EXERCISE TRAINING IN PATIENTS WITH SEVERE HEART FAILURE

BODY-WEIGHT SUPPORTED TREADMILL TRAINING IN PATIENTS WITH SEVERE HEART FAILURE

By

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ABSTRACT

Patients with severe heart failure (HF) are often excluded from exercise training studies due to their potentially unstable nature and severe exercise intolerance. Steady state cycling and walking have been the most common interventions and it is unknown whether these training modalities are appropriate and safe for patients with severe HF as they can produce significant cardiovascular stress. Body-weight supported treadmill (BWST) training may be beneficial in patients with severe HF by improving the periphery while minimizing cardiac loading.

The purpose of this study was to: 1) assess the safety and feasibility of BWST training in severe HF patients and 2) to evaluate the effect of BWST training on functional capacity, health-related quality of life (HRQL), cardiopulmonary function, and blood vessel function.

Three male patients with severe HF participated in the study. On study entry and at the end of 24 sessions of physician supervised BWST training, patients completed a cardiopulmonary exercise test, two HRQL questionnaires, a 6-Minute Walk Test (6-MWT), and a Doppler ultrasound study.

Although there were no study-related adverse events, only one subject (Patient 1) was able to complete post-testing. However, all three patients seemed to demonstrate a general trend towards increased exercise tolerance. By the seventeenth exercise session, the BWS was reduced to zero for Patient 1. In addition, Patient 1 achieved an average

walking speed of 2.0 km/hr and was completing 34 minutes of walking with minimal rest periods by the end of the training program. Patients 2 and 3 also responded to the training as evidenced by a slight increase in exercise duration. However due to fluctuations in their health status, they did not have any substantial improvement.

Patient 1 experienced substantial increases in functional capacity: a 64% increase in VO_2 peak (7.2 to 11.7 ml/kg/min); a 33% increase in peak power output (300 to 400 kpm/min); a 37% increase in V_E peak (28 to 39 L/min); and a 28% increase in 6-MWT distance (223.5 to 286m). In addition, Patient 1's NYHA-FC improved after training from class III to II. A significant training effect was also evident by reductions in HR at rest (96 to 79 bpm) and during submaximal exercise (100 kpm/min) (105 to 84 bpm). HRQL also tended to improve for Patient 1.

Based on these findings and observations, two conclusions can be made. First, patients with severe HF can safely participate in BWST training and may derive considerable benefits. Second, the feasibility of training patients with severe HF is highly dependent on their cardiac condition and other co-morbidities remaining stable enough to allow consistent training.

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1.0 REVIEW OF LITERATURE

1.1 Review of Heart Failure

1.1.1 Introduction

Patients with heart failure (HF) are limited in their activities of daily living by varying degrees of dyspnea and fatigue. Heart failure originates from a weakened heart which is unable to pump enough blood to meet the requirements of the metabolizing tissues (Colluci & Braunwald, 1997) and is associated with a high degree of morbidity and mortality. Heart failure is the first or second leading cause of hospitalization among patients over 65 years of age in developed countries (Adams, 2001) and the number of HF hospital admissions is growing (McMurray and Stewart, 2000). In addition, approximately one third of patients are readmitted within six months of discharge, making HF a major economic burden (McMurray and Stewart, 2000). A recent population-based study investigated prognosis and determinants of survival in 38, 702 patients who were hospitalized for HF for the first time in Ontario between 1994-1997 (Jong, Vowinckel, Liu & Gong, 2002). The results of this study are believed to more accurately represent the status of HF patients than previously published clinical trials since unselected community-dwelling patients were involved. This study determined that 30-day and 1-year case-fatality rates were 11.6% and 33.1%, respectively. Age was associated with a stepwise increase in risk of death, and males had significantly lower 1-year survival rates than females. In addition, chronic comorbidities independently

increased mortality rates. Unfortunately, the most prominent finding was that the prognosis for patients with heart failure, despite advances in treatment, remains poor.

1.1.2 Epidemiology

A review by Cowie and colleagues (1997) examined epidemiological studies listed on the Medline Literature Database from 1966 to 1995. The incidence of HF for people under 65 years of age was 1/1000 and 0.4/1000 a year for men and women, respectively. Over 65 years, the incidence rose to 11/1000 for men and 5/1000 a year for women. The prevalence of HF for people under 65 years of age was 1/1000 for both men and women and for those over 65 years, the prevalence was 40/1000 for men and 30/1000 for women (Cowie et al., 1997). Unfortunately, the yearly number of HF cases has been increasing over the past few decades (McMurray & Stewart, 2000). In fact, projections suggest that the prevalence will increase two to three fold by the year 2010 (Adams, 2001). This trend can be mostly attributed to the aging population and the greater extent of HF in the elderly. However, it is also believed that recent developments in medicine have reduced the mortality rates for acute myocardial infarction and therefore have increased the number of people at risk for HF (Cowie et al., 1997; McMurray, Petrie, Murdoch, & Davie, 1998; McMurray & Stewart, 2000).

1.1.3 Pathophysiology

The pathophysiology of HF involves a complex interaction of various cardiac and circulatory compensatory mechanisms with short and long time constants (Zelis, Sinoway, Leuenberger, Clemson & Davis, 1991). Packer (1992) described the dynamic processes involved in the development of HF due to left ventricular systolic dysfunction. The process begins with an initiating factor (myocardial infarction, viral infection, prolonged hypertension or valvular disease) which results in the loss of a critical amount of functional myocardial cells. In response, hemodynamic and neurohormonal systems are activated to augment contractile force and preserve cardiac function. First, as a result of the ventricle's inability to empty during systole, there is increasing diastolic tension (preload) on the non-injured parts of the heart. This is offset by enhancing the contraction force through the Frank-Starling mechanism (dilation). Second, the reduced ventricular ejection into the aorta stimulates the sympathetic nervous system therefore increasing beta-adrenergic stimulation of the non-injured myocardial cells. This leads to an increase in both the force and frequency of contraction. Together these compensatory strategies provide chronotropic and inotropic support for the damaged heart (Packer, 1992).

Unfortunately, over the long term these compensatory mechanisms result in increased wall stress which can distort the architecture and increase the energy expenditure of the heart. These adverse changes are avoided by two adaptive strategies involving both ventricular and atrial responses. First, in response to the increase in diastolic wall stress of the ventricles, myofibrillar proteins are synthesized. The

subsequent increase in wall thickness reduces the ventricular strain and dilation by distributing the excess stress among a greater number of sarcomeres. This hypertrophy reduces the energy expenditure of the heart. Second, the actions of the sympathetic nervous system are suppressed by the increase in diastolic wall stress in the atria. Atrial stretch stimulates 1) atrial baroreceptors which inhibit sympathetic activity and 2) secretion of atrial natriuretic peptide (ANP) which inhibits release of noradrenaline and has a direct vasodilator and natriuretic effect which reduces the hemodynamic load on the heart. Collectively, these mechanisms reduce stress on the heart and help offset the adverse consequences of ventricular dilation and sympathetic activation (Packer, 1992).

Overall, cardiac function is restored to pre-injury levels at minimal energetic cost through these positive inotropic and stress-reducing mechanisms. Long-term activation of these mechanisms however, compromises their beneficial effects and predisposes to later decompensation. In particular, the ability to manage wall stress is jeopardized as prolonged ventricular distension leads to thinning, necrosis and fibrosis of the ventricular wall. Moreover, inhibition of sympathetic outflow is impeded and ANP release reduced as prolonged atrial distension impairs the baroreceptor endings and depletes ANP stores. Overall, this represents a loss of the circulation's ability to limit ventricular wall stress and sympathetic drive, and ventricular dilation progresses, sympathetic tone predominates and heart failure begins (Packer, 1992).

Secondary to the loss of stress-reducing mechanisms, there is a loss of the positive inotropic mechanisms as the heart becomes increasingly dependent on inotropic processes to maintain cardiac function. Initially, because of progressive dilation,

sarcomeres are maximally stretched and further increases in preload do not enhance systolic ejection. The Frank-Starling curve becomes both depressed and flattened to the point that increases in ventricular volume do not result in increases in ejection. Next, the positive inotropic effects of endogenous and exogenous catecholamines become progressively less potent as down-regulation and uncoupling (from effector enzyme) of beta-adrenergic receptors occurs. This happens in conjunction with an increased sensitivity of alpha-adrenergic stimulation in the peripheral vessels which increases the pressure and volume in the heart thus increasing cardiac load. Ultimately the heart has less capacity to contract, and its limited capacity must be used to overcome stress instead of eject blood, thus compromising cardiac output (Packer, 1992).

In response to the reduction in cardiac output, perfusion to vital organs must be maintained by peripheral mechanisms such as peripheral vasoconstriction and sodium retention (Packer, 1992). These adaptive strategies represent a shift in circulatory priorities such that the main objective is not to support cardiac function as with healthy individuals, but to maintain systemic perfusion pressures.

Overall, long-term hemodynamic stress and neurohormonal activation depress cardiac function but also cause necrosis of healthy myocardial cells. The combination of these deleterious processes creates a progressively deteriorating state ultimately leading to terminal HF (Packer, 1992).

1.2 Health-Related Quality of Life

In general, quality of life is assessed by well-being and the ability to function in daily life (Tandon, Stander & Schwarz, 1989). Although it is difficult to specifically define health-related quality of life (HRQL), common domains found in most conceptualizations are health, physical function, psychological function, social interactions and symptoms and their consequences (Grady, 1993; Wenger, 1989).

Patients with HF report physical limitations, reduced activities of daily living and the inability to work as a result of their condition (Grady, 1993). Compared to the general population and patients with and without chronic conditions (i.e. hypertension and diabetes), patients with HF have the poorest HRQL as measured by health perceptions, physical functioning, role functioning and social functioning (Blackwood, Mayou, Garnham, Armstrong & Bryant, 1990; Dracup, Walden, Stevenson & Brecht, 1992; Quittan, Sturm, Wiesinger, Pacher & Fialka-Moser, 1999; Stewart et al., 1989).

1.3 Exercise Capacity

Exercise intolerance, associated with dyspnea and fatigue, is the principal symptom experienced by patients with HF. To date, the most common and reliable method of measuring exercise capacity in HF has been through cardiopulmonary exercise testing with direct measurement of oxygen consumption (VO_2). Since patients with HF rarely achieve a true maximal VO_2 (VO_{2max}), investigators most commonly use peak VO_2 (VO_{2peak}). Exercise testing provides an accurate assessment of functional capacity that can be used to determine prognosis and to evaluate responses to various therapeutic

interventions (Hanson, 1994; Shephard, 1997; Sullivan & Hawthorne, 1995). Based on the results from many HF studies, the peak oxygen consumption of patients with HF ranges from approximately 7 to 20 ml/kg/min. Compared to healthy men and women over the age of 60, the average HF patient would fall in the 1st percentile of exercise capacity (American College of Sports Medicine [ACSM], 1995).

Although VO_2 peak is commonly used, there are several limitations, including subjective endpoints, varying protocols and modalities, little concordance with activities of daily living, and the requirement of trained personnel and expensive equipment (Sullivan & Hawthorne, 1995). An alternative method of measuring functional capacity in HF is a self-paced walking test that determines the distance achieved in a specified time, e.g. the 6 minute walk test (6-MWT). This test is thought to be more closely related to activities of daily living, requires less trained personnel, less equipment and is inexpensive. In addition, this test is more appropriate for frail, elderly and severely limited patients with heart failure (Guyatt et al., 1985; Lipkin, Scriven, Crake & Poole-Wilson. 1986). Guyatt et al. (1985) were the first group to assess the 6-minute walk test in patients with HF. They found that it was well tolerated by patients, produced stable results after the first two walks and the results were reproducible and correlated with conventional measures of functional status and exercise capacity. Moreover, Guyatt et al. (1985) concluded that the modest correlation between the 6-MWT and VO_2 peak suggests that the walking test may be more a measure of a patient's ability to perform activities of daily living than exercise capacity alone. A similar study by Lipkin et al. (1986) found comparable results, however the authors mentioned that this test is less

discriminating than measurement of oxygen consumption and may be best used for assessing treatment and for serial monitoring of patients with moderate or severe HF. More recent studies have demonstrated that the 6-MWT strongly and independently predicts morbidity and mortality in patients with left ventricular dysfunction (Bittner et al., 1993) and has a weak inverse correlation with disease-specific quality of life (as measured by the Minnesota Living with Heart failure Questionnaire) and New York Heart Association Functional Classification (NYHA-FC) (Demers, McKelvie, Negassa & Yusuf, 2001). Lipken et al. (1986), reported that patients with HF walk significantly shorter distances than age matched normals. That is, the 6-MWT distance achieved by age-matched normals was 683m whereas HF patients with NYHA-FC II and III symptoms walked a mean distance of 562m and 402m, respectively. Patients with more severe symptoms (i.e. NYHA-FC III and IV) have been shown to walk considerably shorter distances (Dracup et al., 1992). Based on these results and those of other studies, patients with HF demonstrate a reduced functional capacity which is associated with an impaired ability to perform activities of daily living.

1.4 Determinants of Exercise Capacity

Based on the pathophysiology of HF, a reasonable assumption is that exercise capacity is limited by central hemodynamic function. This has proven to be an oversimplification based on the consistent finding that there is essentially no correlation between exercise tolerance and indices of cardiac function in patients with HF (Chati et al., 1994; Conn, Williams & Wallace, 1982; Franciosa, Park & Levine, 1981; Minotti et

al., 1991; Smith, R. et al., 1993; Volteranni et al., 1994). For example, Conn et al. (1982) found no relation between resting left ventricular ejection fraction (LVEF) and exercise capacity, noting that a patient with a LVEF of 25% exercised to 4.6 METS while a patient with a LVEF of 13% achieved 9.5 METS. Furthermore, improvements in cardiac function, through administration of dobutamine (a synthesized catecholamine) (Maskin, Forman, Sonnenblick, Frishman & LeJemtel, 1983; Wilson, Martin & Ferraro, 1984a) and cardiac transplantation (Stratton, Kemp, Daly, Yacoub & Rajagopalan, 1994b) have occurred without improvements in exercise capacity. Based on these findings, researchers have investigated the peripheral determinants of exercise capacity in patients with HF.

1.5 Skeletal Muscle Metabolic Abnormalities

1.5.1 Evidence from local exercise studies

^{31}P nuclear magnetic resonance (^{31}P-NMR) spectroscopy is a non-invasive technique which allows assessment of intra-cellular pH and phosphocreatine (PCr) utilization, indices of glycolytic activity and of mitochondrial respiratory control (Adamopoulos & Coats, 1991). Several ^{31}P-NMR studies investigating local muscle metabolism have shown that HF patients demonstrate a greater dependence on anaerobic metabolism during exercise than controls. Specifically, several studies have found greater levels of PCr depletion and larger reductions in pH for HF patients compared to healthy normals during submaximal forearm or finger flexion exercise (Kemp et al., 1996; Massie et al., 1988; Massie et al., 1987a and b; van der Ent et al., 1998; Wiener et

al., 1986; Wilson et al., 1985b) and leg exercise (Chati et al., 1996; Hanada et al., 2000; Kemp et al., 1996; Mancini et al., 1989; Mancini, Ferraro, Tuchler, Chance & Wilson, 1988; Mancini et al., 1992; Okita et al., 1998).

The impact of HF on PCr resynthesis has not been defined. Some investigators have demonstrated prolonged PCr resynthesis in all study patients (Hanada et al., 2000; Mancini et al., 1992; van der Ent et al., 1998), whereas others have found either delayed PCr resynthesis in only a small minority of subjects (Massie et al., 1987a and b), or normal PCr resynthesis (Chati et al., 1996; Wilson et al., 1985b). The investigation of PCr resynthesis rate by ^{31}P-NMR is technically unreliable, so this may account for the conflicting results (Chati et al., 1994).

