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

by

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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.
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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] Prevalence 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 pathophysiological 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-\(\alpha\)) 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-\(\alpha\), 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-\(\alpha\) can cause hyperinflammatory reactions and tissue injury and is associated with non-survival in septic patients.[45] Excessive TNF-\(\alpha\) 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
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. Some researchers have found no change in serum/plasma markers of IL-8 following concentric exercise alone, e.g., bicycle ergometry or rowing. 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.

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. 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. 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”.

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. Although it is not clear, some studies have shown that IL-10 levels can increase up to 27-fold following strenuous 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. 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.
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 “nondematous 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-\( \alpha \), 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™) 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 VO2 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/VO2 reserve and 2 minute recovery bouts at 40% Heart Rate Reserve/VO2 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™ 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).
Interleukin-6 (IL-6) as a function of time. Means +/- SD.
* main effect for Immediate Post value (p < 0.05).

<table>
<thead>
<tr>
<th>Sampling Time</th>
<th>Interleukin-6 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
</tr>
<tr>
<td>Immediate Post</td>
<td>3</td>
</tr>
<tr>
<td>6 hours</td>
<td>4</td>
</tr>
<tr>
<td>24 hours</td>
<td>8</td>
</tr>
<tr>
<td>48 hours</td>
<td>4</td>
</tr>
</tbody>
</table>

Steady State

Interval

Figure 1: Interleukin 6
Figure 2: Interleukin 8

Interleukin-8 (IL-8) as a function of time. Means +/- SD.

<table>
<thead>
<tr>
<th>Sampling Time</th>
<th>Interleukin-8 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
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</tr>
<tr>
<td>Immediate Post</td>
<td>0.0</td>
</tr>
<tr>
<td>6 hours</td>
<td>0.5</td>
</tr>
<tr>
<td>24 hours</td>
<td>1.0</td>
</tr>
<tr>
<td>48 hours</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- Steady State
- Interval
Figure 3: Interleukin 10

Interleukin-10 (IL-10) as a function of time.
Means +/- SD.
* main effect for 24 Hour Post value (p < 0.05).

<table>
<thead>
<tr>
<th>Sampling Time</th>
<th>Interleukin-10 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
</tr>
<tr>
<td>Immediate Post</td>
<td>1</td>
</tr>
<tr>
<td>6 hours</td>
<td>2</td>
</tr>
<tr>
<td>24 hours</td>
<td>3</td>
</tr>
<tr>
<td>48 hours</td>
<td>4</td>
</tr>
</tbody>
</table>

Steady State
Interval

Graph showing Interleukin-10 levels over time with means +/- standard deviation.
Figure 4: Tumor Necrosis Factor alpha

Tumor Necrosis Factor - alpha (TNF-a) as a function of time. Means +/- SD.
Figure 5: C-Reactive Protein

C-Reactive Protein (CRP) as a function of time. Means +/- SD.
Figure 6: Heart Type Fatty Acid Binding Protein

H-Type Fatty Acid Binding Protein (H-FABP) as a function of time. Means +/- SD.
Figure 7: Myoglobin

Myoglobin (MGB) as a function of time. Means +/- SD. * main effect for 6 Hours Post value (p < 0.05).

Sampling Time

Baseline  Immediate Post  6 hours  24 hours  48 hours

Myoglobin (pg/mL)

Steady State

Interval
Figure 8: Myoglobin to H-FABP Ratio

Delayed Onset of Muscle Soreness (DOMS) as a function of time. Means +/- SD.

Sampling Time

Delayed Onset of Muscle Soreness (DOMS)

Steady State

Interval
Figure 10: Lower Extremity Functional Scale

Lower Extremity Functional Scale (LE Fxn) as a function of time. Means +/- SD.

* main effect for 24 Hour & 48 Hour Post value (p < 0.05).

