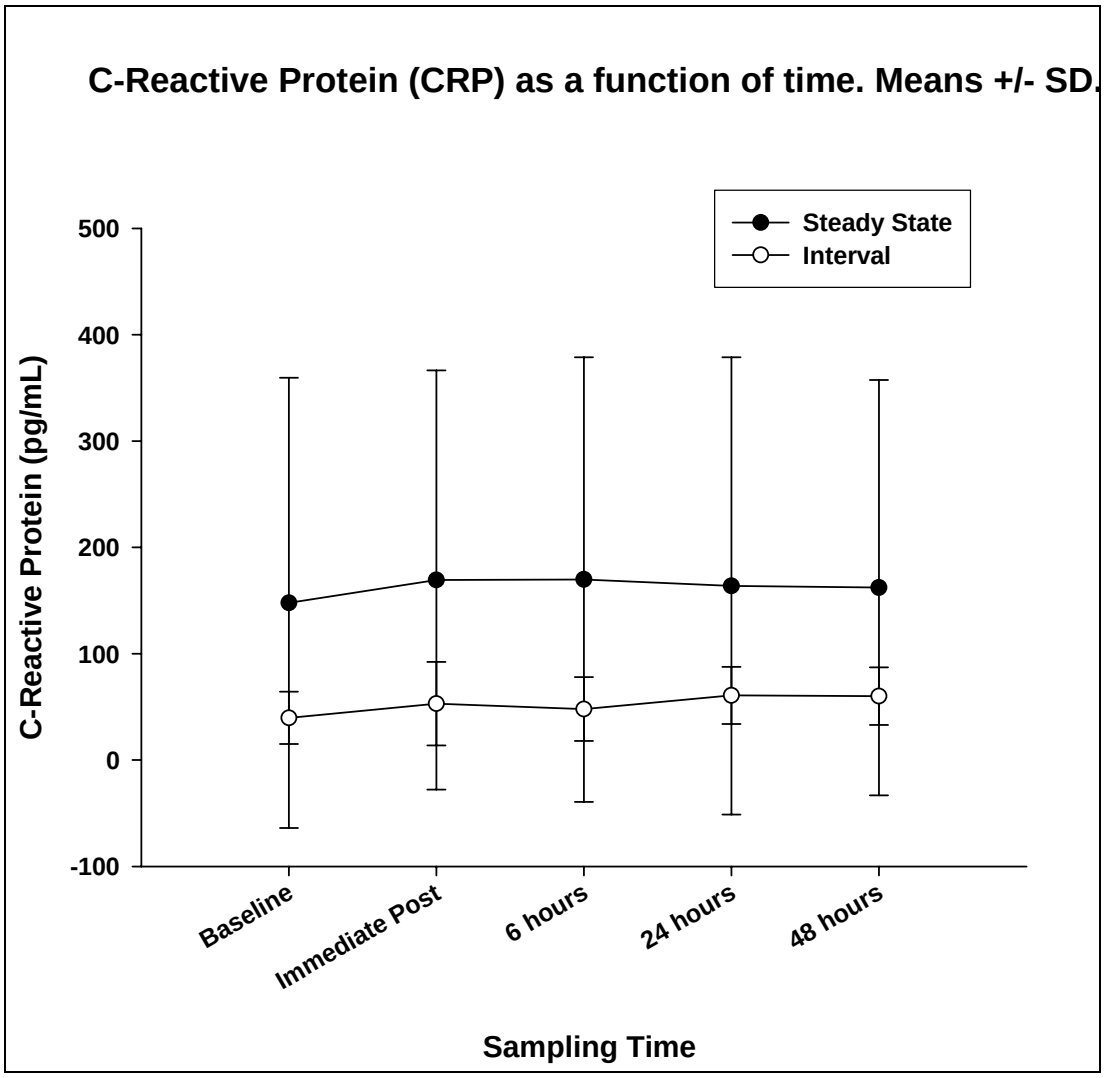


Figure 6: Heart Type Fatty Acid Binding Protein

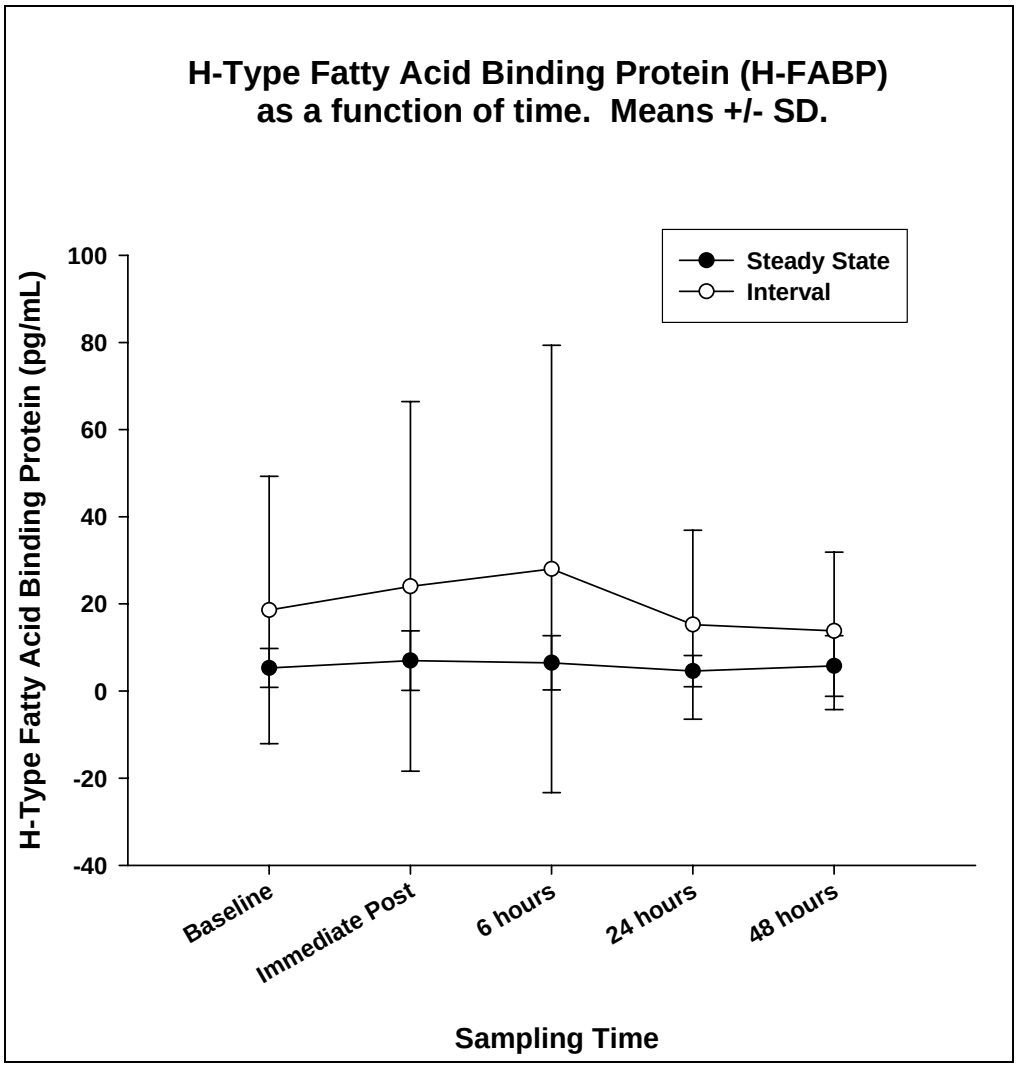


Figure 7: Myoglobin

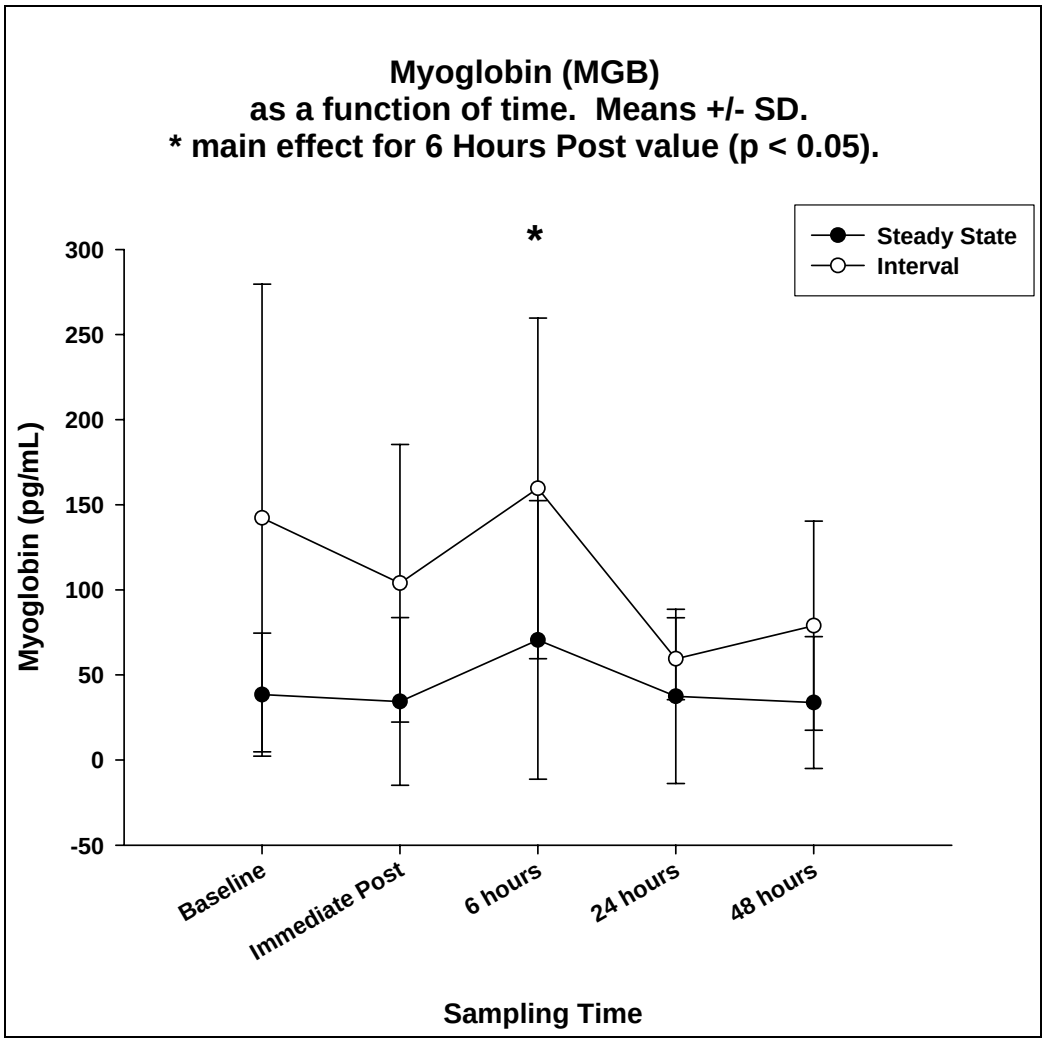


Figure 8: Myoglobin to H-FABP Ratio

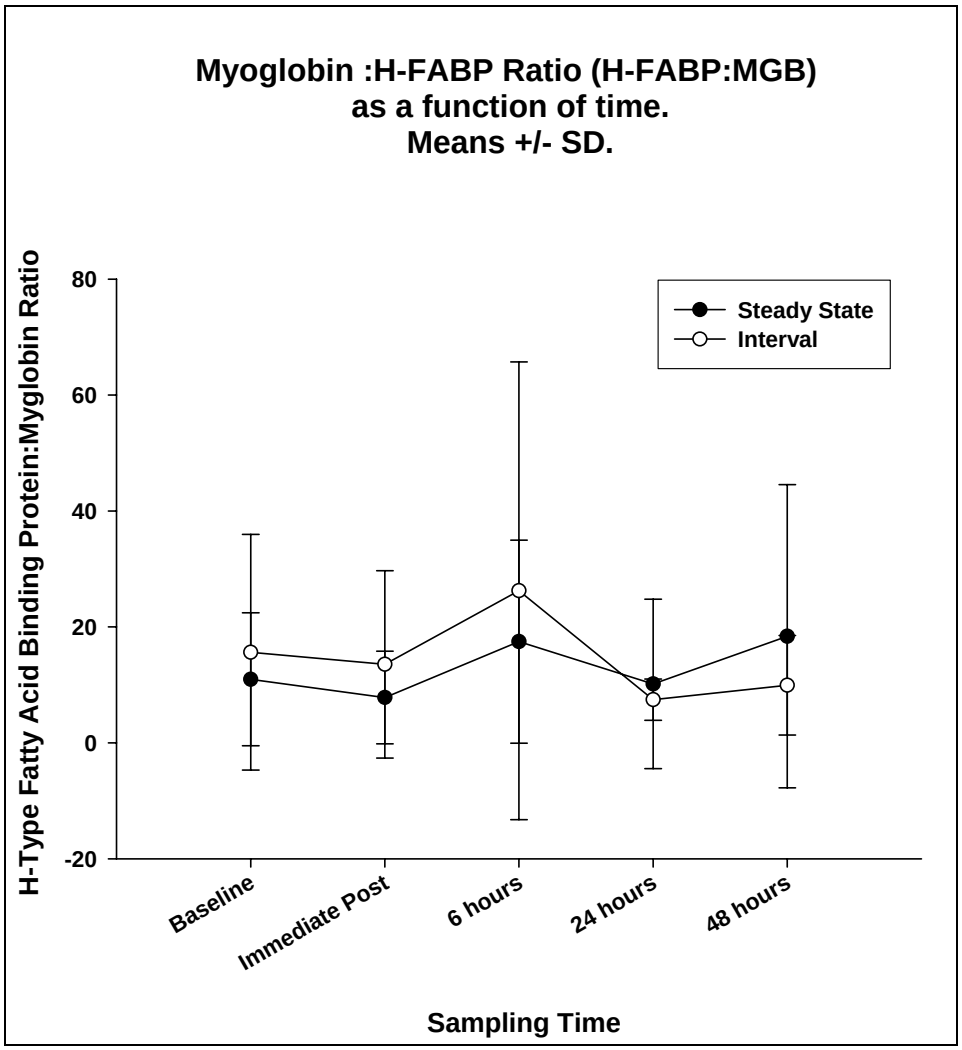


Figure 9: Delayed Onset Muscle Soreness

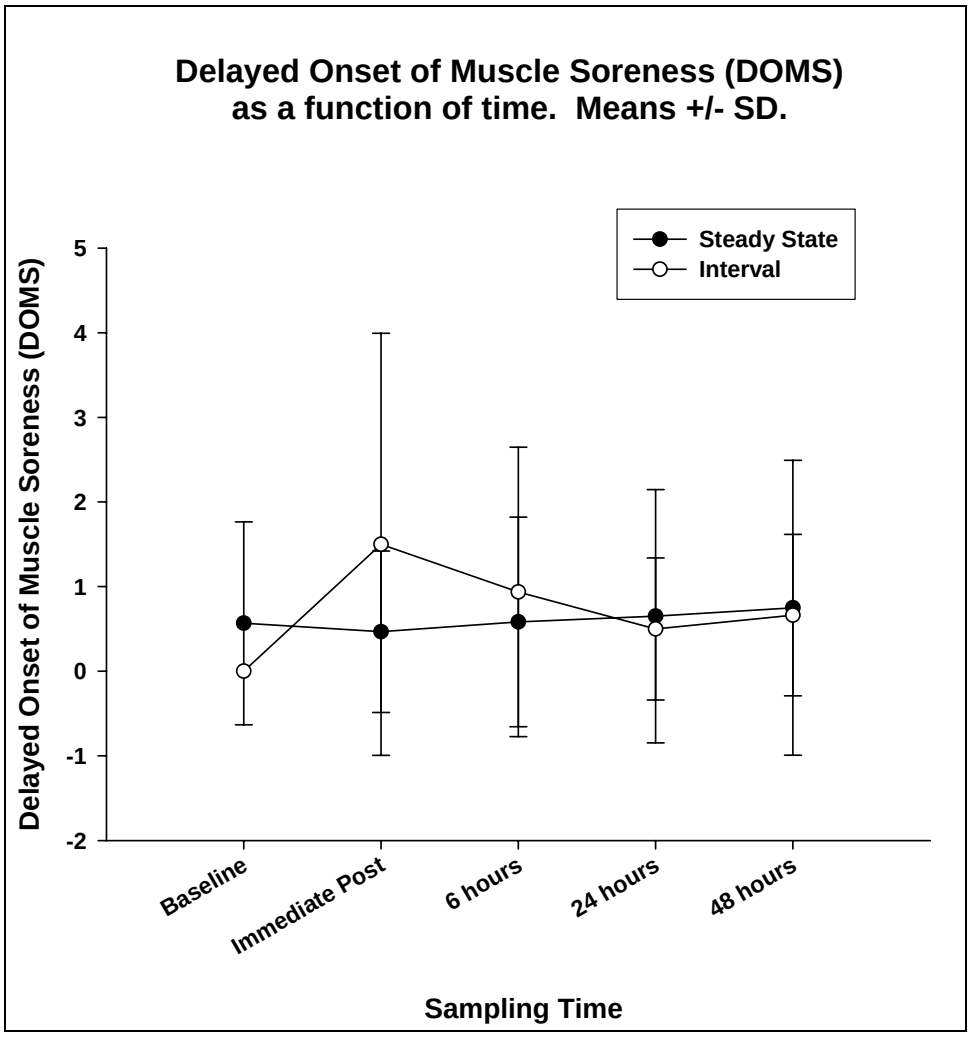


Figure 10: Lower Extremity Functional Scale

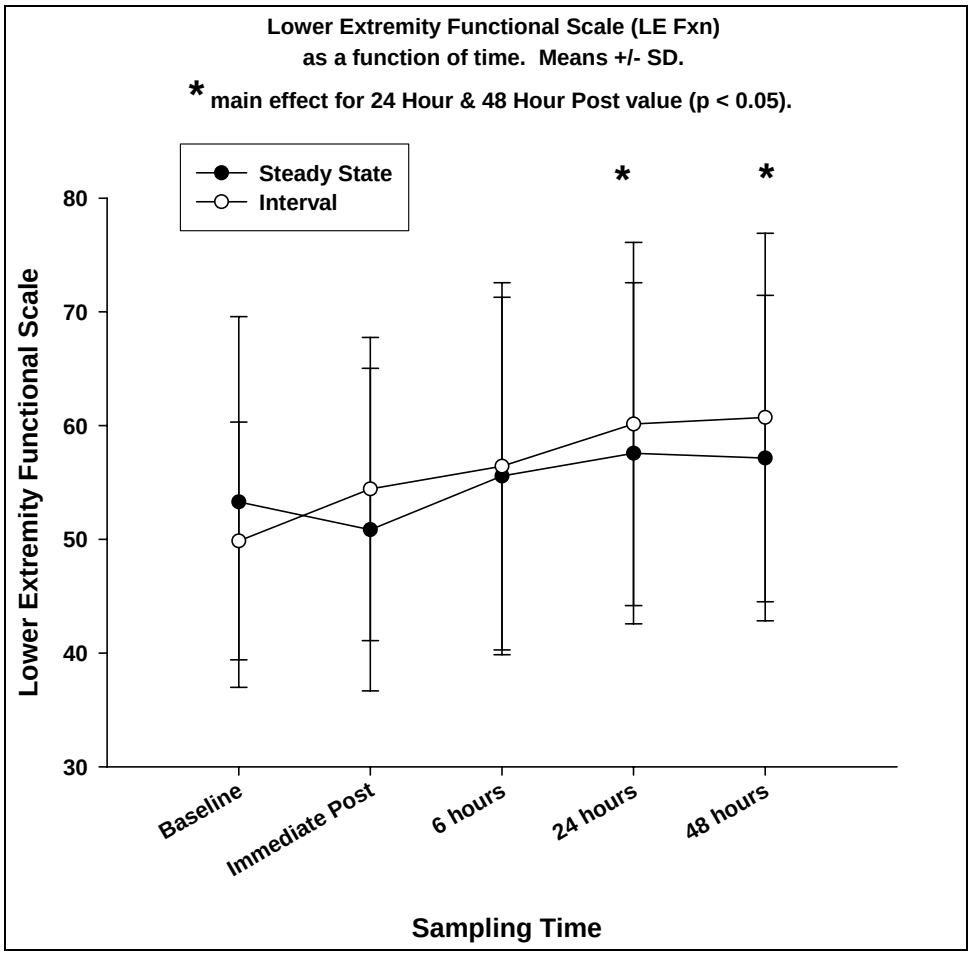


Figure 11: Peak Concentric Muscle Torque

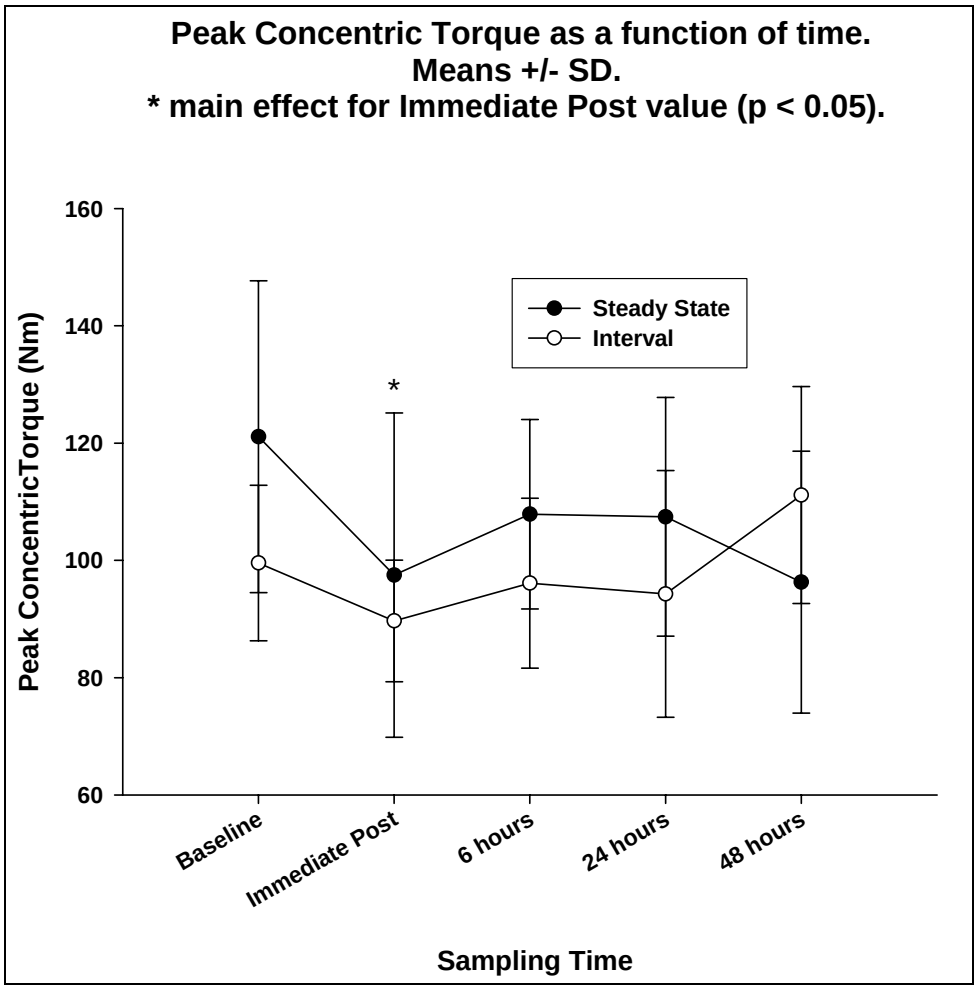
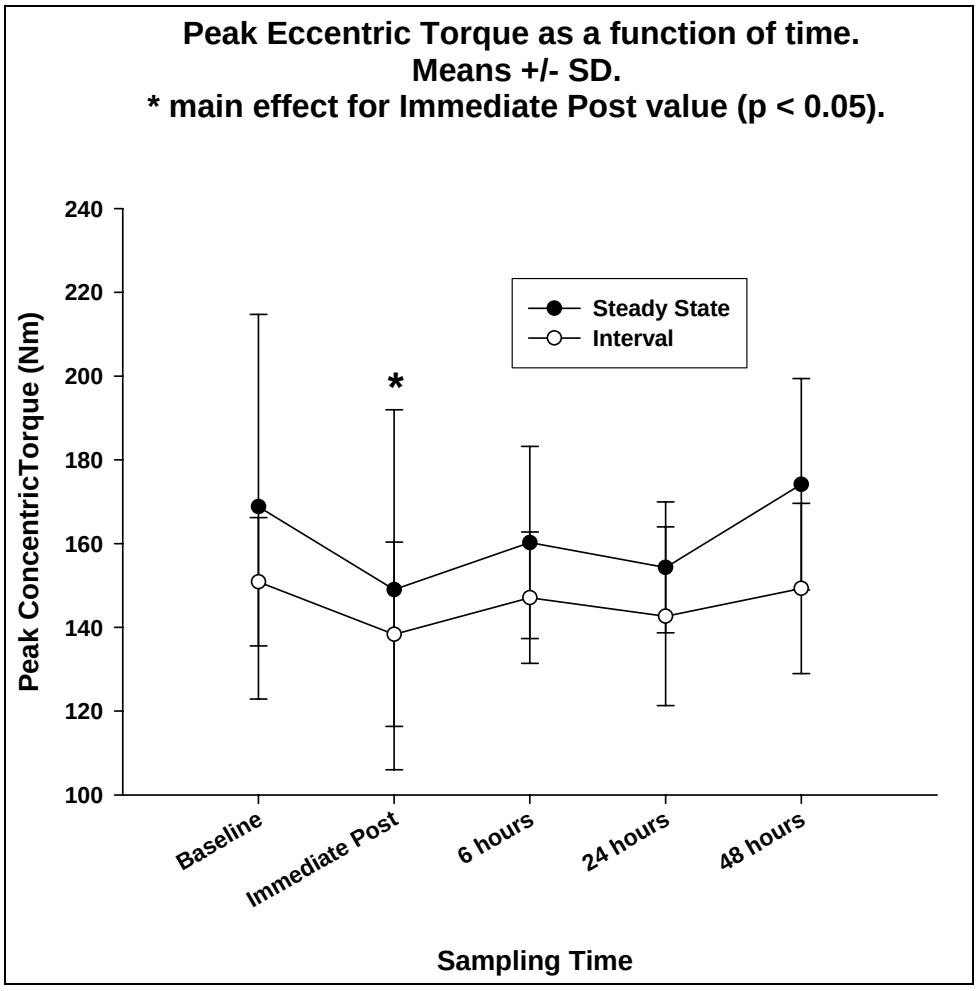


Figure 12: Peak Eccentric Muscle Torque



DISCUSSION

The present study demonstrated that there were no differences between the interval training group and the steady-state training group for markers of skeletal muscle injury or inflammatory activation following a single bout of either steady-state or interval training in sedentary individuals with heart failure. Both groups demonstrated significant increases in myoglobin 6 hours post exercise and interleukin 10 at 24 hours post exercise. Both groups demonstrated a significant decrease in both peak concentric and eccentric muscle torque in the immediately post exercise period. However, neither group demonstrated prolonged decrements in concentric or eccentric torque, biochemical markers of inflammation or skeletal muscle injury, or in delayed onset of muscle soreness. Significance was found in both groups for the lower extremity functional scale from baseline to the 24 hour and 48 hour time periods following the training bout.