Findings from ^{31}P-NMR investigations are supported by studies which have employed blood sampling (Andrews, Walsh, Evans, Curtis & Cowley, 1997; Shoemaker, Naylor, Hogeman & Sinoway, 1999). For instance, Andrews and colleagues (1997), using a forearm model of muscle metabolism, found significant abnormalities of skeletal muscle metabolism in patients with HF as evidenced by elevated lactate and ammonia responses during exercise when compared to controls.

Overall, results from local exercise studies using ^{31}P-NMR or blood sampling support the notion that HF patients exhibit a greater dependence on glycolytic metabolism and thus a reduced capacity for oxidative ATP synthesis during small muscle mass exercise. Several of these studies have also found a significant correlation between the abnormal metabolism observed during local exercise (i.e. rapid PCr depletion and intracellular muscle acidosis) and systemic exercise capacity and symptomatic status

(Andrews et al., 1997; Chati et al., 1996; Chati et al., 1994; Massie et al., 1987a; Okita et al., 1998). However, these results must be interpreted with caution. A correlation does not signify cause and effect, therefore it cannot be concluded with certainty that the skeletal muscle metabolic abnormalities seen during small muscle exercise in HF underly the exertional fatigue noted during systemic exercise in this population.

1.5.2 Evidence from systemic exercise studies

In an attempt to overcome the limitations of local exercise studies, several authors have investigated systemic exercise. Although the results are highly variable they do not entirely support the local studies. For example, skeletal muscle biopsy results from systemic exercise studies have shown that at peak exercise, HF patients have lower skeletal muscle lactate concentrations and less PCr depletion than controls (Schaufelberger, Eriksson, Held & Swedberg, 1996; Sullivan, Green & Cobb, 1991). These results suggest that factors other than the magnitude of lactic acidosis or high-energy phosphate depletion are important in mediating fatigue during exercise in heart failure. These results are supported by a study which investigated the effects of Dichloracetate (a drug that decreases lactate formation) on maximal exercise performance in HF patients and found that intramuscular lactate accumulation was not responsible for the muscular fatigue (Wilson, Mancini, Ferraro & Egler, 1988). Slightly different results were obtained by Nävari, Leinonen and Härkönen (1992) in that comparable magnitudes of skeletal muscle PCr depletion and lactate accumulation were seen in HF patients and controls at peak exercise.

Clearly there are some discrepancies in the literature. Studies employing small muscle mass exercise have demonstrated significantly higher lactate accumulation and PCr depletion in HF patients compared to controls. In contrast, systemic exercise studies have produced conflicting results to the extent that some authors have suggested that factors other than the magnitude of PCr depletion and lactate accumulation influence exercise tolerance in HF.

In an attempt to resolve the discrepancies, Okita and colleagues (1998) investigated skeletal muscle metabolism during both local and systemic exercise by ^{31}P-NMR and venous blood sampling. The results of their systemic exercise protocol (cycle ergometer) support the results of the local training studies in that PCr depletion occurred at a lower workload for HF patients than normals and was accompanied by a greater reduction in pH. The authors concluded that skeletal muscle metabolism is the limiting factor during maximal systemic exercise and thus is an important determinant of exercise capacity in patients with HF.

In conclusion, although there are some discrepancies in the literature, increased skeletal muscle anaerobic metabolism appears to be a contributing factor to the reduced exercise tolerance in HF patients. It remains to be determined whether this abnormal metabolism is due to reduced skeletal muscle perfusion or to intrinsic skeletal muscle alterations associated with reduced oxidative phosphorylation.

1.6 Skeletal Muscle Blood Flow

1.6.1 Evidence for reduced blood flow

During exercise in a healthy person, blood flow to working skeletal muscles is increased by increasing the muscle perfusion pressure through enhanced cardiac function and vasoconstriction in non-exercising tissues, and through vasodilation in the exercising muscles. In chronic HF, reduced skeletal muscle blood flow has been associated with exercise intolerance, however, there is uncertainty regarding which of the above responses necessary for adequate blood flow is impaired.

Evidence for reduced skeletal muscle blood flow in HF has been derived from numerous studies employing different blood flow measurement techniques. Reduced exercise leg blood flow has been observed in HF patients during submaximal and/or maximal cycling using the thermodilution technique (Sullivan, Knight, Higginbotham & Cobb, 1989; Sumimoto et al., 1996), local isotope washout technique (Sorensen, Wroblewski, Galatius & Kastrup, 1999), near-infrared (NIR) spectroscopy (Matsui et al., 1995), and Doppler ultrasound (Isnard et al., 1996). Impaired leg blood flow has also been shown at rest and/or during recovery from cycling by thermodilution (Sullivan et al., 1989; Sumimoto et al., 1996), plethysmography (Cowley et al., 1986), NIR spectroscopy (Matsui et al., 1995), local isotope washout (Sorensen et al., 1999) and Doppler ultrasound techniques (Isnard et al., 1996). Forearm exercise studies utilizing plethysmography and Doppler ultrasound have found comparable results (Arnold et al., 1991; Longhurst, Gifford & Zelis, 1976; Zelis, Longhurst, Capone & Mason, 1974b).

In a study by Isnard et al. (1996), using Doppler ultrasound and submaximal leg exercise, it was determined that HF patients exhibited lower leg blood flows at rest and during exercise than controls. They also noted that HF patients maintained arterial pressures at rest and during exercise at the expense of higher leg vascular resistance. Maintained arterial perfusion pressure and blood flow to non-exercising regions, as well as increased leg vascular resistance, have been noted in the majority of blood flow studies. This suggests that working limb hypoperfusion may be a protective strategy for maintaining arterial pressure and blood flow to vital organs in the setting of reduced cardiac performance.

Evidence of increased oxygen extraction in HF patients during exercise has also been observed during forearm (Longhurst et al., 1976; Zelis et al., 1974b) and submaximal leg exercise (Sullivan et al., 1989). Despite this, oxygen consumption was not maintained and anaerobic metabolism predominated.

1.6.2 Role of reduced blood flow in exercise intolerance

The role of reduced blood flow in limiting exercise performance in HF has also been investigated. In 1993, Kraemer and colleagues established that forearm blood flow during reactive hyperemia was closely associated with peak oxygen uptake in patients with HF (Kraemer, Kubo, Rector, Brunsvold & Bank, 1993). In a similar study by Jondeau et al. (1993) it was noted that calf peak hyperemic flow was linearly related to peak oxygen consumption but forearm peak hyperemic flow was not. The authors speculated that the regional vascular specificity may be due to a more pronounced

deconditioning of the leg muscles versus the arm muscles because activity in larger muscle groups is associated with greater exertional symptoms and therefore may be preferentially avoided. In contrast, Volteranni et al. (1994) found no correlation between exercise capacity and quadriceps resting and peak blood flow as measured by plethysmography. Despite these dissimilar results, several studies have reported a strong correlation between reduced limb blood flow and systemic exercise capacity (Anker et al., 1997; Cowley et al., 1986; Sorensen et al., 1999; Sullivan et al., 1989; Wilson, Martin, Schwartz & Ferraro, 1984b).

1.6.3 Mechanisms behind reduced blood flow

A tempting conclusion based on the pathophysiology of HF would be that the reduced skeletal muscle blood flow results from inadequate cardiac pump function leading to arterial hypotension. Indeed this was shown in a study by Magnusson et al. (1997) where patients were able to maintain sufficient blood flow to working muscles when only a small muscle mass was exercised. Engagement of more muscle mass resulted in hypoperfusion in spite of a good vasodilatory capacity, leading the authors to conclude that low pumping capacity in HF is the primary determinant of skeletal muscle hypoperfusion. However, several studies have noted a vasodilatory impairment in this population independent of cardiac performance (Hayoz et al., 1993; LeJemtel, Maskin, Lucido & Chadwick, 1986; Wilson et al., 1984a; Zelis, Mason & Braunwald, 1968). One of the first studies to demonstrate this was Zelis and group (1968) where HF patients demonstrated a markedly reduced response to a variety of endogenous and exogenous

vasodilator stimuli. In addition, a study which used dobutamine to improve cardiac output found no improvement in skeletal muscle blood flow during exercise in HF thus implying that an intrinsic defect at the muscle level is responsible (Wilson et al., 1984a). If reduced skeletal muscle blood flow is due to an abnormality in vascular function, what is the underlying mechanism?

1.6.4 Mechanisms behind vasodilatory impairment

1.6.4.1 Reduced vascular compliance (structural vascular alterations)

Vascular compliance reflects the relationship between changes in pressure to the resulting changes in diameter. A reduction in vascular compliance has been observed in HF in studies of the aorta (Pepine, Nichols & Conti, 1978), carotid artery (Lage et al., 1994); brachial artery (Arnold et al., 1991; Finkelstein, Cohn, Collins, Carlyle & Shelley, 1985), radial artery (Giannattasio et al., 1995) and peripheral microcirculation (Sorensen et al., 1999; Wroblewski, Norgaard, Haunso & Kastrup, 1995). For example, Arnold et al. (1991) observed increased stiffness and reduced compliance in the brachial artery of HF patients as measured by bidemensional pulsed Doppler. Giannattasio and group (1995) found that the degree of reduced compliance was related to the severity of the disease and Sorensen et al. (1999) demonstrated that skeletal muscle distensibility in HF patients is related to maximal skeletal muscle blood flow. Furthermore, Sorenson et al. (1999) found that maximal skeletal muscle blood flow correlated to exercise time, therefore, the microvascular stiffness in HF patients may, through its impact on blood flow, be a determinant of exercise capacity.

Potential causes for reduced vascular compliance are kidney salt and water retention (Zelis, Delea, Coleman & Mason, 1970; Zelis, Lee & Mason, 1974a; Zelis & Mason, 1970), sympathetic nervous system and renin-angiotensin system activation (will be addressed below), and vessel structural abnormalities (Lage et al., 1994; Lindsay et al., 1994; Wroblewski et al., 1995).

1.6.4.2 Impaired endothelial function (functional vascular alterations)

The endothelium, which is located between the lumen and the underlying media of the vascular wall, modulates vascular tone through the release of endothelium-derived relaxing factor (EDRF), also known as nitric oxide (NO). NO is released in response to either neurotransmitters (e.g. acetylcholine and bradykinin) or as the result of physical stimulation (e.g. increases in cardiac output leading to increased shear stress on the vascular wall) (Drexler & Hornig, 1996; Ferrari, Bachetti, Agnoletti, Comini & Curello, 1998; Kiowski, Sütsch, Schalcher, Brunner & Oechslin, 1998; Treasure & Alexander, 1993). The endothelium also modulates vasoconstriction through the release of potent endothelium-derived contracting factors, thromboxane A_2, superoxide anion, prostaglandin H_2, and the most potent of which is endothelin (Treasure & Alexander, 1993).

Because of its role in modulating vascular tone, the endothelium has been implicated as a possible source for the reduced blood flow and vascular abnormalities detected in HF. In other words, endothelial dysfunction may be the reason for impaired blood flow in HF. Endothelial dysfunction refers to an altered vasodilatory capacity either at rest or after administration of various endothelium-dependent stimuli (Ferrari et

al., 1998). Several investigations have shown that the acetylcholine stimulated increase in blood flow is blunted in HF (Drexler et al., 1992a; Katz et al., 1992; Katz, Schwartz, Yuen & LeJemtel, 1993; Lindsay et al., 1996) suggesting that endothelium-dependent vasodilation is attenuated. Further support for endothelial impairment has been shown through blunted responses to serotonin (Maguire, Nugent, McGurk, Johnston & Nicholls, 1998), methacholine (Kubo, Rector, Bank, Williams & Heifetz, 1991) and substance P (Lindsay et al., 1996). The role of NO specifically has also been investigated and numerous studies indicate that impaired NO activity is involved in the depressed vasodilation in HF (Kanaya, Nakamura, Kobayashi & Hiramori, 1999; Katz, Krum, Khan & Knecht, 1996; Maguire et al., 1998; Rector et al., 1996; Smith, C. et al., 1996) while an equal number of studies have suggested otherwise (Habib, Dutka, Crossman, Oakley & Cleland, 1994; Kubo et al., 1994; Negrao et al., 2000; Winlaw et al., 1994). Drexler et al. (1992a), demonstrated that release of NO appeared to be reduced on stimulation but basal release was maintained. These results could explain the mixed findings from other studies.

Endothelin has been shown to be elevated in HF patients and appears to account for some of the circulatory abnormalities observed in this population (Kiowski et al., 1995; Krum, Goldsmith, Wilshire-Clement, Miller & Packer, 1995; Krum & Katz, 1998; Love, Haynes, Gray, Webb & McMurray, 1996; McMurray, Ray, Abdullah, Dargie & Morton, 1992; Wei et al., 1994). Also of note is that prostaglandin, a vasodilator released from the endothelium, may play a distinct role in HF by offsetting the increased vasoconstriction caused by other factors (Dzau et al., 1984; Lang, Chomsky, Butler,

Kapoor & Wilson, 1997a; Punzengruber, Stanek, Sinzinger & Silberbauer, 1986; Townend, Doran, Lote & Davies, 1995).

1.6.4.3 Increased neurohormonal activation

Vascular function may be impaired in HF due to enhanced neurohormonal activation, that is, prolonged activation of the sympathetic, renin-angiotensin, and vasopressin systems. Several investigators have shown increased sympathetic activation in HF at rest (Leimbach et al., 1986; Levine, Francis, Goldsmith, Simon & Cohn, 1982) and during exercise (Chidsey, Harrison & Braunwald, 1962; Francis, Goldsmith, Ziesche & Cohn, 1982). However, the effect of prolonged sympathetic activation on vascular function at rest and during exercise in HF has yet to be elucidated. A small number of studies have found that enhanced sympathetic drive in HF has no bearing on resting and working skeletal muscle vasoconstriction or blood flow (Wilson, Ferraro & Wiener, 1985a; Wilson, Frey, Mancini, Ferraro & Jones, 1989; Zelis et al., 1968) while other researchers have found that sympathetic activation does alter vasculature function and working muscle blood flow (Grassi et al., 1995; Lage et al., 1994; Lang, Rayos, Chomsky, Wood & Wilson, 1997b). For example, Lage et al. (1994) determined that in HF, plasma norepinephrine concentration was directly correlated with Young's modulus of elasticity (an index of vessel stiffness). The authors concluded that sympathetic nervous system activation may contribute to reduced vessel compliance in patients with HF.

Similarly, there is strong evidence supporting increased activity of the renin angiotensin system in HF (Genest, Granger, De Champlain & Boucher, 1968; Laragh,

1986; Levine et al., 1982; Newby et al., 1998), however its role in limb circulation during exercise in HF has not been established (Wilson & Ferraro, 1985). Likewise, elevated vasopressin has been observed (Riegger, Liebau & Kochsiek, 1982) but there is no evidence to define its role during exercise in this population. More research is required to determine the relationship between the neurohumoral factors and vascular function and exercise intolerance in HF.

