THE EFFECTIVENESS OF 12 WEEKS HOME BASED EXERCISE INTERVENTON IN CHRONIC HEART FAILURE PATIENTS

by

HEDIEH SAFIYARI

B.H.K., The University of British Columbia, 2002

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

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

(HUMAN KINETICS)

THE UNIVERSITY OF BRITISH COLUMBIA

August 2005

ABSTRACT

Heart failure is a chronic and progressive disorder that is a major public health problem in Canada that is associated with significant morbidity, mortality and frequent hospital admission and health care costs.

The purpose of this investigation was to evaluate the effectiveness of a supervised home-based exercise training program involving a combination of interval and resistance training.

Forty patients with chronic heart failure (CHF) were recruited, stratified (according body mass, aerobic fitness, age and CHF classification) and randomized to either control (CONT; n = 20) or experimental (EXP; n = 20) conditions. Measures of aerobic fitness (VO_2peak (as a percentage of predicted)) and cardiorespiratory responses at anaerobic threshold measured by cardiopulmonary test using a cycle ergometer, endurance capacity using the 6-min walk test, and Quality of Life using Minnesota Living with Heart Failure Questionnaire, were taken at baseline and after 12-weeks. The EXP group underwent a 12-week interval and resistance training program. The CONT patients were asked to maintain usual activities of daily living. Twenty-nine patients completed the trial (CONT = 15; EXP = 14).

Statistical analysis showed significant improvements after 12 weeks of training in aerobic fitness (46 ± 9% vs. 54 ± 12%, respectively), endurance capacity (267 ± 39 m vs. 288 ± 45 m, respectively), and Quality of Life (50 ± 20 vs. 40 ± 17, respectively) in EXP. There were also significant improvement in VO_2 peak, VCO_2, tidal volume (Vt) and power output (PO) at ventilatory anaerobic threshold in EXP.
There were no significant changes in CONT.

A home-based rehabilitation program involving interval and resistance training is associated with improved aerobic capacity and Quality of Life in patients with CHF. This research has important implications for the treatment of CHF.

Table of Contents

List of Charts

List of Tables

List of Figures

Acknowledgement

Special acknowledgement goes to my supervisor, Dr. Jack Taunton, who provided me with lot of guidance and support. My heartfelt acknowledgement goes to the members of my committee, Dr. Darren Warburton and Dr. Andrew Ignaszewski, who spent a lot of time and energy in order to make this research study a success. I also like to extend my acknowledgement to the funding provided by Sports Medicine that facilitated this study. Lastly but not least, fond acknowledgement should go to my husband Bob for his timeless encouragement and support.

Chapter 1:Introduction

1.1. Statement of problem

Heart failure is a chronic and progressive disorder that is a major public health problem in Canada. It is associated with significant morbidity, mortality, frequent hospital admission and health care costs. It currently afflicts over 350,000 people in Canada, and mortality rates range from 25% to 40% one-year post diagnosis (26). Despite gains in the treatment and prevention of cardiovascular disease, Chronic Heart Failure (CHF) has been increasing steadily over the past several years, with over 50, 000 new cases occurring annually. In fact, it is the only major cardiovascular disorder that is increasing in both incidence and prevalence (70). There are costs associated with repeated hospitalizations, complex treatment regimens and pharmacological intervention. Often, people cannot work, resulting in a loss to productivity. The chronic nature of heart failure increases the need for social services and the costs associated with social support, which is proven to be a financial strain to health care. According to Health Canada's 1998 report, Economic Burden of Illness in Canada, cardiovascular diseases costs the Canadian economy over $18 billion a year (55).

For a long time, avoidance of exertional physical activity has been advocated in all forms and stages of heart failure to prevent further deterioration of the remaining functional capacity of the heart; however, the opposite has been proven in the recent years (60). Interest was shown by many researchers in the possibility that some forms of exercise therapy, either localized or systemic, could benefit the peripheral manifestations of CHF and thereby modifies the symptoms of patients with CHF. Recently it has even been suggested that regular training could have beneficial effects on disease progression and survival. The growing literature on exercise physiology in chronic heart failure supplies some answers, as well as raising a number of important questions with regard to the most appropriate exercise protocols for heart failure patients.

Owing to the multi-factorial nature of the disease, treatment of heart failure is extremely challenging and patients require close monitoring and therefore supervised program is considered to be effective. Although, non-supervised home exercise programs have gained popularity largely for economic reasons in recent years, they can be problematic if there are no follow-ups. It was shown that many patients may be unwilling or unable to follow an appropriate exercise prescription, adherence to the program may be compromised or there may be safety issues that arise for some patients (30).

The factors need to be addressed are: (1) the most beneficial training protocol for this high risk group of patients and (2) the safest and most effective way of supervision and follow-ups to enhance compliance. Although previous trials provide some answers, there are still some contradictory findings. Search for different methods of training in order to gain optimal result exists (30).

1.2. Purpose of the Research

The purpose of this research is to seek an appropriate means of exercise training program including monitoring, education and follow-ups to ensure the effectiveness of the program for patients with heart failure.

Supervised home-based intervention is believed to be effective by providing formal exercise prescription and having follow-ups on patients by health care professionals to ensure safety and compliance. As the chronic heart failure patients are significantly limited functionally, even a small increase in exercise capacity could dramatically reduce a patient's dependency (62). Therefore, in an increasingly competitive health care climate, training could be a highly cost effective resource in chronic heart failure.

1.5. Research Question/ Hypothesis

It was hypothesized that a 12 week supervised home-based intervention, by including individualized and specifically tailored monitored exercise training, education and follow-ups, would render, primarily, the following result:

(1) Significant improvement in cardiorespiratory responses, especially VO_2 max

(2) The exercise capacity improves significantly by enhancing the walking ability.

(3) There would be more negative symptoms reported by the patients via the Minnesota Living with Heart Failure Quality of Life Questionnaire. Therefore, the quality of life of patients who followed the 12 week program will increase significantly.

It was also hypothesized that the proposed intervention will result in:

(1) Significant improvement in metabolic, ventilatory, gas-exchange and cardiovascular responses at anaerobic threshold and at peak exercise as a result of 12 week intervention.

Chapter 2: Review of Literature

2.1. Pathophysiology of Heart Failure

Cardiac failure is a condition in which the output of the heart is not adequate to meet the needs of the body, either at rest or with exercise. This is usually accompanied by an increased filling pressure and/or volume (29). Acute heart failure is not a single entity, occurring during diastole or systole. Heart failure can be caused by factors originating from the heart (i.e., intrinsic disease or pathology) or from external factors that place excessive demands upon the heart. Chronic heart failure results from the heart undergoing adaptive responses to a precipitating cause, and it is this cardiac response that ultimately may lead to impaired function (29).

Myocardial contractility (inotropy) and relaxation (lusitropy) are impaired in most patients with heart failure. A change in ejection performance or stroke volume can result from either a change in contractility or afterload, for any given end diastolic volume. For instance, following a myocardial infarction, a decrease in left ventricular performance could be secondary to either a decrease in contractility due to the loss of the functioning myocytes, an increase in systemic vascular resistance, or both (28).

2.1.1. Impaired ejection: depressed myocardial contractility in the failing heart

A change in myocardial contractility is readily demonstrated as a shift in the Starling Curve, which simply documents a change in the amount of work done at any given end-diastolic fibre length (29). This means that heart can operate on any of the "family of starling curves," each of which represents a different inotropic state. A positive inotropic intervention, which by definition increases work capacity at any given end-diastolic volume (or fibre length), shifts the heart to a new, higher starling curve, while a negative inotropic intervention, by causing a downward shift in the starling curve, reduces the work of the heart at any given end-diastolic volume(29).

2.1.2. Impaired filling: relaxation abnormalities in the failing heart

Ventricular filling can be impaired by four types of lusitropic abnormality: (A) slowed relaxation with decreased rate of pressure fall during isovolumic relaxation; (B) slowed relaxation with delayed filling during early diastole; (C) incomplete relaxation with impaired filling throughout diastole; (D) decreased compliance (increased stiffness) (72).

2.2. Altered Loading in Heart Failure

Congestive heart failure as a result of left ventricular systolic dysfunction reflects myocardial injury, leading to a depressed contractile state (29). In response to depressed cardiac performance and decreased cardiac output, the body takes steps to maintain normal perfusion to vital organs by activating the sympathetic nervous system and the rennin-angiotensin-aldestrone endocrine volume-regulatory response which is linked to hemodynamic changes. As a result, renal sodium and water retention increases preload, sympathetic alpha adrenergic vasoconstriction increases afterload, and myocardial inotropic beta adrenergic stimulation increases the contractile state and drives tachycardia (72). In short term, a normal forward cardiac output is maintained. In long term, the increased loads on an already dysfunctional heart lead to a further deterioration of cardiac performance (72).

2.2.1. Neurohormonal responses to exercise in heart failure

As cardiac function decreases, the heart depends on three major compensatory mechanisms in order to maintain adequate cardiac output (8, 53). Although these responses will maintain cardiac function at relatively normal levels for a period of time, they all have limited capacity. The sympathetic nervous system is activated within seconds of a change in cardiac output, and serves as an immediate support mechanism (8). Plasma norepinephrine concentration and many other neurohormones and cytokines are known to be increased in patients with heart failure with even limited exercise due to having higher basal levels of plasma norepinephrine at resting state (23). It was observed however that maximal plasma norepinephrine levels during exercise in patients with heart failure failed to achieve the much higher peak values observed in strenuously exercised normal subjects (23).

2.2.2. Hemodynamic response to heart failure

The result of myocardial injury, with its compensatory remodelling, is an alteration in ventricular function and the subsequent impaired contraction and relaxation (71). Acute or chronic decompensated heart failure is present when symptoms at rest are due to high filling pressure and/or depressed cardiac index. Blood pressure can vary depending on the systemic vascular resistance. Either normal or abnormal hemodynamics at rest may be shown in a patient with a low ejection fraction, depending on vascular tone or volume (28).

2.2.3. Physiologic response to heart failure

Impairment with activity is the hallmark of symptoms of heart failure. Reasons for reduced peak oxygen consumption with exercise include impaired augmentation of cardiac output (heart rate x stroke volume), pulmonary congestion, or skeletal muscle de-conditioning (28).

2.2.3.1. Impaired cardiac output

Cardiac output is increased during exercise in the normal heart. In heart failure, cardiac output does not increase much due to impaired heart rate and the failure of stroke volume to increase. Heart rate is impaired due to depletion of nore-adrenaline and stroke volume fails to increase because the Frank Starling mechanism is impaired, there is less contractility and ventricle eject less well against arterial pressure(71). Impaired cardiac output is linked to breathlessness which causes pulmonary congestion (71).

2.2.3.2. Pulmonary Congestion

Because of the intimate relationship between cardiac and pulmonary function with respect to anatomy and physiologic processes, pulmonary abnormalities quickly appear in heart failure patients whose symptoms include congestion. Reduction in peak expiratory flow rate (PEFR), forced expiratory volume (FEV), and the expiratory volume: vital capacity ratios are all well described in congestive heart failure (71). Ventilatory levels are higher than expected at any given workload or level of carbon dioxide production. Respiratory muscle strength is reduced in patients with severely symptomatic congestive heart failure and correlates with their complaints of dyspnoea and with peak exercise oxygen uptake (71).