Interleukin 6 Baseline

The current study supports data from previous studies that found baseline levels of IL-6 were elevated in patients with moderate CHF compared to values found in control subjects (3.04 +/- 2.28 vs. 1.1 +/- .8).[23, 99, 100, 121-123] Interleukin 6 concentrations have been related to severity of left ventricular dysfunction and to the degrees of activation of the rennin-angiotensin systems in patients with HF. [11, 23, 49, 58, 100, 124, 125] The raised levels of IL-6 correlate with decreased cardiac functional class, lowered ejection fraction and poorer prognosis and most recently with the progression and deterioration of HF.[49] Interleukin 6 is produced by, not only immune

cells and immune accessory cells, but also by cardiovascular components such as endothelial cells, vascular smooth-muscle cells and ischemic myocytes.[49]

Interleukin 6 Exercise

Numerous studies have shown IL-6 markedly increases after exercise without muscle damage.[55, 56, 65, 126-129] Plasma IL-6 increases in an exponential fashion with exercise and is related to exercise intensity, duration, and the mass of the muscle recruited, and endurance capacity.[55, 56, 65, 127-129] Recent research has demonstrated that IL-6 is produced by contracting skeletal muscles and is released into the circulation in large quantities.[55, 56, 65, 126-129] Bruunsgard and Pedersen suggest in their article on age-associated elevations in cytokine production that current research shows that pure concentric exercise without any muscle damage also induces marked production of IL-6.[60] Steenberg et al were also able to demonstrate that during exercise the net skeletal muscle IL-6 production increases strikingly and can account for the exercise-related high plasma IL-6 concentration[130, 131] Steenberg looked at IL-6 levels after 5 hours of one legged knee extension exercise in healthy untrained males (mean age of 26 years) and found that there was a gradual increase in arterial plasma IL-6 concentration with exercise, but a more substantial increase in IL-6 concentration occurred after 3 hours of exercise (Resting IL-6 level .74 pg/mL (.67 – 1.5) to 14.13 pg/mL (11.62 – 16.75).[131] In the current study, we did not see the vast increases in exercise IL-6 as per Steenberg, but this is likely related to the relatively short duration of exercise in this study (20 minutes vs. 5 hours). Additionally, Steenberg suggests that there is the possibility that one stimulus of IL-6 production by skeletal muscle is the force of the contraction.[131] In Steenberg's research, he estimated that the relative workload was as low as 40% of maximal work but suggested it was not

possible to transfer these high production values to models where a large fraction of muscle mass is engaged in the concentric exercise as the weight-specific power output is higher than in running or cycling.[131] However, data in the current study are consistent with the research that demonstrates IL-6 increases in response to concentric muscle actions, i.e., cycle ergometry that utilizes primarily concentric vs. eccentric muscle contractions. Given that a cycle ergometer was used in the current study whereby there were no appreciable eccentric muscle contractions, only concentric muscle action, our data support Pedersen's and Steenberg's hypothesis of local muscle production of IL-6 from concentric contractions. Although there were no significant differences between the SS or IT group in the present study, the SS group had higher IL-6 levels at all time points. These results are not surprising given that with the IT protocol, there are recovery intervals with a relatively low workload, i.e., 40% of HRR/VO2 reserve for 50% of the conditioning phase, built in to the exercise bout.

Other researchers, however, have speculated that IL-6 secretion is stimulated during exercise, possibly by catecholamines. Kinugawa et al found positive correlations between changes in IL-6 and changes in plasma catecholamines in control subjects only.[122, 123] These researchers were not able to demonstrate significance between IL-6 and changes in catecholamines in the HF subjects.[122, 123] Kinugawa et al suggested that the lack of significance may be due to the high resting sympathetic activity blunting the IL-6 response during exercise in patients with CHF.[122, 123] Data from work done by Ostrowski et al also suggest that there is a correlation between intensity of exercise and increased plasma IL-6.[126, 132] These researchers were able to demonstrate a correlation between heart rate and IL-6.[126, 132] Given that beta blockade is a first line treatment in HF, it is possible that increases in IL6 as a

result of increased heart rate would be blunted in the current study, given that all participants were on beta blocker medication. However, a recent study by Pedersen, Steensberg and Schjerling suggest that adrenaline plays only a minor role in the exercise-induced increase in plasma IL-6.[128] Research by Parthenakis et al. also looked at the relation of cardiac sympathetic innervation to proinflammatory cytokine levels in patients with HF secondary to dilated cardiomyopathy.[133] These researchers showed a significant correlation with increased values of cytokine levels, supporting the hypothesis that impaired cardiac adrenergic activation leads to a loss of the inhibitory effect of the sympathetic nervous system on TNF-α production contributing to the elevated plasma levels of cytokines.[133]

Recently some investigators have suggested that elevations in IL-6 in response to exercise may play an anti-inflammatory role, principally by inhibiting the production of TNF-α.[55] Tumor Necrosis Factor alpha has direct inhibitory effects on insulin signaling and the ability of IL-6 to inhibit TNF-α production may represent a mechanism whereby exercise enhances insulin sensitivity.[55] In the current study, IL-6 (but not TNF-α) showed a significant increase immediately following the exercise bout but returned to baseline by 6 hours. This is consistent with other researchers who state that maximal IL-6 levels are found immediately after the exercise followed by a rapid decline.[55, 56, 65, 127-129] Ostrowski's findings also support that an increase in plasma IL-6 can be detected after only 30 minutes of running and showed a steady increase throughout running and then a steady decline immediately after running.[132] The level of IL-6 increases with the duration of exercise as well as is related to the intensity of exercise.[132] In the current study, the relative exercise intensity for this group of HF participants was set at a minimum of a moderate intensity (based on

participants ratings of perceived exertion). However, in some cases the relative intensity was much higher as indicated by some individual responses rating the perceived exertion at 6 to 7. Therefore, although the absolute intensity of the exercise bout may appear low to a healthy, unimpaired individual, the relative intensity was quite high for this group of study participants.

The significance of exercise-induced increases in proinflammatory cytokines is not entirely clear. Based on the literature, exercise-induced increases in IL-6 contribute to the maintenance of glucose homeostasis during prolonged exercise in normal subjects.[65,127-132,136] There is indirect evidence that muscle-derived IL-6 inhibits the effects of proinflammatory cytokines.[60] Pedersen et al state that "muscle-derived IL-6 is likely to work in a hormone-like fashion, exerting its effect on the liver and adipose tissue, thereby contributing to the maintenance of glucose homeostasis during exercise and mediating exercise-induced lipolysis.[60] Muscle-derived IL-6 may also work to inhibit the effects of proinflammatory cytokines such as TNF-α, thereby protecting against insulin.[60] In the current study, although IL6 increased immediately post exercise, TNF-α did not show any significant increases following the exercise bout. It is possible that IL6 had an inhibitory function on TNF-α in the current study as suggested by other researchers.[60]

Interleukin 8 Baseline

Kohut et al state that IL-8 is elevated in the serum of Type II diabetics and is a predictor of cardiovascular death and future coronary heart disease in older adults.[134] Additionally, Dominguez-Rodriguez and colleagues found that high levels of IL-8 predict heart failure in patients with anterior myocardial infarction treated with percutaneous

coronary intervention (PCI).[61] Larsen et al found baseline levels of IL-8 to be elevated in males with NYHA class II to III stable, ischemic HF (mean age 67 +/-8 years) when compared to age and sex-matched healthy controls.[135] In the current study, it is not clear why baseline levels of IL-8 were not elevated in this sample of HF patients especially in the presence of elevated baseline levels of other cytokines (i.e., TNFα, IL-6 and CRP). It is possible that etiology of HF may have an influence on the expression of this cytokine.

Interleukin 8 Exercise

Bruunsgaard and Pedersen state that concentrations of chemokines (e.g., IL-8) are elevated after strenuous exercise.[60] Suzuki et al report that IL-8 is released into the circulation under prolonged, severe exercise conditions as well as brief, high intensity exercise.[44] Large increases in IL-8 (2.6 – 6.7 times, 92% increase) immediately post exercise have been demonstrated by other researchers following long duration activities such as marathons or ultra marathons.[126, 136] Other researchers report no change in IL-8 levels after an anaerobic training session that involved healthy male subjects performing one 60 second all-out exercise test followed by a 10 minute rest and then eight, 10 second all-out tests with a 4:50 rest in between them on a cycle ergometer.[137]

Interestingly, other researchers have found no change in plasma/serum markers of IL-8 following concentric exercise alone, e.g., bicycle ergometry or rowing.[135] Akerstrom et al investigated the muscle-derived production of IL-8 following concentric exercise and concluded that there was high local expression of IL-8 but only a small, transient release of IL-8 in the plasma.[62] A recent study by Chan et al investigated

both IL-6 and IL-8 in 8 healthy males (mean age 24 years) after 60 minutes of cycling exercise with either a normal or reduced intramuscular glycogen content.[138] These researchers found that IL-6 increased after 40 minutes but IL-8 was no different from rest or at any point during exercise.[138] Additionally, Mucci et al looked at 11 untrained and 11 endurance trained males cycle to exhaustion.[139] These researchers found no change in IL-8 during, or 5 minutes post exercise, but a 50% and 35% increase immediately post, respectively in both groups.[139] In the current study, immediate post exercise was within the 1st hour following the exercise bout. If IL-8 increases by 50% on immediate cessation of exercise, this window would have been missed and the increase in IL8 levels would not have been detected.

The results of the current study support Akerstrom's and Mucci's data as there were no significant changes of IL-8 from baseline measures to any time point following the exercise bout. This is likely the result of the relatively short duration (i.e., 20 minutes) of exercise, the overall lower intensity of exercise and the nature of the muscle contractions (i.e., concentric) during bicycle ergometry.

Interleukin 10 Baseline

Interleukin 10 (IL-10) is believed to be one of the most important anti-inflammatory cytokines.[23] It is known to down-regulate the production of TNF-α & IL-6 and other cell-mediated immune responses.[23] Circulating IL-10 concentrations have been reported to be either increased or decreased in CHF patients compared to healthy age-matched controls.[43] Most recently research by Stumpf et al looked at serum levels of IL-10 in patients with advanced heart failure compared to age-matched controls and found significantly reduced plasma levels of IL-10 in advanced heart failure

2.3 +/- 1.9 pg/ml compared to healthy controls 5.2 +/- 2.3.[43] The current study demonstrates significantly reduced IL-10 levels (1.8 +/- 1.4 pg/mL) when compared to the healthy controls in the research by Stumpf et al. Interestingly, Stumpf et al also looked at the ratio of TNF-α to IL-10 and found it to be significantly higher in the CHF group vs. the control group (3.2 +/- 1.2 vs. .4 +/- .2). In the current research, the ratio of TNF-α to IL-10 was identical to Stumpf's data (3.2 +/- 2.4) indicating an immunological imbalance in favor of inflammation in this study group of CHF patients.[43]

Interleukin 10 Exercise

Activity-induced IL-10 is produced by stretching and compressing the epithelial cells, as well as in response to high levels of IL-6.[45] Kasapis et al report the relative change in IL-10 following strenuous exercise follows a similar time-course as IL-6, albeit, to a much lesser degree.[59] However, there is no consensus on the effect of strenuous exercise on levels of plasma/serum IL-10.[66, 69, 88-90] Some authors report increases in IL-10 following strenuous exercise (up to 27-fold) while others report no change.[66, 69, 88-90] Peake et al investigated the effects of running at moderate intensity (60% VO_{2max}), high intensity (85% VO_{2max}) and downhill (-10%) at 60% VO2max in 9 well-trained male runners mean age 28 years.[63, 140] The results of this study demonstrated that IL-10 did not increase significantly after the moderate intensity or the downhill running trials, but only after the high intensity trial.[63, 140] Brenner et al looked at healthy moderately fit males (mean age 24.9 years) and the response of IL-10 during maximal exercise, circuit resistance exercise and prolonged cycling (2 hours)[66]. These researchers found that IL-10 did not change from baseline in any of the three exercise conditions.[66] Suzuki et al. in his research also found that there were no detectable changes in levels of IL-10 following 10 minutes of maximal

exercise.[44] These researchers suggest that IL-10 is only released into the circulation under prolonged severe exercise conditions.[44]

The results of the current study demonstrate that IL-10 did not change significantly from baseline levels. Given that the relative intensity of both the SS and IT exercise bouts would be considered “moderate”, this research supports the research of Peake et al, Brenner et al and Suzuki et al.

Tumor Necrosis Factor alpha Baseline

Elevation of proinflammatory cytokine levels in HF is consistent with previously reported findings.[23, 43, 100, 101, 121, 123] Stumpf et al found plasma Tumor Necrosis Factor alpha (TNF-α) levels to be significantly higher in patients with CHF than in healthy controls (6.5 +/- 2.9 pg/ml compared with 2.5 +/- 1.8 pg/ml).[43] In the current study, the baseline TNF-α levels were also elevated when compared to the healthy control subjects in Stumpf’s research (5.9 +/- 3.3 pg/ml vs. 2.5 +/- 1.8 pg/ml) supporting Stumpf and other researchers (Anker, Toth, Kinugawa) findings that TNF-α levels are increased in advanced heart failure patients.[23, 43, 99-101, 121, 123]

Tumor Necrosis Factor alpha Exercise

In a recent review paper on cytokine kinetics, Suzuki et al state that more than half of the existing studies examining TNF-α could not confirm significant increases after exercise.[44] Bruunsgaard & Pedersen et al, also state that most studies show no effect of exercise on TNF-α levels after strenuous exercise.[51, 60, 74, 128, 141] In Ostrowksi’s research with male endurance trained runners, he also found no differences between the pre-exercise plasma TNF-α level and any of the later samples (2.5 hours

of treadmill running at 75% VO_{2max}).[126, 132] Kinugawa et al found an increase in both IL-6 and TNF-α levels immediately following maximal exercise in both patients with mild to moderate CHF and in normal controls.[123] Kinugawa concluded that increases in basal IL-6 & TNF-α levels are associated with high sympathetic nervous system activity and exercise intolerance in patients with mild to moderate HF.[123] In the current study, there was no significant change in TNF-α levels in either the SS or the IT group at any time point following the exercise bout. Suzuki et al state that TNF-α is rapidly cleared from the circulation into the urine as a result of a short half-life (14 to 18 minutes).[44] If TNF-α is rapidly expelled into the urine it is possible that the immediate post blood sample within one hour of cessation of exercise would have missed this window especially if the increase in TNF-α levels were relatively small given the duration and intensity of the exercise bout. The results from the present study are consistent with the above research findings that exercise does not affect TNF-α levels.

C-Reactive Protein Baseline

C-Reactive Protein (CRP) is produced by hepatocytes in response to a variety of inflammatory cytokines and has been shown to be a nonspecific marker of systemic inflammation. The serum concentration of high sensitivity (hs) CRP is known to be an independent predictor of adverse cardiovascular events, including death, the need for transplantation and worsening CHF requiring hospitalization.[142-147] In the current study, the baseline hsCRP values were extremely high, possibly indicating the severity of the heart dysfunction and/or other comorbid conditions that accompany a HF population. In research by Stumpf et al, they reported that hsCRP was significantly elevated in their group of CHF patients with the highest levels found in the NYHA class

IV patients, as well as in the ischemic versus dilated cardiomyopathy group (16.7 +/- 8.9 compared to 7.3 +/- 3.8 mg/L).[43] In the current research, the mean hsCRP baseline values were 9.38 +/- 15 ug/L.