1.6.5 Evidence against reduced blood flow

Although the weight of evidence suggests that skeletal muscle blood flow is reduced in patients with HF and probably contributes to altered muscle metabolism during exercise, a noteworthy collection of studies has produced evidence to suggest otherwise (Arnold et al., 1990; Mancini et al., 1988; Massie et al., 1988; Massie et al., 1987a and b; Minotti et al., 1991; Shoemaker et al., 1999; Sullivan & Cobb, 1991; Wiener et al., 1986; Wilson, Martin, Ferraro & Weber, 1983; Wilson, Wiener, Fink & Ferraro, 1986; Wilson, Mancini & Dunkman, 1993; Wilson et al., 1984a). For instance, several studies have observed similar blood flows between HF patients and control subjects (Arnold et al., 1990; Wilson et al., 1986), and numerous studies have demonstrated that no association exists between the metabolic abnormalities observed in HF and impaired blood flow (Massie et al., 1987a; Shoemaker et al., 1999; Wiener et al., 1986). Similarly, a study using ^{31}P-NMR and different types of exercise (Mancini et al., 1988), stair climbing versus plantar flexion, found that metabolic abnormalities were more pronounced during plantar flexion. The authors inferred that intrinsic skeletal

muscle defects rather than muscle underperfusion must be responsible based on the assumption that stair climbing produces a greater cardiovascular stress, thus is more likely to be associated with insufficent muscle blood flow. Two additional studies (Massie et al., 1988; Minotti et al., 1991) using an ischemic model, found that under identical blood flow conditions, HF patients still exhibited greater reductions in pH and PCr than controls. The failure of exercise capacity to rise acutely in the face of enhanced peripheral blood flow (Wilson et al., 1984a; Wilson et al., 1983) suggests that although impaired blood flow may be a significant contributor to the abnormal metabolism and concomitant exercise intolerance observed in HF, other factors must be involved.

Potential reasons for the discrepancies in the literature are: small versus large muscle mass and upper limb versus lower limb protocols, lack of standardized exercise intensities, limitations and differences in blood flow measurement techniques and differences in heart failure severity.

In summary, reduced skeletal muscle blood flow likely contributes to the early onset of anaerobic metabolism in HF and therefore contributes to the exercise intolerance experienced by this population. However, since several researchers have found that blood flow was not the primary limiting factor to exercise capacity, other mechanisms must be involved in producing the reduced oxidative capacity, i.e. intrinsic skeletal muscle alterations.

1.7 Intrinsic Skeletal Muscle Alterations

1.7.1 Fibre atrophy and reduced muscle mass

Skeletal muscle atrophy and a correlation between skeletal muscle atrophy and exercise capacity has been reported in a considerable number of HF studies using various techniques, for example, magnetic resonance imaging (MRI) (Mancini et al., 1992; Minotti et al., 1993); dual energy x-ray absorptiometry (Miyagi, Asanoi, Ishizaka, Kameyama & Sasayama, 1991 and Toth, Gottleib, Fisher & Poehlman, 1997), computerized tomographic scanning (CT scan) (Anker et al., 1997; Harrington et al., 1997; Volteranni et al., 1994), muscle biopsies (Massie, Simonini, Sahgal, Wells & Dudley, 1996; Vescovo et al., 2000), and rat studies (Delp, Duan, Mattson & Musch, 1997; Siminoni et al., 1996). Some biopsy studies have shown that there is substantially greater atrophy of Type II fibres than Type I fibres in patients with HF (Massie et al., 1996; Mancini et al., 1989; Sullivan, Green & Cobb, 1990). This is in contrast to healthy subjects, where following a period of inactivity there is similar atrophy of all fibre types (Lindboe & Platou, 1982). By measuring VO_2 peak in HF patients during lower limb only versus lower and upper limb exercise, Jondeau et al. (1992) demonstrated that patients with HF are able to substantially increase VO_2 peak during upper and lower body exercise versus lower body only exercise. This is in contrast to healthy subjects, where combined upper and lower limb exercise is unable to increase VO_2 peak over that achieved during lower limb only exercise. These results indirectly indicate that insufficient active muscle mass and not cardiac output is a predominant limiting factor during maximal exercise in patients with HF.

It is important to note that not all studies have provided support for muscle atrophy as the basis for the metabolic irregularities seen in HF. A muscle biopsy study by Schaufelberger et al. (1997) found that fibre area was not altered in patients with HF compared to normal subjects, however, the authors suggested that the differing results may be attributed to varying levels of physical activity in the subject pool.

In conclusion, it appears that even though skeletal muscle atrophy is present in numerous HF patients, it is not the sole reason for the metabolic alterations seen in this population.

1.7.2 Altered muscle function

Despite reductions in muscle mass, some groups have reported a preservation of muscle strength accompanied by a reduction in muscular endurance in patients with HF (Harridge, Magnusson & Gordon, 1996; Minotti, Christoph & Massie, 1992; Minotti et al., 1993). For example, in the study by Minotti and group (1993), HF patients had similar knee extensor isometric strength to maximal cross-sectional area ratio suggesting that the force generated per cross-sectional area of muscle was not impaired. The authors concluded that any reductions in strength were due to smaller muscle size and not reduced strength per muscle fibre. In this same study however, dynamic endurance of the knee extensors was found to be significantly reduced in HF patients. It was suggested that the fibre type shift noted in HF (i.e. shift from type I to type II) may account for the reduced dynamic endurance in the presence of maintained muscular strength. In contrast, Harrington and colleagues (1997 and 2001) have shown a reduced strength per unit

muscle cross sectional area (Harrington, Anker & Coats, 2001; Harrington & Coats, 1997). Moreover, the demonstration of a strong correlation between quadriceps muscle strength and exercise capacity indicated that impaired muscle function may contribute to the reduced systemic exercise tolerance. In fact, among HF patients and control subjects with similar exercise capacities, no significant differences in muscle size or function were observed, further implicating leg muscle dysfunction in the exercise intolerance of HF. These results are supported by Volteranni and group (1994) who found that right quadriceps strength was the most important individual correlate of exercise tolerance as measured by peak oxygen consumption. If there is an apparent reduction in strength per unit muscle cross-sectional area, it may be due to increased fat content which would cause an overestimation of cross sectional area and thus an underestimation of strength per unit muscle. Possible anatomic arrangement alterations of muscle fibres may also play a role (Harrington & Coats, 1997).

1.7.3 Structural abnormalities

1.7.3.1 Fibre type shift

There is a general consensus that a shift from type I (high aerobic-oxidative activity) to type II (low aerobic-oxidative activity) fibres occurs in patients with HF. For instance, several biopsy studies have shown a smaller percentage of type Ia fibres and a larger percentage of type IIb fibres in HF patients compared to controls (Drexler et al., 1992b; Mancini et al., 1989; Massie et al., 1996; Schaufelberger et al., 1997; Sullivan et al., 1990; Vescovo et al., 1996; Vescovo et al., 2000) and these results are supported by

data from animal investigations (Delp et al., 1997; De Sousa et al, Veksler, Bigard, Mateo & Ventura-Clapier, 2000; Simonini et al., 1996). An important finding noted in a small number of the biopsy studies is that although there was an increased percentage of type IIb fibres, the area of these fibres was also reduced (Mancini et al., 1989; Massie et al., 1996; Sullivan et al., 1990). This increase in percentage accompanied by a decrease in area makes the overall impact of the shift difficult to resolve.

^{31}P-NMR studies also support the above findings in that the metabolic changes support a shift from slow oxidative fibres to fast glycolytic fibres which are more susceptible to acidosis and fatigue and exhibit greater reductions in PCr (Kemp et al., 1996; Massie et al., 1987b; Massie et al., 1988).

Further evidence for a fibre type shift was observed in a study investigating whole muscle contractile characteristics and fatigue resistance. It was found that patients with HF possess muscles that are faster to contract and less resistant to fatigue, properties which are characteristic of type II and IIb fibres (Harridge et al., 1996). Finally, the fibre type shift in HF has been associated with reduced exercise capacity (Sullivan et al., 1990; Vescovo et al., 1996; Vescovo et al., 2000).

1.7.3.2 Reduced capillarization

The literature regarding capillarization in patients with HF is inconclusive. Two studies have shown no differences between HF and healthy controls in the number of capillaries surrounding each fibre (Mancini et al., 1989; Massie et al., 1996), whereas two studies (Schaufelberger et al., 1997; Sullivan et al., 1990) and one animal study (De Sousa et al., 2000) have shown a decrease in the number of capillaries surrounding each

muscle fibre. In addition, differences in capillary density have been noted such that three studies have found no differences in capillary density compared to controls (Mancini et al., 1989; Massie et al., 1996; Schaufelberger et al., 1997), while two studies have noted a reduction of capillary density in HF patients (Drexler et al., 1992b; Sullivan et al., 1990).

Evaluation of capillary density is problematic due to sampling errors, measurements are proportional to the number of type I and II fibres, and results are influenced by alterations in fibre atrophy (Lindsay et al., 1994). In addition, a recent study noted that females with HF had slightly increased capillary densities while men showed significant reductions (Duscha, Annex, Green, Pippen & Kraus, 2002). These results imply that findings from earlier studies may have been confounded by gender differences. Clearly, more conclusive results are needed before the role of capillary density in HF can be determined.

1.7.3.3 Reduced mitochondrial density

An extensive ultrastructural analysis of 57 patients with HF demonstrated that the volume density of mitochondria and the surface density of mitochondrial cristae were significantly reduced compared to healthy individuals (Drexler et al., 1992b). These results indicate a decreased oxidative capacity in skeletal muscle in HF. It is of interest that the decreases in volume density and cristae surface density of mitochondria occurred predominantly in patients with severe impairment and were significantly related to reduced exercise capacity. Reduced mitochondrial content has also been shown by reduced succinate dehydrogenase activity which is an estimate of mitochondrial content (Massie et al., 1996). In addition, a strong relation between succinate dehydrogenase

activity and VO_2 peak was observed in HF patients but not for controls implying that impairment of aerobic-oxidative enzyme capacity may be significant in contributing to exercise capacity in HF.

1.7.4 Biochemical alterations

1.7.4.1 Reduced oxidative enzyme activity

Numerous investigations have demonstrated that oxidative enzyme activity is reduced in the HF state (Delp et al., 1997; De Sousa et al., 2000; Duscha et al., 2002; Mancini et al. 1989; Schaufelberger et al., 1997; Schaufelberger et al., 1996; Siminoni et al., 1996; Sullivan et al., 1990; Sullivan et al., 1991). Sullivan et al. (1990) demonstrated reduced mitochondrial enzyme activity at rest, as indicated by reductions in the activity of succinate dehydrogenase, citrate synthase and 3-hydroxylacyl-CoA-dehydrogenase. No differences were found between HF subjects and controls for glycolytic enzymes. An exercise study by the same group extended these results (Sullivan et al., 1991) by demonstrating that reduced skeletal muscle aerobic enzyme activity was a determining factor in the metabolic response to submaximal exercise in HF as indicated by an inverse relationship between blood lactate accumulation and oxidative enzyme activity. A study by Drexler et al. (1992b) also found an impairment in aerobic enzyme activity (as evidenced by a reduction in cytochrome oxidase activity) however they also observed a relationship between this reduction in enzyme activity and exercise capacity.

Overall it appears that in HF there is a reduction in the activity of oxidative enzymes. These alterations undoubtedly contribute to the modified metabolism observed in this population.

1.7.4.2 Intracellular Ca^{2+} accumulation and slowed pump activity

Patients with HF have been shown to have an increase in triads (triadic junctions of two L tubule cisternes and one terminal T tubule cisterne), which represent a measure of intracellular and extracellular calcium transport (Drexler et al., 1992b). This finding raises the possibility that increased Ca^{2+} overload may be occurring in the muscle and thus could contribute to the altered metabolism. In support of this finding, data from a study by Peters et al. (1997) indicated that such a skeletal muscle defect is in part due to a decreased protein expression of the predominant skeletal muscle sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) isoform. Support for this finding came from a similar rat study which showed that the SERCA-2a isoform protein was reduced by 16% and the SERCA-2a messenger RNA was reduced by 59% in rats with postinfarction HF (Simonini, Chang, Yue, Long, & Massie, 1999). Finally, down regulation of Na^{+}-K^{+} pumps in oxidative skeletal muscle may play an important role in exercise intolerance in HF since impairment of these pumps could interfere with contractile performance through reductions in membrane excitability (Musch, Wolfram, Hageman & Pickar, 2002).

In conclusion, it appears that intrinsic skeletal muscle abnormalities contribute to the metabolic abnormalities and reduced exercise tolerance observed in HF. The origin of these abnormalities has yet to be clarified, however deconditioning appears to be the most probable candidate.

1.8 What is the Origin of these Changes?

It has been established that patients with HF have abnormal skeletal muscle metabolism during exercise. Furthermore, this altered metabolism appears to be associated with various intrinsic skeletal muscle changes and reduced skeletal muscle blood flow, both of which have been associated with reduced exercise capacity. However, researchers have yet to resolve the cause of these changes. There are several postulated mechanisms, including, physical deconditioning (Chati et al., 1996; Drexler et al., 1992b; Mancini et al., 1989), changes in ventricular function (Chati et al., 1996), caloric protein malnutrition (Wilson & Mancini, 1993), alterations in skeletal muscle innervation (Mancini et al., 1989), neurohumoral effects (Drexler & Coats, 1996), increased plasma levels of tumor necrosis factor (Levine, Kalman, Mayer, Fillit & Packer, 1990), a metabolic myopathy (De Sousa et al., 2000), and elevated cortisol levels (Wilson & Mancini, 1993).

Of all the possible mechanisms, the majority of evidence appears to support physical deconditioning as the basis for the metabolic abnormalities seen in patients with HF. However, it is difficult to determine how deconditioning is involved. As described by Minotti et al. (1990), "[in patients with HF], muscle fatigue is the primary determinant of exercise capacity. Consequently, activity is limited to avoid fatigue, which undoubtedly causes deconditioning and leads to a cycle of progressively worsening exercise tolerance." This description reveals the complex interrelationship between deconditioning and HF.

If the reduced oxidative capacity in HF patients is indeed the result of deconditioning, it would seem reasonable that comparable abnormalities would be present in persons with sedentary lifestyles. In addition, disuse studies on healthy individuals should show similar trends.

There are many similarities between the abnormalities associated with HF and those seen in physical deconditioning. In both conditions, there is exercise intolerance, sympathetic hyperactivity, wasted skeletal muscles, decreased fibre size and depleted oxidative enzymes (Adamopoulos & Coats, 1991). For example, in a study by Chati et al. (1996) using ^{31}P-NMR, skeletal muscle metabolism in sedentary but otherwise healthy subjects was similar to that of HF subjects. Likewise, Harrington et al. (2001) demonstrated that asymptomatic patients with severely impaired left ventricular systolic function did not have the peripheral abnormalities observed in symptomatic patients. These results suggest that the peripheral changes in HF are not an inevitable consequence of left ventricular dysfunction but may be the result of patients avoiding activity because of symptoms. Although physical deconditioning may play a primary role in stimulating the peripheral limitations in heart failure, the normal physiological consequences of disuse (Berg, Dudley, Hather & Tesch, 1993; Lindboe & Platou, 1982) are moderate compared to those associated with HF. Therefore, most studies show that the peripheral changes in HF cannot be entirely explained by deconditioning alone (Duscha et al., 2002; Massie et al., 1996; Sullivan et al., 1990; Vescovo et al., 1996).

2.0 EXERCISE TRAINING AND HEART FAILURE

Traditionally, bed rest was advocated for HF patients and exercise training interventions were only applied to patients with stable coronary artery disease with no evidence of HF (Smith, TW, Braunwald, E, & Kelly, R, 1988). Research as early as 1979 (Lee, Ice, Blessey & Sanmarco, 1979) however, has established that exercise training in stable HF patients is safe, feasible and results in significant patient benefits.

Findings from over sixty training studies involving HF patients were reviewed. HF training studies have employed a variety of training protocols including cycling, walking, arm cycling, rowing, calisthenics, localized muscle training, and cardioresistance training. Stable HF patients with mild to moderate symptoms (NYHA-FC I-III) have been predominantly used as subjects in these studies.