2.2.3.3. Skeletal muscle de-conditioning

Exercise intolerance is influenced by abnormalities at several levels, including the lungs, skeletal muscle, peripheral resistance vessels, and vascular endothelium. Abnormalities of mitochondrial function in skeletal muscles have been observed in congestive heart failure patients. Exercise places additional demands on the heart and the circulatory system, because of the increase in oxygen-dependent metabolic energy requirements and in cellular respiratory waste products that need to be eliminated. During exercise, cardiac output demands are 5-10 times greater than those needed at rest. Theoretically, normal subjects have a well-integrated oxygen delivery pathway, which moves oxygen from the ambient air to the skeletal muscle mitochondria and quickly carries carbon dioxide and acid by-products of respiration to the expired air or urine (71). Decreased blood flow to exercising muscle resulting from diminished cardiac output in skeletal muscle bed is important contributing factor in heart failure.

Intrinsic abnormalities of skeletal muscle have been identified that could account for the abnormal metabolic profile independent of blood flow. Sullivan et al. (64) have identified an increase in fast twitch type II b fibres and a decrease in the slow twitch type I fibres in patients with congestive heart failure. These differences were accompanied by reductions aerobic oxidative enzymes activity in patients with congestive heart failure (64). Other investigators also demonstrated a shift in muscle fibre distribution with increased percentage of the fast twitch easy fatigable type II b fibres in heart failure when compared to normal subjects (39).

2.3. Response to Exercise in heart failure

A patient with heart failure and an impaired increase of cardiac output with activity, compared with a normal individual, may have a fixed stroke volume and an increased resting heart rate. This could result in an increase in oxygen consumption with exercise when tissue extraction of oxygen (change in AVO_2) can no longer increase (28).

2.3.1. Heart failure response to different modes of interval exercise

As patients with chronic heart failure are characterized during exercise by a rapid decline of phosphocreatine, reduced aerobic capacity, and decreased muscle strength (1, 39), interval exercise has been shown to overcome the premature muscle fatigue seen during high work rate training and help prepare patients for coping with activities of daily living (46). It was demonstrated that short-term training of only 3 weeks resulted in a marked delay of ventilatory threshold. The amount of improvement in oxygen uptake was similar to that reported after 24 weeks of aerobic training using three interval exercise modes with different ratios of work/ recovery phases (30/60 s, 15/60 s and 10/60 s) and different work rates during cycle ergometer exercise in patients with moderate CHF (46).

The rationale for developing interval training methods for cardiac patients was to apply a more intense stimulus on peripheral muscles than that obtained during steady-state training methods, but without inducing greater cardiovascular stress. This is possible by using short bouts of work phases in repeated sequence, followed by short recovery phases. It is possible that intermittent nature of interval training allows the left ventricle to accommodate to an enhanced venous return associated with the high muscle work rates. This new training modality proved safe since no ST segment depression or serious ventricular arrhythmias occurred during testing or training and no worsening of the heart failure was suggested by clinical studies as a result of interval training (47). Higher intensity stimulus at intensity levels of 75% of peak VO_2 and ventilatory threshold was shown to be more beneficial in reversing the alteration in skeletal muscle ultra-structure, biochemistry, and fibre type as well as in peripheral perfusion that occurred in patients with heart failure (47).

2.4. Pharmacological effect

Because of the intimate relationship between cardiac and pulmonary function with respect to anatomy and physiologic processes, it is not surprising that pulmonary abnormalities quickly appear in heart failure patients whose symptoms include congestion (71). Reduction in peak respiratory flow rate, forced expiratory volume and expiratory volume: vital capacity ratios are evident in settings of congestive heart failure. These abnormalities are responsible for exertional dyspnea and increased ventilatory response (71).

Performance of the failing heart and the congestion state can be improved by either increasing contractility or decreasing afterload. However, a drug that increases contractility (i.e. inotropic drugs such as digoxin) will increase myocardial VO_2 whereas a drug that reduces afterload (i.e. vasodilators such as Ace inhibitors) will decrease myocardial VO_2 (28).

Arterial vasodilators reduce afterload by decreasing vascular resistance to blood flow. Reducing afterload decreases ventricular wall stress and can improve ventricular performance. Cardiac output will increase, resulting in an improvement of congestion. The combination of diuretics, vasodilators, and arterial vasodilators can result in marked improvement in ventricular performance in many patients with decompensated congestive heart failure (71). Acutely hemodynamic changes that occur by drug therapy should be considered and therefore keeping the patients on the same medications and dosage during an exercise intervention is vital in order to avoid attenuation of the result of the study due to the drug interference (71).

2.5. Patient's Characteristics

It was shown that most patients with stable chronic heart failure in New York Heart Association (NYHA) classes I to III could enter a physical training program (Appendix A). Although, a lesser improvement in exercise tolerance was seen in patients with more severe chronic heart failure (NYHA class III) because of the more depressed capacity to train. But the improvement in peak VO_2 and exercise duration were similar in NYHA classes II and III, confirming that even in high-risk chronic heart failure patient's training could be beneficial (25). The recommendations for developing an exercise program are typically aimed at chronic heart failure patients with an ejection fraction less than 40% (21). There is no minimal left ventricular ejection fraction criteria for exercise training and it also has not been published anywhere that patients with an ejection fraction above 40% do not benefit from an exercise training program (21).

It has been reported that both female and male patients with coronary artery disease and chronic heart failure can obtain benefit from exercise training (20). Age, also, was not shown to be a contraindication, as patients older than 70 years are able to train, although less benefit was shown in terms of exercise tolerance (20).

Looking at different aetiologies, it was shown that patients with ischemic heart failure showed lower improvement in peak VO_2 in comparison with patients with idiopathic dilated cardiomyopathy, but not in exercise duration or NHYA class (20). In general, it appears that the benefit of training is not dependent on the aetiology of heart failure. Some contraindications exist to exercise training and it is important to be familiar with them in order to avoid putting patients with heart failure at risk (Appendix B).

2.6. Length of the training program

It has been shown recently that the functional gains of training are positively influenced by the duration of the program. Looking at the rate of exercise progression, initial improvements of aerobic capacity and symptoms, in traditional programs, occurred at 4 weeks and the maximum time required to attain peak responses in physical and cardiopulmonary variables was 16 and 26 weeks, respectively, than responses plateau (30). Benefits are shown to be higher after 12 weeks than after 6 weeks of exercise (18) and also higher after 24 weeks than after 12 weeks;

although, compliance to a long exercise program of 24 weeks could not be always as high as a 12 week program (31). Improvements in VO_2 after 16 weeks of training have also been evident in comparison to shorter period of training for 6 weeks (20).

In general, most studies supported a 12 weeks exercise intervention to be beneficial and result in significant improvement in the patient's outcome by increasing peak VO_2, besides having a high compliance rate (9, 18, 41, 42).

2.7. Training protocol (mode of training)

Different studies have used different modalities to find the answer to so many unsolved questions about the more appropriate training protocol for CHF patients. Differences exist, up to this date, in terms of the number of exercise sessions/week, the duration of each exercise session, and the type and intensity of exercises.

2.7.1 Aerobic training

It has to be taken in to consideration that the pathology and exercise tolerance of patients with chronic heart failure only allow a few of such selected activities. Cycle ergometer training allows exercising at very low workloads, allows a continuous monitoring of heart rate, rhythm and blood pressure. In contrast a wide range of workloads in walking offers a promising applicability for patients at a broad range of exercise tolerance (21). It has been suggested that low speeds of <50 m/min, require a low exercise tolerance of 0.3 W/kg body weight (24), and a faster speed of 100m/min require an exercise tolerance of 0.8-0.9 W/kg (4).

Looking at other cardiovascular activities, it has been shown that head-up immersion and the hydrostatically induced volume shift result in an increased volume loading of the left ventricle, with increase of heart volume, and pulmonary capillary wedge pressure, during swimming; thus, it is not recommended for the chronic heart failure patients with diastolic and systolic dysfunction to swim (36).

2.7.1.1. Interval versus steady state exercise

It has been shown that left ventricular ejection fraction increase significantly and by the same amount during the course of a 15 minute interval training exercise than during the steady state exercise performed at the same average power output (21). Mean arterial blood pressure and heart rate were shown to remain similar to that seen in steady-state exercise, while blood lactate was significantly higher during interval exercise, showing a greater peripheral training stimulus (45). Thus, the rationale for developing interval training methods for cardiac patients is to apply a more intense exercise stimulus on peripheral muscles than that obtained during steady-state training methods, but without inducing greater cardiovascular stress (21). It was shown that chronic heart failure patients with very low baseline aerobic capacity demonstrated an improvement in ventilatory threshold (VT) (24% on average) and peak VO_2 (20% on average) (48). The improvement was observed after only 3 weeks of interval cycle ergometer training at different modes and levels (50%, 70%, 80% of predetermined maximal capacity) (48). Other studies showed similar findings by using steady state method, but after much longer training periods (8-24 weeks) (7, 30).

As it was suggested, work phases of 30 s and recovery phases of 60 s, using an intensity of 50% of maximum short-term exercise capacity for work phases are useful (21). Other combinations of work/recovery phases such as 15s/60s and 10s/60s with 70% and 80% of maximum short-term exercise capacity were also proven to be tolerable (46). Depending on the work/recovery interval chosen, about 10-12 work phases can be performed per 15 minutes training session (46).

2.7.2. Resistance exercise training

Up to recently, there has been a reluctance to apply resistance exercise because of potential harmful cardiovascular responses which were found primarily during sustained isometric hand grip exercise lasting > 3 minutes (56). There was a fear that resistance training may increase hemodynamic burden, decreases myocardial perfusion, or cause wall motion abnormalities or arrhythmias (40). However, it was found with further studies that rhythmic strength exercise appears to be a promising training method for chronic heart failure patients by helping to maintain venous return, reducing systemic vascular resistance, maintaining muscle blood flow, and meeting muscle metabolic need (21).

In a study comparing hemodynamic responses to both resistance exercise and continuous aerobic exercise (cycling) of similar relative intensities, the resistance modality was associated with favourable responses (43). Other studies of 8 and 12 weeks showed improvement in functional capacity and muscular strength in chronic heart failure patients following a circuit weight training program (38, 57). Studies using combined endurance/strength training showed to be superior to endurance training alone concerning improvement of left ventricular function, peak VO_2, and strength parameters. It appears that for stable CHF patients, a greater benefit can be derived from this training modality (17).

2.8. Frequency and duration

There have been a lot of differences in duration and frequency of exercise applied, in chronic heart failure patients, ranging from 10 to 60 minutes sessions, and performed between 3-7 times per week (7, 12, 30, 46). Chronic heart failure patients with functional capacity of <3 METS (approximately 25-40 W) seem to benefit from multiple short daily exercise sessions of 5-10 minutes (25, 46). Patients with a functional capacity of 3-5 METS (approximately 40-80 W), one or two sessions/day of 15 minutes each seems to be appropriate. For patients with functional capacity of >5 METS, 3-5 sessions per week for 20-30 min each are recommended (21) (Appendix C).