C-Reactive Protein Exercise

Research on the effect of strenuous exercise on CRP levels is limited. Gleeson et al state that CRP increases in response to exercise that is associated with muscle damage and/or inflammation.[85] However, research by Croisier et al that investigated exercise-induced muscle damage and the interleukin response in healthy male subjects (mean age 24 years) found that CRP levels were essentially unchanged after two exercise bouts of maximal eccentric contractions of the knee flexors and extensors despite significant increases in IL-6.[64] Levels of CRP have been found to increase during strenuous exercise, immediately post-exercise, 24 hours, 48 hours and at 7 days; however, results are inconsistent.[44, 59, 63, 66, 140] Kasapis et al in their systematic review conclude that, “there is a short-term, transient increase in serum CRP after strenuous exercise, produced by an exercise-induced acute phase response mediated by the cytokine system and mainly IL-6”.[59]

Heart type - Fatty Acid Binding Protein Baseline

Recent studies indicate that progressive deterioration of ventricular function in patients with CHF is associated with ongoing myocardial injury.[148] Increased ventricular wall tension and volume overload are detected mainly by elevated levels of B-type Natriuretic Peptide (BNP) (or NT-ProBNP) which have been shown to accurately reflect heart failure severity as classified by the New York Heart Association (NYHA).[149] However, Pelsers states that minor necrosis of cardiomyocytes is very

often not detected by coronary angiogram and the cytoplasmic and myofibrillar proteins (i.e., H-FABP) are evaluated as sensitive markers for minor myocardial injury in patients with CHF.[150] For clinical reference, Pelsers suggests 6 ug/L H-FABP as a cut-off value for detection of myocardial injury.[148] Baseline values for H-FABP in the current study suggest that minor myocardial injury was present as evidenced by mean values of 11 ug/L in this participant sample in both the SS and the IT group. Pelsers (2004) states that elevated plasma levels of H-FABP do not carry positive predictive value but only a negative predictive value for future events (81.3%) when H-FABP level is below the clinical reference value of 6 ug/L.[148] Additionally, Pelsers states that the effect of aging can influence the plasma concentration of H-FABP, which given the average age of the participants in the current study it is likely that advancing age would have contributed to the elevated values seen.[148]

Myoglobin Baseline

Baseline levels of myoglobin were similar to values obtained from the unpublished data of Pelsers et al, 2008 (90.35 +/- 110 vs. 77.45 +/- 50.34). Compared to baseline values of healthy individuals, the myoglobin values in the current study were elevated.[148, 151] In a recent study evaluating cachexia in cancer patients, Weber et al found mean plasma myoglobin values to be 48% below that of controls in cachexic patients.[151] In the current study, participants were not evaluated for HF-related cachexia but given the elevated myoglobin levels it is unlikely that the participants were demonstrating muscle wasting. The elevated myoglobin levels are likely attributed to what Pelsers refers to as “ongoing myocardial injury”.[148] As with H-FABP, increases in myoglobin have also been attributed to advancing age. Therefore, it is likely that the

increased age of the participants in the current study, also contributed to the elevated values of myoglobin.[84, 150, 152]

H-FABP and Myoglobin Exercise

Plasma levels of H-FABP have been shown to increase after physical activity in healthy subjects.[84, 148] Sorichter et al also demonstrated that after 20 minutes of downhill running that the pattern of release of H-FABP into and clearance from the blood is similar to that of myoglobin.[84, 148] In the current study, both H-FABP and myoglobin increased from baseline values and reached their peak by 6 hours following the exercise bout. This relatively rapid increase and clearance from the blood following exercise is supported by previous research by both Pelsers and Sorichter.[84, 148]

Myoglobin to H-FABP Ratio Baseline

As per baseline elevated levels of H-FABP indicating cardiac muscle injury, the baseline levels of the ratio between myoglobin and H-FABP indicate that a small amount of cardiac muscle damage was present prior to the exercise intervention (ratio 2-10). These results are not surprising given that this participant sample consisted mostly of individuals with NYHA class II to III HF with ejection fractions less than 35%, indicating moderate to severe HF.

Myoglobin to H-FABP Ratio Following Exercise

It is now widely accepted that training can result in varying degrees of microtrauma to muscle, connective tissue and/or bones and joints and is referred to as “adaptive microtrauma that may be regarded as an initial phase along an “injury continuum”.[153] This microinjury is referred to as “adaptive” as it is widely believed

that the microtrauma results in a mild inflammatory response, with the final purpose of healing.[153]. Lakier Smith suggests that exercise that requires elevated local demands, such as high intensity cycling, may induce pockets of ischemia, resulting in ischemic/reperfusion injury.[153] Adaptive microtrauma is also proposed in joint structures undergoing high volume repetitions (e.g., cycling).[153] The mode of exercise used in the current study i.e., cycle ergometer with primarily concentric muscle actions, is therefore likely to have resulted in the limited markers of muscle tissue damage or inflammation. In the current study there were small increases in the ratio of myoglobin to H-FABP suggestive of a small amount of skeletal muscle injury. However, these changes did not achieve statistical significance between groups and only occurred in a few of the participants (4 participants at 6 HR – POST; 1 participant at 24 HR – POST; 3 participants at 48 HR – POST). On an individual basis, some individuals demonstrated either slight cardiac or skeletal muscle damage at baseline (4 participants cardiac muscle injury; 5 participants skeletal muscle injury). Individual data suggest that skeletal muscle damage was transient in nature. In the current study, both Myoglobin and FABP returned to baseline within 24 hours, which Pelsers suggests is due to the relatively short half-life of FABP and Myoglobin and is related to the rapid renal clearance of both of these markers.[150]

Delayed Onset of Muscle Soreness Questionnaire (DOMS)

Participants were asked to rate the amount of muscle soreness that was being experienced at all time points following the exercise bout using a visual analogue scale and body diagram following the performance of a stand-to-sit exercise. Although delayed onset muscle soreness is known to peak at 24 to 72 hours post damage-inducing exercise, neither group, nor individual rated any degree of muscle soreness

from the single exercise bout on a cycle ergometer.[154] Gleeson et al demonstrated that an exercise bout that induced DOMS & biochemical indices of muscle damage (8 untrained men and women performed a single step test for 40 minutes) was associated with an acute phase response with elevation of serum CRP.[85] In the current study, there was no increase in CRP at any time period, nor an increase in DOMS. Further, repeated measures of peak concentric torque did not support skeletal muscle damage following the exercise bout.

Lower Extremity Functional Scale

The acute mood effects associated with participation in single session of exercise and the effect of regular exercise has been demonstrated in a number of studies.[109, 155-158] Interestingly, in this study the effect of a single bout of exercise was enough to cause a significant increase in the perception of lower extremity function in both groups at most time points. It is possible that the "perception of function" may be enhanced from even a single bout of exercise. Pedersen et al have demonstrated that Interleukin 6 has numerous effects on brain function, such as influencing the activity and function of the neurons.[55] In a recent study by these same researchers they were not able to demonstrate a net release or uptake of IL6 after 15 minutes of exercise.[55] However, a small release of IL6 from the brain was observed after 60 minutes of exercise and when a second bout of exercise was performed there was a fivefold increase in IL6 at the end of the second bout of exercise.[55] These researchers concluded that IL6 is released from the brain after prolonged exercise and is influenced by the duration of exercise rather than increase in body temperature.[55] In the current study, the exercise bout lasted a total of 35 minutes. It is not clear whether this intermediate amount of time would be enough to stimulate the brain production of IL6 or

if even IL6 plays any role in acute mood effects, but this may be of interest in future research.

Peak Concentric Isokinetic Torque

Exercise intolerance and muscle weakness in heart failure is well documented.[159-162] Previous researchers have described a reduction in muscle strength and mass which correlates with exercise capacity.[99, 101, 102, 121, 163] Isokinetic dynamometry provides a method of dynamically evaluating skeletal muscle function. In the current study, an age-matched healthy control group was not used but when baseline measures of peak concentric isokinetic torque were compared against normal values for healthy, similar aged males, at a similar angular velocity (i.e., 30° per second) a 26% decrement in peak isokinetic concentric torque was observed (146.8 (Nm) +/- 40 vs. 109 (Nm) +/- 22).[164] However, the comparison of results from the current study to a group of healthy control subjects from an unrelated study should be observed with caution. Toth et al study looked at immune activation and skeletal muscle mass and found that there was a significant decrease in both peak isokinetic and isometric knee extensor strength in males with HF compared to age-matched controls.[100] He found that higher levels of IL6 & TNFα were associated with reduced knee extensor and forearm grip strength and suggests that heart failure is associated with reduced skeletal muscle strength that is not due to muscle atrophy.[100]

Concentric training protocols are typically associated with strength reductions of 10-30% in peak concentric torque immediately after the exercise and are generally restored within a few hours post-exercise.[18] The highest degrees of strength loss and prolonged recovery occur following high-force eccentric exercise.[18] When compared

to baseline values, strength loss following high-force eccentric exercise, e.g., maximal eccentric contractions, can generate up to 50-65% loss of force-generating capacity.[18]

Despite findings of reduced skeletal muscle strength, as measured by the peak concentric isokinetic torque on the KinCom^{TM}, the results of the current study did not demonstrate the typical pattern of skeletal muscle injury following SS or IT. There was an initial decrease in force production immediately following the exercise bout but this force decrement did not persist to later time periods. This finding is consistent with results typical of concentric training protocols.[18]

The results from this study suggest that there was initial muscle fatigue following the exercise bout but not skeletal muscle injury. The fatigue was short-lived and the strength values returned to near baseline following the initial reduction in peak torque.

Peak Eccentric Isokinetic Torque

The current investigation is the first to look at peak eccentric isokinetic torque in individuals with HF. As a result, there is no HF data with which to compare results from this study. Recent studies looking at peak eccentric muscle torque in patients with chronic obstructive pulmonary disease found a preservation of eccentric quadriceps muscle strength when compared against a similarly healthy age-matched population.[165] However, the current study did not use a comparison control group and therefore, no inferences can be made in this regard. Peak eccentric torque measurements in the current study demonstrated a similar pattern of force loss to peak concentric torque immediately post exercise bout but then returned back to near baseline levels at all other time points post exercise.

Baseline Correlations

Significant correlations between CRP and interleukins 6 and 8 were found in the current study. The strength of the relationship between CRP and IL6 can be explained by the r-square value in which 34% of the variance in CRP can be explained by changes in IL6, while 55% of the variance in CRP can be explained by IL8. These relationships are not surprising given that CRP and IL6 have both been associated with increased severity of left ventricular dysfunction and increased NYHA functional class.and that high levels of IL8 have been shown to predict heart failure in patients following anterior myocardial infarction. [49, 51, 60, 61] All participants in the current study had ejection fractions less than 35% and were primarily classified in the NYHA functional classes II to III, indicating moderate to severe heart failure. Additional support for this finding is data from recent investigations that suggests that CRP may function to markedly exaggerate the actions of IL6 from endothelial cells and therefore, the increased vascular production of IL6 may represent a positive feedback loop for the continued production of CRP from the liver.[57-59] Previous studies have also demonstrated dynamic changes in plasma IL8 level along with CRP.[166] Interleukin 8 has also been shown to be induced by a number of stimuli, including proinflammatory cytokines, insulin resistance and obesity.[167-169]

PRACTICAL IMPLICATIONS

Exercise training plays an essential role in the optimal treatment for patients with HF with clear evidence of an overall reduction in mortality. Conclusions taken from the ExTraMATCH Collaborative (Exercise training meta-analysis of trials in patients with chronic heart failure) suggest that further research should focus on optimizing exercise programmes in patients with HF. The results from this investigation will contribute to this area of knowledge with important implications for exercise training in rehabilitation programs and future studies for patients with heart failure. If the early inflammatory response is excessive, an appropriate persistence of anti-inflammatory compensation will result in later immune suppression, which can lead to further progression or worsening of HF. Therefore, prescribing exercise that does not contribute to the inflammatory cascade is of utmost importance in this population. The results of this investigation suggest that when either SS or IT exercise is prescribed at a similar volume of exercise on a cycle ergometer, there are no indicators of excessive activation of the inflammatory system or skeletal muscle injury beyond adaptive microtrauma. These findings suggest that either SS or IT may be an appropriate method of training for optimizing improvements in aerobic capacity in patients with HF.

Limitations of the study/Future Research

The number of patients in the present study was small and the participants were all male, which precludes any general inference of results. Further research into skeletal muscle injury and inflammatory activation with a larger sample that includes female patients with HF is warranted, especially given that females are known to respond differently to skeletal muscle injury than males.[72] Additionally, the present

study did not look at different types of exercise, only cycle ergometry. Research that investigates activities with a greater weight-bearing load and/or eccentric component would contribute further to our knowledge in this area. Lastly, this study lacked a control group which limited the ability to make comparisons against the response of healthy, age-matched individuals to the same intervention.

Previous research has demonstrated relationships between quality of life measures and exercise. Although the present study did not directly measure quality of life, it is possible that the "perception of function" may be enhanced from even a single bout of exercise, as evidenced by the increased scores for both groups over most time periods on the lower extremity functional scale. Results from this study indicate that there is a need for future research looking into the effects of a single exercise bout on the actual and perceived effect on lower extremity function and quality of life.