2.1 Exercise Training and Functional Capacity

An increase in exercise capacity as measured by peak oxygen consumption has been observed in essentially all HF training studies. Investigations which observed no changes in VO_2 peak generally involved peripheral muscle training (Cider et al., 1997; Hare et al., 1999; Pu, Johnson, Forman, Piazza & Fiatarone, 1997) or may not have used an adequate training stimulus (Giannattasio et al., 2001). In addition, one study noted that only men with HF exhibited improved oxygen consumption while female participants did not (Willenheimer, Erhardt, Cline, Rydberg & Israelsson, 1998). Most studies have also noted increased exercise time, peak work rate, reduced heart rate at rest

and submaximal exercise, a delayed anaerobic threshold as well as improved ventilation during graded exercise testing.

Similarly, studies employing the 6-MWT as a measure of functional capacity have reported significant increases in walking distance following training in HF (Kavanagh et al., 1996; Kostis, Rosen, Cosgrove, Shindler & Wilson, 1994; Meyer et al., 1997c; Parnell, Holst & Kaye, 2002; Sindone, Sammel, Keech, Macdonald & Keogh, 1998; Tyni-Lenné, Gordon, Jansson, Bermann & Sylvén, 1997). Studies which did not find significant increases in walking distance involved resistance training (Hare et al., 1999) or found a significant improvement in HF without a significant difference between HF and control subjects (McKelvie et al., 2002).

Functional class (as reported by New York Heart Association Functional Classification) has also been shown to improve following exercise training in HF (Delagardelle, Feiereisen, Krecké, Essamri & Beissel, 1999; Hambrecht et al., 1998; Hambrecht et al., 2000; Hambrecht et al, 1995; Kavanagh et al., 1996; Kiilavuori, Souijärvi, Nävari, Ikonen & Leinonen, 1996; Lee et al., 1979; Meyer et al., 1997c; Quittan et al., 1999; Sindone et al., 1998).

2.2 Exercise Training and HRQL

Improved QOL as measured by the Minnesota Living with Heart Failure Questionnaire has not been consistently shown in training studies. Two studies have shown improvement (Belardinelli, Georgiou, Cianci & Purcaro, 1999; Parnell et al., 2002) whereas a number of studies have shown no improvement in QOL following

training using this measurement tool (Keteyian et al., 1999; McKelvie et al., 2002; Wilson, Groves & Rayos, 1996). The discrepant findings may be due to insufficient sample sizes (Keteyian et al., 1999), poor compliance to the exercise program (McKelvie et al., 2002) and problems with the questionnaire approach (Wilson et al., 1996). However, studies which used other questionnaires, have suggested improved QOL after exercise training in the HF population (Coats, Adamopoulos, Meyer, Conway & Sleight, 1990; Giannuzzi et al., 1997; Kavanagh et al., 1996; Koch, Douard & Broustet, 1992; Oka et al., 1998; Sindone et al., 1998; Squires, Lavie, Brandt, Gau & Bailey, 1987; Tyni-Lenné et al., 1997; Wielenga et al., 1999; Willenheimer et al., 1998).

2.3 Exercise Training and Cardiac Function

One of the first studies to investigate exercise training in HF found a dramatic increase in physical work capacity without any improvement or deterioration in resting left ventricular function (Lee et al., 1979). This study, along with many studies to follow, provided evidence that patients with HF can benefit from training programs while experiencing little or no changes in ventricular function (Adamopoulos et al., 1993; Belardinelli et al., 1999; Belardinelli, Georgiou, Scocco, Barstow & Purcaro, 1995b; Delegardelle et al., 1999; Dubach et al., 1997a and b; Giannattasio et al., 2001; Jetté, Heller, Landry & Blümchen, 1991; Koch et al., 1992; Kostis et al., 1994; Magnusson et al., 1996; McKelvie et al., 2002; Parnell et al., 2002; Pu et al., 1997; Sullivan, Higginbotham & Cobb, 1988; Willenheimer et al., 1998).

Studies that have found significant improvements in cardiac function have shown increases in maximum cardiac output (Coats et al., 1992; Dubach et al., 1997a; Dziekan et al., 1998), increases in contractility (Belardinelli, Georgiou, Ginzton, Cianci & Purcaro, 1998), increases in LVEF (Belardinelli et al., 1998; Giannuzzi et al., 1997; Kellerman et al., 1990), and diastolic filling (Belardinelli, Georgiou, Cianci & Purcaro, 1996; Belardinelli et al., 1995a). Hambrecht et al. (1995) found that after six months of aerobic training, HF patients demonstrated significant improvements in maximal cardiac output and a reduction in left ventricular end-diastolic dimension (LVEDD), however, the significant increase in exercise capacity was predominantly due to an increased oxidative capacity of skeletal muscle. A more recent study by the same group (Hambrecht et al., 2000) demonstrated improvements in ventricular function as indicated by increased resting and peak exercise stroke volumes, increased maximum cardiac output, reduced LVEDD, and improved resting left ventricular ejection fraction. The authors also found a significant reduction in total peripheral resistance which was significantly correlated with the changes in stroke volume and LVEDD, suggesting that regular exercise may reduce afterload which may then lead to significant improvements in stroke volume and reduced cardiomegaly. Similar results from the Exercise in Left Ventricular Dysfunction Trial (ELVD Trial) (Giannuzzi et al., 1997) demonstrated that exercise training attenuates unfavorable remodeling as observed by reduced wall motion abnormalities and increased left ventricular ejection fraction (increase of 12%). The authors proposed that these changes may have been due to a "true" increase in contractile performance, via a decrease

in ventricular wall stress through peripheral adaptations and/or improved myocardial perfusion.

In general it appears that HF patients can benefit from exercise training without necessarily achieving significant increases in cardiac function. Thus, improvements in exercise capacity may be primarily due to peripheral adaptations.

2.4 Exercise Training and Skeletal Muscle Metabolism

Numerous studies have established that some of the metabolic abnormalities associated with HF can be reversed by exercise training as evidenced by reduced blood lactate at rest and/or during submaximal exercise (Barlow et al., 1994; Belardinelli et al., 1995b; Hambrecht et al., 1995; Kiilavuori et al., 1996; Meyer et al., 1996; Sullivan et al., 1988; Tyni-Lenné et al., 1997). Enhanced regulation of skeletal muscle metabolism during exercise after training has also been shown through smaller reductions in PCr (Adamopoulos et al., 1993; Ohtsubo et al., 1997; Stratton et al., 1994a), pH (Adamopoulos et al., 1993; Ohtsubo et al., 1997; Stratton et al., 1994a), an enhanced PCr recovery rate (Adamopoulos et al., 1993; Kleuss, Welsch, Properzio, Scott & Pollack, 1996; Stratton et al., 1994) and smaller increases in ADP (Adamopoulos et al., 1993; Minotti et al., 1990). These results suggest an increased capacity for oxidative metabolism and a decreased reliance on glycolysis.

2.5 Exercise Training and Blood Flow

The effect of exercise training on exercising muscle blood flow and vascular function has been investigated in HF. A decrease in total peripheral resistance (Coats et al., 1992; Hambrecht et al., 2000) has been noted, but not in all studies (Dubach et al. 1997a). Vasodilatory capacity and blood flow of limb resistance vessels has also been increased with exercise training in some studies (Demopoulos et al., 1997; Hambrecht et al., 1998; Hare et al., 1999; Katz, Yuen, Bijou & LeJemtel, 1997; Maiorana et al., 2000b) whereas others have shown no increase (Dziekan et al., 1998; Minotti et al., 1990; Ohtsubo et al., 1997). Studies of radial artery function (Giannattasio et al., 2001; Hornig, Maier & Drexler, 1996; Linke et al., 2001) and femoral venous blood flow (Hambrecht et al., 1995; Sullivan et al., 1988) have also demonstrated enhanced vasodilatory function and blood flow in patients with HF following exercise training. Some investigators have argued that the enhanced vasodilation is confined to the trained area (Demopoulos et al., 1997; Hornig et al., 1996) while others support a generalized circulatory effect (Linke et al., 2001; Maiorana et al., 2000b).

2.5.1 Mechanisms of increased blood flow

2.5.1.1 Improved vascular compliance

To date, the effect of exercise training on arterial compliance in HF has only been investigated in a single study (Parnell et al., 2002). Eight weeks of walking, light hand weights and stationary cycling produced a significant increase in systemic arterial compliance as determined by flow through the ascending aorta.

2.5.1.2 Improved endothelial function

The weight of evidence appears to support improved endothelial function as the mechanism behind the enhanced blood flow and improved vasodilation. Several studies have observed increased acetylcholine-mediated vasodilation (Hambrecht et al., 1998; Katz et al., 1997; Maiorana et al., 2000b) and an enhanced blood flow reduction in response to L-NMMA (Hambrecht et al., 1998; Hornig et al., 1996). Moreover, numerous studies have shown that the adaptation to exercise training is localized to the endothelium as there were unaltered smooth muscle responses to nitroglycerin (Linke et al., 2001; Niebauer et al., 1998) and sodium nitroprusside (Hornig et al., 1996; Maiorana et al., 2000b). Finally, Hambrecht and group (2000) found a correlation between reduced total peripheral resistance and ACh induced (endothelium-dependent) vasodilation of skeletal muscle vasculature suggesting that exercise training may exert its primary effects on the endothelium of the peripheral vasculature.

2.5.1.3 Reduced neurohormonal activation

Exercise training has also been associated with a shift from sympathetic to vagal modulation of cardiac function as evidenced by increased heart rate variability (Coats et al., 1992; Kiilavuori, Toivonen, Nävari & Leinonen, 1995) and reduced neurohormone levels (Belardinelli et al., 1995b; Braith, Welsch, Feigenbaum, Kleuss & Pepine, 1999; Coats et al., 1992; Hambrecht et al., 2000; Maskin, Reddy, Gulanick & Perez, 1986). Studies which failed to show changes in sympathetic drive (Barlow et al., 1994; Cider et al., 1997; Ohtsubo et al., 1997) may be explained by either the type (localized muscle

training), intensity, or environment (home-based versus supervised) of training. No studies have shown an association between the increase in vascular function and the shift from sympathetic to vagal modulation. For instance, Hambrecht et al. (1995 and 2000) failed to show any correlation between the change in catecholamine levels and reduced peripheral resistance after exercise training. Based on these results, other determinants of vasodilatory capacity must be involved, such as reduced compliance, activation of the renin-angiotensin system, increased endothelin levels and endothelial dysfunction.

2.6 Exercise Training and Intrinsic Skeletal Muscle Alterations

2.6.1 Increased muscle mass and reduced fibre atrophy

Localized muscle training in HF has been shown to increase the cross-sectional area of the forearm (Katz et al., 1997), calf (Ohtsubo et al., 1997) and quadriceps muscles (Magnusson et al., 1996). In contrast, Minotti et al. (1990) found no change in cross-sectional area of the forearm following localized wrist flexor training perhaps due to an inadequate training stimulus. Increases in mean fibre area have also been observed in the vastus lateralis of patients with HF following exercise training (Belardinelli et al., 1995b; Magnusson et al., 1996; Tyni-Lenné, Janson & Sylven, 1999). Based on these results it appears that exercise training, specifically localized muscle training, can improve muscle mass and reduce the number of atrophied fibres. Furthermore, the training-induced increase in muscle fibre area has been shown to be significantly correlated with increases in peak oxygen uptake (Tyni-Lenné et al., 1999).

2.6.2 Improved muscle function

Not surprisingly, the increases in muscle size have been associated with increases in muscle function. Numerous studies have demonstrated increases in muscle strength (Delagardelle et al., 1999; Hare et al., 1999; Katz et al., 1997; Koch et al., 1992; Magnusson et al., 1996; Maiorana et al., 2000a; McKelvie et al., 2002; Ohstubo et al., 1997; Pu et al., 1997; Stratton et al., 1994a; Tyni-Lenné et al., 1999) as well as increases in muscle endurance (Delagardelle et al., 1999; Hare et al., 1999; Minotti et al., 1990; Pu et al., 1997) in HF patients following various types of exercise training.

2.6.3 Structural and biochemical alterations

2.6.3.1 Fibre type shift

Data regarding the effects of training on fibre type distribution are inconsistent. Two studies have found unaltered fibre type distributions following knee extensor training (Magnusson et al., 1996) and cycling (Belardinelli et al., 1995b) whereas Hambrecht et al. (1997) found a "reshift" from Type II fibres to Type I fibres which was significantly correlated with increases in peak oxygen uptake. Tyni-Lenné and group (1999) investigated the effects of knee extensor training in females with HF and found that at baseline, although the HF patients showed greater atrophy, there was no significant difference in the mean number of type I fibres between the females with HF and healthy, age-matched controls. Furthermore, exercise training decreased the relative number of type I fibres with a shift to type II fibres. Clearly more studies are needed to

understand the effects of exercise training on fibre type distribution in HF in both men and women.

2.6.3.2 Capillarization

As mentioned earlier, the cross-sectional data regarding capillary density and HF patients is inconclusive. The same uncertainty exists about the effects of training on capillary density in this population. Magnusson et al. (1996) showed a significantly increased capillary per fibre ratio and increased capillary density in HF patients after eight weeks of supervised knee extensor training. Conversely, Belardinelli and colleagues (1995b) found no change in the capillary per fibre ratio and only a slight, non-significant increase in capillary density after eight weeks of supervised, low intensity cycling. Clearly, more research is necessary.

2.6.3.3 Increased mitochondrial density and oxidative enzyme activity

Exercise training studies of patients with HF have demonstrated an increase in the volume density of mitochondria which was significantly correlated with an improvement in maximum exercise capacity (peak oxygen consumption) (Belardinelli et al., 1995b; Hambrecht et al., 1995). In addition, exercise training has produced an increase in oxidative enzyme activity (Gordon, Tyni-Lenné, Jansson, Jensen-Urstad & Kaijser, 1999; Magnusson et al., 1996; Tyni-Lenné et al., 1997).

2.7 Summary and Statement of Purpose

In HF, exercise tolerance is predominantly limited by dyspnea and fatigue resulting from cardiac limitations, peripheral vascular factors, hormonal disturbances,

ventilatory disorders and skeletal muscle abnormalities (McKelvie et al., 1995; Shephard, 1997; Wielenga, Coats, Mosterd & Huisveld, 1997). Traditionally, bed rest was advocated for HF patients and exercise training interventions were only applied to patients with stable coronary artery disease with no evidence of HF (Smith, TW, Braunwald, E, & Kelly, R, 1988). HF research as early as 1979 (Lee et al., 1979) however, has established that stable HF patients can benefit from exercise training. Exercise training in patients with stable HF with mild to moderate symptoms (NYHA-FC II and III) has resulted in improvements in exercise performance, autonomic function, skeletal muscle impairments, and HRQL (Meyer, 2001). It remains to be determined whether severe HF patients (NYHA class III-IV) may benefit from such training programs as they have essentially been excluded from previous studies due to their potentially unstable nature and severe exercise intolerance. Additionally, as supported by a recent review (Meyer, 2001), exercise training should focus on training the periphery without significant increases in cardiac loading. The majority of studies have employed steady state cycle ergometry or treadmill training protocols which may not be applicable to patients with severe HF.

The body-weight supported treadmill (BWST) is ideal for persons with weak leg muscles and impaired cardiovascular function because it has a parachute-like harness which partially lifts a person while they are walking on a treadmill. BWST training has been shown to be safe and effective in a variety of patient populations, including, spinal cord injured, stroke, brain damage, cerebral palsy and multiple sclerosis. Results have included increased walking capacity, enhanced walking efficiency, and improved

functional independence (Laufband Therapy Symposium, 2000). There have been no studies to date examining the role of BWST training in HF patients.

BWST training may be beneficial in patients with severe HF by enhancing walking capacity while minimizing cardiac loading. With body weight support, it is likely that steady state walking may be performed at greater speeds and for longer periods of time than could otherwise be achieved by unsupported walking, thus promoting peripheral benefits.

The purpose of this study was to: 1) assess the safety and feasibility of BWST training in severe HF patients and 2) to evaluate the effect of BWST training on functional capacity, health related quality of life, cardiopulmonary function, and blood vessel function.