2.9. Exercise intensity

With regard to the intensity of the exercise program, it has been proven that supervised moderate exercise programs help to improve exercise capacity and quality of life in heart failure patients who have a stable condition (11, 14, 62).

It was suggested by a trial that the reason why moderate exercise training improves the outcome of the patients could be due to the fact that relatively higher functional capacity after exercise training may be a stimulus for more active lifestyle. That contributes to the maintenance of a higher peak VO_2 (6). Another possible explanation was that by prolonging exercise conditioning, myocardial perfusion improves and therefore less cardiovascular events may occur (6). Although, these evidences were supportive of the moderate exercise intensity, some limitations existed to the study, as there was no measurement taken of the changes in skeletal muscle oxidative capacity or changes in autonomic balance after exercise training. These factors combined with a small sample size could have overestimated the importance and the role of the improvement in myocardial perfusion in predicting a lower rate of cardiac events in trained patients with ischemic cardiomyopathy (6).

Adverse effects, though, have been shown by vigorous exercise training. It was suggested that vigorous exertion might trigger sudden death (3). High intensity training (70-80% of peak oxygen uptake) might lead to acute heart failure and episodes of sustained ventricular tachycardia and participants may be required to withdraw from training as a result (7).

Although most studies have used aerobic programs in which patients aimed at achieving 50% to 75% of maximum heart rate with exercise, less demanding protocols are beneficial as well. An easier pace was recommended in earlier years and it was argued that programs of low intensity produce an improvement in aerobic capacity with a smaller risk/benefit ratio (7). Other studies supported the fact that a low level (corresponding to 40-50% maximal VO_2) program may be more advantageous than a program at higher workloads (corresponding to 70-80% maximal VO_2) (7, 18, 33). The reasoning for choosing lower exercise intensity was that it could reduce the risk of left ventricular dilation minimizing the ventricular wall stress. Thus, the intensity of the exercise program must be carefully chosen to avoid complications.

2.11. Changes associated with exercise

2.11.1. Cardiorespiratory responses

It is shown that exercise tolerance, defined as time to exhaustion at sub-maximal intensity, can increase in the range of 26% to 37% after exercise training (32). Individuals report less fatigue, more energy, and more endurance after training programs. This improvement in exercise capacity is directly related to increase in peak VO_2. It was shown by many studies that peak VO_2 is reduced in patients with heart failure and it is believed that exercise training improves peak oxygen uptake (13, 64). The mechanisms responsible for the exercise training-induced increase in peak VO_2 represent improved myocardial function, as evidenced by increases in peak cardiac output response (19). The measurement of VO_2 max has been a useful supplementary criterion not only for the selection of patients for heart transplant but also for its timing. Maximal exercise performance exceeding 14ml/kg/min predicts a 1-year survival of greater than 90 % (which is higher than 1 year survival after heart transplant, so that it can be safely postponed) (61).

Exercise training at low intensity (40% of VO_2) was shown to improve VO_2 in patients with mild chronic heart failure by 22-25% (7). There has also been a wide range of improvement of peak oxygen uptake from 9% to 18% (5, 12, 20, 42, 66) in studies that used moderate intensity aerobic at 60% of heart rate reserve for 3-4 months (21). However, these improvements were not reported to be consistent in all studies of the same length for 3-4 months (67, 69).

Improvements in peak exercise capacity and an improved ability to tolerate sub-maximal exercise represent clinically important outcome in response to exercise training; therefore, it is important to investigate the most appropriate protocol, condition and number of people that would result in a significant improvement in peak VO_2. Changes in other cardiorespiratory parameters besides peak VO_2 are expected. A hospital based trial showed a 10% improvement in power output after 12 weeks moderate aerobic training (32). Progressive supervised aerobic walking programs for longer period of 52 weeks also demonstrated 10-15% increase in power output (30).

Minute ventilation (VE) was increased anywhere from 3%-13% after 12 weeks of aerobic training according different trials (12, 32, 66). Increase in O_2 Pulse was also evident after 12 weeks of moderate aerobic training (32). There were changes in cardiorespiratory responses at derived anaerobic threshold at peak exercise. Patients performed 12 weeks of aerobic training using different modalities for 20 minutes three times a week, showed 15% improvement in the derived anaerobic threshold at peak exercise (66). Other studies of similar length (12 weeks) showed 9% increase in derived ventilatory anaerobic threshold with moderate aerobic training for 3 times a week (32).

2.11.2. Quality of life

Measurement of health related quality of life (HRQL) in heart failure patients provides important information in addition to a clinical evaluation (11). Patients with heart failure experience progressive disability and decline in health related quality of life, which are associated with dyspnea and fatigue during routine activities of daily living, as well as having depression and feelings of isolation (20). Exercise training could be an effective treatment to improve quality of life. It is thought that as patients become more tolerant of exertion, they experience less fatigue and dyspnea and become more comfortable performing tasks of daily living (16).

Specific intervention should be aimed at improving quality of life in those most severely affected. It has been suggested that moderate exercise training improves functional capacity and quality of life in patients with chronic heart failure (6). Many trials showed exercise training improves quality of life and reduces limitations caused by symptoms of heart failure with left ventricular dysfunction by exercising CHF patients moderately for 12 weeks (14, 42). Oka et al. reported 3 of 4 domains of quality of life were improved by a 12 week, in-home moderate intensity walking and resistance training program. Significant improvements in fatigue, mastery, and emotional function, and clinical improvement were reported (50).

However, significant improvements in quality of life with exercise have not always been suggested. Some studies have shown very little change or no change at all in quality of life as a result of exercise training (51, 67, 68). Inconsistent findings necessitate investigating the type of exercise program that would increase the quality of life in chronic heart failure patients, by reducing their symptoms.

2.11.3. Exercise capacity

Exercise intolerance is a well-known component of heart failure and is a major limiting factor in terms of functional status and quality of life for patients with heart failure, where excessive muscle fatigue and breathlessness creates problems.

Six minutes walk test (6' WT) is shown to be a simple measure of functional capacity. According to a trial by Owen et al (51), exercise capacity was shown to improve significantly from 209±99 m to 231±99 m using the 6' WT, after 12 weeks of moderately exercising 15 heart failure patients of 75 years of age by going through circuit stations. The EXERT trial also reported a significant increase in 6-minute walk distance compared with baseline at 3 months for the exercising group (22±5m), by performing aerobic and resistance training in a supervised home based program using 60-70% of max HR for exercise intensity (42). Exercise tolerance was also shown to increase from 13.9 +/- 1.0 to 16.5 +/- 1.0 minutes (18% improvement) by 8 week trial exercising 17 men following a moderate aerobic training using bicycle 5 times a week (12). A 17% increase in exercise tolerance was reported by a controlled trial exercising 134 heart failure patients for up to 16 weeks using cycle ergometer for at least 20 minutes 4-5 times a week (20). Progressive, supervised aerobic walking programme for longer period of 52 weeks also supported improvement in 6 minutes walk up to 15% (30).

Although improvements are shown in the exercise tolerance by the 6' WT, they are inconsistent and it remains unclear which method of training would improve the walking distance in comparison to other forms of training.

2.12. Follow-ups, Patient education and self-management

Exercise training must be diligently monitored and terminated when an acute decrease in blood pressure, onset of angina, significant dyspnoea and fatigue, and feeling of exhaustion, and/or serious exercise-induced rhythm disorders are observed.

Not all studies are clear on whether a home-based exercise program is as safe as a hospital supervised training program. Beneficial effects of a home-based exercise program in chronic heart failure was first reported by Coats et al. (12); however, complete data concerning the compliance of all patients were not available.

Home-based intervention for heart failure patients was supported by many trials. Individualized instructional session, patient education and one on one follow-up were shown to be very effective (11, 50, 62). Close nurse directed follow ups were shown to reduce readmission by 13% and reduced hospitalization by 36% according to one trial and therefore a trend towards a mean annual reduction in health care costs per patient of US$1300 (11).

Recent large trials have confirmed the effectiveness of a supervised home based intervention by specifically providing exercise prescription for each individual. Extra Match collaborative trial (22) by analyzing nine separate clinical trials, involving over 800 heart failure patients, concluded that heart failure patients randomized to exercise achieved a significant increase in survival, as well as a significant decrease in hospital admissions. This large clinical trial confirmed the importance of formal exercise training rather than a general program with no guidance (22). The HF- ACTION (Heart Failure—A Controlled Trial Investigating Outcomes of Exercise Training) study, the latest ongoing 5 year large multi center trial by involving 3,000 patients, is also trying to promote supervised home based exercise training by the hypothesis that patients who participate in an exercise program with supervised visits will do significantly better than those who are simply put on standard medication therapy and encouraged to exercise. The overall death rate and the number of hospitalizations are expected to decrease by over 20% over two years (27).

Most home based trials suggested that active sensitive listening and open communication improve patient compliance and clinical outcomes in most studies, increase satisfaction with care, save clinician's time, and lower the risk of malpractice suits (37). Actively involving patients in the management of their chronic illness by giving them responsibility and helping the patient control the pace of change, and planning a strategy for self care have been also shown to improve compliance (34).

Chapter 3: Methodology

3.1. Study Participants

Out of all the patients who were screened at the Heart Failure Outpatient Clinic at St. Paul's Hospital, a total of 40 patients were recruited and randomized in to two equal groups of experimental (n=20) and control (n=20) group. They were stratified based on age, body mass index (BMI), initial VO_2 max (within the past 6 months) and functional class. After recruiting 4 patients at a time, they were matched based on the above criteria and randomized in to either control or experimental group. The person who was recruiting the patients was blinded to the group assignment.

Eleven of these patients, 6 from the experimental group and 5 patients from the control group did not complete the study due to either complications or inability to complete the tests. Altogether, 29 men and 10 women were studied (Table 1).

3.2. Inclusion Criteria:

(1) 45-75 years of age; consisting of both men and women

(2) Left ventricular (LV) systolic ejection fraction of < 40%

(3) VO_2 max of < 69% predicted for age

(4) History of heart failure

(5) Stable condition for at least a month

(6) NYHA classes I-III

(7) Stable dose of medication

(8) Patients who reside out side of lower mainland or those who do not have access and resources to a structured exercise program.

(9) Study approval by University of British Columbia and St. Paul's Hospital Ethic Committee.

3.3. Exclusion criteria:

(1) Musculoskeletal limitation

(2) Chronic obstructive pulmonary disorder (COPD) or other pulmonary disorders that limit exercise

(3) Patients who require change of medication

(4) Existing contraindications to exercise training

(5) Patients who are already involved in an exercise program such as healthy heart exercise program (Appendix B).

3.4. Study design

The study was a randomized controlled trial. Both, St. Paul's Hospital and UBC ethical review boards approved the protocol, and all patients provided written informed consent. After the recruitment and randomization of both groups, the experimental group (n = 20) underwent a combined interval walking and resistance training program and the control group (n = 20) underwent "usual activity" for 12 weeks.