Table 1. Participant Characteristics

*** Denotes P < .05**

Variable	Steady-State Training Group (n=7)	Interval Training Group (n=7)
Age (years)	60.1 ± 6.7	57.9 ± 9.8
Height (cm)	177.7 ± 5.3	177.7 ± 5.4
Weight (kg)	96.3 ± 23.4	96.0 ± 13.5
BMI (kg/m^2)	30.2 ± 5.34	30.5 ± 4.6
Ejection Fraction	.236 ± .069	.300 ± .108
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	14.9 ± 5.3	12.43 ± 3.8
Diabetes Mellitus		
Type 1 DM	1	2
Type 2 DM	1	1
New York Heart Association Class		
Class 1	2	0
Class 2	4	5
Class 3a	1	2
Diagnosis		
Ischemic	3	4
Valvular	1	0
Dilated	1	0
Idiopathic	0	3
Rhythm		
NSR	3	6
Atrial Fibrillation/Flutter	1	0
Paced	3	1
Ventricular Pacemaker	2	2
AICD	3	4
HF Onset (years)		
< 1year	0	1
1 – 5 years	5	3
6 – 10 years	1	2
11 – 20 years	1	1
NT-Pro BNP (pg/ml)		
500 – 1000	4	2
1001 – 2000	1	1
2001 – 3000	1	1
3001 – 4000	1	1
4001 – 5000	0	1
5001 – 10,000	0	1
> 10,000	1	0
Hemoglobin		
Low	1	2
Normal	6	5
Medications		
ASA	4	4
Beta Blocker (CoReg, Atenolol, Monocor,	7	6

Bisoprolol)		
ARB (Spironolactone, Atacand)	5	4
Digoxin	4	4
Diuretic (Lasix)	6	7
Amiodarone (Antiarrhythmic)	1	2
Cholesterol-lowering (Lipitor, Crestor, Simvastatin)	2	3
Anti-coagulant (Coumadin)	5	4
Plavix	0	1
Ace Inhibitor (Altace)	3	2
Calcium Channel Blocker (Captopril, Accupril, Norvasc)	2	1
Vasodilators, (Nitroglycerine: patch, spray, tablets; Hydralazine)	2	1
Hyperglycemic Agents (Metformin, Glyburide, Insulin)	2	3
Other (Testosterone, Eltroxin, Synthroid, Pantolec, Allopurinol, Effexor, Welbutrin, Celexa, Cholchicine, Valium, Halcion)	5	3

Values are means ± SD

Table 2. Training Workloads

Individual Data

Steady-State Training Group					
	Exercise Prescription		Actual Workloads		
Participant	65% Heart Rate Reserve	65% Peak Watts	Heart Rates	Rating of Perceived Exertion	Watts
01	122 bpm	20 Watts	105 – 119 bpm	3 – 4	20 Watts
02	113 bpm	36 Watts	107 – 108 bpm	3.5	36 Watts
03	133 bpm	78 Watts	92 – 100 bpm	3 – 4	78 Watts
04	89 bpm	39 Watts	93 – 102 bpm	4 – 7	39 Watts
10	103 bpm	92 Watts	115 – 123 bpm	4 – 5	92 Watts
15	99 bpm	52 Watts	99 – 113 bpm	3.5 – 6	52 Watts
17	98 bpm	65 Watts	98 – 101 bpm	4 – 6	65 Watts
Interval Training Group					
	Exercise Prescription		Actual Workloads		
Participant	40% Heart Rate Reserve & 90% Heart Rate Reserve	40% Peak Watts & 90% Peak Watts	Heart Rates	Rating of Perceived Exertion	Watts
05	77 bpm & 84 bpm	14 Watts & 32 Watts	96 – 99 bpm*	4 – 7	14 Watts & 32 Watts
06	79 bpm & 97 bpm	34 Watts & 77 Watts	78 – 96 bpm*	3 – 6	34 Watts & 77 Watts
07	74 bpm & 90 bpm	20 Watts & 44 Watts	85 – 104 bpm*	1 - 3	20 Watts & 44 Watts
08	74 bpm & 84 bpm	42 Watts & 94 Watts	94 – 111 bpm*	2 & 4 - 5	42 Watts & 94 Watts
11	92 bpm & 105 bpm	32 Watts & 72 Watts	82 – 92 bpm & 92- 102 bpm	3 – 4 up to 7 last 5 minutes	32 Watts & 72 Watts
12	No target Range	29 Watts & 65 Watts	110 bpm*	4 – 6	20 Watts & 65 Watts
13	64 bpm & 80 bpm	48 Watts & 108 Watts	79 – 85 bpm*	4 – 5	64 watts & 108 Watts

*** Heart Rates elevated throughout interval**

Group Data

Training Watts	Mean	Standard Deviation
All Participants	54.07143	19.7424
Steady-State Group	56.0000	23.2451
Interval Training Group	52.1429	17.1894

Table 3. Correlation Matrix

*** Marked correlations are significant at p < .05000**

	EF	VO2	Ht	Wt	NT Pro BNP	Age
EF	1.00	0.22	-0.12	-0.29	0.46	0.02
VO2	0.22	1.00	-0.42	-0.63	0.29	0.64
Ht	-0.12	-0.42	1.00	0.59	0.36	-0.01
Wt	-0.29	-0.63	0.59	1.00	-0.47	-0.067
BMI	-0.29	-0.61	0.41	0.98	-0.62	-0.77
NT PRO BNP	0.46	0.29	0.36	-0.47	1.00	*0.65
Age	0.02	0.64	-0.01	-0.67	*0.65	1.00

*** Marked correlations are significant at p < .05000**

	CRP	FABP	IL6	IL8	IL10	MGB	Ratio	TNFa
CRP	1.00	0.00	*0.59	*0.74	0.35	-0.28	-0.23	0.29
FABP	0.00	1.00	-0.08	0.19	0.13	0.44	-0.22	-0.06
IL6	*0.59	-0.08	1.00	0.44	0.13	-0.01	-0.17	0.38
IL8	*0.74	0.19	0.44	1.00	0.36	-0.08	-0.19	0.20
IL10	0.35	0.13	0.13	0.36	1.00	0.02	0.14	0.09
MGB	-0.28	0.44	-0.01	-0.08	0.02	1.00	0.52	-0.05
Ratio	-0.23	-0.22	-0.17	-0.19	0.14	0.52	1.00	-0.31
TNFa	0.29	-0.06	0.38	0.20	0.09	-0.05	-0.31	1.00

Table 4. Baseline levels of Cytokines (Values are means ± SD)

Cytokine	Study Participants (N = 14) (males)	Values in Healthy Population	Values in CHF population
CRP (ug/mL)	9.3805 +/- 14.9641	Plasma 2.0 ug/mL +/- .56 (males)[100]	Plasma 5.11 +/- 1.26 (males)[100] Serum 3.57 +/-2.7 (females also)[71] Serum 19 +/- 4 ug/mL (males & females)[170]
IL 6 (pg/ml)	3.043 +/- 2.276	Plasma 31 +/- 37 (1 female)[38] Serum 1.3 +/- .2 (age matched controls mean age 57.2 +/-1.7 (females also)[123] Serum 1.2 +/- .4 [171] Plasma 1.92 +/- .38 (males)[100] Plasma .98 +/-.19 (males)[121] Plasma 1.47 +/- .23 (males & females)[133] Plasma 1.1 +/- .8 (males age 62)[10]	Plasma 23 +/- 22 (1 female)[38] Serum 2.4 +/- .3 (females also)[123] Serum 1.5 +/- .6 [171] *Plasma 3.96 +/- .76 (males)[100] Serum 9.82 +/- 14.6 (females also)[71] Plasma non-cachectic CHF 2.81 +/- .42 (males)[121] Plasma cachectic CHF 3.92 +/- .70 (males)[121] Plasma 4.6 +/- 2.7 (males & females age 56 +/- 9)[133] Serum 1.7 pg/ml +/- .14 (males & females)[170] Plasma 4.6 +/- 3.9 (males age 67)[10]
IL 8 (pg/ml)	0.468 +/- 0.665	Plasma ~3.8 – 4.0 +/- .8 [139] Plasma – not detectable (males 62 years)[10]	Plasma 12.7 +/- 9.2 (males age 67)[10] Serum 15.2 +/- 3.5 & 25.9 +/- 4.2 after AMI (males & females)[61]

IL 10 (pg/ml)	1.815 +/- 1.389	Plasma 5.2 +/- 2.3 (males & females mean age 63.6)[43]	Plasma 2.3 +/- 1.9 (males & females) (mean age 66.9 +/- 12.6; class 2 – 4)[43]
TNFα (pg/ml)	5.905 +/- 3.278	Plasma 2.5 +/- 1.8 [43] Plasma 1.4 +/- 0.4 (1 female)[38] Serum 2.7 +/- .2 [123] Serum .8 (males)[124] Serum .9 +/- .2 [33] Plasma 1.52 +/- .15 (males)[100] Plasma 7.0 +/-.8 (males) [121] Plasma 1.5 +/- .12 (males & females age 56 +/- 9)[133] Plasma 7.3 +/- 3 (Larsen et al) (males)	Plasma 6.5 +/- 2.9 [43] Plasma 2.72 +/- 1.5 (1 female)[38] Serum 3.8 +/- .2 [123] Serum 2.0 (males)[124] Serum 2.2 +/- .2 [33] Plasma 1.91 +/- .30 (males)[100] Serum 8.43 +/- 3.6 (females also)[71] Plasma non-cachectic CHF 6.9 +/- .8 (males)[121] Plasma cachectic CHF 14.6 +/- 2.8 (males)[121] Plasma 2.79 +/- .9 (males & females age 56 +/- 9)[133] Plasma 28.7 +/- 18.5 (males age 67)[135]
H - FABP (ug/L)	11.939 +/- 21.356	Plasma *6.0 ug/L [148]	Plasma **11.0 ug/L [148]
Myoglobin (ug/L)	90.353 +/- 106.464	Plasma 60 ug/L [148]	80 ug/L +/- 77.45 (Pelsers unpublished data)
Myoglobin:H-FABP Ratio	7.6	Heart muscle damage Mg:FABP ratio 2-10[148]	Skeletal muscle damage Mg:FABP ratio 20-70 (depending on type of muscle)[148]

* Cut-off value for healthy subjects

**Median level in total CHF group (Pelsers, 2004)

Table 5. Peak Concentric Isokinetic Torque Knee Extensors (Values are means ± SD)

Study Participants (N = 14 Males)	Comparison to Healthy Population	Comparison to HF population	Comparison to COPD Population
Dominant Leg - 109 (Nm) +/- 22 Angular speed 30° per second 100° to 20° knee flexion (90° ROM)	**Toth et al, 2005 (10 Males)** Dominant Leg - 121 (Nm) +/- 11) Angular speed 90° per sec 0° to 90° ROM (extension to flexion) [100]	**Toth et al 10, 2005 (10 Males)** Dominant Leg - 88 (Nm) +/- 10 Angular speed 90° per sec 0 to 90° ROM (extension to flexion) [100]	**Mathur et al, 2007 (9 males, 11 women average age 68 years)** Dominant Leg 61 (Nm) +/- 18 Angular speed of 30° per second 100° to 20° knee flexion (90° ROM) [175]
	Ostchega et al (411 non-Hispanic white males) Dominant Leg 144 (Nm) Angular speed 60° per second ROM not stated [172]	**Quittan et al (33 Males, 5 females)** Dominant & Non-Dominant Leg 115.6 (Nm) +/- 7.2 Angular speed of 60° per second ROM not stated [176]	
	Skelton et al, 2002 (women "nonfallers" > 65 years of age) Weakest Leg 162.5 (Nm) +/- 44.6 Angular speed 100° per second ROM 20° to 90° [173]	**Clark et al, 1997 (10 ?males?)** Both Dominant & Nondominant Leg 123.6 (Nm) +/- 30 Angular speed of 30° per second 80° to 10° knee flexion [164]	
	Sunnerhagen et al, 2000 (males 40 – 79 years) Right Leg: 40 – 49 years: 198 (Nm) 50 – 59 years: 163 (Nm) 60 – 69 years: 157 (Nm)		

70 – 79 years: 136 (Nm)
Angular speed 60° per second ROM not stated [174]
Mathur et al, 2007 (9 males, 11 females)
Dominant Leg 85 (Nm) +/- 24
Angular speed of 30° per second
100° to 20° knee flexion (90° ROM) [175]
Clark et al, 1997 (10 ?males?)
Both Dominant & Nondominant Leg 146.8 (Nm) +/- 40
Angular speed of 30° per second
80° to 10° knee flexion [164]

Table 6. Peak Eccentric Isokinetic Torque Knee Extensors (Values are means ± SD)

Study Participants (N = 14)	Comparison to Healthy Population	Comparison to HF population	Comparison to COPD Population
Dominant Leg – 159 (Nm) +/- 32 Angular Speed 30° per second 100° to 20° knee flexion (90° ROM)	**Skelton et al, 2002 (women "nonfallers" > 65 years of age**) Weakest Leg 306.3 (Nm) +/- 91.3 Angular speed 100° per second ROM 20° to 90° [173]	**No available research for comparison**	**Mathur et al, 2007 (9 males, 11 women average age 68 years)** Dominant Leg – 109 (Nm) +/- 26 Angular speed of 30° per second 100° to 20° knee flexion (90° ROM) [175]
	Sunnerhagen et al, 2000 (males 40 – 79 years) Right Leg: 40 – 49 years: 230 (Nm) 50 – 59 years: 193 (Nm) 60 – 69 years: 182 (Nm) 70 – 79 years: 175 (Nm) Angular speed 60° per second ROM not stated [174]		
	Mathur et al, 2007 (9 males, 11 females x age 64 years) Dominant Leg 139 (Nm) +/- 45 Angular speed of 30° per second 100° to 20° knee flexion (90° ROM) [175]		

REFERENCES

1. Rich, M.W., *Multidisciplinary heart failure clinics: are they effective in Canada?* CMAJ, 2005. **173**(1): p. 53-4.

2. Wilson, E., *Congestive heart failure: A national priority.* Can J Cardiol, 2001. **17**(12): p. 1243-4.

3. Mann, D.L. and M.B. Reid, *Exercise training and skeletal muscle inflammation in chronic heart failure: feeling better about fatigue.* J Am Coll Cardiol, 2003. **42**(5): p. 869-72.

4. *American College of Sports Medicine's Resource Manual of Guidelines for Exercise Testing and Prescription.* 5th ed. ed. 2005: Lippi Williams & Wilkins.

5. Pina, I.L., et al., *Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention.* Circulation, 2003. **107**(8): p. 1210-25.

6. Coates, A., *What causes the sympt of heart failure?* Heart, 2001. **86**: p. 574-578.

7. Coates, A., *Origin of symptoms in patients with cachexia with special reference to weakness and shortness of breath.* Int J Cardiol, 2002. **85**: p. 133-139.

8. Coats, A.J., *The "muscle hypothesis" of chronic heart failure.* J Mol Cell Cardiol, 1996. **28**(11): p. 2255-62.

9. Fuchs, M. and H. Drexler, *Chronic heart failure and proinflammatory cytokines: possible role of physical exercise.* Exerc Immunol Rev, 2004. **10**: p. 56-65.

10. Larsen, A.I., et al., *Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure. Correlation between skeletal muscle alterations, cytokines and exercise capacity.* Int J Cardiol, 2002. **83**(1): p. 25-32.

11. Cicoira, M., et al., *Skeletal muscle mass independently predicts peak oxygen consumption and ventilatory response during exercise in noncachectic patients with chronic heart failure.* J Am Coll Cardiol, 2001. **37**(8): p. 2080-5.

12. Deschenes, *Effects of aging on muscle fibre type and size.* Sports Med., 2004. **34**: p. 809-24.

13. Magnusson, G., et al., *Peak skeletal muscle perfusion is maintained in patients with chronic heart failure when only a small muscle mass is exercised.* Cardiovasc Res, 1997. **33**(2): p. 297-306.