The substantive hypothesis states that this training program will produce: (1) an increase in functional capacity (i.e. increased 6 Minute Walk Test (6MWT) distance and improved NYHA-FC); (2) improved Health Related Quality of Life (HRQL); (3) enhanced cardiopulmonary function (i.e. increased peak oxygen uptake (VO_{2peak}), reduced resting and submaximal heart rate (HR), increased exercise time, and improved ventilation (V_E)); and (4) enhanced blood vessel function (increased vascular compliance).

3.0 METHODS

3.1 Subjects

Four patients with severe HF were enrolled into the study. The patients were recruited through the Heart Function Clinic at McMaster University Medical Centre, Hamilton, Ontario.

Patients were included if they met the following criteria: (1) age 18 years and over; (2) NYHA class III or IV; (3) 6-MWT distance less than 300m; (4) stable on Beta-blockers and ACE Inhibitors for at least 4 weeks; and (5) ability to read and comprehend English.

Exclusion criteria were as follows: (1) angina CCS III or more; (2) documented left main artery stenosis (≥50%) on coronary angiogram; (3) stroke with significant residual deficit; (4) significant abnormal lung function; (5) arthritis or any other significant orthopedic limitation; and (6) significant peripheral vascular disease.

3.2 Study Design

This was a non-randomized, non-controlled clinical study. The study protocol was reviewed and received ethics clearance through the Hospital Research Ethics Board and all patients gave informed, written consent before participating.

On study entry and at the end of 24 sessions of physician supervised BWST training, patients completed a cardiopulmonary exercise test, two Health Related Quality of Life questionnaires, a 6MWT, and an Echo Doppler study. All testing procedures were completed in a two week period before and after training in the following sequence:

Day 1: The HRQL questionnaires were completed. These questionnaires were always completed prior to any other testing.

Day 2: The screening 6MWT test was completed. This was only performed prior to training as it was a screening test for participation in the study.

Day 3: The cardiopulmonary exercise test was completed. (If this test followed a 6-MWT (i.e. prior to training), there were at least two days between the two tests).

Day 4: The Echo Doppler study and the pre-test 6-MWT were completed. These tests followed the cardiopulmonary exercise test by at least three days and the Echo Doppler study was performed prior to the 6-MWT.

3.3 Experimental Procedures

3.3.1 Health-related quality of life

The questionnaires were self-administered in a standardized fashion in a private room. Patients were asked to complete two questionnaires: The SF-36 Health Survey and The Minnesota Living with Heart Failure Questionnaire (MLHFQ) (see Appendix A). The SF-36 contains 8 subscales: physical functioning, physical role limitations, social functioning, bodily pain, general mental health, emotional role limitations, vitality, general health, and health transition. Although the interobserver reliability of this questionnaire has not been specifically assessed in HF patients, normative data are available for patients with HF (Ware, 1993). The SF-36 was used for this study because it assesses a wider variety of aspects of QOL that are not included in the MLHFQ (Wenger, 1989). This questionnaire was analyzed as described by Ware (1993) and

transformed scores (scale of 0 to 100) were calculated so that comparisons could be made to normative data. Transformed scores were calculated using the following formula:

$$\textbf{Transformed Score} = \frac{\textbf{(Actual raw score – lowest possible raw score*)}}{\textbf{Possible raw score range*}} \times 100$$

* From Ware, 1993

The MLHFQ includes 21 questions and has a total score, a physical dimension score and an emotional dimension score. This questionnaire has been shown to be both reliable and valid and is disease specific in that it assesses common limitations associated with HF (Rector & Cohn, 1992; Rector, Kubo & Cohn, 1993). The total score is calculated by summing the results from all 21 questions, the physical dimension score is the sum of questions 2-7, 12 and 13 and the emotional dimension score is the sum of questions 17-21.

3.3.2 Functional capacity

A 6-MWT was used to assess functional capacity. This test was performed as a screening measure as well as for pre- and post-testing. Patients were instructed to walk a 20 metre course with the aim of covering as much distance as possible in six minutes. Markers were located along the walking course at 1.5 metre intervals. Patients were permitted to stop, rest and then continue when ready, as needed throughout the walk. During these rest periods, the clock was not stopped. Standardized encouragement was given to the patients at approximately 30 second intervals (e.g. "you are doing well" or "keep up the good work") and the time was called out every two minutes. At the

completion of six minutes, the patients were told to "stop" and the total distance walked was measured to the nearest 0.5 metre. A five minute rest period before and after the walk test was included.

Functional capacity was also assessed by the New York Heart Association Functional Classification (NYHA-FC). The NYHA-FC evaluates functional capacity by assessing symptoms of dyspnea and fatigue during ordinary physical activities. Since this scale is based on the rater's perception of the patient's functional capacity it is somewhat subjective. However, this was controlled for by having the attending cardiologist evaluate all patients using standard descriptions (see Appendix B).

3.3.3 Cardiopulmonary function

A symptom-limited cardiopulmonary exercise test was conducted before and after the 8 weeks of training. The test was performed in the Cardiorespiratory Laboratory at McMaster University Medical Centre. The test was performed on a Quinton upright electronically braked computerized cycle ergometer and the exercise protocol involved one minute stages with increases of 100 kpm/min for each minute. During the test, a 12-lead electrocardiogram (ECG) was recorded with a Marquette system as well as arterial blood pressure at the end of each minute by a cuff sphygmomanometer. Expired gases were analyzed breath by breath using an AVL (Compact 3) gas analyzer. Cardiopulmonary function was determined through peak oxygen consumption (VO_{2peak}), heart rate (HR), peak minute ventilation (V_{Epeak}), and peak power output.

3.3.4 Carotid and femoral blood vessel function

The Echo Doppler measurements were performed by an experienced imaging technician. Arterial diameters and flow velocities for the right carotid and common femoral arteries were measured using simultaneous B-mode and pulsed Doppler ultrasound (GE Vingmed System FiVe) with a high-resolution linear-array transducer (5-10MHz). Blood flow velocity measurements were performed at an insonation angle of between 60 and 68 degrees and were corrected for the insonation angle. The sample volume gate was adjusted to cover the width of the vessel and thus blood velocity distribution in the artery of interest (Gill, 1985). Blood pressure measurements were taken via an automatic inflatable blood pressure cuff placed around the left upper arm (Dinamap Pro 100, Critikon Inc. 1999, Tampa, Florida). Arterial compliance was determined by combining arterial ultrasound imaging with simultaneous blood pressure measurements. Electrocardiogram (ECG) measurements were taken throughout.

Measurements were taken with subjects in a quiet, resting, supine position. A good image (cineloop) of the right carotid artery was obtained at approximately 1.5 cm before the bifurcation to determine the arterial diameter during both systole and diastole. Lumen diameter was defined as the distance between the far-wall boundary, corresponding to the interface between the lumen and intima, and a near-wall boundary, corresponding to the interface of the adventitia and media. Concurrently, Doppler measurements of blood flow velocities were collected for 1 minute. Blood pressure measurements were taken during this time frame as well. The same protocol was used to determine systolic and diastolic diameter and blood flow velocities of the right common

femoral artery. The ultrasound images were obtained below the inguinal ligament, approximately 2-3 cm above the bifurcation into the profundus and superficial branches.

All data were recorded on a super VHS videotape and digitally stored on the Doppler machine for later off-line analysis. Arterial diameters were measured from the digitally stored images using the Echopac Software (GE Medical). This involved examining each digital image within a heart beat to determine the maximum (systolic) and minimum (diastolic) arterial diameter. Two independent investigators measured arterial diameters, and the results were averaged.

Mean blood velocity was also analyzed from digitally stored images of the velocity profiles in each artery. The velocity was taken as the mean flow obtained over several cycles.

The following calculations were used:

Mean Arterial Diameter = (1/3Ds) + (2/3Dd) (mm)

Pulse Pressure = Ps-Pd (mmHg)

Blood flow was calculated using cross-sectional area (CSA) and blood velocity by:

(Mean Blood Velocity x 10) x (CSA/10 000) x 60 x 1000 (ml/min)

Compliance was calculated using the Stiffness Index:

Stiffness Index = [ln(Ps/Pd)]/[(Ds-Dd)/Dd)] (no units)

Where Ps and Pd are systolic (maximum) and diastolic (minimum) pressures and Ds and Dd are systolic (maximum) and diastolic (minimum) diameters.

3.4 Exercise Training

A Woodway (Woodway, USA) Lokosystem treadmill with a dynamic counterbalance weight pulley system was used for BWST training. It has a parachute-like harness which partially lifts a person while they are walking on a treadmill and is therefore ideal for persons with weak leg muscles and impaired cardiovascular function.

Patients trained on the BWST 2-3 days per week until they completed 24 exercise sessions. All patients started at 2 days per week and were graduated to 3 days per week after approximately 6 sessions or 3 weeks. The training duration began at approximately 15 minutes per session with the BWS at 40%. The treadmill speed was set at a comfortable but challenging walking speed based on individual subject abilities. Initial walking speeds ranged from 1.2 km/kr to 2.5 km/hr. Initially, the exercise was performed in 3 minute intervals (i.e. 5x3 minutes) separated by 2-5 minutes of rest depending on subject needs. These interval times were adjusted based on a rating of perceived exertion score (Borg 1-10 RPE scale) (see Appendix C). The goal of the program was for patients to be exercising at an RPE of 3 to 4 ("moderate" to "somewhat severe"). If patients achieved a score of below 3 (i.e. "slight" effort or less), the exercise interval times were increased as tolerated. Treadmill speed was adjusted as needed to maintain a comfortable but challenging walking speed at all times. The BWS was reduced by 10% if 30 minutes of walking was completed. With each BWS, interval times were adjusted to maintain an RPE score of 3 or 4. If unsupported walking was achieved, the harness was still worn by the subject for balance support.

During rest periods, patients remained in the harness, seated on a chair positioned on the treadmill. Water and juice were provided ad libitum.

Safety Precautions. All training sessions were supervised by a physician and an exercise supervisor (trained in automatic external defibrillation and Basic Cardiac Life Support). A "crash cart" was in the training area containing appropriate medications, resuscitation equipment, and an automatic external defibrillator.

Throughout each training session, ECG was monintored continuously and BP (by an automatic inflatable blood pressure cuff) was measured immediately before and after each exercise bout.

4.0 RESULTS

4.1 Patient Characteristics

Seven patients (6 males, 1 female) were approached to participate in the study. Two patients chose not to participate and one patient, after verbally agreeing to participate, underwent heart transplant surgery. Three of the four patients enrolled in the study participated in the training sessions. Patient 4 was admitted to hospital prior to completing all pre-testing and was not discharged throughout the course of the study. Data from Patient 4 will not be included since only the questionnaires and screening 6-MWT were completed. Baseline characteristics for the 3 patients who participated in the training sessions are presented in Table 1. Patients were taking standard anti-failure medications which were not altered throughout the duration of the study (see Appendix D). Of the three patients who enrolled in the study, only one patient (Patient 1) was able to undergo post-testing. However, all patients completed at least 17 of the 24 exercise sessions. The results from this study will be presented in a case study format and changes will be discussed qualitatively since statistical analyses were not performed.

Table 1: Baseline Patient Characteristics

Patient	Age	Gender	NYHA-FC	VO_{2peak} (ml/kg/min)	LVEF (%)	Etiology of HF	Duration of HF (years)
Patient 1	80	M	III	7.2	35	IHD	2
Patient 2	80	M	IV	9.9	35	IHD	2
Patient 3	62	M	III	9.4	20-25	IHD	2

IHD, Ischemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association- Functional Classification

4.2 Adverse Events

The training program was well tolerated by all patients and there were no investigation-related complications during the study. Adverse events unrelated to the study included one syncopal episode requiring hospital admission, one sudden death and one hospital admission for myocardial infarction and ischemic foot resulting in below-knee amputation.

4.3 Results for Patient 1

Patient 1 completed 23 of the 24 training sessions in 9 weeks and 3 days. The last training session had to be cancelled due to a conflict with the testing schedule.

4.3.1 HRQL questionnaires

Results from the MLHFQ show that Patient 1 exhibited increased QOL after training as shown by decreased values for all scores (the total score decreased from 55 to 13, the physical score from 24 to 5 and the emotional score from 13 to 4) (see Table 2).

Table 2: Minnesota Living with Heart Failure Questionnaire

	Patient 1		Patient 2	Patient 3
Subscale	**Pre**	**Post**	**Pre**	**Pre**
Total	55	13	62	63
Physical Dimension	24	5	35	28
Emotional Dimension	13	4	5	12

Results from the SF-36 showed that training improved physical functioning, general mental health, vitality and general health. There appeared to be no change for

bodily pain and social functioning. Patient 1 reported worse values for role limitations (both physical and emotional) after training (see Tables 3 and 4).

Table 3: SF-36 (Raw Scores)

	Patient 1		Patient 2	Patient 3
Subscale	**Pre**	**Post**	**Pre**	**Pre**
Physical Functioning	15	17	12	13
Role Limitations (Physical)	7	4	5	4
Social Functioning	10	9	7	5
Bodily Pain	10.4	12	9.4	7.2
General Mental Health	17	24	28	22
Role Limitations (Emotional)	6	3	5	3
Vitality	14	19	15	7
General Health	16.4	23.4	20.4	10
Health Transition	3	3	3	3

Table 4: SF-36 (Transformed Scores)

	Patient 1		Patient 2	Patient 3	HF normative
Subscale	**Pre**	**Post**	**Pre**	**Pre**	**data***
Physical Functioning	25	35	10	15	47.54
Role Limitations (Physical)	75	0	25	0	34.37
Social Functioning	100	87.5	62.5	37.5	71.31
Bodily Pain	84	100	74	52	62.67
General Mental Health	56.7	80	92	73.3	74.68
Role Limitations (Emotional)	100	0	66.7	0	63.67
Vitality	50	75	55	15	44.29
General Health	57	92	77	25	47.05
Health Transition	50	50	50	50	n/a

* Ware, 1993

4.3.2 6-MWT distance and NYHA - functional classification

As shown by Table 5, Patient 1 appeared to have an increase in 6-MWT distance from 223.5m to 286.0m after training. NYHA-FC was reported as III at baseline and II after training.

Table 5: 6-Minute Walk Test (distance in metres)

Patient	Screening	Pre	Post	Difference
Patient 1	166.0	223.5	286.0	62.5
Patient 2	101.0	108.0		
Patient 3	228.0	270.0		

4.3.3 Cardiopulmonary function

Patient 1 exhibited improved cardiopulmonary function after training as seen by a decreased resting heart rate (96bpm to 79bpm) and heart rate at submaximal exercise (100kpm/min) (105bpm to 84bpm). Peak power output increased from 300 to 400 kpm/min and VO_2 peak and V_E peak increased from 7.2 to 11.7 ml/kg/min and 28 to 39 L/min, respectively (see Table 6).

Table 6: Cardiopulmonary Exercise Test Results

	Patient 1		Patient 2	Patient 3
Variable	**Pre**	**Post**	**Pre**	**Pre**
Resting HR (bpm)	96	79	77	88
Submaximal HR (bpm) (100kpm/min)	105	84	88	90
Peak HR (bpm)	120	120	95	100
Peak Power Output (kpm/min)	300	400	200	300
Peak Power Output (% of max. predicted*)	35	47	21	32
VO_{2peak} (ml/kg/min)	7.2	11.7	9.9	9.4
VE_{peak} (L/min)	28	39	34	42
RER_{peak}	0.80	0.93	0.94	1.08

HR, heart rate, VO_2, oxygen consumption, VE, minute ventilation, RER, respiratory exchange ratio

*kpm predicted maximum = $1506*(height*0.01)^{2.7}*age^{-.46}$ (Killian, K, McMaster University Medical Centre, Hamilton)

4.3.4 Carotid and femoral blood vessel function

BWST training seemed to produce a reduction in resting femoral and carotid blood flow. Carotid and femoral diameters and vascular compliance as measured by the stiffness index were unaffected by training (Table 7).