Experimental group- The experimental group underwent formal exercise prescription at the intake clinic before starting and they also were prescribed individualised exercise program to follow. They were followed and educated by a clinical exercise specialist by telephone, Internet and fax on a weekly basis for a period of 12 weeks. The cardiovascular part of the training was different for each patient since it was specifically designed based on the patient's current condition, VO_2 max, activity level and medication. Patients were given heart rate monitors in order to exercise at a safe training zone and pedometer, a small device anchored to a patient's lower leg and calibrated to his/her stride to record time and distance walked (i.e., number of steps and miles). Each patient was asked to complete an activity log for each exercise session and was instructed on: 1) walking at the given training heart rate zone by recording the heart rate monitor data, 2) Keep record of ratings of perceived exertion, exercise performed, duration of exercise, and any symptoms experienced, 3) wearing the pedometer for walking and recording the distances walked.

The mode of cardiovascular training was walking in order to keep it easily accessible to patients. Patient were instructed on how to change their intensity of walking following their heart rate from faster bouts (i.e.75% of max HR) to slower bouts (i.e. 50% of max HR) of training in order to perform an interval training program to keep it challenging and stimulating rather than walking at a continuous pace. For most patients with moderate exercise capacity, they started walking from 3 times a week progressing to daily walks up to 60 minutes. Those starting with a poor exercise capacity were asked to walk twice a day for a shorter time initially progressing to a longer walk once a day.

They were also given tubing for resistance training along with pictures and instructions. Demonstration and proper instruction on how to perform resistance training for upper and lower body with the tubing following a proper technique, repetition and sets were provided. The resistance training program involved using tubing and performing up to 10 different exercises for overall body strength. The progression of the resistance training was once a week for the first 4 weeks, twice a week for the week 4-8 and three times a week for week 8-12. The repetitions stayed the same (15 reps); but resistance was increased by lengthening the tubes for more resistance. Number of sets was also increased from 1 to 3 sets by week 12.

Control group- The control group or the usual care group (n=20) maintained their habitual activity level and were not provided any formal exercise prescription and follow-ups at the heart failure clinic. They were simply encouraged to continue exercising moderately regularly by the nurse at the intake clinic without being given any specific guidelines.

3.5. Exercise protocol and progression

3.5.1. Interval training

Patients with low exercise capacity started interval training with 2 to 3 minutes of walking followed by a minute of rest, until they could do 10 to 15 minutes of exercise. The frequency for these patients was walking twice a day for the first 2-3 weeks up to three times a week. They then worked up to 5 minutes of fast walk followed by 2 minutes of rest for a total of 20 to 25 minutes of exercise per session for week 3-4 for up to 4 times per week. Longer bouts of fast walk were continued for up to 6 minutes alternated by 4 minutes of a slow walk for 30-40 minutes for week 4-8 up to 5 times a week and progressed to 7-8 minutes of fast walk alternated by 1-2 minutes of slow walk for 45- 60 minutes for week 8-12 daily for most patients. Patients who had higher exercise capacity started from 20-25 minutes initially (1min fast: 3 min slow) for the first 2 weeks, progressed to 30 minutes (2min fast: 2 min slow) for week 2-4, 40-45 minutes (4 min fast:2 minutes slow) for week 5-6, 50 minutes (5 minutes fast: 2 minutes slow) for week 7-8 and 55-60 minutes (7-8 minutes fast: 1 minutes slow) for week 9-12. The frequency started from 3 times a week for the first 3 weeks, 4 times a week for week 4-6, 5 times a week for week 7-8 and up to 6-7 times a week for week 9-12.

In order to provide an adequate training stimulus, the intensity varied anywhere between 50 to 85% of heart rate reserve (HRR). Patients worked up to 80-85% VO_2 max during high intensity portion of their training when they were walking at a brisk pace and down to 40-50 % $VO_{2\ max}$ during the slow recovery. There was at least 5-10 min of warm-up and cool down at a slower speed of 40% of their max HR. The intensities controlled by patient' heart rate and a rate of perceived exertion (RPE) was adjusted individually as they progressed.

3.5.2. Resistance Training

A series of total body strength training (six upper bodies and four lower bodies) were performed progressing from 1-3 days a week as well, by using elastic bands. Patients were instructed on how to perform Chest press, seated row, frontal and lateral shoulder raises, bicep curl, triceps press down, squat, leg curl, leg adduction and leg abduction. The number of repetitions (15 reps) stayed the same through out the program for 12 weeks, but the resistance increased by adjusting the length of the elastic band (shortening it for more resistance) and the number of sets progressed from 1 to 3 sets by the end of the program. Patients started by using the elastics once a week for one set for week 1-4, twice a week for 2 sets for week 4-8 and up to 3 times a week for 3 sets for week 8-12 maintaining 15 repetitions and increasing the resistance from 40% to approximately 75% of 1 repetition maximum over the 12 weeks will be performed. The heaviest resistance finished through a full range of motion was the patient's 1- repetition maximum of each exercise.

3.5.3. Follow-up protocol

In addition to having an initial exercise prescription, the experimental group (n=20) were followed by an exercise specialist on a weekly basis by phone, fax or email. They were given instructions on: 1) how to know they are exercising at the right intensity by using RPE and dyspnoea scale; 2) how to use heart rate monitors and train within the prescribed training zone; 3) how to use and calibrate pedometers to record walking distance; 4) how to perform resistance training using tubing by providing manuals with pictures and demonstrating the exercises and; 5) finally, recognizing signs that require the patient to stop exercising and acquiring immediate medical attention.

The patients were asked to keep a record on their activities, their perceived exertion, heart rate, waking distance/time and signs and symptoms on each exercising day on a log sheet in order to report back. Each patient within the experimental group was contacted by the exercise specialist initially for 3 times a week for the first month, followed by twice a week for the second month and then once a week for the third month. They each averaged about 10-15 minutes follow-ups on each participant within the experimental group for 12 weeks, in addition to 30-40 minutes of initial consultation. On each contact, the completed log sheets were reported to the exercise specialist by patients and they were provided with feedback and motivation.

3.6. Parameters Measured and the Rationale for Their Selection

The primary outcome measures were changes in VO_2 max, walking ability and quality of life. In addition, changes in other cardiopulmonary measures at peak such as power output, heart rate, O_2 pulse, respiratory quotient, and minute ventilation were investigated. Metabolic, ventilatory, gas-exchange and cardiovascular changes at anaerobic threshold were also calculated. Cardiopulmonary exercise test using a cycle ergometer was used to assess any changes in all these cardiopulmonary parameters.

The reason for choosing this technique was because cardiopulmonary exercise (CPX) testing is arguably now believed to be the 'gold standard' for evaluation of cardiopulmonary function and supersedes ECG treadmill studies, which are focused on detection of ischemia. The focus of CPX is measurement of ventricular function, respiratory function and cellular function via measurement of gas exchange, as well as detection of myocardial ischemia. CPX is the most cost effective method of evaluating the pathophysiology of both the cardiovascular and respiratory systems; in addition it is totally non-invasive.

A 6 minutes walk test (6 MWT) was administered to evaluate the walking ability of the patients by measuring the distance each patient can complete in 6 minutes. The results of the 6MWT were concordant with changes in symptoms, suggesting that it may be used as supportive evidence for symptom benefit. This test is shown to be of value in patients with more advanced heart failure, where it may function as a maximal exercise test (35). Other sources have confirmed that the self-paced 6 min walking test as a sub-maximal exercise test has been adopted in measuring exercise capacity in patients with chronic diseases (44, 52). The advantages of the 6 min walking test compared with other exercise tests is that it is simple, safe, and non-expensive to perform.

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used to examine any changes in the quality of life of the patient over 12 weeks (Appendix D). This questionnaire was chosen because it is commonly used at clinical settings for patients with heart failure and it has been used in many studies. It is a measure of the patients' perceptions of the effects of congestive heart failure on their lives. This 21-item, self-administered questionnaire comprehensively covers physical, socioeconomic and psychological impairments that patients often relate to their heart failure. A score based on how each person ranks each item on a common scale is used to quantitative the extent of impairment and how it is affected by therapeutic intervention. This patient self-assessment may provide an important perspective on congestive heart failure and the efficacy of medical therapy.

3.7. Measurement Technique and Protocol

The method available for the cardiopulmonary test was an electronically braked cycle ergometer (Sensormedics 800S). All CPX personnel were blinded to patient assignment. On an upright position, the patient underwent 3 minutes rest; 3 minutes unloaded pedaling, exercise-phase pedaling at 60 rpm, and 2 minutes recovery pedaling at 40 rpm. During the exercise phase, work rate was increased at 10 W/min in a ramp pattern up to symptom-limited maximum. Every 2 minutes, 12-lead electrocardiogram (ECG), blood pressure (BP), and oxygen saturation were recorded. Exercise was terminated due to: 1) patient's request, 2) ECG changes associated with myocardial ischemia (ST-segment depression > 2 mm), 3) systolic BP > 200 mm Hg, 4) diastolic BP > 100 mm Hg, and 5) physical exhaustion, dyspnoea, or calf/thigh pain.

Air expired during exercise testing was analyzed using a Horizon II Metabolic System. Direct measurement and calculations were used to determine peak VO_2, carbon dioxide production (VCO_2), ventilation, oxygen (O_2) pulse, and respiratory exchange ratio. Ventilatory derived anaerobic threshold (V-AT) was determined using the V-slope method. This measure, in which VCO_2 is plotted as a function of VO_2, can be used to detect the beginning of excess carbon dioxide production caused by the buffering of H^+ that arise from lactic acid (32).

The 6 min walk test (6 MWT) was conducted using a predefined course in one of the hallways of St. Paul's Hospital with small distance markers. A distance of 33 meter around the hallway was measured and the evaluation was based on how many times the patient was able to complete the designated distance in 6 minutes. The tester walking with patients around the hallway used a timer and was blinded to the patient assignment. This test was performed in a standardized manner in an un-crowded area assisted by a control person without any knowledge of which treatment the patient has been randomized to. The 6 MWT was performed both prior to and after the completion of study for both experimental and control groups.

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was given to both experimental and control groups prior to the study at the heart function clinic at the same time as the patient recruitment for the study by the exercise specialist. At the completion of the study, patients were given the questionnaire to fill out by the lab technician where they had gone for cardiopulmonary testing.

3.8. Data Analysis

Descriptive and inferential statistical analyses of all data were conducted using Statistica 6 and sigma plot was used for the figures. The alpha level of significance was set at 0.05. All measurements subjected to inferential analyses were reported as mean. A 2 (Group) x 2 (Time) factorial design with repeated measure on the second factor was used for the current study. A 2x2 ANOVA was used to monitor significant changes in each dependent variable in the control group versus the experimental group over the 12 weeks treatment protocol. The primary dependent variables included VO_2 max (ml/kg/min), 6 minutes walk test (meters) and negative symptoms obtained from Minnesota Living with Heart Failure Quality of Life Questionnaire. The Secondary dependent variables were the followings at peak: work (watts), HR (bpm), O_2

pulse (ml/beat), RQ, VE (L/min). The changes in metabolic, ventolitory, gas-exchange, and cardiovascular parameters at anaerobic threshold were also calculated. Each of these variables was compared at base line and at the end of the study between both groups of experimental and control group.