14. Williams, A.D., et al., *Reduced exercise tolerance in CHF may be related to factors other than impaired skeletal muscle oxidative capacity.* J Card Fail, 2004. **10**(2): p. 141-8.

15. Ventura-Clapier, R., E. De Sousa, and V. Veksler, *Metabolic myopathy in heart failure.* News Physiol Sci, 2002. **17**: p. 191-6.

16. Couillard, A., et al., *Evidence of local exercise-induced systemic oxidative stress in chronic obstructive pulmonary disease patients.* Eur Respir J, 2002. **20**(5): p. 1123-9.

17. McArdle, A., A. Vasilaki, and M. Jackson, *Exercise and skeletal muscle ageing: cellular and molecular mechanisms.* Ageing Res Rev, 2002. **1**(1): p. 79-93.

18. Clarkson, P.M. and M.J. Hubal, *Exercise-induced muscle damage in humans.* Am J Phys Med Rehabil, 2002. **81**(11 Suppl): p. S52-69.

19. Lieber, R.L. and J. Friden, *Mechanisms of muscle injury gleaned from animal models.* Am J Phys Med Rehabil, 2002. **81**(11 Suppl): p. S70-9.

20. MacIntyre, D.L., et al., *Presence of WBC, decreased strength, and delayed soreness in muscle after eccentric exercise.* J Appl Physiol, 1996. **80**(3): p. 1006-13.

21. MacIntyre, D.L., et al., *Markers of inflammation and myofibrillar proteins following eccentric exercise in humans.* Eur J Appl Physiol, 2001. **84**(3): p. 180-6.

22. Sorichter, S., B. Puschendorf, and J. Mair, *Skeletal muscle injury induced by eccentric muscle action: muscle proteins as markers of muscle fiber injury.* Exerc Immunol Rev, 1999. **5**: p. 5-21.

23. Anker, S.D. and S. von Haehling, *Inflammatory mediators in chronic heart failure: an overview.* Heart, 2004. **90**(4): p. 464-70.

24. Farber, M.O. and E.T. Mannix, *Tissue wasting in patients with chronic obstructive pulmonary disease.* Neurol Clin, 2000. **18**(1): p. 245-62.

25. Koechlin, C., *Does systemic inflammation trigger local exercise-induced oxidative stress in COPD?* Eur Respir J, 2004. **23**: p. 538-544.

26. Reid, M.B., *Invited Review: redox modulation of skeletal muscle contraction: what we know and what we don't.* J Appl Physiol, 2001. **90**(2): p. 724-31.

27. Roveda, F., et al., *The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial.* J Am Coll Cardiol, 2003. **42**(5): p. 854-60.

28. Adamopoulos, S., et al., *Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure.* J Am Coll Cardiol, 2002. **39**(4): p. 653-63.

29. Adamopoulos, S., et al., *Physical training reduces peripheral markers of inflammation in patients with chronic heart failure.* Eur Heart J, 2001. **22**(9): p. 791-7.

30. Braith, R.W., *Exercise training in patients with CHF and heart transplant recipients.* Med Sci Sports Exerc, 1998. **30**(10 Suppl): p. S367-78.

31. Conraads, V.M., et al., *Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease.* Eur Heart J, 2002. **23**(23): p. 1854-60.

32. ExTraMATCH, *Exercise Training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH).* Br Med J, 2004(January): p. 1-7.

33. Gielen, S., et al., *Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure.* J Am Coll Cardiol, 2003. **42**(5): p. 861-8.

34. Larsen, A.I., et al., *Effect of exercise training in patients with heart failure: a pilot study on autonomic balance assessed by heart rate variability.* Eur J Cardiovasc Prev Rehabil, 2004. **11**(2): p. 162-7.

35. Meyer, K., et al., *Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures.* Med Sci Sports Exerc, 1997. **29**(3): p. 306-12.

36. Meyer, K., et al., *Effects of exercise training and activity restriction on 6-minute walking test performance in patients with chronic heart failure.* Am Heart J, 1997. **133**(4): p. 447-53.

37. Niebauer, J., et al., *Home-based exercise training modulates pro-oxidant substrates in patients with chronic heart failure.* Eur J Heart Fail, 2005. **7**(2): p. 183-8.

38. Niebauer, J., et al., *Exercise training in chronic heart failure: effects on pro-inflammatory markers.* Eur J Heart Fail, 2005. **7**(2): p. 189-93.

39. Warburton E, M.S., *Skeletal muscle training in people with chronic heart failure or chronic obstructive pulmonary disease.* Physio Can., 2004. **56**: p. 143-157.

40. Wisloff, U., et al., *Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study.* Circulation, 2007. **115**(24): p. 3086-94.

41. Corra, U., et al., *Chronic heart failure-related myopathy and exercise training: a developing therapy for heart failure symptoms.* Curr Probl Cardiol, 2003. **28**(9): p. 521-47.

42. Libera, L.D. and G. Vescovo, *Muscle wastage in chronic heart failure, between apoptosis, catabolism and altered anabolism: a chimaeric view of inflammation?* Curr Opin Clin Nutr Metab Care, 2004. **7**(4): p. 435-41.

43. Stumpf, C., et al., *Decrease of serum levels of the anti-inflammatory cytokine interleukin-10 in patients with advanced chronic heart failure.* Clin Sci (Lond), 2003. **105**(1): p. 45-50.

44. Suzuki, K., et al., *Systemic inflammatory response to exhaustive exercise. Cytokine kinetics.* Exerc Immunol Rev, 2002. **8**: p. 6-48.

45. Winkelman, C., *Inactivity and inflammation: selected cytokines as biologic mediators in muscle dysfunction during critical illness.* AACN Clin Issues, 2004. **15**(1): p. 74-82.

46. Meadows K, H.J., Stewart C., *Tumor necrosis factor-alpha-induced apoptosis is associated with suppression of insulin-like growth factor binding protein-5 secretion in differentiating murine skeletal myoblasts.* J Cell Phyiol., 2000. **183**: p. 330-337.

47. Patiag, D., et al., *Effects of tumour necrosis factor-alpha and inhibition of protein kinase C on glucose uptake in L6 myoblasts.* Clin Sci (Lond), 2000. **99**(4): p. 303-7.

48. St. Pierre B, T.J., *Differential response of macrophage subpopulations to soleus muscle reloading after rat hindlimb suspension.* J Appl Physiol, 1994. **77**: p. 290-297.

49. Kanda, T. and T. Takahashi, *Interleukin-6 and cardiovascular diseases.* Jpn Heart J, 2004. **45**(2): p. 183-93.

50. Tomiya, A., et al., *Myofibers express IL-6 after eccentric exercise.* Am J Sports Med, 2004. **32**(2): p. 503-8.

51. Bruunsgaard, H., et al., *Predicting death from tumour necrosis factor-alpha and interleukin-6 in 80-year-old people.* Clin Exp Immunol, 2003. **132**(1): p. 24-31.

52. Murray, D.R. and G.L. Freeman, *Proinflammatory cytokines: predictors of a failing heart?* Circulation, 2003. **107**(11): p. 1460-2.

53. Adamopoulos, S., et al., *Effects of growth hormone on circulating cytokine network, and left ventricular contractile performance and geometry in patients with idiopathic dilated cardiomyopathy.* Eur Heart J, 2003. **24**(24): p. 2186-96.

54. Haddad, F., et al., *IL-6-induced skeletal muscle atrophy.* J Appl Physiol, 2005. **98**(3): p. 911-7.

55. Pedersen, B.K. and M. Febbraio, *Muscle-derived interleukin-6--a possible link between skeletal muscle, adipose tissue, liver, and brain.* Brain Behav Immun, 2005. **19**(5): p. 371-6.

56. Pedersen, B.K., A. Steensberg, and P. Schjerling, *Exercise and interleukin-6.* Curr Opin Hematol, 2001. **8**(3): p. 137-41.

57. Modur, V., et al., *Retrograde inflammatory signaling from neutrophils to endothelial cells by soluble interleukin-6 receptor alpha.* J Clin Invest, 1997. **100**(11): p. 2752-6.

58. Goldhammer, E., et al., *Exercise training modulates cytokines activity in coronary heart disease patients.* Int J Cardiol, 2005. **100**(1): p. 93-9.

59. Kasapis, C. and P.D. Thompson, *The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review.* J Am Coll Cardiol, 2005. **45**(10): p. 1563-9.

60. Bruunsgaard, H. and B.K. Pedersen, *Age-related inflammatory cytokines and disease.* Immunol Allergy Clin North Am, 2003. **23**(1): p. 15-39.

61. Dominguez-Rodriquez A, A.-G.P., Garcia-Gonzalez M, and Ferrer J., *Prognostic value of interleukin-8 as a predictor of heart failure in patients with myocardial infarction and percutaneous intervention.* Int J Cardiol., 2005. **Article in Press**.

62. Akerstrom, T., et al., *Exercise induces interleukin-8 expression in human skeletal muscle.* J Physiol, 2005. **563**(Pt 2): p. 507-16.

63. Peake, J.M., et al., *Exercise-induced muscle damage, plasma cytokines, and markers of neutrophil activation.* Med Sci Sports Exerc, 2005. **37**(5): p. 737-45.

64. Croisier, J.L., et al., *Effects of training on exercise-induced muscle damage and interleukin 6 production.* Muscle Nerve, 1999. **22**(2): p. 208-12.

65. Pedersen, B.K., et al., *The metabolic role of IL-6 produced during exercise: is IL-6 an exercise factor?* Proc Nutr Soc, 2004. **63**(2): p. 263-7.

66. Brenner, I.K., et al., *Impact of three different types of exercise on components of the inflammatory response.* Eur J Appl Physiol Occup Physiol, 1999. **80**(5): p. 452-60.

67. Camus, G., et al., *Mild endotoxaemia and the inflammatory response induced by a marathon race.* Clin Sci (Lond), 1997. **92**(4): p. 415-22.

68. Chan, M.H., et al., *Cytokine gene expression in human skeletal muscle during concentric contraction: evidence that IL-8, like IL-6, is influenced by glycogen availability.* Am J Physiol Regul Integr Comp Physiol, 2004. **287**(2): p. R322-7.

69. Gannon, G.A., et al., *Circulating levels of peripheral blood leucocytes and cytokines following competitive cycling.* Can J Appl Physiol, 1997. **22**(2): p. 133-47.

70. MacIntyre, D., et al., *Presence of WBC, decreased strength, and delayed soreness in muscle after eccentric exercise.* J Appl Physiol, 1996. **80**(3): p. 1006-13.

71. LeMaitre, J.P., et al., *Change in circulating cytokines after 2 forms of exercise training in chronic stable heart failure.* Am Heart J, 2004. **147**(1): p. 100-5.

72. MacIntyre, D.L., et al., *Different effects of strenuous eccentric exercise on the accumulation of neutrophils in muscle in women and men.* Eur J Appl Physiol, 2000. **81**(1-2): p. 47-53.

73. Mackinnon, L., in *ACSM's Resources for Clinical Exercise Physiology.* 2002, Lippincott Williams & Wilkins. p. 192-205.

74. Bruunsgaard, H., et al., *Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage.* J Physiol, 1997. **499 (Pt 3)**: p. 833-41.

75. Gleeson, N., et al., *Effects of prior concentric training on eccentric exercise induced muscle damage.* Br J Sports Med, 2003. **37**(2): p. 119-25; discussion 125.

76. Hyatt, J.P. and P.M. Clarkson, *Creatine kinase release and clearance using MM variants following repeated bouts of eccentric exercise.* Med Sci Sports Exerc, 1998. **30**(7): p. 1059-65.

77. Nosaka, K. and P.M. Clarkson, *Changes in indicators of inflammation after eccentric exercise of the elbow flexors.* Med Sci Sports Exerc, 1996. **28**(8): p. 953-61.

78. Nosaka, K., M. Newton, and P. Sacco, *Muscle damage and soreness after endurance exercise of the elbow flexors.* Med Sci Sports Exerc, 2002. **34**(6): p. 920-7.

79. Nosaka K, S.K., Newton M, Sacco P., *How long does the protective effect on eccentric-induced muscle damage last?* Med Sci Sports Exerc, 2001. **33**: p. 1490-1495.

80. Warren, G.L., et al., *Excitation-contraction uncoupling: major role in contraction-induced muscle injury.* Exerc Sport Sci Rev, 2001. **29**(2): p. 82-7.

81. Pelsers M, H.W., Glatz J., *Fatty acid binding proteins as plasma markers of tissue injury.* Clinca Chimica Acta., 2004. **Article in Press.**

82. Van Nieuwenhoven F, K.A., Wodzig W, Hermens W, Kragen H, Maessen J et al., *Discrimination between myocardial and skeletal muscle injury by assessment of the plasma ratio of myoglobin over fatty acid binding protein.* Circulation, 1995. **92**: p. 2848-2854.

83. Azzazy, H.M., M.M. Pelsers, and R.H. Christenson, *Unbound free fatty acids and heart-type fatty acid-binding protein: diagnostic assays and clinical applications.* Clin Chem, 2006. **52**(1): p. 19-29.

84. Sorichter S, M.J., Koller A, Pelsers M, Puschendorf B, Glatz J., *Early assessment of exercise-induced skeletal muscle injury using plasma fatty acid binding protein.* Br J Sports Med, 1998. **32**: p. 121-124.

85. Gleeson M, A.J., Brooks S, Cave R, Lewis A, Griffiths H., *Haematological and acute-phase responses associated with delayed onset muscle soreness in humans.* Eur J Appl Physiol, 1995. **71**: p. 137-142.

86. Akimoto, T., et al., *Effect of brief maximal exercise on circulating levels of interleukin-12.* Eur J Appl Physiol, 2000. **81**(6): p. 510-2.

87. Margeli A, S.K., Tsironi M, Hantzi E, Matalas A, Vrettou C et al., *Dramatic elevation of interluekin-6 and acute-phase reactants in athletes participating in the ultradistance foot race spartathlon: severe systemic inflammatio and lipoprotein changes in protracted exercise.* J Clin End Met., 2005. **90**: p. 3914-3918.

88. Nieman, D.C., et al., *Influence of vitamin C supplementation on oxidative and immune changes after an ultramarathon.* J Appl Physiol, 2002. **92**(5): p. 1970-7.

89. Nieman, D.C., et al., *Cytokine changes after a marathon race.* J Appl Physiol, 2001. **91**(1): p. 109-14.

90. Pistilli E, N.D., Henson D, Kaminsky D, Utter A, Vinci D, Davis J, Fagooaga O and Nehlsen-Cannarella S., *Influence of age on the immune changes in runners following a marathon.* J Aging and Physical Activity, 2002. **10**.