Table 7: Carotid and Femoral Blood Vessel Function

	Patient 1		Patient 2	Patient 3
Variable	**Pre**	**Post**	**Pre**	**Pre**
Carotid Blood Flow (ml/min)	1305.0	1153.3	error	666.7
Femoral Blood Flow (ml/min)	491.3	335.4	499.6	119.8
Carotid Compliance (Stiffness Index)	13.2	15.8	6.5	8.0
Femoral Compliance (Stiffness Index)	10.8	11.5	6.2	7.1
Carotid Mean Diameter (mm)	8.5	8.6	7.6	8.0
Femoral Mean Diameter (mm)	7.3	7.8	7.6	7.1

4.3.5 Exercise training progression

By the seventeenth exercise session, the BWS for Patient 1 was reduced to zero (Figure 1). In addition, Patient 1 tolerated a gradual increase in speed up to the eighth training session at which point the maximum walking speed that was both comfortable and challenging was achieved (2.2 to 2.4 km/hr) (Figure 2). Thereafter the speed was maintained so that BWS and training duration could be manipulated. Patient 1 also showed a steady increase in exercise duration (15 to 34 minutes) with an accompanying decrease in rest interval times (10 to 5 minutes) (Figure 3).

4.4 Results for Patient 2

Patient 2 completed 17 of the 24 exercise training sessions in 7 weeks. The remaining training sessions and the post-testing measures could not be performed because Patient 2 was admitted to hospital with a second-degree heart block and congestive heart failure. After a pacemaker was inserted and he was discharged home, Patient 2 experienced sudden death. Since post-testing was not performed on this subject, only baseline values will be reported, and a comparison to data from other studies will be made in the discussion.

4.4.1 HRQL questionnaires

See Tables 2 and 3 for pre-testing data.

4.4.2 6-MWT distance and NYHA - functional classification

Patient 2 covered 108.0m during the baseline 6-MWT (Table 5). NYHA-FC was III-IV at baseline and remained so throughout 17 training sessions.

4.4.3 Cardiopulmonary function

At baseline, Patient 2 achieved a VO_2 peak of 9.9ml/kg/min and V_E peak of 34L/min. Maximum power output was 200kpm/min, or 21% of predicted maximum. Resting HR was 77 bpm and HR at submaximal exercise (100kpm/min) was 88bpm (Table 6).

4.4.4 Carotid and femoral blood vessel function

For baseline results see Table 7. Data for carotid artery blood flow could not be analyzed due to a calibration error.

4.4.5 Exercise training progression

A comparison between the first and 17th training session shows that Patient 2 had essentially no change in the duration of exercise (8 to 9 minutes) or rest (10 to 9 minutes) intervals (Figure 3). There was no change in BWS throughout training (40%) (Figure 1), and a slight increase in walking speed (1.0 to 1.4 km/hr) (Figure 2). It should be noted that the last training session does not represent the "best" values for Patient 2 as there were constant fluctuations in his performance.

4.5 Results for Patient 3

Patient 3 completed 23 of the 24 exercise training sessions in 10 weeks and 3 days. The last day of training and all post-testing measures could not be performed because Patient 3 was admitted to hospital for myocardial infarction and ischemic foot resulting in below-knee amputation. Since post-testing was not performed on this subject, only baseline values are reported, and a comparison to data from other studies will be made in the discussion.

4.5.1 HRQL questionnaires

See Tables 2 and 3 for pre-testing data.

4.5.2 6-MWT distance and NYHA - functional classification

Patient 3 covered 270.0m during the 6-MWT at baseline (Table 5). NYHA-FC was III at baseline and did not change during the training period.

4.5.3 Cardiopulmonary function

At baseline, Patient 3 achieved a VO_2 peak of 9.4ml/kg/min and V_E peak of 42L/min. Maximum power output was 300kpm/min or 32% of predicted maximum. Resting HR was 88 bpm and HR at submaximal exercise (100kpm/min) was 90bpm (Table 6).

4.5.4 Carotid and femoral blood vessel function

For baseline results see Table 7.

4.5.5 Exercise training progression

A comparison of the first and 23rd training sessions shows that Patient 3 had an increase in training duration (15 to 21 minutes) with a decrease in rest interval time (20 to 7 minutes) (Figure 3). Patient 3 had no reduction in BWS (40%) (Figure 1) and essentially no change in walking speed (2.5 to 2.1 km/hr) (Figure 2). It should be noted that Patient 3 exhibited considerable day to day variability in training performance with several days producing better performance than the results of the last day.

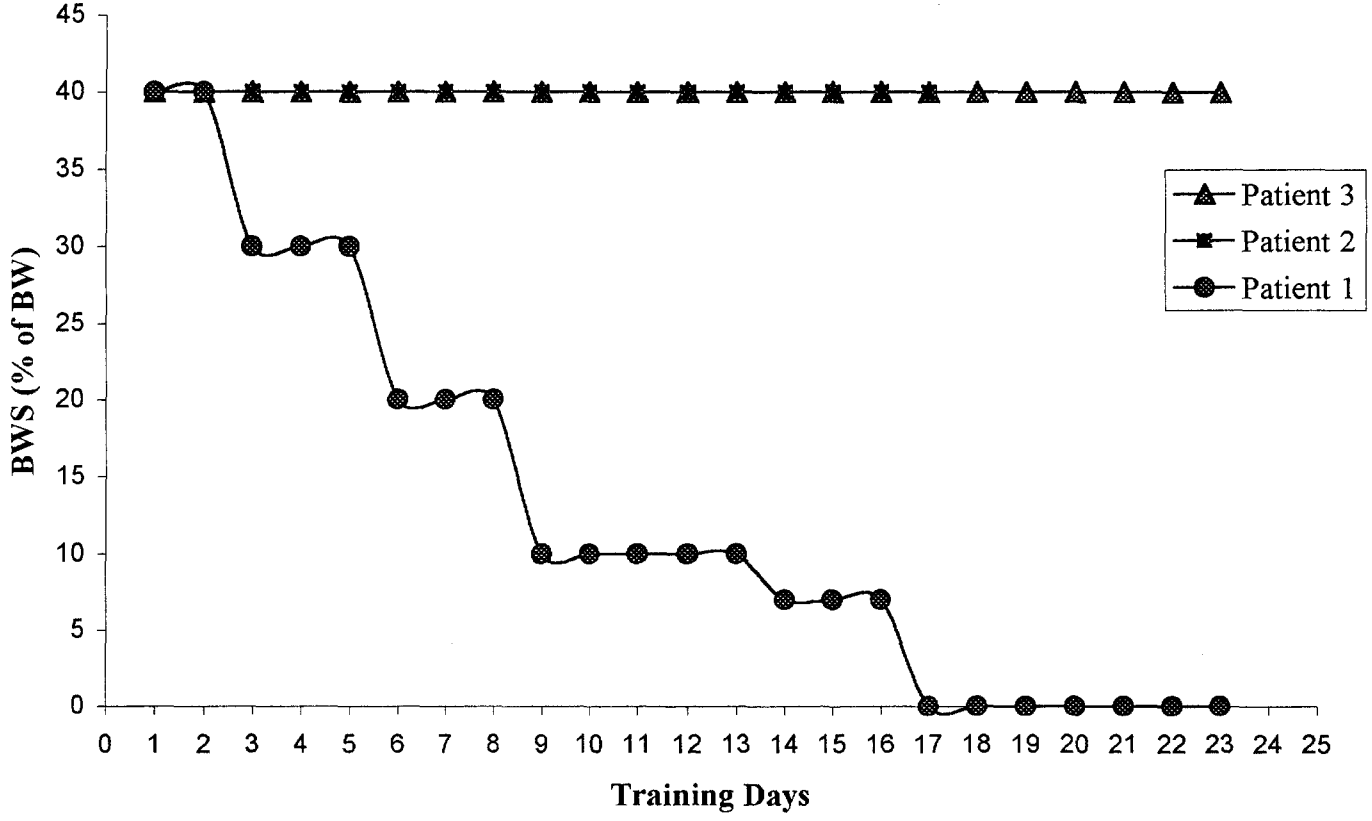

Figure 1: Body-weight support for all training days for all three subjects

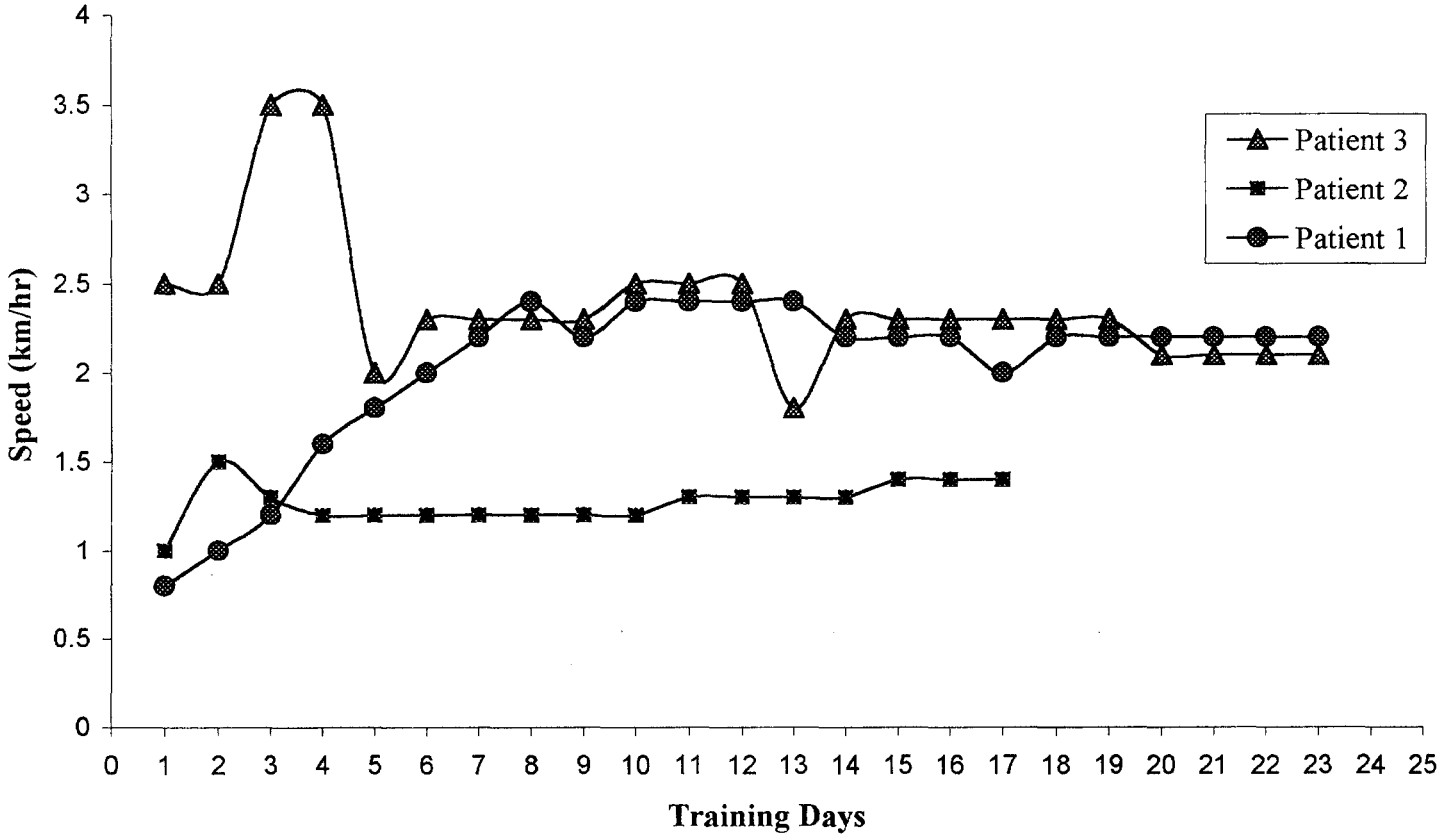

Figure 2: Speed of treadmill for all training days for all three subjects

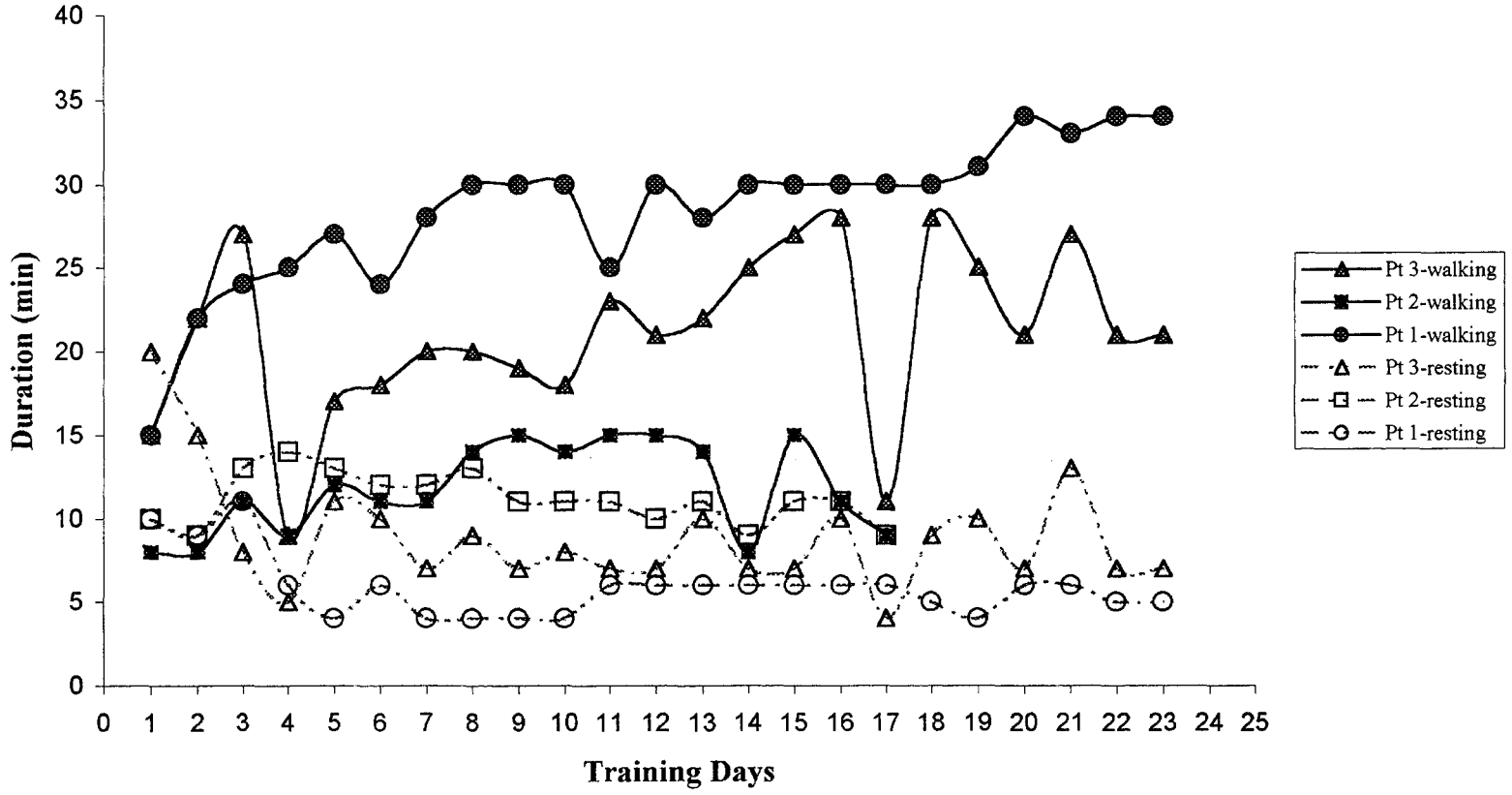

Figure 3: Duration of exercise and rest intervals for all training days for all three subjects

5.0 DISCUSSION

The purpose of this study was two-fold. First, to determine if exercise training is safe and feasible in severe HF patients and second, to determine if body-weight supported treadmill training is an effective training modality for this population.