Chapter 4: Results

4.1. Patient Characteristics

Among patients who completed the study, no significant differences in demographic characteristics were seen between the two study groups after randomization (Table 1). The New York Heart Association Class, which is an indicator of the functional ability of patients with heart failure, was the same between both groups with the same mean for both. The mean for the initial VO_2 max was also similar in both groups and the patients were matched based on 10% difference in VO_2 max predicted for age. The patients were not matched based on gender since gender differences were shown to be non-existent in therapy, procedure use, and outcomes in patients who have a diagnosis of congestive heart failure (CHF) according to a recent Canadian study (58). Women and men were reported to have similar yearly numbers of re-hospitalization for CHF and emergency room visits and clinical outcomes in women and men who had CHF were also similar (58).

Among 40 patients who were recruited initially, there were 29 men and 11 women. The average age for both groups was 58.3 +/- 7.5 years; body mass index was 29.6 +/- 4.7; and initial % predicted peak vo_2 was 47.15 +/- 10.45%. The ejection fraction for both groups was < 40% with a mean of 26.9 +/- 8.5 %. There were more patients with NYHA functional class II; 6 patients had functional class I and the other 6 had class III functional class. Patients from both groups (experimental= 20, control = 20) were stratified based on age, body mass index, initial aerobic capacity (VO_2 max) and New York Heart Association Heart (NYHA) functional class. Of the 40 patients randomly assigned at baseline, 29 completed the study and 11 dropped out (Figure 1).This statistical equivalency remained even after the drop out data was removed from the analysis, indicating that the drop outs occurred in a randomly fashion.

4.2. Event Rate

4.2.1. Major Adverse Events. No major adverse events occurred during or immediately following exercise testing or training sessions. Over the course of the study, major adverse events in the experimental group included: 1 heart transplant in the third month, 1 Coronary Artery Bypass Graft (CABG) in the 5th month as a result of unstable angina after the 2nd month of exercise training, 1 inotrope admission in the second month and 1 defibrillator implantation in the 3rd month. Major adverse events in the control group included: 1 CABG x4 in the third month and 1 sudden cardiac death. The major adverse events occurred were due to comorbidities and the nature of heart failure, and not due to the training program.

4.2.2. Minor Clinical Events. Minor clinical events (i.e. effects of comorbidities, etc.) did not necessitate patient's withdrawal from the study, but interrupted the 12-week program. Five patients (25%) in the training group compared to 3 patients (15%) in the control group experienced minor clinical events. Minor events in the experimental group included: 1 bronchitis resulting in breathing difficulties, 1 stroke requiring period of rehabilitation, 1 hypoglycemic episodes, 1 asthmatic causing breathing difficulties and 1 car accident causing injuries requiring period of rehabilitation. Minor events in the control group included: 1 long period flue requiring recovery time, 1 breathing difficulties and 1 back problem.

4.3. Compliance to Training

The overall mean compliance rate for the 12-week program was calculated as the total actual time spent walking, as measured in minutes by the pedometer, for the 12 weeks, divided by the total prescribed walking time in minutes for 12 weeks. The overall mean compliance with the exercise training prescription was 77 +/- 19.73%. Only two patients had an overall mean compliance of 100% by strictly following the training program over 12 weeks. The reasons for poor compliance for most patients were comorbid conditions that occurred during the period of training. Those patients who did not experience complications, followed the training program strictly by keeping diaries of recorded heart rate, distance walked measured by pedometer, frequency and time performed. Fifteen patients completed the intervention at 12 weeks, but the training program took up to 20 weeks for some of the patients who experienced complications. On average, including those who had limiting conditions, all patients completed the intervention in 15.24 +/- 3.83 weeks because of all the interruptions that occurred during the study due to comorbid conditions and also inability for some patients to perform the post testing right at 12 weeks because of living out side of lower mainland.

4.4. Changes in cardiorespiratory responses during peak exercise

4.4.1. Changes in absolute and relative VO_2 at peak

It was hypothesized that the VO_2 max would increase significantly ($p < 0.05$) as a result of home-based exercise training for the experimental group after 12 weeks. This variable was tested at baseline and at week 12 by performing a cardiopulmonary test using a cycle ergometer. Statistical analysis showed significant improvement in % predicted, relative and absolute VO_2 max. The effect size of group x time was significant for the % predicted VO_2 max in the experimental group as it was reported to be $F (1, 27) = 4.86$, $p= 0.036$ and improved from 46 +/- 9% to 54 +/- 12 % versus the improvement that control group had from 48 +/- 11 % to 49 +/- 12 %. The effect of group x time was also shown to be significant in the experimental group for relative VO_2 max as it was reported to be $F (1, 27) = 5.36$, $p= .03$ and improved from 13 +/- 4 to 15 +/- 3 ml/kg/min as oppose to the control group who remained the same at 13 +/- 3 ml/kg/min with no improvement. The absolute VO_2 increased from 0.88 +/- 0.37 to 0.98 +/- 0.36 L/min after 12 weeks of training in the experimental group which was also shown to be significant, $p<0.05$. Therefore the hypothesis that was predicting a significant improvement in both relative and absolute VO_2 peak is accepted (Figure 1 & 2).

4.4.2. Changes in PO, HR, O_2 pulse, RQ and VE at peak

It was believed that all cardiorespiratory measures will improve respectively as a result of a 12 week home based intervention significantly, $p< 0.05$.

Work (watts) improved slightly in the experimental group and decreased in the control group from baseline to post-intervention. The heart rate (bpm) remained relatively the same at baseline and after the intervention in the experimental group and decreased slightly in the control group. O_2 pulse (ml/beat) increased in both groups respectively to the same magnitude with slightly greater improvement in the experimental group. Respiratory quotients (RQ) were similar in both groups. It was reported to be constant both at baseline and post intervention for the experimental and control group comparing before and after the intervention. Minute Ventilation (VE) (l/min) was increased in both groups after the intervention; this change was greater in experimental group; although, not significant.

In general, changes in maximal cardiorespiratory responses at peak included greater increase in work (watts), O_2 pulse and minute ventilation (VE) after 12 weeks of training in the experimental group compare to the control group. However, these changes were not proven to be significant (Table 2).

4.5. Changes in Six Minute Walk Test (6MWT)

It was hypothesized that the ability to walk in 6 minutes would increase significantly ($p < 0.05$) as a result of home-based exercise training for the experimental group after 12 weeks. This variable was tested at baseline and at week 12 performing a 6 minutes walk test, walking around a pre-designated 33-m hallway in St. Paul's Hospital and counting the number of the times that will be finished in 6 minutes. Statistical analysis showed the effect size of group x time to be significant as $p<0.05$, it was reported to be $F (1, 28) = 11.6$, $p= 0.002$.

The walking distance was increased from 267 +/- 39 to 288 +/- 45 m after 12 weeks of training in the experimental group as oppose to the reduction that was shown in the control group from 252 +/- 26 to 247 +/- 29 m comparing the baseline to the end of the study. Therefore, the hypothesis with regard to significant improvement in exercise tolerance as a result of home based exercise training after 12 weeks is accepted (Figure 3).

4.6. Changes in Quality of Life

It was hypothesized that the quality of life would increase significantly ($p < 0.05$) as a result of home-based exercise training for the experimental group after 12 weeks as a result of experiencing less negative symptoms. This variable was tested at baseline and at week 12 by having the patients to fill out a self-administered Minnesota Living with Heart Failure Questionnaire.

There was a significant improvement in the negative symptoms (40+/- 17 vs. 50 +/- 20) in the experimental group after 12 weeks of training in comparison to the control group who reported a slight increase in the negative symptoms (41 +/- 23 vs. 44 +/- 22) Therefore, the hypothesis that predicted an improvement in quality of life as a result of lower negative symptoms is accepted (Figure 4).

4.7. Changes at ventrilatory derived anaerobic threshold

It was hypothesized that there will be a significant improvement ($P<0.05$) after 12 weeks of home-based intervention in cardiovascular responses (HR, HR % max, O_2 pulse), metabolic responses (work, relative VO_2 (VO_2 /K), absolute VO_2 (VO_2), VCo2 & RQ), ventilatory responses (Vt, VE, RR) and gas exchange responses (Veo_2 and $Veco_2$).

Most metabolic measures were increased significantly ($P<0.05$) at anaerobic threshold after 12 weeks of home based exercise intervention. There was a significant increase ($P<0.05$) in work (watts), absolute VO_2 (L/min), relative VO_2 (ml/kg/min), VCO_2 (L/min) in the experimental group as oppose to the control group who showed a slight decrease in these measures after 12 weeks. Respiratory quotient (RQ) decreased in both, experimental and control group after 12 weeks of intervention in comparison to the baseline; however it was not reported to be significant ($P<0.05$).

The only ventilatory measure that was increased significantly ($p<0.05$) at 12 weeks in the experimental group was Tidal Volume (Vt)(L) whereas the control group showed a decrease in Vt (L). The changes in minute ventilation (VE) (L/min) and respiratory rate (RR) (BPM) were not significant. None of the measures of gas exchange (Veo_2 and $Veco_2$) were improved significantly as a result of the home-based intervention. None of the cardiovascular measures improved significantly ($p<0.05$) as a result of 12 weeks intervention. Heart rate, heart rate % and O_2 pulse (ml/beat) increased in experimental group compare to the control group that showed a decrease, however these changes were not significant (Table 2).

In general, there was significant increases ($p<0.05$) in metabolic responses (work, relative and absolute VO_2 and VCO_2) at anaerobic threshold as a result of 12 week home-based exercise interventions.

Chart 4.1. Patients screened, consented, randomized, and completed.

