

Chapter 2:
Review of Literature

Introduction

Congestive heart failure (CHF) is one of the leading causes of morbidity and mortality in the United States. One of the hallmark syndromes is a significant reduction in exercise capacity (Coats, 1996). This reduction in exercise capacity has been attributed to various pathological changes in the patient during the development of this condition. CHF has been currently defined 'as a reduction in the ability of the myocardium to meet the metabolic needs of the body' (Schoen 1994). However, to view this condition in this simplistic manner, diminishes the severity of the changes that occur to many of the tissues during CHF. For instance, the previous statement does not address that fact that there are multiple changes in the types of collagen expressed in the myocardium (Schoen, 1994), nor does it address the fact that there are large increases in the occurrence of peripheral edema (Schoen, 1994). This definition only addresses the condition from the perspective of one organ (*i.e* heart), whereas a CHF patient will have alterations in a variety of tissues, which can affect the functional capacity of the individual. For example, there are known changes in the lungs and vasculature, which could affect the oxygen delivery and blood flow, respectively. Therefore, when one is attempting to understand this disease it should include consideration of tissues other than just the myocardium.

One of the most common clinical signs of CHF is a significant reduction in exercise capacity, yet currently there is no clear reason why this occurs. The early onset of fatigue has often been attributed to a reduction in peripheral blood flow, secondary to a dysfunctional myocardium. However, recent evidence suggests that this may be too simplistic an explanation (Volterrani et al. 1994, Lunde et al. 1998). This review will attempt to describe evidence of alterations in skeletal muscle due to CHF. It will also

attempt to explain why these alterations could possibly contribute to the reduction in exercise capacity. This review will also address the possibility of reversing the changes in skeletal muscle through exercise training to recover some of the functional capacity.

Myocardium and exercise capacity

Numerous studies show that many tissues are functionally and structurally changed during CHF (Delp et al. 1997, Bernocchi et al. 1996, Schoen, F. J. 1994), yet few tissues are more studied frequently than the myocardium. The myocardium shows many dramatic changes during CHF, such as ventricular hypertrophy and myofilament disarray (Schoen, 1994). CHF is characterized by a diminished cardiac output, which seems to be due to a decreased distensibility and decreased force production of the myocardium (Schoen, 1994). Some have suggested that the reduction in force production occurs due to a decrease in the number of active cross-bridges, thereby reducing overall force output of the myocardium, which results in a reduction in cardiac output. Also, there is a concurrent increase in the amount of fibrosis, which could affect the distensibility of the heart. This increase in fibrosis is indicated by the increase in the amount of collagen expressed within the myocardium. Elevated amounts of collagen significantly decrease the distensibility of the myocardium creating a situation in which the myocardium is less elastic. Therefore, if there is a reduction in the force generating capacity due to fibrosis or an alteration in the contractile machinery, it may cause a reduction in cardiac output. A reduction in cardiac output can lead to a reduction in blood delivered to the peripheral tissues during exercise, creating a situation in which the skeletal muscle is receiving inadequate oxygen and other nutrients. It should also be noted that in a healthy patient, cardiac output does have a

significant correlation with exercise capacity demonstrating that there is an existing relationship between exercise and a healthy myocardium (Franciosa et al. 1981, Coats, 1996). Therefore, the changes in the myocardium that occur during CHF would significantly contribute to the altered exercise capacity of the patient. However, as previously stated, during CHF there are multiple changes occurring to multiple tissues. Therefore changes in other tissues may also be contributing to a reduction in exercise capacity.

Is the heart really the limiting factor?

Many have suggested that it would be too simplistic to consider that reductions in functional or exercise capacity are due to altered functioning of the myocardium. In fact, it has been well documented that various indicators of cardiovascular function (e.g. ejection fraction) do not correlate well with overall exercise capacity in CHF patients, even though there are strong correlations in healthy subjects (Volteranni et al. 1994). For example, Franciosa et al. (1981) demonstrated that measurements of left ventricular performance did not correlate well with exercise duration times in CHF patients. More specifically their study showed that exercise duration times and ejection fraction did not correlate ($r=-0.06$). Subsequent studies have demonstrated similar effects in that many measurements of hemodynamic function did not show significant correlations with peak oxygen consumption ($VO_{2\text{ peak}}$) (Minnoti et al. 1991, Minnoti and Massie 1992). These studies suggest that during the development of CHF there is a dissociation in the relationship between exercise capacity and hemodynamic measurements. Therefore, it is

likely that there are other factors contributing to diminished exercise capacity of CHF patients.