91. Friden, J. and R.L. Lieber, *Structural and mechanical basis of exercise-induced muscle injury.* Med Sci Sports Exerc, 1992. **24**(5): p. 521-30.

92. Faulkner J, B.S., Zerba E., *Muscle atrophy and weakness with aging: contraction-induced injury as an underlying mechanism.* Biological Science and Medical Sciences., 1995. **50 (Spec)**: p. 124-129.

93. Grimby, G., *Muscle performance and structure in the elderly as studied cross-sectionally and longitudinally.* J Gerontol., 1995. **50 (Spec)**: p. 17-22.

94. Zerba, E., T.E. Komorowski, and J.A. Faulkner, *Free radical injury to skeletal muscles of young, adult, and old mice.* Am J Physiol, 1990. **258**(3 Pt 1): p. C429-35.

95. Devor S, F.J., *Regeneration of new fibres in muscles of old rats reduces contration-induced injury.* J Appl Physiol, 1999. **87**: p. 750-756.

96. Arbustini E, R.A., Pasotti M, Azan G, Opasich C, Campana C., *Cardiomyology: An attempt to link structural cardiac and skeletal muscle damage in patients with dilated cardiomyopathy.* Eur Heart J, 2004. **6**: p. F40-F53.

97. Warren, G.L., et al., *Eccentric contraction-induced injury in normal and hindlimb-suspended mouse soleus and EDL muscles.* J Appl Physiol, 1994. **77**(3): p. 1421-30.

98. Kasper C, T.L., Gaines J., *Skeletal muscle damage and recovery.* AACN Clin Issues, 2002. **13**: p. 237-247.

99. Anker, S.D., et al., *Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting.* J Am Coll Cardiol, 1997. **30**(4): p. 997-1001.

100. Toth, M.J., et al., *Immune activation is associated with reduced skeletal muscle mass and physical function in chronic heart failure.* Int J Cardiol, 2006. **109**(2): p. 179-87.

101. Anker S, M.R., *Insights into the pathogenesis of chronic heart failure: immune activation and cachexia.* Curr Opin Cardiol., 1999. **14**: p. 211-225.

102. Anker, S.D., et al., *Wasting as independent risk factor for mortality in chronic heart failure.* Lancet, 1997. **349**(9058): p. 1050-3.

103. Anker SD, C.T., Ponikowski P, Harrington D, Swan JW, Kox WJ et al., *Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia.* Circulation, 1997. **96**: p. 526-534.

104. Vescovo, G., et al., *Apoptosis in the skeletal muscle of patients with heart failure: investigation of clinical and biochemical changes.* Heart, 2000. **84**(4): p. 431-7.

105. Delagardelle, C., et al., *Strength/endurance training versus endurance training in congestive heart failure.* Med Sci Sports Exerc, 2002. **34**(12): p. 1868-72.

106. Delagardelle, C., et al., *Objective effects of a 6 months' endurance and strength training program in outpatients with congestive heart failure.* Med Sci Sports Exerc, 1999. **31**(8): p. 1102-7.

107. Gordon, A., et al., *Improved ventilation and decreased sympathetic stress in chronic heart failure patients following local endurance training with leg muscles.* J Card Fail, 1997. **3**(1): p. 3-12.

108. Pu C, J.M., Forman D, Hausforff J, Roubenoff R, Foldvari M, Fielding R, Singh M., *Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure.* J Appl Physiol, 2001. **90**: p. 2341-2350.

109. van den Berg-Emons R, B.A., Bussmann H, Sam H., *Does aerobic training lead to a more active lifestyle and improved quality of life in patients with chronic heart failure?* Eur J Heart Fail, 2004. **6**: p. 95-100.

110. *American College of Sports Medicine's Guidelines for Testing and Prescription.* 7th ed. ed. 2005: Lippincott Williams & Wilkins.

111. Meyer, K., et al., *Effects of short-term exercise training and activity restriction on functional capacity in patients with severe chronic congestive heart failure.* Am J Cardiol, 1996. **78**(9): p. 1017-22.

112. Akima, H., et al., *Effect of short-duration spaceflight on thigh and leg muscle volume.* Med Sci Sports Exerc, 2000. **32**(10): p. 1743-7.

113. Filippatos, G.S., et al., *Studies on apoptosis and fibrosis in skeletal musculature: a comparison of heart failure patients with and without cardiac cachexia.* Int J Cardiol, 2003. **90**(1): p. 107-13.

114. Hulsmann M, Q.M., Berger R, Crevanna R, Springer C, Nuhr M et al., *Muscle strength as a predictor of long-term survival in severe congestive heart failure.* Eur J Heart Fail, 2004. **6**: p. 101-107.

115. Schulze, P.C., et al., *Functional and morphological skeletal muscle abnormalities correlate with reduced electromyographic activity in chronic heart failure.* Eur J Cardiovasc Prev Rehabil, 2004. **11**(2): p. 155-61.

116. Meyer, K., *Exercise training in heart failure: recommendations based on current research.* Med Sci Sports Exerc, 2001. **33**(4): p. 525-31.

117. Meyer, K., et al., *Comparison of left ventricular function during interval versus steady-state exercise training in patients with chronic congestive heart failure.* Am J Cardiol, 1998. **82**(11): p. 1382-7.

118. Warburton, D.E., et al., *Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease.* Am J Cardiol, 2005. **95**(9): p. 1080-4.

119. Wollert, K.C. and H. Drexler, *The role of interleukin-6 in the failing heart.* Heart Fail Rev, 2001. **6**(2): p. 95-103.

120. Wollert, K.C. and H. Drexler, *Growth hormone and proinflammatory cytokine activation in heart failure. Just a new verse to an old sirens' song?* Eur Heart J, 2003. **24**(24): p. 2164-5.

121. Anker, S.D., et al., *Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure.* Eur Heart J, 1999. **20**(9): p. 683-93.

122. Kinugawa, T., et al., *Neurohormonal determinants of peak oxygen uptake in patients with chronic heart failure.* Jpn Heart J, 2003. **44**(5): p. 725-34.

123. Kinugawa, T., et al., *Interleukin-6 and tumor necrosis factor-alpha levels increase in response to maximal exercise in patients with chronic heart failure.* Int J Cardiol, 2003. **87**(1): p. 83-90.

124. Cicoira, M., et al., *High tumour necrosis factor-alpha levels are associated with exercise intolerance and neurohormonal activation in chronic heart failure patients.* Cytokine, 2001. **15**(2): p. 80-6.

125. Cicoira, M., et al., *Body mass index, prognosis and mode of death in chronic heart failure: results from the Valsartan Heart Failure Trial.* Eur J Heart Fail, 2007. **9**(4): p. 397-402.

126. Ostrowski, K., P. Schjerling, and B.K. Pedersen, *Physical activity and plasma interleukin-6 in humans--effect of intensity of exercise.* Eur J Appl Physiol, 2000. **83**(6): p. 512-5.

127. Pedersen, B.K., et al., *Searching for the exercise factor: is IL-6 a candidate?* J Muscle Res Cell Motil, 2003. **24**(2-3): p. 113-9.

128. Pedersen, B.K., et al., *Exercise and cytokines with particular focus on muscle-derived IL-6.* Exerc Immunol Rev, 2001. **7**: p. 18-31.

129. Pedersen, B.K., A. Steensberg, and P. Schjerling, *Muscle-derived interleukin-6: possible biological effects.* J Physiol, 2001. **536**(Pt 2): p. 329-37.

130. Steensberg, A., et al., *Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content.* J Physiol, 2001. **537**(Pt 2): p. 633-9.

131. Steensberg, A., et al., *Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6.* J Physiol, 2000. **529 Pt 1**: p. 237-42.

132. Ostrowski, K., et al., *A trauma-like elevation of plasma cytokines in humans in response to treadmill running.* J Physiol, 1998. **513 (Pt 3)**: p. 889-94.

133. Parthenakis R, P.A., Prassopoulos V, Papadimitriou E, Nikitovic D, Karkavitsa N, and Vardas P., *Relation of cardiac sympathetic innervation to proinflammatory cytokine levels in patients with heart failure secondary to idiopathic dilated cardiomyopathy.* Am J Cardiol, 2003. **91**: p. 1190-1194.

134. Kohut ML, M.D., Russell DW, Konopka DN, Cunnick JE, Franke WD et al., *Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of Beta-blockers, BMI, and psychosocial factors in older adults.* Brain, Behavior and Immunity, 2006. **20**: p. 210-209.

135. Larsen, A.I., et al., *Effect of aerobic exercise training on plasma levels of tumor necrosis factor alpha in patients with heart failure.* Am J Cardiol, 2001. **88**(7): p. 805-8.

136. Ostrowski K, R.T., Asp S, Schjerling P, Pedersen B., *Chemokines are elevated in plasma after strenuous exercise in humans.* Eur J Appl Physiol, 2001. **84**: p. 244-245.

137. Meyer, T., et al., *Anaerobic exercise induces moderate acute phase response.* Med Sci Sports Exerc, 2001. **33**(4): p. 549-55.

138. Chan, C.P., et al., *Rapid analysis of fatty acid-binding proteins with immunosensors and immunotests for early monitoring of tissue injury.* Biosens Bioelectron, 2005. **20**(12): p. 2566-80.

139. Mucci, P., et al., *Interleukins 1-beta, -8, and histamine increases in highly trained, exercising athletes.* Med Sci Sports Exerc, 2000. **32**(6): p. 1094-100.

140. Peake, J.M., et al., *Plasma cytokine changes in relation to exercise intensity and muscle damage.* Eur J Appl Physiol, 2005. **95**(5-6): p. 514-21.

141. Bruunsgaard, H., *Effects of tumor necrosis factor-alpha and interleukin-6 in elderly populations.* Eur Cytokine Netw, 2002. **13**(4): p. 389-91.

142. Anand, I.S., et al., *C-reactive protein in heart failure: prognostic value and the effect of valsartan.* Circulation, 2005. **112**(10): p. 1428-34.

143. Kavsak, P.A., et al., *Elevated C-reactive protein in acute coronary syndrome presentation is an independent predictor of long-term mortality and heart failure.* Clin Biochem, 2007. **40**(5-6): p. 326-9.

144. Krum, H., et al., *Statins and symptomatic chronic systolic heart failure: a post-hoc analysis of 5010 patients enrolled in Val-HeFT.* Int J Cardiol, 2007. **119**(1): p. 48-53.

145. Osman, R., et al., *Critical appraisal of C-reactive protein throughout the spectrum of cardiovascular disease.* Vasc Health Risk Manag, 2006. **2**(3): p. 221-37.

146. Rosen B, C.M., Khurram N, Bluemke D, Edvardsen T, Fernandes V, Lai S, Russell T and Lima J., *Relationship between c-reactive protein levels and regional left ventricular function in asymptomatic individuals.* J Am Coll Cardiol, 2007. **49**(5): p. 594-600.

147. Yin, W.H., et al., *Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure.* Am Heart J, 2004. **147**(5): p. 931-8.

148. Pelsers, *Fatty acid binding protein as plasma marker for tissue injury.*, in *Cardiovascular Research Institution*. 2004, Maastricht University: Maastricht. p. 181.

149. Remme, W.J. and K. Swedberg, *Comprehensive guidelines for the diagnosis and treatment of chronic heart failure. Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology.* Eur J Heart Fail, 2002. **4**(1): p. 11-22.

150. Pelsers, M.M., et al., *Brain- and heart-type fatty acid-binding proteins in the brain: tissue distribution and clinical utility.* Clin Chem, 2004. **50**(9): p. 1568-75.

151. Weber, M.A., et al., *Myoglobin plasma level related to muscle mass and fiber composition: a clinical marker of muscle wasting?* J Mol Med, 2007. **85**(8): p. 887-96.

152. Chen, I.W., et al., *Age-, sex-, and race-related differences in myoglobin concentrations in the serum of healthy persons.* Clin Chem, 1980. **26**(13): p. 1864-8.

153. Lakier Smith, L., *Overtraining, excessive exercise, and altered immunity: is this a T helper-1 versus T helper-2 lymphocyte response?* Sports Med, 2003. **33**(5): p. 347-64.

154. Close, G.L., et al., *The emerging role of free radicals in delayed onset muscle soreness and contraction-induced muscle injury.* Comp Biochem Physiol A Mol Integr Physiol, 2005. **142**(3): p. 257-66.

155. Jankowska, E.A., et al., *The 12-week progressive quadriceps resistance training improves muscle strength, exercise capacity and quality of life in patients with stable chronic heart failure.* Int J Cardiol, 2007.

156. Laederach-Hofmann, K., et al., *Comprehensive rehabilitation in chronic heart failure--better psycho-emotional status related to quality of life, brain natriuretic peptide concentrations, and clinical severity of disease.* Clin Invest Med, 2007. **30**(2): p. E54-62.

157. Meyer, K. and K. Laederach-Hofmann, *Effects of a comprehensive rehabilitation program on quality of life in patients with chronic heart failure.* Prog Cardiovasc Nurs, 2003. **18**(4): p. 169-76.

158. van Tol, B.A., et al., *Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis.* Eur J Heart Fail, 2006. **8**(8): p. 841-50.

159. Harrington, D., et al., *Skeletal muscle function and its relation to exercise tolerance in chronic heart failure.* J Am Coll Cardiol, 1997. **30**(7): p. 1758-64.

160. Harrington, D., et al., *Effect of reduced muscle bulk on the ventilatory response to exercise in chronic congestive heart failure secondary to idiopathic dilated and ischemic cardiomyopathy.* Am J Cardiol, 1997. **80**(1): p. 90-3.

161. Harrington, D. and A.J. Coats, *Skeletal muscle abnormalities and evidence for their role in symptom generation in chronic heart failure.* Eur Heart J, 1997. **18**(12): p. 1865-72.

162. Harrington, D. and A.J. Coats, *Mechanisms of exercise intolerance in congestive heart failure.* Curr Opin Cardiol, 1997. **12**(3): p. 224-32.

163. Buller, N.P., D. Jones, and P.A. Poole-Wilson, *Direct measurement of skeletal muscle fatigue in patients with chronic heart failure.* Br Heart J, 1991. **65**(1): p. 20-4.

164. Clark A, R.D., Arbuthnott K., *Relationship between isokinetic muscle strength and exercise capacity in chronic heart failure.* Int J Cardiol, 1997. **59**: p. 145-148.