5.1 Safety of Exercise Training in Patients with Severe Heart Failure

Three patients with severe HF were able to participate in a thrice weekly exercise training program without any study-related adverse events. At no point was a training session stopped due to exercise-induced hypotension, arrythmias or other exercise-related complications. Furthermore, after each training session, patients did not experience worsened symptoms or signs to suggest a negative response to exercise. Based on the response of these three subjects and the few studies which have included patients of this HF class (Belardinelli et al., 1999; Demopoulos et al., 1997; Magnusson et al., 1996; Meyer et al., 1996, 1997a, b and c), it appears that patients with severe HF can safely participate in an exercise training program which does not produce excessive cardiovascular stress. This is in accordance with the review by Meyer (2001) who proposed that patients with HF are eligible for exercise rehabilitation as long as the exercise focuses on the periphery without stimulating a significant cardiovascular load.

5.2 Feasibility of Exercise Training in Severe Heart Failure Patients

5.2.1 The exercise training progression (all three patients)

As mentioned, there were no adverse events associated with exercise training in this study. In fact, the HF patients responded well to exercise training despite the severity of their condition. Although Patient 1 displayed the greatest progress, Patient 3 and Patient 2 also tended to perform better as the exercise training proceeded.

Patient 1's attendance was very consistent in that he completed 23 exercise sessions in just over 9 weeks. By the seventeenth exercise session, the BWS was reduced to zero (see Figure 1). In addition, Patient 1 achieved a maximum walking speed of 2.2 to 2.4 km/hr (average of 2.0 km/hr) (see Figure 2) and was completing 34 minutes of walking with minimal rests by the end of the training program (see Figure 3). Patient 2 also responded to the training, as evidenced by a slow but steady increase in exercise duration. However, as can be seen in Figure 3, Patient 2 was unable to consistently maintain or increase his training time and, in fact, performed very sporadically towards the end as his health deteriorated. Patient 2 was also unable to make any substantial increases in walking speed (average of 1.3 km/hr) (see Figure 2) or tolerate any reductions in BWS (see Figure 1). Similarly, Patient 3 steadily increased his training duration, but he was unable to maintain a consistent exercise time due to his unstable health (see Figure 3). His unstable health also contributed to the fluctuations in walking speed where some days he was able to walk comfortably at 3.5 km/hr while on other days he was challenged by 1.8 km/hr (average of 2.4 km/hr) (see Figure 2). BWS was never reduced for Patient 3.

It is difficult to compare the training progression and intensity from this study to other studies because of the added element of BWS and because the training prescription was based on a rating of perceived exertion versus a percentage of peak heart rate or a predetermined exercise prescription. Nonetheless, all three patients seemed to demonstrate a general trend towards increased exercise tolerance.

5.2.2 BWST training and functional capacity (Patient 1 only)

Patient 1, who completed all post-testing, demonstrated notable improvements in functional capacity. He experienced a 64% increase in VO_2 peak (7.2 to 11.7 ml/kg/min), a 33% increase in peak power output (300 to 400 kpm/min), and a 28% increase in 6-MWT distance (223.5 to 286m). In addition, Patient 1's NYHA-FC improved after training from class III to II. A significant training effect was also evident by reductions in HR at rest (96 to 79 bpm) and during submaximal exercise (100 kpm/min) (105 to 84 bpm) as well as a 37% increase in V_E peak (28 to 39 L/min).

The increase in oxygen consumption (64%) is unexpectedly high compared to previous studies of similar duration which employed patients with less severe HF. Most of these studies showed increases ranging from 8 to 33% (Belardinelli et al., 1998; Davey et al., 1992; Dubach et al., 1997a; Hambrecht et al., 1995; Maiorana et al., 2000a). In addition, studies employing similarly impaired patients have found less dramatic increases (Belardinelli et al., 1999; Demopoulos et al., 1997; Magnusson et al., 1996). There are numerous potential explanations for the dramatic increase. Patient 1 may have given a less than maximal effort during the baseline cardiopulmonary test but then put

forth a greater effort for the post-test, thus producing an exaggerated improvement. This seems unlikely considering that for both the pre and post-exercise tests, Patient 1 achieved the same peak HR (see Table 6). Second, the dramatic increase may be explained by the confounding effect of natural post-surgery recovery. Forty-four days prior to enrolling in this study, Patient 1 underwent quadruple coronary artery bypass surgery with aortic valve replacement. His dramatic increase in exercise capacity may be due to the additional effect of the natural recovery process following surgery. However a study by Goebbels et al. (1998) reported that patients with depressed ventricular function (LVEF <40%) one month following myocardial infarction or coronary artery bypass surgery did not spontaneously improve VO_2 peak after an additional two months of traditional care. Conversely, patients with normal ventricular function (LVEF >50%) appeared to spontaneously improve exercise capacity even if they were not involved in exercise training. Patient 1 exhibited depressed ventricular function (LVEF = 35%) one month post-surgery (see pre-testing LVEF, Table 1) and had persistent HF following surgery requiring prolonged post-operative hospitilization. This suggests that his dramatic increase in exercise capacity may not have been confounded by the natural recovery process following bypass surgery. Finally, assuming that Patient 1's baseline VO_2 peak was accurate, it has been shown that patients with the most severely depressed exercise capacity at baseline stand to achieve the greatest improvements in peripheral aerobic capacity (Meyer et al., 1997a). It should be noted however, that the European Heart Failure Training Group (1998) reviewed the progress of 134 heart failure patients enrolled in physical training trials and concluded that patients with more severe heart

failure have a more depressed capacity to train and therefore achieve a lesser improvement in exercise tolerance. This latter finding may not be applicable to the present study as BWST training was specifically employed to increase the patient's "capacity" to train.

Assuming that Patient 1's increase in VO_2 peak was accurate, the practical significance of this increase is what is most important. By looking at the METs (metabolic cost) of various activities, it is interesting to note that with a VO_2 peak of 7.2ml/kg/min or 2 METs, Patient 1 would be challenged (i.e. at peak effort) while performing activities such as tub bathing, cooking, and riding a power lawn mower. With a VO_2 peak of 11.7ml/kg/min or approximately 3 METs, Patient 1 could perform the previous activities with less of a challenge or participate in activities such as light gardening, general housework or pushing a light power mower. Therefore, although Patient 1's increase in peak oxygen consumption only translates to an increase of one MET, it represents a significant increase in the number of activities in which he can participate.

The 28% increase in 6-MWT distance by Patient 1 in this study is comparable to previous reports which have observed increases between 5 and 20% (Kavanagh et al., 1996; Kostis et al., 1994; Parnell et al., 2002; Sindone et al., 1998; Tyni-Lenné et al., 1997) however all of these studies included patients with NYHA-FC II-III symptoms and baseline distances considerably higher than Patient 1 (e.g. 474m from Parnell et al., 2002). Meyer et al. (1997c) reported a baseline 6-MWT distance of 232m which is comparable to Patient 1's baseline value (223.5m) however they noted a 65% increase in

6-MWT distance after training. Functional walking may have improved more dramatically in Meyer's (1997c) study due to the more intense interval training.

5.2.3 BWST training and HRQL (Patient 1 only)

In addition to the improvement in functional capacity, Patient 1 demonstrated enhanced HRQL as measured by the MLHFQ. Patient 1 improved all scores on the MLHFQ such that his total score decreased from 55 to 13, physical score from 24 to 5 and emotional score from 13 to 4 (see Table 2). This is a greater improvement than seen by Belardinelli et al. (1999) and Parnell et al. (2002) where after training, patients' total scores improved from 52 to 39 and 46 to 24, respectively.

As shown in Table 4, results from the SF-36 survey are varied in that Patient 1 appeared to demonstrate the greatest improvement in general health (57 to 92) followed by vitality (50 to 75), general mental health (56.7 to 80) and physical functioning (25 to 35). These improvements were accompanied by essentially no change in social functioning (100 to 87.5) and bodily pain (84 to 100) and poorer results with respect to role limitations, both physical (75 to 0) and emotional (100 to 0). These results are surprising because it was expected that the biggest improvements would be seen in the domains related to physical activity (physical functioning, role limitations associated with physical problems and social functioning). Quittan et al. (1999) reported significant improvements in these domains in subjects with HF after three months of aerobic training. Although Patient 1 showed improvement in physical functioning after training, he reported greater role limitations due to physical problems and there appeared to be no

change in social functioning. These results are inconsistent with the substantial improvement in physical performance shown by the increase in VO_2 peak and 6-MWT distance. It should be noted however, that Patient 1's baseline results are not consistent with previous reports of patients with HF. For example, compared to normative data from the SF-36 health survey for patients with HF (Ware, 1993) and the baseline results from Quittan et al. (1999), Patient 1 reported substantially better scores for role limitations due to physical problems (SF-36 norm, 34.37, Quittan et al., 53.5, Patient 1, 75) and social functioning (SF-36 norm, 71.31, Quittan et al., 76.0, Patient 1, 100). In fact, Patient 1's scores for these two domains are better than expected for a normal male aged 65 and over (Ware, 1993). These elevated baseline results are difficult to explain considering the profound physical impairment observed in this subject at baseline. Moreover, Patient 1's baseline value for physical functioning (25) is substantially worse than baseline data reported by Ware (1993) (47.54) and Quittan et al. (1999) (60.6).

Overall, the results from the questionnaires are hard to interpret as the MLHFQ reported substantial improvement in HRQL for all scores after training while the SF-36 depicts a situation of improved general health with unchanged or even worsened physical function. The MLHFQ may better represent the changes in HRQL as it is specific to HF-related issues, i.e. ankle swelling, shortness of breath and medications.

5.2.4 BWST training and blood vessel function (Patient 1 only)

BWST training did not alter blood flow through the carotid or femoral arteries in Patient 1. Carotid and femoral vascular compliance measured by the stiffness index were

also unaffected by training. These findings are difficult to compare to the eight week training study by Parnell et al. (2002) which involved measurements of systemic arterial compliance as determined by flow through the ascending aorta. The present study was unable to determine aortic blood flow due to technical limitations. Nonetheless, although Parnell and group (2002) observed increased systemic arterial compliance following exercise training, central and peripheral pulse wave velocity (inversely related to compliance) and the augmentation index (indication of pulse wave reflection) were unchanged. These results support the findings from the current study as central (carotid) and peripheral (femoral) compliance were found to be unaltered by training.

5.2.5 BWST training and activities of daily living (all three patients)

In addition to the QOL questionnaires, patients were occasionally asked throughout the study if they noticed any improvements in their ability to perform activities of daily living. Despite its anecdotal nature, this question stimulated very interesting and valuable answers (see Appendix D). Patient 1, who exhibited substantial increases in VO_2 peak and functional walking, consistently answered that his activities of daily living were completely unaffected by training. Similarly Patient 3 reported that he had not noticed any improvements with his daily activities. Patient 2 reported on several occasions that his "walking was much better" and that he felt it was easier to get up out of chairs at home. All subjects mentioned that improvements would be hard to detect since their daily activities were so limited.

5.2.6 Comparison of baseline data to previous studies and normative data

It is important to compare the condition of the participants in the present study to previous studies before a conclusion is made regarding the feasibility of exercise training in patients with "severe" HF. Four training studies up till now have included patients with severe HF (Belardinelli et al., 1999; Demopoulos et al., 1997; Magnusson et al., 1996; Meyer et al., 1996, 1997a, b and c). Patients from these studies were classified as NYHA-FC II to IV and had mean baseline oxygen consumptions ranging from 11.5 to 15.7 ml/kg/min. The present study involved patients with baseline VO_2 peak values of 7.2, 9.4 and 9.9 ml/kg/min (see Table 6). One training study reported a mean baseline VO_2 peak value of 0.69 L/min (Tyni-Lenné et al., 1999). This translates to approximately 9.5 ml/kg/min after accounting for the mean body weight (73 kg) of the subjects. However this study only included females, who generally exhibit lower oxygen consumptions than males, even in healthy populations. Previous training studies employing the 6-MWT have reported baseline distances ranging from 232m to 503m (Kavanagh et al., 1996; Kostis et al., 1994; Meyer et al., 1997c; Parnell et al., 2002; Sindone et al., 1998; Tyni-Lenné et al., 1997). The present study had baseline 6-MWT distances of 108, 223.5 and 270m (see Table 5). In terms of HRQL, total scores for the MLHFQ have ranged from 28 to 56 (lower score represents better HRQL) (Belardinelli et al., 1999; Keteyian et al., 1999; McKelvie et al., 2002; Parnell et al., 2002; Wilson et al., 1996), while subjects in this study started with baseline total values of 55, 62 and 63 (Table 2). Only one training study reported the other dimensions of this questionnaire, i.e. physical and emotional dimensions (Keteyian et al., 1999). This study reported a

mean baseline value for the physical and emotional scores as 11 and 5, respectively. The current study found baseline values for the physical dimension of 24, 35 and 28 and for the emotional dimension, 13, 5 and 12 (Table 2). As mentioned, Patient 1's SF-36 baseline results are not consistent with previous reports of patients with HF, however, all three patients reported substantially lower baseline scores for physical functioning (see Table 4) compared to the normative data from Ware (1993) and baseline results from Quittan et al. (1999). In addition, Patient 3 reported lower baseline values (versus Ware, 1993) for all subscales except for general mental health (see Table 4) while Patient 2 reported lower values for physical role limitations and social functioning, higher scores for general mental health, vitality, general health and bodily pain and a similar value for emotional role limitations. Therefore, with respect to the domains related to physical activity (i.e. physical functioning, role limitations associated with physical problems and social functioning) the patients in this study generally reported poorer results compared to other patients with HF (Quittan et al., 1999; Ware, 1993).

Based on the above comparisons, the subjects in the current study appear to be the most severely debilitated HF patients ever involved in exercise training. Given this consideration, it is even more interesting that exercise training was well tolerated and was not associated with any adverse events. However, despite the fact that there were no study-related adverse events, two of the three patients were unable to consistently attend and participate in training sessions due to the inherent instability associated with this degree of HF. Several training sessions were missed due to episodes of worsening HF symptoms, frequent illness (e.g. cold), and problems associated with comorbidities (e.g.

diabetes). In addition, exercise sessions were often modified as patients presented with problems prohibiting them from participating. For example, subject Patient 3 presented with hypotension (e.g. 71/59) on several days of training which either prohibited training or dramatically restricted the amount of training. Likewise, on several occasions Patient 2 was so fatigued at the beginning of a training session that only two minutes of walking could be performed accompanied by significant rest intervals. Although these patients responded well to the training and demonstrated slight signs of improvement (i.e. training progression), the effectiveness of the training stimulus was limited by inconsistent attendance and irregular performance. Thus, exercise training can be beneficial in patients with severe HF however the effectiveness of the program is constrained by the fluctuating health status of these patients.

5.3 Is the BWST an effective mode of training for patients with severe HF?

Body-weight supported treadmill training has never been applied to patients with heart failure. Founded on the positive findings from other populations, such as people with spinal cord injuries (i.e. increased walking capacity, enhanced walking efficiency, and improved functional independence), this study sought to determine whether HF patients would benefit from this form of training. BWST training alleviates the stress of supporting the entire weight of the body therefore it may reduce cardiovascular stress while still allowing peripheral muscle training. In addition, the reduced demand for cardiac work may allow for a more efficient distribution of blood flow to working muscle groups.