<table>
<thead>
<tr>
<th>Sampling Time</th>
<th>Lower Extremity Functional Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30</td>
</tr>
<tr>
<td>Immediate Post</td>
<td>40</td>
</tr>
<tr>
<td>6 hours</td>
<td>50</td>
</tr>
<tr>
<td>24 hours</td>
<td>60</td>
</tr>
<tr>
<td>48 hours</td>
<td>70</td>
</tr>
</tbody>
</table>

- **Steady State**
- **Interval**
Figure 11: Peak Concentric Muscle Torque

Peak Concentric Torque as a function of time. Means +/- SD.
* main effect for Immediate Post value (p < 0.05).
Figure 12: Peak Eccentric Muscle Torque

Peak Eccentric Torque as a function of time. Means +/- SD. * main effect for Immediate Post value (p < 0.05).
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-$\alpha$ 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-$\alpha$. [55] Tumor Necrosis Factor alpha has direct inhibitory effects on insulin signaling and the ability of IL-6 to inhibit TNF-$\alpha$ production may represent a mechanism whereby exercise enhances insulin sensitivity.[55] In the current study, IL-6 (but not TNF-$\alpha$) 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
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.
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% VO₂max), high intensity (85% VO₂max) 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$_{2\text{max}}$).[126, 132] Kinugawa et al found an increase in both IL-6 and TNF-$\alpha$ 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-$\alpha$ 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-$\alpha$ levels in either the SS or the IT group at any time point following the exercise bout. Suzuki et al state that TNF-$\alpha$ is rapidly cleared from the circulation into the urine as a result of a short half-life (14 to 18 minutes).[44] If TNF-$\alpha$ 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-$\alpha$ 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-$\alpha$ 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™, 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Steady-State Training Group (n=7)</th>
<th>Interval Training Group (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.1 ± 6.7</td>
<td>57.9 ± 9.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.7 ± 5.3</td>
<td>177.7 ± 5.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>96.3 ± 23.4</td>
<td>96.0 ± 13.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.2 ± 5.34</td>
<td>30.5 ± 4.6</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>.236 ± .069</td>
<td>.300 ± .108</td>
</tr>
<tr>
<td>VO₂peak (mL·kg⁻¹·min⁻¹)</td>
<td>14.9 ± 5.3</td>
<td>12.43 ± 3.8</td>
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<tr>
<td>Diabetes Mellitus</td>
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<tr>
<td>Type 1 DM</td>
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<tr>
<td>Type 2 DM</td>
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<td>1</td>
</tr>
<tr>
<td>New York Heart Association Class</td>
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<tr>
<td>Class 1</td>
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<tr>
<td>Class 2</td>
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<td>5</td>
</tr>
<tr>
<td>Class 3a</td>
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</tr>
<tr>
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<td>Fibrillation/Flutter</td>
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<td>HF Onset (years)</td>
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<td>&lt; 1 year</td>
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<td>1 – 5 years</td>
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<td>3</td>
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<td>6 – 10 years</td>
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<td>2</td>
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<td>11 – 20 years</td>
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<td>NT-Pro BNP (pg/ml)</td>
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<td>500 – 1000</td>
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<td>&gt; 10,000</td>
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<td>Hemoglobin</td>
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<tr>
<td>Beta Blocker (CoReg, Atenolol, Monocor,</td>
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<td>6</td>
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<tr>
<td>Drug Category</td>
<td>Count</td>
<td>Standard Deviation</td>
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<td>Bisoprolol</td>
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<td>ARB (Spironolactone, Atacand)</td>
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<td>Digoxin</td>
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<td>Amiodarone (Antiarrhythmic)</td>
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<td>Cholesterol-lowering (Lipitor, Crestor, Simvastatin)</td>
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<td>Anti-coagulant (Coumadin)</td>
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<td>Plavix</td>
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<td>Ace Inhibitor (Altace)</td>
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<td>Calcium Channel Blocker (Captopril, Accupril, Norvasc)</td>
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<td>Vasodilators, (Nitroglycerine: patch, spray, tablets; Hydralazine)</td>
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<tr>
<td>Hyperglycemic Agents (Metformin, Glyburide, Insulin)</td>
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<td>3</td>
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<tr>
<td>Other (Testosterone, Eltroxin, Synthroid, Pantolec, Allopurinol, Effexor, Welbutrin, Celexa, Cholchicine, Valium, Halcion)</td>
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<td>3</td>
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</table>

Values are means ± SD
## Table 2. Training Workloads
### Individual Data
#### Steady-State Training Group