Human skeletal muscle and CHF

By examining various published studies one can find that even though exercise capacity does not correlate well with hemodynamic measures, it does correlate with indices of peripheral muscular function. For example, peripheral muscle endurance and strength show significant correlations with exercise capacity in CHF patients (Volteranni et al. 1994, Minnoti et al. 1991, Buller et al. 1991, Franciosa et al. 1981). This has been demonstrated on numerous occasions using both voluntary or stimulated contractions (Buller et al. 1991) of the peripheral musculature with intact or restricted blood flow (Minotti et al. 1991). For example, Minotti et al. (1991) have indicated that muscular endurance is severely compromised in CHF patients and is a major contributor to the reduction in exercise capacity. This study also demonstrated that muscular endurance and exercise capacity (i.e. $VO_{2\text{ peak}}$) were significantly correlated ($r=0.90$). Interestingly, in the healthy subjects the same correlation was poor ($r=0.37$). This suggests that in part, the exercise capacity of these patients may be limited by altered functioning of the skeletal muscle during CHF. However, it is currently unclear why or how the functional properties of the skeletal muscle change. Therefore, it is important to determine what functional or structural changes may contribute to the alterations in muscular performance and hence exercise intolerance.

Multiple investigations have suggested that there are many alterations in the skeletal muscle which could have a detrimental effect on its functioning. The most

obvious of these changes include decreased muscle strength and endurance. Minotti et al. (1991) described that CHF patients were unable to maintain a similar force output over same period of time when compared to the control group. Specifically, they produced 25% less force at the same time point compared to the control group. Also, Buller et al. (1991) found that the quadriceps muscle group of CHF patients produced 31% less force than age-matched control subjects. In animal studies, Williams and Ward (1998) and Perrault et al. (1993) both showed depressed twitch and tetanic tensions after stimulation. Therefore it is apparent that patients afflicted with CHF suffer from reductions in muscular strength and muscular endurance, which could contribute to the reduced overall exercise capacity. Mancini et al. (1991) indicated that changes are simply due to skeletal muscle atrophy. However, if one carefully evaluates this study it can be determined that muscular size was never measured, rather calculated from various equations. More recently Lang et al. (1997) found little evidence of leg muscle atrophy in the CHF patients compared to the control subjects when using dual-energy X-ray absorptiometry (DEXA). Finally, Williams and Ward (1998) and Perrault et al. (1993) showed decreases in force persist when normalized by wet muscle mass or cross sectional area (CSA), respectively. Other than specific muscle atrophy, what changes could occur in the skeletal muscle which would contribute to these alterations?

Changes in skeletal muscle metabolism

Numerous published studies have shown that skeletal muscle of CHF patients demonstrates increased reliance on glycolytic metabolism at the expense of oxidative metabolism. Studies have shown that CHF patients experience elevated lactate

concentrations, increased utilization of phosphocreatine (PCr) and increased rates of acidosis development during lower levels of exercise intensity compared to control patients (Bernocchi et al. 1996, Massie et al. 1987). Okita et al. (1998) found using ^{31}P magnetic resonance spectroscopy that PCr depletion occurred at a much lower peak VO_2 than in the control patients. It should be noted that they found no differences in the rate of fatigue development, which is contrary to most other CHF studies. In contrast, Sullivan et al. (1991) demonstrated that fatigue development during peak exercise is not associated with greater PCr depletion or lactate accumulation when compared to normal subjects. This suggests that muscular fatigue occurred with similar changes in indicators of glycolytic metabolism between the two groups, suggesting that onset early onset of fatigue in the CHF patients was not due to metabolic changes. Taken together these studies indicate that changes in muscle metabolism do not fully account for the exercise capacity changes seen during CHF. It also should be pointed out that it is unlikely that reductions in muscular strength are due to changes in muscle metabolism. Therefore, there are reductions in muscle strength and endurance during CHF, however it is still unclear as to why this reduction occurs.

Are the skeletal muscle changes related to reduced activity?