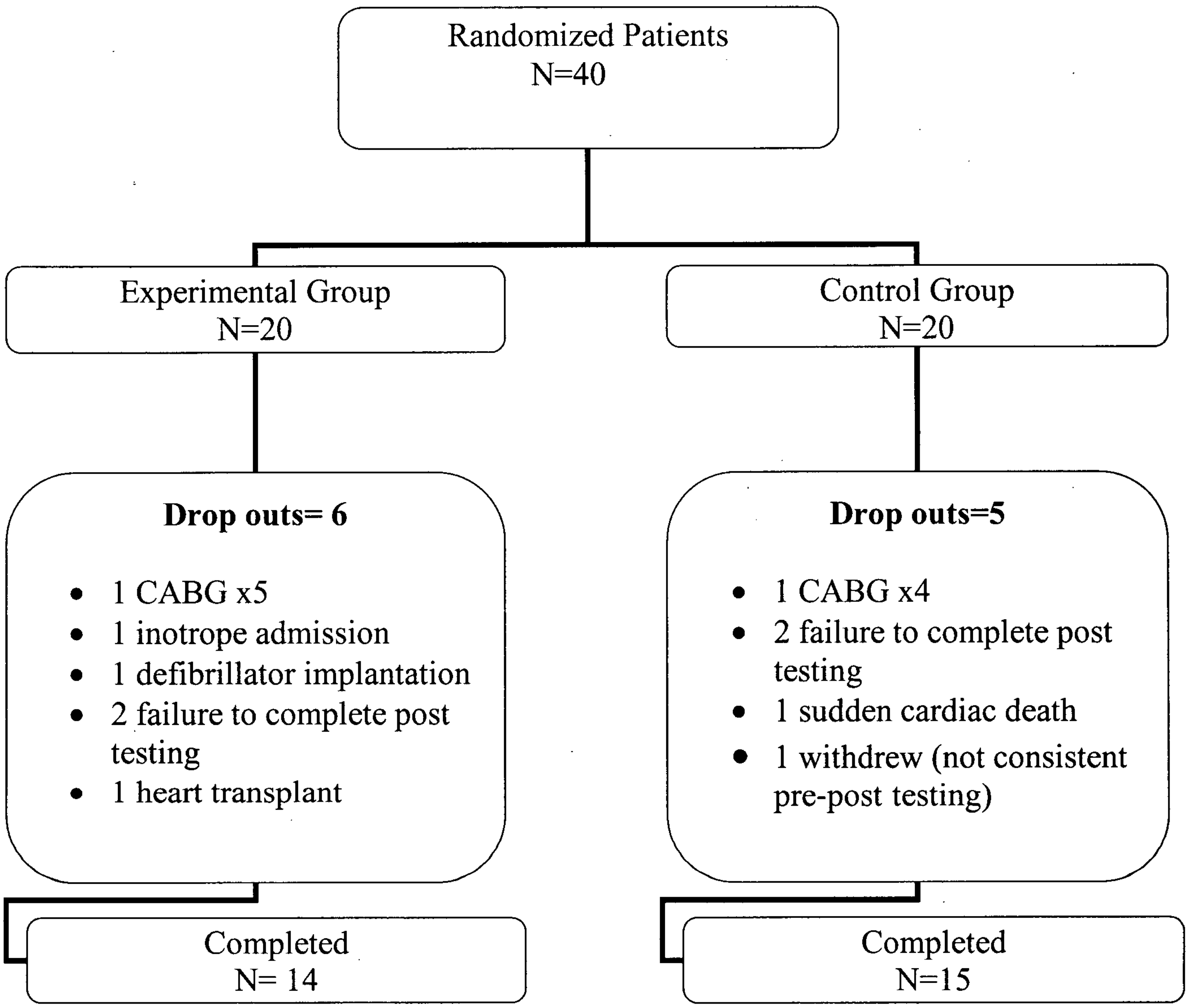


Table 4.1. Baseline demographic and clinical characteristics (n = 40)

Variables	Training group (n = 20)	Control group (n =20)	*P*
Male/female	15/5 (75/25)	14/6(70/30)	NS
Race			
White	19 (95)	17(85)	NS
Latin	0	1(5)	NS
Asian	1(5)	2(10)	NS
Age (y)	57.8 +/- 8.1	58.9 +/- 6.9	NS
Aetiology			
Ischemic	7 (35)	5 (25)	NS
Idiopathic	9 (45)	13 (65)	NS
Other	4 (20)	2 (10)	NS
BMI (kg/m^2)	30.3 +/- 4.4	28.9 +/- 4.9	NS
NYHA			
Class I	3 (15)	3 (15)	NS
Class II	14 (70)	14 (70)	NS
Class III	3 (15)	3 (15)	NS
Initial peak Vo_2 (% predicted)	46.7+/-10.1%	47.6+/-10.8%	NS
Ejection Fraction	27.8 +/- 8.8 %	26.0 +/- 8.3 %	NS
Medications			
Diuretics	14 (70)	10 (50)	NS
ACE inhibitors	13 (65)	13 (65)	NS
Angiotensin receptor blocker	9 (45)	9 (45)	NS
II	5 (25)	5 (25)	NS
Nitrates	19 (95)	20 (100)	NS
β-Blockers	18 (90)	18 (90)	NS
Digitalis	3 (15)	6 (30)	NS
Antiarrythmics	1 (5)	5 (25)	NS
Calcium Channel blocker	16 (80)	15 (75)	NS
Anticoagulant	10(50)	12 (60)	NS

Values are given as mean ± SD or n (%). *BMI*, Body mass index; *NYHA*, New York Heart Association; NS= Not Significant

Table 4.2. Changes in cardiorespiratory responses in control and experimental group over 12 weeks intervention (N=29)

	Base	*Post*	*P*
PO			
Experimental	96.85 +/- 31.01	97.35 +/- 29.88	NS
Control	79.20 +/- 25.43	72.13 +/- 29.64	NS
HR			
Experimental	110.57 +/- 17.87	110.57 +/- 22.54	NS
Control	105.53 +/- 34.29	97.53 +/- 27.64	NS
O_2 Pulse			
Experimental	10.70 +/- 4.12	11.82 +/- 3.74	NS
Control	10.60 +/- 3.64	11.35 +/- 3.56	NS
RQ			
Experimental	1.23 +/- 0.09	1.23 +/- 0.09	NS
Control	1.17 +/- 0.12	1.17 +/- 0.11	NS
VE			
Experimental	64.92 +/- 15.04	68.92 +/- 19.07	NS
Control	57.61 +/- 23.35	59.59 +/- 19.53	NS

Values are means+/- SD; NS= Not significant
PO=power output (watts); HR= heart rate (bpm); O_2 Pulse = Oxygen Pulse (ml/beat)
RQ=respiratory quotient; VE= minute ventilation (l/min)

Table 4.3. Cardiovascular responses at Anaerobic threshold in control and experimental group over 12 weeks intervention (N=29)

	Base	***Post***	***P***
Work			
Experimental	56+/- 21	62 +/- 25.30*	0.0010
Control	53.93 +/- 21.41	42.66 +/- 14.58	NS
VO_2 /kg			
Experimental	10.09 +/- 3.14	11.17 +/- 2.91*	0.039
Control	10.10 +/- 2.76	9.37 +/- 2.42	NS
VO_2			
Experimental	0.88 +/- 0.37	0.98 +/- 0.36*	0.019
Control	0.84 +/- 0.28	0.763 +/- 0.21	NS
VCO_2			
Experimental	0.88 +/- 0.35	0.98 +/- 0.38*	0.014
Control	0.85 +/- 0.28	0.74 +/- 0.19	NS
RQ			
Experimental	1.002 +/- 0.04	0.08 +/- 0.08	NS
Control	1.01 +/- 0.07	0.99 +/- 0.10	NS
VE			
Experimental	33.05 +/- 8.04	35.26 +/- 12.90	NS
Control	32.93 +/- 9.70	30.43 +/- 6.76	NS
RR			
Experimental	23.90 +/- 5.72	22.42 +/- 4.98	NS
Control	23.84 +/- 5.53	24.15 +/- 5.67	NS
Vt			
Experimental	1.44 +/- 0.47	1.60 +/- 0.53*	0.013
Control	1.43 +/- 0.48	1.31 +/- 0.36	NS
VEO_2			
Experimental	40.15 +/- 11.04	36.43 +/- 6.02	NS
Control	40.50 +/- 8.67	42.29 +/- 13.58	NS
$VECO_2$			
Experimental	40.19 +/- 9.72	36.65 +/- 4.99	NS
Control	39.80 +/- 7.41	42.36 +/- 9.91	NS
HR			
Experimental	91.78 +/- 12.46	94.85 +/- 21.67	NS
Control	96.2 +/- 38.10	86.20 +/- 24.38	NS
HR% max			
Experimental	59.64 +/- 12.41	62.64 +/- 18.52	NS
Control	65.20 +/- 24.42	62.40 +/- 18.96	NS
O_2 Pulse			
Experimental	9.77 +/- 4.19	10.54 +/- 3.06	NS
Control	9.28 +/- 3.78	8.96 +/- 2.89	NS

Values are means+/- SD; NS= Not significant, * $p< 0.05$ significant vs. baseline
Work =power output (watts); Relative V02 (V02/kg) = ml/kg/min; Absolute Vo2= L/min; VCO2 = L/min; RQ=respiratory quotient; VE= minute ventilation (l/min); RR= respiratory rate (bpm); Vt= Liters; HR= heart rate (bpm); O_2 Pulse = Oxygen Pulse (ml/beat)

Figure 4.1. Changes in max aerobic power in control and experimental group over 12 weeks intervention
*** Significant increase in the experimental group**

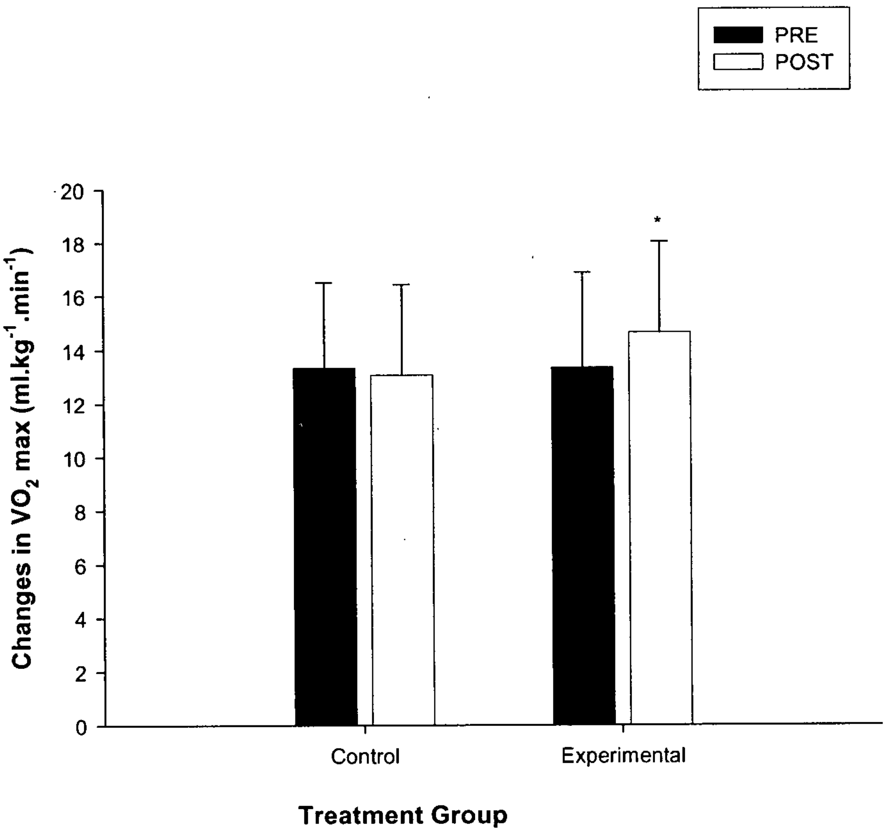


Figure 4.2. Changes in % predicted VO_2 max in control and experimental group over 12 week intervention