<table>
<thead>
<tr>
<th>Participant</th>
<th>Exercise Prescription</th>
<th>Actual Workloads</th>
<th>Heart Rates</th>
<th>Rating of Perceived Exertion</th>
<th>Watts</th>
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<tbody>
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<td></td>
<td>65% Heart Rate Reserve</td>
<td>65% Peak Watts</td>
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<tr>
<td>01</td>
<td>122 bpm</td>
<td>20 Watts</td>
<td>105 – 119 bpm</td>
<td>3 – 4</td>
<td>20 Watts</td>
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<tr>
<td>02</td>
<td>113 bpm</td>
<td>36 Watts</td>
<td>107 – 108 bpm</td>
<td>3.5</td>
<td>36 Watts</td>
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<tr>
<td>03</td>
<td>133 bpm</td>
<td>78 Watts</td>
<td>92 – 100 bpm</td>
<td>3 – 4</td>
<td>78 Watts</td>
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<tr>
<td>04</td>
<td>89 bpm</td>
<td>39 Watts</td>
<td>93 – 102 bpm</td>
<td>4 – 7</td>
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<tr>
<td>10</td>
<td>103 bpm</td>
<td>92 Watts</td>
<td>115 – 123 bpm</td>
<td>4 – 5</td>
<td>92 Watts</td>
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<tr>
<td>15</td>
<td>99 bpm</td>
<td>52 Watts</td>
<td>99 – 113 bpm</td>
<td>3.5 – 6</td>
<td>52 Watts</td>
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<tr>
<td>17</td>
<td>98 bpm</td>
<td>65 Watts</td>
<td>98 – 101 bpm</td>
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<td>65 Watts</td>
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#### Interval Training Group

<table>
<thead>
<tr>
<th>Participant</th>
<th>Exercise Prescription</th>
<th>Actual Workloads</th>
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<tbody>
<tr>
<td></td>
<td>40% Heart Rate Reserve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90% Heart Rate Reserve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40% Peak Watts &amp; 90% Peak Watts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart Rates</td>
<td>Rating of Perceived Exertion</td>
</tr>
<tr>
<td>05</td>
<td>77 bpm</td>
<td>14 Watts</td>
</tr>
<tr>
<td>06</td>
<td>79 bpm</td>
<td>34 Watts &amp; 77 Watts</td>
</tr>
<tr>
<td>07</td>
<td>74 bpm</td>
<td>20 Watts &amp; 44 Watts</td>
</tr>
<tr>
<td>08</td>
<td>74 bpm</td>
<td>42 Watts &amp; 94 Watts</td>
</tr>
<tr>
<td>11</td>
<td>92 bpm</td>
<td>32 Watts &amp; 72 Watts</td>
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<tr>
<td>12</td>
<td>No target Range</td>
<td>29 Watts &amp; 65 Watts</td>
</tr>
<tr>
<td>13</td>
<td>64 bpm</td>
<td>48 Watts &amp; 108 Watts</td>
</tr>
</tbody>
</table>

* Heart Rates elevated throughout interval
<table>
<thead>
<tr>
<th>Group Data</th>
<th>Training Watts</th>
<th>Mean</th>
<th>Standard Deviation</th>
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<tr>
<td>All Participants</td>
<td>54.07143</td>
<td>19.7424</td>
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<tr>
<td>Steady-State Group</td>
<td>56.0000</td>
<td>23.2451</td>
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<td>Interval Training Group</td>
<td>52.1429</td>
<td>17.1894</td>
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</tbody>
</table>
Table 3. Correlation Matrix

* Marked correlations are significant at p < .05000

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<tr>
<th></th>
<th>EF</th>
<th>VO2</th>
<th>Ht</th>
<th>Wt</th>
<th>NT Pro BNP</th>
<th>Age</th>
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</thead>
<tbody>
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<td>EF</td>
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<td>-0.12</td>
<td>-0.29</td>
<td>0.46</td>
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<tr>
<td>VO2</td>
<td>0.22</td>
<td>1.00</td>
<td>-0.42</td>
<td>-0.63</td>
<td>0.29</td>
<td>0.64</td>
</tr>
<tr>
<td>Ht</td>
<td>-0.12</td>
<td>-0.42</td>
<td>1.00</td>
<td>0.59</td>
<td>0.36</td>
<td>-0.01</td>
</tr>
<tr>
<td>Wt</td>
<td>-0.29</td>
<td>-0.63</td>
<td>0.59</td>
<td>1.00</td>
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<tr>
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<tr>
<td>NT PRO</td>
<td>0.46</td>
<td>0.29</td>
<td>0.36</td>
<td>-0.47</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>BNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*0.65</td>
</tr>
<tr>
<td>Age</td>
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<td>-0.01</td>
<td>-0.67</td>
<td>*0.65</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Marked correlations are significant at p < .05000