While it would be easy to suggest that these muscular alterations (*i.e.* MHC and metabolic changes) in the skeletal muscle are simply due to the decrease in activity of the patient as a result of CHF. In fact, some of these changes are very similar to what one would see with models which mimic states of decreased activity (*i.e.* spinal cord injury). However, there is considerable evidence to suggest that these effects are not simply due to

decreased levels of activation of the muscle, rather it seems to be specific to CHF. For example, it has been shown that phenotypic (*i.e.* MHC) changes in the skeletal muscle of human CHF patients are much more dramatic than changes that occur in completely bed-ridden individuals (Vescovo et al. 1996). It has also been shown in two separate studies that spontaneous cage activity of rats afflicted with CHF are not different from healthy control rats even though their phenotypes (*i.e.* MHC and sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA)) of their musculature are different (Simonini et al. 1996a, Simonini et al. 1999). The data of Bigard et al. (1998) suggests that hindlimb suspension is only capable of reproducing the MHC changes in the muscle and not all of the mitochondrial changes associated with CHF. These studies suggest that models of reduced activity cannot reproduce skeletal muscle changes known to occur in CHF. Therefore, it seems unlikely that these changes are completely due to reduced activity. However, it should be noted that there are no direct data examining specific muscle activation (*i.e.* electromyographic activity (EMG)), therefore it is not possible to completely rule out the possibility that reduced activity of some muscles may lead to changes in structure and function. Therefore, recent evidence strongly suggests that reduced activity is not a major factor mediating the changes known to occur in skeletal muscle during CHF.

Reduced peripheral blood flow and skeletal muscle alterations

Another factor to consider is the assumption that skeletal muscle changes in CHF are due to a chronic reduction in blood flow to the peripheral musculature. However, this seems unlikely. Vescovo et al. (1998) showed no significant correlations between alterations in skeletal muscle blood flow and changes in skeletal muscle protein expression

in rats afflicted with CHF. Also, numerous investigations have indicated that the reductions seen in basal or resting blood flow in rats afflicted with CHF are minimal. For example, Musch and Terrell (1992) found no differences in resting blood flow to various peripheral muscles of rats afflicted with CHF. It should also be noted that skeletal muscle changes are different in human patients afflicted with peripheral artery disease (PAD) compared to those subjected to CHF. For example, there is an increase in the number of slow fibers during PAD compared to the increase in fast fibers seen in CHF patients (Hiatt, 2000). So, in a condition where blood flow is chronically comprised, skeletal muscle changes are occurring in the opposite direction compared to that which is seen in CHF. Also, Minotti et al. (1991) have shown that skeletal muscle endurance in CHF patients is reduced independent of changes in limb blood flow. This study normalized the blood flow between CHF and control groups by making the leg muscle ischemic, via a blood pressure cuff, and found that the CHF group still exhibited a reduction in endurance capacity. Therefore, this suggests that a reduction in blood flow may not be the sole cause of the alterations in function of the skeletal muscle.

Skeletal muscle excitation-contraction coupling and fatigue

In the past, our lab and others have argued that skeletal muscle fatigue occurs in healthy individuals due to alterations or disruptions in excitation-contraction coupling (ECC) (Williams et al. 1998, Ward et al. 1998, Allen et al. 1995). ECC is a major process in striated muscle involving multiple steps that help regulate force production. A disruption of this process (i.e. exercise or pharmacological intervention) has been shown to cause alterations in the force production and endurance capacity of the muscle (Ward et

al. 1998). Therefore, it seems reasonable to suggest that during the development of CHF there may be subsequent alterations in ECC, which could contribute to alterations in skeletal muscle function.

Briefly, ECC is the process in which the nerve releases acetylcholine (ACh) into the neuromuscular junction, where it binds to the ACh receptor. This allows for the formation and propagation of an action potential, which travels down the t-tubule, until it reaches the voltage sensor. The activation of the voltage sensor allows for subsequent activation of the ryanodine receptor (RyR) or Ca^{2+} release channel, which is located on the sarcoplasmic reticulum (SR). Ca^{2+} is then released into the myoplasm from the SR, the organelle which acts as a Ca^{2+} storage sink. As the myoplasmic Ca^{2+} concentration rises from nanomolar (nM) to micromolar (μM) concentrations, activation of the contractile apparatus occurs. The contractile apparatus is made up of the thin or actin filament and the thick filament. This activation occurs by Ca^{2+} binding to TnC, which is located on the thin filament. The binding of Ca^{2+} acts as a trigger promoting the transition from a 'weak' binding state to a 'strong' binding, force generating state between the actin and myosin filament. After Ca^{2+} binds to TnC there is a subsequent release of an inorganic phosphate molecule, which is produced from the hydrolysis of ATP by the myosin ATPase and a subsequent rise in force production. The SR then resequesters free Ca^{2+} in the myoplasm via the Ca^{2+} -ATPase, which is also known as sarco/endo-plasmic reticulum calcium ATPase (SERCA). The rate of Ca^{2+} taken up by the SERCA pump directly contributes to the rate of muscular relaxation. The rate of SR Ca^{2+} uptake is also different depending upon the isoform of SERCA expressed. More specifically, it is known that SERCA isoforms are differently regulated in that SERCA 2 has associated with it phospholamban