As anticipated, the BWST facilitated walking in patients with severe HF. This was evident by the fact that patients were able to walk on the BWST with less symptoms than when they entered the rehabilitation centre (see Appendix D). For example, Patient 3 required a seated rest for approximately every minute of walking while entering the rehabilitation centre whereas on the BWST he could complete at least three minutes of walking without a rest. Likewise, Patient 2 needed to be wheeled into the rehabilitation center because of his severe leg fatigue whereas on the BWST he could complete two to three minutes of walking before requiring a rest. Patient 1 also exhibited significant shortness of breath while entering and exiting the building but on the BWST he did not demonstrate this at any point.

To evaluate the effect of BWS, on Patient 1's eleventh exercise session, the BWS (10%) was removed. Due to increasing shortness of breath, significant leg fatigue, and at the subject's request, the BWS was reintroduced. This response suggests that even 10% BWS facilitates walking in patients with severe HF. An additional benefit of the BWST was that it provided balance for the subjects while walking. All three subjects demonstrated altered balance while performing the 6-MWT and while walking in and out of the rehabilitation center. For this reason, even when Patient 1 was able to walk without any BWS, the harness was still utilized.

5.4 Summary and Recommendations

Based on the findings and observations of this study, two conclusions can be made. First, patients with severe HF can safely participate in BWST training and may derive considerable benefits. Second, the feasibility of training in patients with this degree of HF is highly dependent on their cardiac condition and other co-morbidities remaining stable enough to allow consistent training.

Future studies are needed to establish when HF patients are beyond the point when exercise training is no longer practical or safe, and to determine the minimal training stimulus required to achieve benefit. Perhaps severe HF patients would benefit more from a home-based training program. Transportation would no longer be an issue and exercises could be performed throughout the day as opposed to a specific time period. Also, exercises could be based around activities of daily living (e.g. opening containers, stair climbing, standing up from a seated position) versus traditional forms of training which may not necessarily improve a person's ability to perform the activities required to live independently. Nonetheless, home-based training programs require that the patient be stable enough to engage in physical activity without supervision and a major benefit of supervised training programs is the added attention and social interaction. Without a doubt, for patients with severe HF, maximizing the benefits of exercise training while minimizing the potential risks, is a challenging task, which will most likely require unique exercise prescriptions based on individual patient needs.

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APPENDIX A: HRQL QUESTIONNAIRES

Living with Heart Failure Questionnaire
(Rector et al., 1986)

Did your heart failure prevent you from living as you wanted during the past month by:

	No		**Very little**		**Very Much**	
1. Causing swelling in your ankles, legs etc	0	1	2	3	4	5
2. Making your working around the house or yard difficult?	0	1	2	3	4	5
3. Making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
4. Making you sit or lie down to rest during the day?	0	1	2	3	4	5
5. Making you tired, fatigued or low on energy?	0	1	2	3	4	5
6. Making your working to earn a living difficult?	0	1	2	3	4	5
7. Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
8. Making you short of breath?	0	1	2	3	4	5
9. Making your sleeping well at night difficult?	0	1	2	3	4	5
10. Making you eat less of the foods you like?	0	1	2	3	4	5
11. Making you going places away from home difficult?	0	1	2	3	4	5
12. Making your sexual activities difficult?	0	1	2	3	4	5
13. Making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
14. Making it difficult for you to concentrate and remember things?	0	1	2	3	4	5
15. Giving you side effects from medications?	0	1	2	3	4	5
16. Making you worry?	0	1	2	3	4	5
17. Making you feel depressed?	0	1	2	3	4	5
18. Costing you money for medical care?	0	1	2	3	4	5
19. Making you feel a loss of self-control of your life?	0	1	2	3	4	5
20. Making you stay in a hospital?	0	1	2	3	4	5
21. Making you feel you are a burden to your family or friends?	0	1	2	3	4	5

SF-36 Health Survey

INSTRUCTIONS:

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is **(circle one)**:

Excellent.....1
Very good.....2
Good.....3
Fair.....4
Poor.....5

2. **Compared to one week ago,** how would you rate your health in general **now?**

Much better now than one week ago..... 1
Somewhat better now than one week ago.....2
About the same as one week ago.....3
Somewhat worse now than one week ago.....4
Much worse now than one week ago.....5

3. The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much? (circle **one** number on each line)

	Yes, limited a lot	*Yes, limited a little*	*No, not limited at all*
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c) Lifting or carrying groceries	1	2	3
d) Climbing **several** flights of stairs	1	2	3
e) Climbing **one** flight of stairs	1	2	3
f) Bending, kneeling, or stooping	1	2	3
g) Walking **more than a mile**	1	2	3
h) Walking **several blocks**	1	2	3
i) Walking **one block**	1	2	3
j) Bathing or dressing yourself	1	2	3

4. During the **past week**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**? (circle **one** number on each line)

	Yes	*No*
a) Cut down on the **amount of time** you spent on work or other activities	1	2
b) **Accomplished less** than you would like	1	2
c) Were limited in the **kind** of work or other activities	1	2
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the **past week**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as felling depressed or anxious)? (circle **one** number on each line)

	Yes	*No*
a) Cut down the **amount of time** you spent on work or other activities	1	2
b) **Accomplished less** than you would like	1	2
c) Didn't do work or other activities as **carefully** as usual	1	2

6. During the **past week**, to what extent have your physical health or Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all.....1
Slightly.....2
Moderately.....3
Quite a bit.....4
Extremely.....5

7. How much **bodily** pain have you had during the **past week**?

None.....1
Very mild.....2
Mild.....3
Moderate.....4
Severe.....5
Very Severe.....6

8. During the **past week**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all.....1
A little bit.....2
Moderately.....3
Quite a bit.....4
Extremely.....5

9. These questions are about how you feel and how things have been with you **during the past week**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past week**...
(circle **one** number on each line)

	All of the time	*Most of the time*	*A good bit of the time*	*Some of the time*	*A little bit of the time*	*None of the time*
a) Did you feel full of pep?	1	2	3	4	5	6
b) Have you been a very nervous person?	1	2	3	4	5	6
c) Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d) Have you felt calm and peaceful?	1	2	3	4	5	6
e) Did you have a lot of energy?	1	2	3	4	5	6
f) Have you felt downhearted and blue?	1	2	3	4	5	6
g) Did you feel worn out?	1	2	3	4	5	6
h) Have you been a happy person?	1	2	3	4	5	6
i) Did you feel tired?	1	2	3	4	5	6

10. During the **past week**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time.....1
Most of the time.....2
Some of the time.....3
A little of the time.....4
None of the time.....5

11. How TRUE or FALSE is **each** of the following statements for you?
(circle **one** number on each line)

	Definitely true	*Mostly true*	*Don't know*	*Mostly false*	*Definitely false*
a) I seem to get sick a little easier than other people.	1	2	3	4	5
b) I am as healthy as anybody I know.	1	2	3	4	5
c) I expect my health to get worse.	1	2	3	4	5
d) My health is excellent.	1	2	3	4	5

APPENDIX B: NYHA FUNCTIONAL CLASSIFICATION

NYHA Class of Failure Definitions:

I. **No objective evidence of limitation:** Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.

II. **Objective evidence of minimal limitation:** Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest, ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.

III. **Objective evidence of moderately severe limitation:** Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest, less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.

IV. **Objective evidence of severe limitation:** Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX C: MODIFIED BORG SCALE

Modified Borg Rating of Perceived Exertion Scale

0	**NOTHING AT ALL**
0.5	**VERY, VERY, SLIGHT (just noticeable)**
1	**VERY SLIGHT**
2	**SLIGHT**
3	**MODERATE**
4	**SOMEWHAT SEVERE**
5	**SEVERE**
6	
7	**VERY SEVERE**
8	
9	**VERY, VERY SEVERE**
10	**MAXIMAL (almost maximal)**

APPENDIX D: RAW DATA

List of Medications for Patient 1

Medication	Dosage
Metolazone	2.5 mg BID
Furosemide	80 mg morning, 60 mg evening
Slow K	3 tabs BID
Spironolactone	25 mg daily
Digoxin	0.25 mg daily
Lipitor	10 mg hs
Celexa	20 mg daily
Flovent	PRN
Atrovent	PRN

List of Medications for Patient 2

Medication	Dosage
Metoprolol	25 mg BID
ASA	81 mg OD
Lasix	40 mg OD
Pravachol	40 mg qhs
EPO treatments	
Chemotherapy	
VALIANT study	

List of Medications for Patient 3

Medication	Dosage
Accupril	10 mg
Metoprolol	25/12.5 mg
Coumadin	
ASA	81 mg OD
Lasix	40 mg BID
Aldactone	25 mg OD
Metformin	500 mg BID
Glyburide	5 mg BID
Nitrodur	0.6 mg qam
Nitrospray	PRN

Training Data for all Three Patients

Patient 3					Patient 2					Patient 1				
	BWS	Duration	Rest	Speed		BWS	Duration	Rest	Speed		BWS	Duration	Rest	Speed
Day 1	40	15	20	2.5	Day 1	40	8	10	1	Day 1	40	15	10	0.8
Day 2	40	22	15	2.5	Day 2	40	8	9	1.5	Day 2	40	22	9	1
Day 3	40	27	8	3.5	Day 3	40	11	13	1.3	Day 3	30	24	11	1.2
Day 4	40	9	5	3.5	Day 4	40	9	14	1.2	Day 4	30	25	6	1.6
Day 5	40	17	11	2	Day 5	40	12	13	1.2	Day 5	30	27	4	1.8
Day 6	40	18	10	2.3	Day 6	40	11	12	1.2	Day 6	20	24	6	2
Day 7	40	20	7	2.3	Day 7	40	11	12	1.2	Day 7	20	28	4	2.2
Day 8	40	20	9	2.3	Day 8	40	14	13	1.2	Day 8	20	30	4	2.4
Day 9	40	19	7	2.3	Day 9	40	15	11	1.2	Day 9	10	30	4	2.2
Day 10	40	18	8	2.5	Day 10	40	14	11	1.2	Day 10	10	30	4	2.4
Day 11	40	23	7	2.5	Day 11	40	15	11	1.3	Day 11	10	25	6	2.4
Day 12	40	21	7	2.5	Day 12	40	15	10	1.3	Day 12	10	30	6	2.4
Day 13	40	22	10	1.8	Day 13	40	14	11	1.3	Day 13	10	28	6	2.4
Day 14	40	25	7	2.3	Day 14	40	8	9	1.3	Day 14	7	30	6	2.2
Day 15	40	27	7	2.3	Day 15	40	15	11	1.4	Day 15	7	30	6	2.2
Day 16	40	28	10	2.3	Day 16	40	11	11	1.4	Day 16	7	30	6	2.2
Day 17	40	11	4	2.3	Day 17	40	9	9	1.4	Day 17	0	30	6	2
Day 18	40	28	9	2.3	Day 18					Day 18	0	30	5	2.2
Day 19	40	25	10	2.3	Day 19					Day 19	0	31	4	2.2
Day 20	40	21	7	2.1	Day 20					Day 20	0	34	6	2.2
Day 21	40	27	13	2.1	Day 21					Day 21	0	33	6	2.2
Day 22	40	21	7	2.1	Day 22					Day 22	0	34	5	2.2
Day 23	40	21	7	2.1	Day 23					Day 23	0	34	5	2.2
# days to complete training:		73			# days to complete training:		49			# days to complete training:		66		

Comments and Observations for Patient 1

Training Day	Comments and Observations
2	Looks comfortable, Patient 1 says he could have walked longer
3	Decreased BWS to 30%, Patient 1 says he feels more muscle effort
5	Whistling while walking on TM, noticeable SOB while walking to car, no SOB on TM
6	Decreased BWS to 20%, Patient 1 didn't notice reduction in BWS
9	Decreased BWS to 10%, slight increase in breathing effort
11	Decreased BWS to 0%, increased SOB and leg effort, Patient 1 requested BWS, subject says that he doesn't notice any benefit due to training, but doesn't "do many activities anyway"
14	Decreased BWS to 7%, good support, Patient 1 says he feels more leg effort, greater challenge
17	Decreased BWS to 0%, no problem with no BWS, slight increase in breathing effort
20	Feels significant leg effort today, no SOB on TM but noticeable while walking to car
22	Patient 1 says he "doesn't notice any benefit but he doesn't challenge himself"

Comments and Observations for Patient 2

Training Day	Comments and Observations
1	BWST walking quite challenging for him, extremely deconditioned, requires lots of rest
4	Patient 2 says he notices more "feeling" in thighs at home
5	Patient 2 was extremely tired today, still put forth a good effort
6	Patient 2 seems to hit a 2 minute "wall"
8	Added extra 2 minute session, tolerated well
9	Able to put harness on without a rest, can stand for longer time before leg fatigue
10	Very tired today, needed frequent rests, Patient 2 says he "feels like his walking is better"
12	Could not complete 3 minutes of walking without rest, has muscle soreness from last day
14	Very tired today, dragged feet while walking, finished early today
15	Legs a little sore today, Patient 2 says he "walks around the house with less effort"
16	Very tired today, slight SOB while walking, extremely tired by end of training, stopped early, Patient 2 says that he "finds it easier to stand up from his chair at home"
17	Very tired today, slight SOB, increased respiratory rate, stopped session early

Comments and Observations for Patient 3

Training Day	Comments and Observations
4	Presented with SOB today, stopped session early, had to rest several times on way in to rehab. centre
5	BP low today, did not get worse with training
6	BP better, trapezius tightness, slight pain in leg at end (intermittent claudication)
8	Presented with SOB today, runny nose and slight cough as well, rested several times on way in to rehabilitation center, kept exercise short
10	BP low today, sudden light headedness, Patient 3 stopped TM with emergency button, session over
11	Patient 3 has not noticed any increases in activities of daily living or QOL, says its hard to tell though because activities are so limited, felt good today during training
12	Walking well today until sharp headache, stopped TM and ended session early
13	Presented with SOB, rested several times on way into rehabilitation center, walked at slow pace on TM and gave extra rest to avoid SOB
14	No problems with SOB today
15	Training went very well today, no problems
16	Seems to hit a 5 minute "wall", added extra 4 minute session, no problem
17	Bad day today, SOB, headache, dry mouth, taken over to hospital to test blood sugar
18	Felt okay today, legs fatigued by last session
19	Rested several times today on way into rehabilitation center due to SOB, SOB progressively worse with exercise, reduced speed, breathing better
20	Slight leg pain during walking, foot cramp, stopped session early
21	Leg better today, feeling good today, does not notice increase in activities at home
22	Feet hurt while walking, limited exercise tolerance, stopped early
23	Horrible foot cramps today, Patient 3 insisted on continuing session, I stopped session when pain became worse

Right Carotid Artery Raw Data

	Patient 1		Patient 2	Patient 3
Variable	**Pre**	**Post**	**Pre**	**Pre**
TAV (cm/s)	37.97	33.01	error	22.33
Maximum Diameter (systolic) (mm)	8.83	8.80	8.02	8.25
Minimum Diameter (diastolic) (mm)	8.40	8.52	7.42	7.82
Systolic Pressure (mmHg)	102	106	115	98
Diastolic Pressure (mmHg)	52	63	68	63

TAV, total average velocity

Right Common Femoral Artery Raw Data

	Patient 1		Patient 2	Patient 3
Variable	**Pre**	**Post**	**Pre**	**Pre**
TAV (cm/s)	19.78	11.70	18.60	5.07
Maximum Diameter (systolic) (mm)	7.53	8.03	7.95	7.38
Minimum Diameter (diastolic) (mm)	7.12	7.68	7.35	6.93
Systolic Pressure (mmHg)	110	110	123	98
Diastolic Pressure (mmHg)	59	65	74	62

TAV, total average velocity