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>FABP</th>
<th>IL6</th>
<th>IL8</th>
<th>IL10</th>
<th>MGB</th>
<th>Ratio</th>
<th>TNFa</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.00</td>
<td>0.00</td>
<td>*0.59</td>
<td>*0.74</td>
<td>0.35</td>
<td>-0.28</td>
<td>-0.23</td>
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</tr>
<tr>
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<td>1.00</td>
<td>-0.08</td>
<td>0.19</td>
<td>0.13</td>
<td>0.44</td>
<td>-0.22</td>
<td>-0.06</td>
</tr>
<tr>
<td>IL6</td>
<td>*0.59</td>
<td>-0.08</td>
<td>1.00</td>
<td>0.44</td>
<td>0.13</td>
<td>-0.01</td>
<td>-0.17</td>
<td>0.38</td>
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<tr>
<td>IL8</td>
<td>*0.74</td>
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<td>-0.19</td>
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<tr>
<td>IL10</td>
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<td>0.13</td>
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<td>0.02</td>
<td>0.14</td>
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<tr>
<td>MGB</td>
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<td>0.44</td>
<td>-0.01</td>
<td>-0.08</td>
<td>0.02</td>
<td>1.00</td>
<td>0.52</td>
<td>-0.05</td>
</tr>
<tr>
<td>Ratio</td>
<td>-0.23</td>
<td>-0.22</td>
<td>-0.17</td>
<td>-0.19</td>
<td>0.14</td>
<td>0.52</td>
<td>1.00</td>
<td>-0.31</td>
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<tr>
<td>TNFa</td>
<td>0.29</td>
<td>-0.06</td>
<td>0.38</td>
<td>0.20</td>
<td>0.09</td>
<td>-0.05</td>
<td>-0.31</td>
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Table 4. Baseline levels of Cytokines (Values are means ± SD)