which imparts slow kinetic properties on SERCA 2 (Sasaki et al. 1992). SERCA 1 does not seem to be associated with phospholamban in skeletal muscle, therefore allowing for higher kinetic properties. SERCA 1, the fast isoform, is normally associated with predominately fast skeletal muscle, while SERCA 2, the slow isoform, is associated with slow/cardiac muscle. It is also known that overall rates of Ca^{2+} uptake are higher in fast skeletal muscle compared to slow skeletal muscle, and the rates of relaxation are elevated in fast muscles compared to slow muscles.

Should any breakdowns or modifications occur in the above listed processes, it is possible they could contribute to altered muscle function thereby promoting a reduction in exercise capacity. It is generally accepted that during the development of fatigue in a healthy individual there are multiple alterations in the ECC process leading to the reduction in force production. This has been demonstrated in multiple labs, using a variety of techniques (Williams et al. 1998, Allen et al. 1995). Therefore, since CHF patients are known to be susceptible to an early onset of muscular fatigue, it seems likely to suggest that there are alterations in the ECC process.

The effects of myosin isoforms on skeletal muscle contractile properties

The thick filament is composed of the myosin heavy chain (MHC) motor protein which is involved in muscular contraction (Talmadge, 2000). The MHC has associated with it the myosin ATPase (M-ATPase). It has been suggested that activity of this M-ATPase, may help to regulate the rate of muscle contraction (Barany, 1967). Currently, it is known that at least four different isoforms (*i.e.* I, IIa, IIx, IIb) of MHC exist in rat hindlimb muscle and three isoforms in human muscle (*i.e.* I, IIa, IIx). The expression of

these MHC within individual muscle fibers is used to determine fiber type composition of various muscles. Numerous studies suggest that there is a progression of maximum contractile velocities in fibers that are expressing certain MHC. More specifically fibers maximally contract from slowest to fastest MHC type $I < IIa < IIx < IIb$ (For review see Reggiani et al. 2000). The maximum speed of contraction of a particular muscle is therefore dependent upon the expression of MHC in that there is an increase in contractile speed of muscle fibers containing high amounts of a given fast isoform (*i.e.* IIa, IIx, or IIb) versus a slow isoform (*i.e.* I) (Bottinelli et al., 1994). For example, whole muscles that contain higher proportions of MHC IIx and IIb will demonstrate higher rates of maximal contractile velocity than muscles containing higher proportions of MHC I and IIa (Talmadge, 2000).

It is widely accepted that the specific MHC isoforms are associated with regulation of contractile velocity and power output of individual muscle fibers. For excellent reviews of specific studies see Fitts and Widrick (1996) and Reggiani et al (2000). Power output curves can be constructed using the muscle force velocity relationship. In fact peak power varies between fibers expressing different MHC, in that power output of fibers increases $I < IIa < IIx < IIb$ (Fitts and Widrick, 1996). Therefore, the overall MHC composition of the muscle not only affects force-velocity relations, but also the overall power output of the muscle.