* Significant improvement in % predicted VO_2 max in experimental group

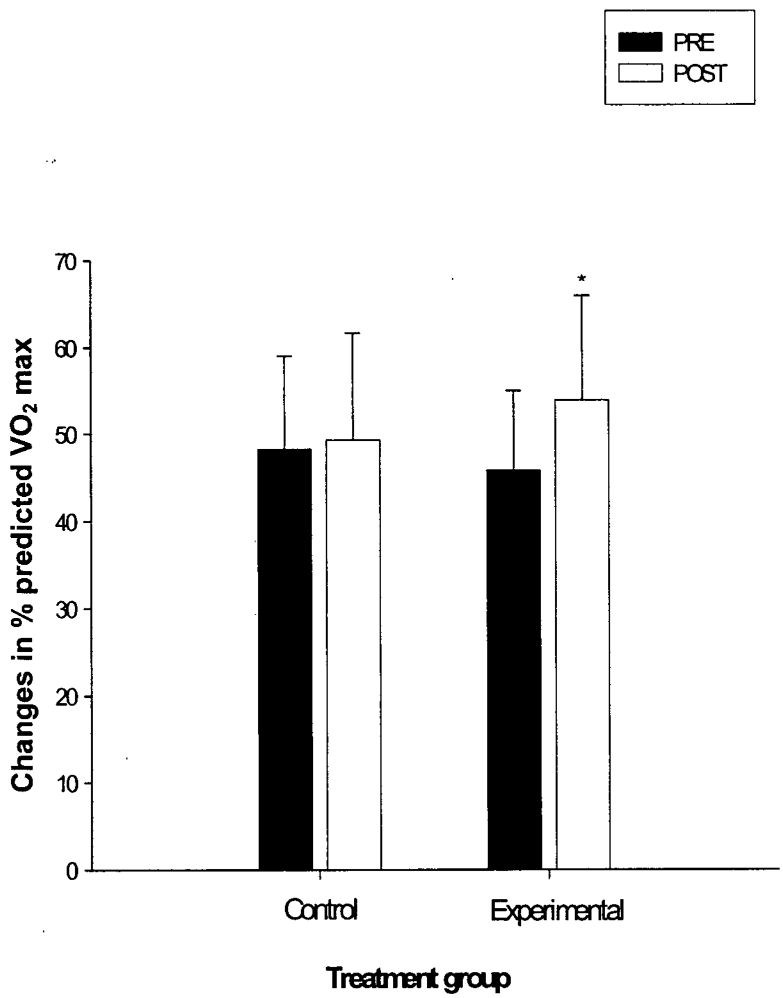


Figure 4. 3. Changes in quality of life presented by negative symptoms in control and experimental group over 12 weeks intervention
*** Significant reduction in negative symptoms**

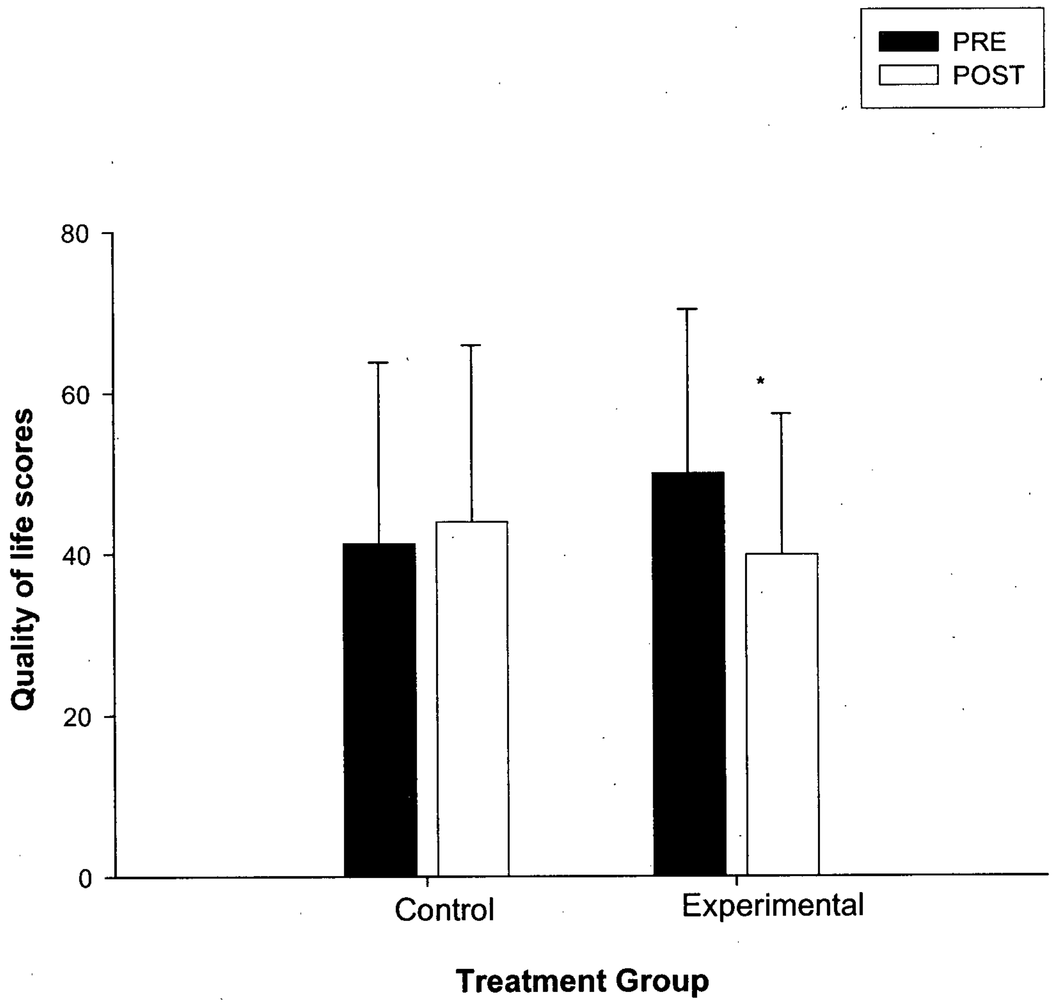
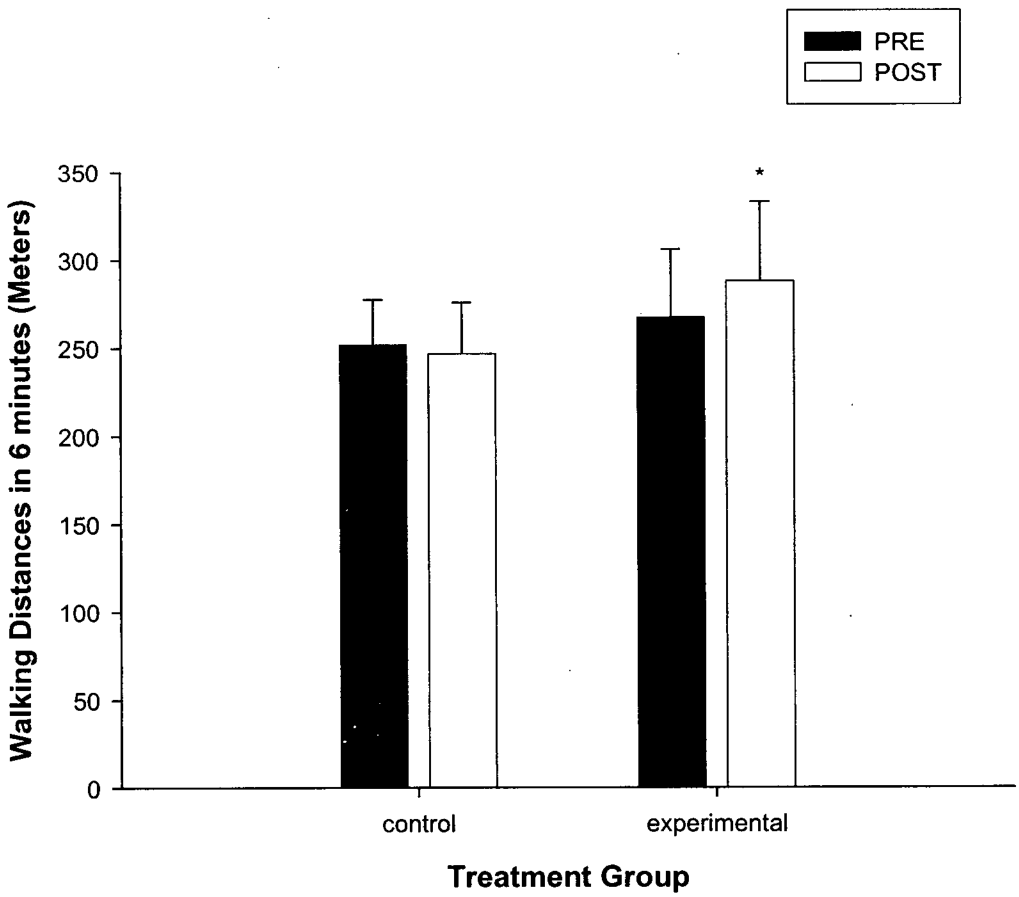


Figure 4.4. Changes in Walking distances in 6 minutes in control and experimental group over 12 weeks intervention
*** Significant improvement in exerimental group**



Chapter 5 : Discussion

The primary objectives of this investigation were to examine an appropriate training method of exercise training and evaluate the effect of home-based supervised exercise program, using a combination of aerobic interval training and resistance training on cardiorespiratory function (VO_2 max), walking ability and also quality of life. The major findings of this investigation are as follows: a) 12 week of supervised exercise training result in a significant improvement in cardiorespiratory function; and b) training induced improvement in cardiac parameters are associated with improvement in functional capacity and quality of life as significant improvements were evident. This study is unique because it is the only study, to best of our knowledge, up to this date that examined the effect of a home based walking program using an interval training method combined with resistance training by including close monitoring and follow-ups on patients. This study proved to be highly safe and effective by showing significant improvement in cardiorespiratory parameters, aerobic fitness (peak VO_2), exercise capacity and quality of life.

5.1. Safety, compliance and follow-ups

Major adverse events were not related to exercise testing or training. In this study, cardiac mortality was reported to be 2% and morbidity was 12% in the experimental group. The rate of hospitalization due to chronic heart failure in the training group was 20% in the exercising group. A recent large meta-analysis of randomized trials to date, following 729 CHF patients for 705 days, supported the safety of exercise training for CHF patients as it gave no evidence that properly supervised medical training programs for patients with heart failure might be dangerous, and indeed there was clear evidence of an overall reduction in mortality and admission to hospital with exercise training (54). Effectiveness and safety of exercise training in patients with heart failure was also confirmed by a systematic of a total of 81 studies that involved 2387 patients exercising and there were no reports of deaths that were directly related to exercise during more than 60,000 patient-hours of exercise training (59). The incidence of minor clinical events has not been reported in previous exercise trials. These events are likely explained by exposure to environmental elements and/or by the effects of coexisting comorbidities rather than the result of the training.

The reasons for dropout in this study were similar to previously reported trials (50, 25). The study's overall dropout rate of randomized patients (27%) is similar to that reported by Hambrecht (23%) (25) and Corvera (21%) (14), but lower than what was reported by Oka (40%) (50). While the home exercise program was well tolerated and well accepted by those patients who participated, they may not represent the greater population of patients with HF. Therefore, further studies are needed to identify barriers to exercise in a larger, representative sample.

The overall compliance rate of all the randomized patients in the experimental group (77%) compared favorably to compliance reports of those investigators who implemented a home-based exercise program (70-74%)(15, 50) and close to other programs of similar length following a standard cardiac rehabilitation program consisting of different aerobic modalities (84%) (66). In fact, the mean compliance of those exercising patients who completed this study was 80%. Two patients had 100% compliance and six patients (30%) dropped out of the exercising group. Poor compliance in some patients in the exercising group can be explained by the clinical effects of comorbidities. Aside from its simplicity, low intensity, and easy accessibility, the home walking exercise program also featured the use of pedometers, heart rate monitors and frequent phone calls, emails as well as some home visits which may have enhanced compliance. Nevertheless, a 12-week home walking and resistance training without home visits also had a higher compliance rate (50).