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Study Participants (N = 14) (males)</th>
<th>Values in Healthy Population</th>
<th>Values in CHF population</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (ug/mL)</td>
<td>9.3805 +/- 14.9641</td>
<td>Plasma 2.0 ug/mL +/- .56 (males)[100]</td>
<td>Plasma 5.11 +/- 1.26 (males)[100]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serum 3.57 +/- 2.7 (females also)[71]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serum 19 +/- 4 ug/mL (males &amp; females)[170]</td>
</tr>
<tr>
<td>IL 6 (pg/ml)</td>
<td>3.043 +/- 2.276</td>
<td>Plasma 31 +/- 37 (1 female)[38]</td>
<td>Plasma 23 +/- 22 (1 female)[38]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum 1.3 +/- .2 (age matched controls mean age 57.2 +/- 1.7 (females also)[123]</td>
<td>Serum 2.4 +/- .3 (females also)[123]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum 1.2 +/- .4 [171] (males)[100]</td>
<td>Serum 1.5 +/- .6 [171]</td>
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<tr>
<td></td>
<td></td>
<td>Plasma 1.92 +/- .38 (males)[121]</td>
<td>Additional plasma levels:</td>
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<tr>
<td></td>
<td></td>
<td>Plasma .98 +/- .19 (males)[121]</td>
<td>Serum 9.82 +/- 14.6 (females also)[71]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma 1.47 +/- .23 (males &amp; females)[133]</td>
<td>Plasma non-cachectic CHF 2.81 +/- .42 (males)[121]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma 1.1 +/- .8 (males age 62)[10]</td>
<td>Plasma cachectic CHF 3.92 +/- .70 (males)[121]</td>
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<tr>
<td>IL 8 (pg/ml)</td>
<td>0.468 +/- 0.665</td>
<td>Plasma ~3.8 – 4.0 +/- .8 [139]</td>
<td>Plasma 4.6 +/- 2.7 (males &amp; females age 56 +/- 9)[133]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma – not detectable (males 62 years)[10]</td>
<td>Serum 1.7 pg/ml +/- .14 (males &amp; females)[170]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasma 4.6 +/- 3.9 (males age 67)[10]</td>
</tr>
<tr>
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<td>Plasma 12.7 +/- 9.2 (males age 67)[10]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Serum 15.2 +/- 3.5 &amp; 25.9 +/- 4.2 after AMI (males &amp; females)[61]</td>
</tr>
<tr>
<td><strong>IL 10 (pg/ml)</strong></td>
<td><strong>Plasma</strong> 5.2 +/- 2.3 (males &amp; females mean age 63.6)[43]</td>
<td><strong>Plasma</strong> 2.3 +/- 1.9 (males &amp; females) (mean age 66.9 +/- 12.6; class 2 – 4)[43]</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>1.815 +/- 1.389</strong></td>
<td><strong>Plasma</strong> 2.5 +/- 1.8 [43]</td>
<td><strong>Plasma</strong> 6.5 +/- 2.9 [43]</td>
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<tr>
<td><strong>5.905 +/- 3.278</strong></td>
<td><strong>Plasma</strong> 1.4 +/- 0.4 (1 female)[38]</td>
<td><strong>Plasma</strong> 2.72 +/- 1.5 (1 female)[38]</td>
<td></td>
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<tr>
<td></td>
<td><strong>Serum</strong> 2.7 +/- 0.2 [123]</td>
<td><strong>Serum</strong> 3.8 +/- .2 [123]</td>
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<tr>
<td></td>
<td><strong>Serum</strong> .8 (males)[124]</td>
<td><strong>Serum</strong> 2.0 (males)[124]</td>
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</tr>
<tr>
<td></td>
<td><strong>Serum</strong> .9 +/- .2 [33]</td>
<td><strong>Serum</strong> 2.2 +/- .2 [33]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Plasma</strong> 1.52 +/- .15 (males)[100]</td>
<td><strong>Plasma</strong> 1.91 +/- .30 (males)[100]</td>
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<td><strong>Plasma</strong> 7.0 +/- .8 (males) [121]</td>
<td><strong>Serum</strong> 8.43 +/- 3.6 (females also)[71]</td>
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<td></td>
<td><strong>Plasma</strong> 1.5 +/- .12 (males &amp; females age 56 +/- 9)[133]</td>
<td><strong>Plasma non-cachectic CHF</strong> 6.9 +/- .8 (males)[121]</td>
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<tr>
<td></td>
<td><strong>Plasma</strong> 7.3 +/- 3 (Larsen et al) (males)</td>
<td>Plasma cachectic CHF 14.6 +/- 2.8 (males)[121]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Plasma</strong> 28.7 +/- 18.5 (males age 67)[135]</td>
<td><strong>Plasma</strong> 14.6 +/- .9 (males &amp; females age 56 +/- 9)[133]</td>
<td></td>
</tr>
<tr>
<td><strong>H - FABP (ug/L)</strong></td>
<td><strong>Plasma</strong> <em>6.0 ug/L</em></td>
<td><strong>Plasma</strong> non-cachectic CHF 14.6 +/- 2.8 (males)[121]</td>
<td></td>
</tr>
<tr>
<td>11.939 +/- 21.356</td>
<td>Plasma 60 ug/L</td>
<td><strong>Plasma</strong> <em>11.0 ug/L</em> [148]</td>
<td></td>
</tr>
<tr>
<td><strong>Myoglobin (ug/L)</strong></td>
<td><strong>Plasma</strong> 80 ug/L +/- 77.45 (Pelsers unpublished data)</td>
<td><strong>Plasma</strong> <strong>11.0 ug/L</strong> [148]</td>
<td></td>
</tr>
<tr>
<td>90.353 +/- 106.464</td>
<td><strong>Plasma</strong> 80 ug/L +/- 77.45 (Pelsers unpublished data)</td>
<td><strong>Plasma</strong> <strong>11.0 ug/L</strong> [148]</td>
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<tr>
<td><strong>Myoglobin:H- FABP Ratio</strong></td>
<td><strong>Heart muscle damage Mg:FABP ratio 2-10[148]</strong></td>
<td><strong>Skeletal muscle damage Mg:FABP ratio 20-70 (depending on type of muscle)[148]</strong></td>
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<tr>
<td>7.6</td>
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* Cut-off value for healthy subjects