Therefore, potential changes in muscle fiber MHC expression can affect overall muscle function and possibly exercise capacity. For instance, it is known that in instances of reduced activity or reduced load there are significant increases in IIx MHC in the soleus muscle, which correspond to increases in maximum rates of contraction velocity

(Talmadge, 2000). These changes also correspond to alterations in power output of the whole muscle. Thus, the changes in MHC expression can have large physiological consequences on muscular performance and therefore possibly effect overall exercise capacity

Skeletal muscle ECC and CHF

Perrault et al. (1993) were the first to publish data suggesting that CHF-induced alterations in skeletal muscle function were accompanied by alterations in ECC. In fact, their data obtained from rats afflicted with CHF show that in single intact fibers there are reductions in the rates of Ca^{2+} release and uptake, and that both are related to reductions in overall force production. Their findings also suggested that the alterations in the Ca^{2+} release and uptake process significantly contributed to decreased rates of contraction and increased rates of relaxation. Following that Williams & Ward (1998) suggested that force production of rat gastrocnemius muscle is clearly altered and unrelated to muscle atrophy. They also showed that the CHF rats had significant alterations in SR Ca^{2+} handling by isolated vesicles, which may have altered the force production capacity of the CHF rats. They found that isolated vesicles from CHF rats showed increased rates of Ca^{2+} release and uptake. The increased rates of uptake also corresponded to increases in Ca^{2+} -ATPase activity. This is an opposite effect to what was found in the results of Perrault et al. (1993). Since, the two investigations used such differing techniques (*i.e.* single fibers vs. isolated vesicles) it is quite possible that the techniques may have caused the differing results. Also, it should be noted that Peters et al. (1997) found decreases in Ca^{2+} -ATPase activities in a genetic rat model of CHF. It is also possible that the differing effects could

be due to the differing levels of heart failure induced, in that Perrault et al. (1993) and Peters et al. (1997) animals were subjected to a greater degree of failure than indicated by Williams and Ward (1998). The two studies do, however, present one common theme in that there are significant alterations in the functioning of the ECC process in skeletal muscle affected by CHF.

Skeletal muscle MHC and SERCA isoform changes during CHF

Others suggest that changes in key structural components may contribute to dysfunctional skeletal muscle in CHF. For example, many studies have shown changes in various protein isoforms involved in ECC and the actual force generating step during the development of CHF. In general there seems to be a transformation in that proteins normally associated with fast muscle (*i.e.* MHC IIx) become more highly expressed in slow muscle. For example, studies by Siminoni et al. (1996a, 1996b) have suggested that there are increases in MHC IIx and IIb mRNA transcripts in the soleus, a predominately slow muscle, during the development of CHF. Also, muscles that contain a heterogeneous mix of slow and fast fibers tend to display a shift towards increased levels of fast expression. For example, Delp et al. (1997) showed that plantaris muscle from CHF rats developed an increase in the proportion of IIb fibers at the expense of IIx fibers. Interestingly, muscles that express a higher content of fast MHC exhibit increased fatigability and altered contractile characteristics compared to muscles which express more slow protein isoforms. While, it is currently unclear as to why fast muscles fatigue more rapidly than slow muscles, this notion suggests that fiber type transformations contribute to the increased rate of fatigue development during CHF.

Corresponding with the MHC changes are alterations in SERCA 1 and 2 expression. However, the data concerning SERCA expression are not as well described and the expression changes seem dependent upon the model used to mimic CHF and the severity of the disorder. Peters et al. (1997) suggested that there were decreases in SERCA 1 mRNA expression and subsequent decreases in SERCA 1 protein levels in a genetic rodent model of CHF. Both of these changes corresponded to decreases in Ca^{2+} -ATPase activity. In contrast, using the coronary ligation model Siminoni et al. (1999) indicated there was a 16 % decrease in SERCA 2 (slow isoform) protein and 59% decrease in SERCA 2 mRNA expression, again suggesting a reduction in slow isoform expression. However, the changes in muscle SERCA expression seem to dependent upon the model used to study CHF and also the severity of CHF. It should be noted that in the Peters et al. (1997) study the rats were in full-decompensated failure before they were euthanized, while the animals in the Simioni et al. (1998) paper were not as severely affected by the CHF. Currently, there are no data on what MHC changes would be seen in the genetic rat model of CHF, therefore it is impossible to fully compare the models. It is possible that the extent and direction of the changes are dependent upon the degree of failure. However, due to disparities in models (i.e. induction of CHF and severity) used to study CHF, realistic evaluation of SERCA changes during CHF still is not possible until more evidence is available.

Is skeletal muscle the limiting factor?