165. Mathur S, M.D., Forster BB, Reid WR, *Influence of exercise-induced injury on knee extension torque in the presence of long-standing quadriceps atrophy: case report.* Physio Can., 2005. **57**: p. 305-313.

166. Qi, X., et al., *Inflammatory cytokine release in patients with unstable angina after coronary angioplasty.* Jpn Heart J, 2002. **43**(2): p. 103-15.

167. Bruun, J.M., et al., *Opposite regulation of interleukin-8 and tumor necrosis factor-alpha by weight loss.* Obes Res, 2002. **10**(6): p. 499-506.

168. Bruun, J.M., et al., *Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-alpha. Effect of weight loss in obese men.* Eur J Endocrinol, 2003. **148**(5): p. 535-42.

169. Hoffmann, E., et al., *Multiple control of interleukin-8 gene expression.* J Leukoc Biol, 2002. **72**(5): p. 847-55.

170. Sola, S., et al., *Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure.* J Am Coll Cardiol, 2006. **47**(2): p. 332-7.

171. Gielen, S., et al., *Exercise training in chronic heart failure: correlation between reduced local inflammation and improved oxidative capacity in the skeletal muscle.* Eur J Cardiovasc Prev Rehabil, 2005. **12**(4): p. 393-400.

172. Ostchega, Y., et al., *Isokinetic leg muscle strength in older americans and its relationship to a standardized walk test: data from the national health and nutrition examination survey 1999-2000.* J Am Geriatr Soc, 2004. **52**(6): p. 977-82.

173. Skelton, D.A., J. Kennedy, and O.M. Rutherford, *Explosive power and asymmetry in leg muscle function in frequent fallers and non-fallers aged over 65.* Age Ageing, 2002. **31**(2): p. 119-25.

174. Sunnerhagen, K.S., et al., *Muscle performance in an urban population sample of 40- to 79-year-old men and women.* Scand J Rehabil Med, 2000. **32**(4): p. 159-67.

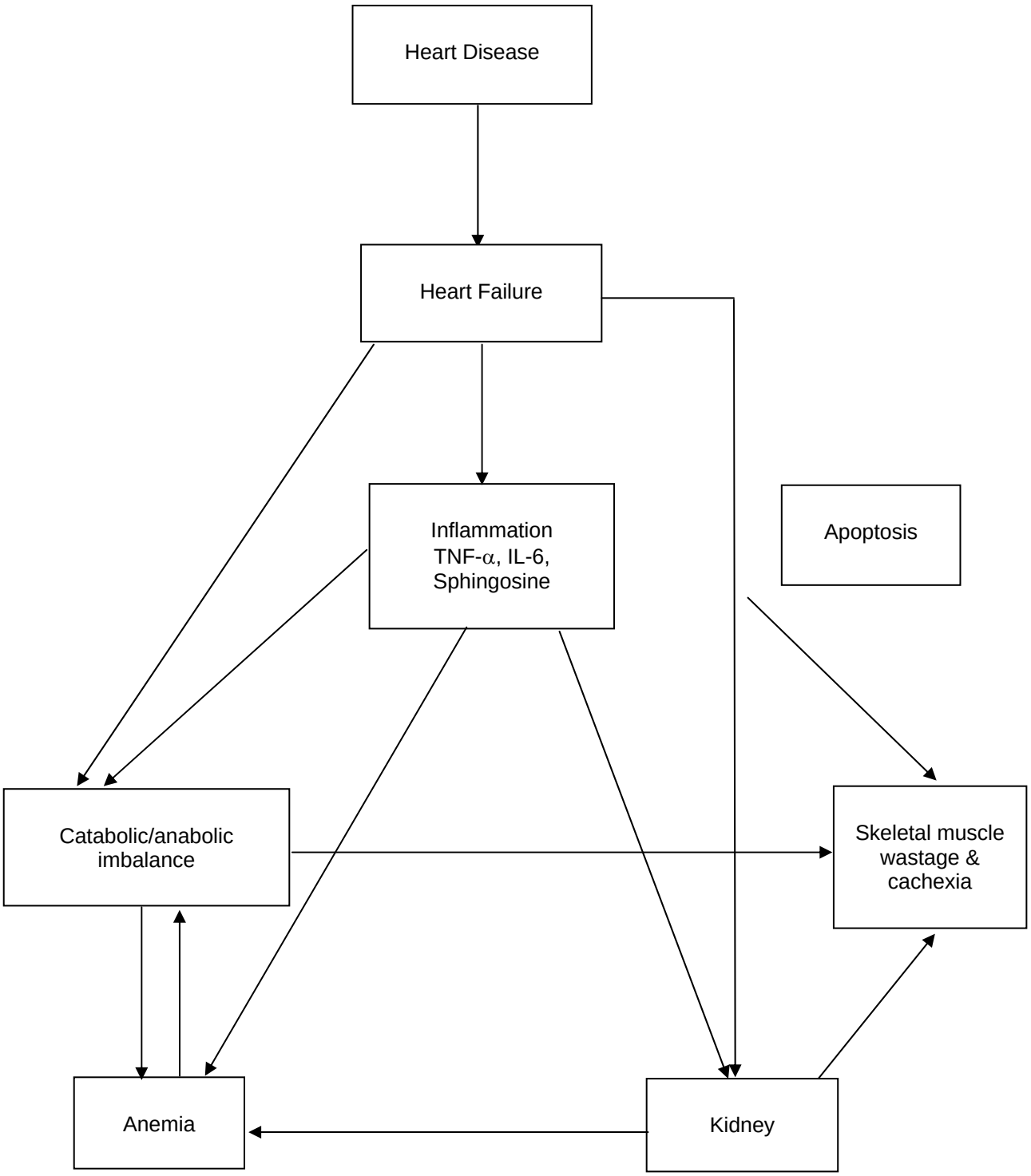
175. Mathur, S., et al., *Preservation of eccentric torque of the knee extensors and flexors in patients with COPD.* J Cardiopulm Rehabil Prev, 2007. **27**(6): p. 411-6.

176. Quittan, M., et al., *Isokinetic strength testing in patients with chronic heart failure--a reliability study.* Int J Sports Med, 2001. **22**(1): p. 40-4.

177. Toumi, H. and T.M. Best, *The inflammatory response: friend or enemy for muscle injury?* Br J Sports Med, 2003. **37**(4): p. 284-6.

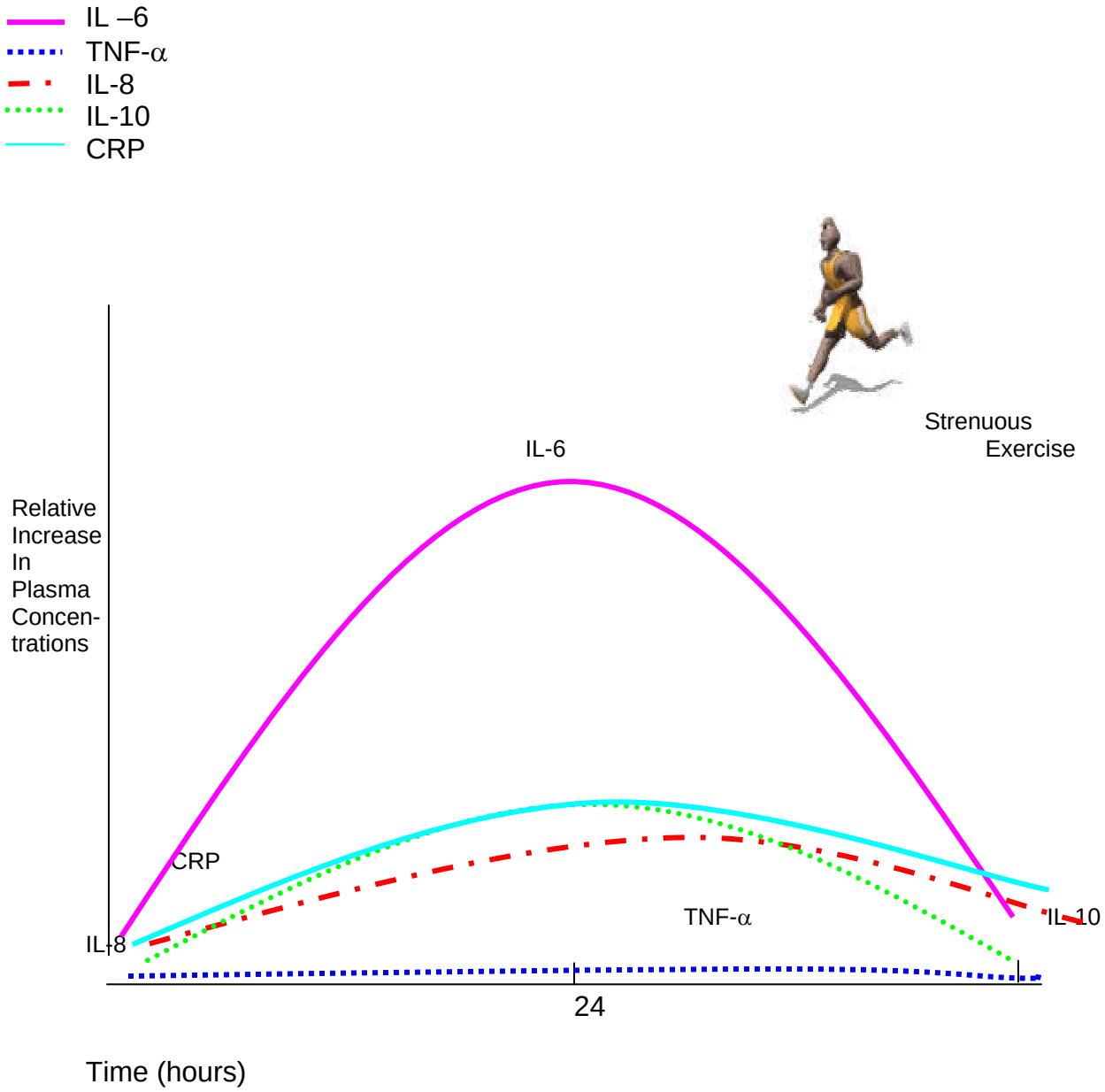
APPENDIX 1

Inflammation, apoptosis and catabolic/anabolic imbalance: a possible link with multiorgan damage in HF. [42]



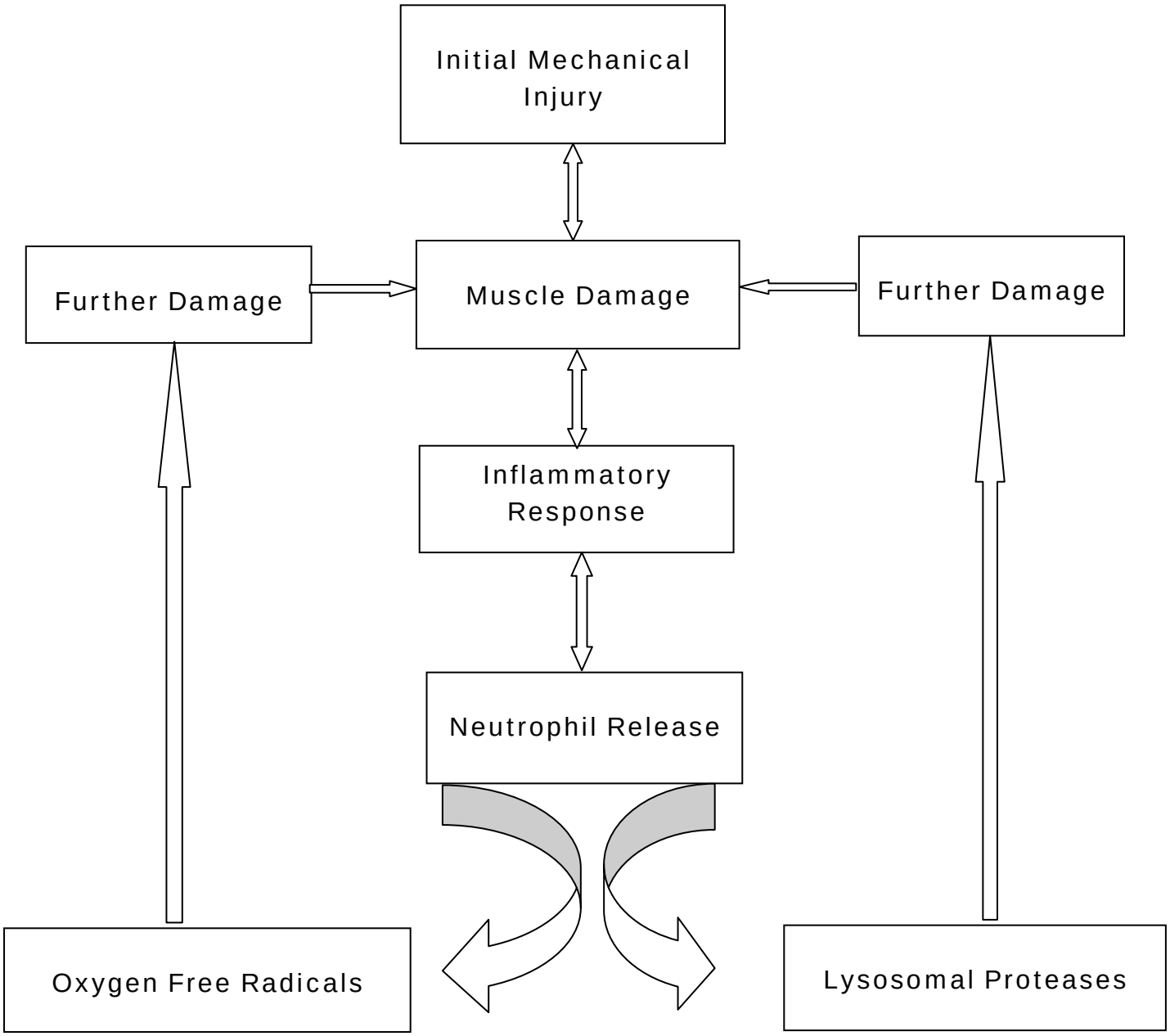
APPENDIX 2

Plasma Cytokine Response to Strenuous Exercise [59]



APPENDIX 3

Proposed Mechanism of the Relation between the Inflammatory Response to Mechanical Injury and Further Muscle Damage.



The initial mechanically induced damage produces myofibre tearing and inflammatory cell infiltration. Neutrophils may promote further damage through the release of oxygen free radicals and lysosomal proteases and elastases.[177]