**Median level in total CHF group (Pelsers, 2004)
<table>
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<th>Study Participants (N = 14 Males)</th>
<th>Comparison to Healthy Population</th>
<th>Comparison to HF population</th>
<th>Comparison to COPD Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant Leg - 109 (Nm) +/- 22</td>
<td>Toth et al, 2005 (10 Males)</td>
<td>Toth et al 10, 2005 (10 Males)</td>
<td>Mathur et al, 2007 (9 males, 11 women average age 68 years)</td>
</tr>
<tr>
<td>Angular speed 30° per second</td>
<td>Dominant Leg - 121 (Nm) +/- 11</td>
<td>Dominant Leg - 88 (Nm) +/- 10</td>
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</tr>
<tr>
<td>100° to 20° knee flexion (90° ROM)</td>
<td>Angular speed 90° per sec 0° to 90°</td>
<td>Angular speed 90° per sec 0 to 90° ROM (extension to flexion)</td>
<td>Dominant Leg 61 (Nm) +/- 18</td>
</tr>
<tr>
<td>Ostcheaga et al (411 non-Hispanic white males)</td>
<td>[100]</td>
<td>[100]</td>
<td>Angular speed of 30° per second</td>
</tr>
<tr>
<td>Skelton et al, 2002 (women “nonfallers” &gt; 65 years of age)</td>
<td>Dominant Leg 144 (Nm)</td>
<td>Non-Dominant Leg 115.6 (Nm) +/- 7.2</td>
<td>[172]</td>
</tr>
<tr>
<td>Weakest Leg 162.5 (Nm) +/- 44.6</td>
<td>Angular speed 60° per second</td>
<td>Angular speed of 60° per second</td>
<td>[176]</td>
</tr>
<tr>
<td>ROM not stated</td>
<td>ROM not stated</td>
<td>100° to 20° knee flexion (90° ROM)</td>
<td></td>
</tr>
<tr>
<td>Sunnerhagen et al, 2000 (males 40 – 79 years)</td>
<td>Clark et al, 1997 (10 males?)</td>
<td>Both Dominant &amp; Nondominant Leg 123.6 (Nm) +/- 30</td>
<td></td>
</tr>
<tr>
<td>Right Leg:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 – 49 years: 198 (Nm)</td>
<td></td>
<td>Angular speed of 30° per second</td>
<td></td>
</tr>
<tr>
<td>50 – 59 years: 163 (Nm)</td>
<td></td>
<td>80° to 10° knee flexion</td>
<td></td>
</tr>
<tr>
<td>60 – 69 years: 157 (Nm)</td>
<td></td>
<td></td>
<td>[164]</td>
</tr>
</tbody>
</table>
### 70 – 79 years: 136 (Nm)

- Angular speed 60° per second
- ROM not stated

[174]

**Mathur et al, 2007**

- (9 males, 11 females)

<table>
<thead>
<tr>
<th>Leg</th>
<th>Torque (Nm) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant Leg</td>
<td>85 (Nm) ± 24</td>
</tr>
<tr>
<td>Angular speed</td>
<td>30° per second</td>
</tr>
<tr>
<td>100° to 20° knee flexion</td>
<td>(90° ROM)</td>
</tr>
</tbody>
</table>

[175]

**Clark et al, 1997**

- (10 ?males?)

<table>
<thead>
<tr>
<th>Leg</th>
<th>Torque (Nm) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both Dominant &amp; Nondominant Leg</td>
<td>146.8 (Nm) ± 40</td>
</tr>
<tr>
<td>Angular speed</td>
<td>30° per second</td>
</tr>
<tr>
<td>80° to 10° knee flexion</td>
<td></td>
</tr>
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</table>

[164]
Table 6. Peak Eccentric Isokinetic Torque Knee Extensors (Values are means ± SD)

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


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

APPENDIX 1

Heart Disease

Heart Failure

Inflammation
TNF-α, IL-6,
Sphingosine

Catabolic/anabolic imbalance

Anemia

Kidney

Apoptosis

Skeletal muscle wastage & cachexia
APPENDIX 2

Plasma Cytokine Response to Strenuous Exercise [59]

IL-6
TNF-α
IL-8
IL-10
CRP

Strenuous
Exercise

Relative Increase
In Plasma
Concentrations

Time (hours)

24

IL-6
CRP
TNF-α
IL-10
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]