Taken together these results, suggest that in mild to severe cases of CHF there are 'slow to fast' transformations with regard to various protein isoforms expressed in skeletal

muscle. Therefore, in patients with CHF, if their muscles become faster, with regards to their phenotype, this may increase their susceptibility to fatigue and alter the physiological function of the muscle. Current data also suggest these alterations in the function of the whole muscle may result from alterations in the ECC process. Alterations in Ca^{2+} handling properties of the SR could be detrimental to the overall function of the muscle, which could therefore contribute to reductions in muscular strength and endurance. Also, changes in muscle MHC expression could affect force-velocity and power output relationships of the muscle. If all these changes contribute to alterations in whole muscle function then it is very likely that overall exercise capacity will be subsequently affected.

Endurance training and CHF

If the factor limiting exercise capacity in CHF patients arises from changes that occur in skeletal muscle, then one should be able to improve functional capacity by reversing these changes. A number of groups have suggested that CHF patients can be safely entered into exercise training programs (Minnoti and Massie, 1992). The majority of exercise programs for CHF patients are related to endurance type activities. Sullivan et al. (1988) showed that 4-6 months of aerobic training increased exercise capacity and blood flow to the periphery. The data also suggested that there were changes in muscle metabolism that occurred after the exercise program, in that there seemed to be less of a reliance on glycolytic metabolism. Also, Hambrecht et al. (1997) demonstrated that endurance training clearly improved $\text{VO}_{2\text{peak}}$ of the CHF patients and therefore the endurance capacity of the patients. The study also demonstrates that multiple muscular changes occurred and that they could have contributed to the changes in exercise capacity.

For example, their study showed that the exercise training produced a ‘re-shift’ in fiber type proportions from fast to slow and also indicated training induced improvements in mitochondrial function. However, it remains unclear if the changes in exercise capacity in the CHF patients were due to adaptations in the myocardium or in the skeletal muscle.

Strength training and CHF

It is interesting to determine whether it is necessary to alter the myocardium in order to change the skeletal muscle. Do skeletal muscle and heart tissue share some sort of cross-talk during CHF, such that cannot adapt without the other adapting? It is impossible to determine if this relationship exists by examining studies that use endurance training with CHF patients. This is because it is well known that endurance training causes multiple improvements in hemodynamic factors, while also changing skeletal muscle function. If it is skeletal muscle causing the reduction in exercise capacity, it may be beneficial to train the skeletal muscle independent of the heart. One way to examine this effect would be to strength train the muscles of individuals with CHF. A study like this would be able to verify or refute the idea that skeletal muscle is the limiting factor contributing exercise intolerance. Strength training would be ideal since it is known to produce muscle phenotypic changes opposite (Adams et al. 1993) to what is seen during CHF and would not cause large changes in the hemodynamic function of the patient. For example, Hare et al. (1999) showed that resistance training in CHF patients improved strength and endurance capacity of the patient, but it also did not alter $VO_{2\text{ peak}}$. This may indicate that training improved the skeletal muscle, possibly without changing hemodynamic factors. Also, Magnusson et al. (1996) showed that high intensity exercise

of the knee extensors in CHF patients resulted in increases in exercise tolerance. These authors also suggested that high intensity training caused changes in the peripheral musculature, in that oxidative enzyme capacity was raised by over 50%. This would suggest that strength training could improve exercise capacity by possibly changing the peripheral muscle without changing hemodynamic function. However, these data only examine one variable involved in skeletal muscle function while it is known that skeletal muscle exhibits multiple changes during CHF that may contribute to the reduced exercise tolerance. Therefore, it is still unclear if strength training can cause adaptations in the muscle without affecting the heart that would subsequently improve exercise capacity.

Summary

One of the major clinical symptoms of CHF is a reduction in exercise capacity. The cause of these changes in exercise capacity still remains unclear. Initially, it was believed that it was simply due to reductions in peripheral blood flow due an altered myocardium. However current evidence suggests that alterations in peripheral muscle function are major factors in the reduced capacity. This is supported by evidence that skeletal muscle during CHF exhibits reductions in muscular strength and endurance. The muscle of CHF patients is also highly fatigable. In fact numerous studies have suggested that intrinsic alterations in skeletal muscle are the primary contributors to exercise intolerance. This is supported by evidence showing that skeletal muscle during CHF develops specific changes in protein isoforms which can affect muscle physiological parameters. These changes in protein expression may lead to known alterations in ECC and therefore the altered functioning of the muscle.

It has been suggested that exercise can improve the function of people afflicted with this condition by reversing the skeletal muscle changes. Therefore, using a muscle specific activity that may specifically reverse these CHF-induced changes may help to return exercise capacity to normal levels.