Follow-ups and the approach that was used towards training are important factors that could have affected the efficiency of this investigation. This study is unique because it documents the occurrence of significant improvement in quality of life, 6 minute walk test and

VO_2 max, as a result of an individualized home-based exercise training following a combination of interval training as a mode of cardiovascular training and resistance training.

This improvement was believed to be due to not only the individualized regimen that was given to each individual but also the follow-ups that were provided on these patients enhanced the compliance. It is believed a diligently monitored exercise training results in a higher compliance and therefore improved outcomes. There was (77%) compliance in the current study and this is attributed to the fact that the executed home based program enforced the patients to comply with the given exercise prescription with close weekly follow-ups, education and motivation. Several week studies supported this approach for a home-based program by showing improvement in quality of life and functional status (12, 15, 50, 62). Patient education and skill building, self-monitoring, social support, telephone follow-ups, and tailoring by active listening and open communication were repeatedly focused as the key in home-based exercise programs (11, 34, 37).

More and more large studies are taking place in an effort to prove the effectiveness of a home based program that is closely monitored. ExTra MATCH trial was one of the most recent largest investigations by looking at effect of supervised home based exercise training on 800 patients with heart failure and showed significant improvement in survival as a result (22). HF-ACTION trial is the largest ongoing trial by involving 3000 patients; improvement in survival and lower hospitalization are expected as a result of supervised home based exercise training (27). These current studies as well as other previous trials, strongly support home-based exercise training program by including proper instructions, close monitoring and interaction with patients via follow-ups (11, 22, 27, 34, 37). However, not all of the existing heart failure clinics offer such a program especially for those patients who do not have access to an exercise program due to either living in rural areas, disability or in general inaccessibility to such programs.

Up to this date, most heart failure clinics still follow the traditional method where they advise patients to perform physical activity in cases that they are unable to attend an exercise program in the area they live at. The guidelines given are very general and not specific for each individual based on their heart rate, medication and current activity level and there is also no regular follow-ups on their physical activity. Knowing that a closely monitored home based exercise program for heart failure patients can improve outcomes and most importantly enhance survival (22, 27), such programs should be implemented.

5.2. Method of training

Several studies investigated an appropriate use of exercise training in order to achieve maximal outcome. Inconsistent findings existed as to which training intensity (low, moderate or high intensity) will have a greater effect on VO_2 max. Low level of physical activity (corresponding to 40-50% maximal VO_2) was believed to be more advantageous than a program at higher workloads (corresponding to 70-80% maximal VO_2) by causing an improvement in aerobic capacity with a smaller risk/benefit ratio by reducing the risk of left ventricular dilation minimizing the ventricular wall stress (7, 18, 33). Use of high intensity program was eliminated by other studies, as adverse effects such as sudden cardiac death, acute heart failure and episodes of sustained ventricular tachycardia may result as a result of exercising at a high intensity (70-80% of peak oxygen uptake) (3, 7).

Most studies used aerobic programs in which patients aimed at achieving 50% to 75% of maximum heart rate with exercise. Improvements in exercise capacity and quality of life have been reported in exercise program following a moderate intensity. The best approach in order to stay within the suggested intensities (50% to 75% of max heart rate) and achieving the optimal result was believed to be interval training, by alternating bouts of low intensity (i.e. 50% of max hear rate) by bouts of high intensity (i.e. 75% of max heart rate) rather than a continuous exercise training, which is what was used in this study (6, 62).

The rationale for developing interval training methods for cardiac patients is to apply an intense exercise stimulus on peripheral muscles than that obtained during steady-state training methods, but without inducing greater cardiovascular stress (45). Blood lactate was shown to be significantly higher during interval exercise, showing a greater peripheral training stimulus (45). Improvement in peak VO_2 was observed after only 3 weeks of interval cycle ergometer training at different modes and levels (50%, 70%, 80% of predetermined maximal capacity) (46) in comparison to studies in which steady state method was used where such improvement was evident after much longer training periods (8-24 weeks) (7, 30). Although, a recent study by Warburton investigating effectiveness of high intensity interval training for the rehabilitation of patients with coronary artery disease revealed that interval training may not necessarily improve peak VO_2 to a greater extent than the traditional continuous rehabilitation program. However, it is believed to lead to adaptations that allow for a greater tolerance to a strenuous exercise challenge, which would benefit performance of many activities of daily living (65).

In addition to using an appropriate intensity of training, the progression of exercise training, frequency and duration is just as important. Patients with heart failure depending on their functional class, medications, exercise capacity and other cardiorespiratory measures are all different from one another. Therefore, a uniform exercise prescription of a certain intensity, frequency and duration might not apply to every one of them. There have been a lot of differences in duration and frequency of exercise applied, in chronic heart failure patients. Chronic heart failure patients with functional capacity of <3 METS (approximately 25-40 W) seem to benefit from multiple short daily exercise sessions of 5-10 minutes (25, 48). Patients with a functional capacity of 3-5 METS (approximately 40-80 W), one or two sessions/day of 15 minutes each seems to be appropriate. For patients with functional capacity of >5 METS, 3-5 sessions per week for 20-30 min each are recommended (21). This enforces the need of an individualized exercise program for these individuals. Therefore the progression of training was prescribed accordingly in the current study and was modified as patients improved. Training intensity was adjusted based on changes in heart rate achieved as a result of exercise as well as the changes in the frequency and duration of the exercise as the fitness level of patients improved.

Besides aerobic interval training, resistance training was also revealed to be beneficial in order to make a training program complete. Combined endurance/strength training was shown to be superior to endurance training alone concerning improvement of left ventricular function, peak VO_2, and strength parameters (17). Knowing the more beneficial outcome for the combined aerobic and resistance training, this method of training was used in the current study by using very light intensity (i.e. tubing) incorporating several muscle groups once a week progressing to three times a week over 12 weeks by increasing the tension and keeping the resistance at 15 repetitions.

5.3. Functional status

Cardiopulmonary test revealed a significant improvement in max VO_2. The magnitude of this improvement (~ 17 %), which is very similar to previous trials that used aerobic exercise modalities such as cycling and walking over a time period of similar length using a moderate intensity at a steady state (5, 7, 12, 20, 32, 42) and higher than the other studies (66). Studies that reported larger improvements in exercise capacity as a result of exercise training have typically taken place over a longer time span. Greater improvements were reported in VO_2 max after 24 weeks than after 12 weeks (31). Although, compliance to a long exercise program of 24 weeks could not be always as high as a 12 week program. It has been reported that heart failure patients with peak VO_2 of 14 ml/kg/min or higher have a better prognosis than those who do not, since having a VO_2 max less than 14 may indicate a need for heart transplant (49).

No significant ($p<0.05$) improvement in cardiorespiratory measures such as increase in power out, heart rate (HR), O_2 pulse, respiratory quotient (RQ) and minute ventilation (VE) was observed. The mean value for power output remained almost the same on average since the improvement was very minor (< 1%). This was different from result of another hospital based trial showed 10% improvement in power output after 12 weeks moderate aerobic training (32). The mean value for heart rate and respiratory quotient were unchanged as well. The change in heart rate was evident (15%) in other trials, but the respiratory quotient remained relatively the same (32).The only measures that improved slightly were increase in O_2 pulse by 10% and minute ventilation (VE) by 6%, which are close to findings of other studies that demonstrated 10% increase in VO_2 & 2% in heart rate (as they represent the change in O_2 pulse (VO_2 /HR) and 3% in minute ventilation (VE) (66). These improvement were also supported by another trial using different modalities of aerobic training for 12 weeks at a moderate intensity; however the changes were shown to be slightly higher for VE (13%) and lower for O_2 pulse (6%) (32)

The walking tolerance significantly improved in the current study (5%). This improvement is very similar to the findings of other supervised studies that followed the patients for 12 weeks using a moderate intensity exercise program (42, 51). In addition, significant correlation exists between the walking tolerance achieved from the 6-minute walk test and VO_2 max obtained from the cardiopulmonary test, which was also shown in other trials (10). However, inconsistency existed among different trials using various modality and intensity of training; thus this study confirmed the use of supervised home based training following a light to moderate interval training format in combination with resistance training.

5.4. Negative symptoms

Inconsistent findings existed with quality of life in patients with heart failure in previous studies. Many trials showed improvement in quality of life with moderate exercise training and reduction in limitations caused by symptoms of heart failure with left ventricular dysfunction by exercising CHF patients after 12 weeks (14, 42, 50) but others (51, 67, 68) argued otherwise. According to the Minnesota Living with Heart Failure Questionnaire in the current study, there was a significant improvement (20%) in quality of life as patients experienced less negative symptoms.

5.5. Changes at Anaerobic Threshold

There was a significant improvement ($p<0.05$) in metabolic responses (work, relative and absolute VO_2 and VCO_2) at anaerobic threshold as a result of 12 week home based exercise interventions. The magnitude of the improvement in the metabolic responses at anaerobic threshold is ~11%. This is closely related to findings of other studies of similar length (3 months) that showed 9-10% increase in the derived ventilatory anaerobic threshold as a result of a standard cardiac rehabilitation program (32, 69) and 15% increase in the anaerobic threshold as a result of aerobic training 3 days a week for at least 20 minutes using different modalities which is identical to the standard cardiac rehabilitation programs (66). Other studies of longer duration of exercise training (16-24 weeks) demonstrated a greater increase in peak vo2 at anaerobic threshold (20%) and delay in ventilatory anaerobic threshold (63).

5.6. Clinical Implication

The current investigation showed significant improvement in aerobic capacity shown by increase in peak VO_2 and 6 minutes walk test as well as significant improvement in quality of life by lessening the symptoms experienced by patients. The two component of this home based supervised program that contributed to this significant improvement were interval and resistance training. What makes this study different from most traditional exercise programs that are performed in several studies and also at the hospitals for the cardiac rehabilitation programs (i.e. healthy heart) is the individualized format of training that is performed in an interval training fashion. The exercise program at most cardiac rehabilitation programs include at least 30 minutes of cardiovascular training usually consisting of different stations such as treadmill, bike and rower training at a continuous intensity within the prescribed training zone (i.e. 50-75% of max heart rate) in addition to series of resistance training exercise for both upper and lower body using tubing or light weights performing high repetitions (i.e. 15-20 reps). These programs are usually 2 times a week but the patients are followed up on their additional home programs as well and each patient's program is individualized based on the exercise prescription received at the beginning on the program.

5.7. Future directions

In an attempt to investigate what could have been done differently or assessed in future research, both interval and the resistance training could have been possibly carried out differently. For the purpose of interval training, shorter bouts of work/recovery phases could be used as combinations of work/recovery phases such as 15s/60s and 10s/60s with 70% and 80% of maximum short-term exercise capacity, as was suggested by earlier studies (46). Other studies also demonstrated use of short work/recovery phases, work phases of 30 s and recovery phases of 60 s, by using a lower intensity of 50% of maximum short-term exercise capacity for work phases (21). A recent trial showed improvement in cardiorespiratory function using similar work/ recovery bouts, using 2 minutes work at high intensity (i.e. 90% of VO_2 max) and 2 minutes active recovery bouts at low intensity (i.e.40% of vo2 max) (65). Although, one of the factors that contributed to the significant improvement in this study was that fact that the aerobic interval training was individualized based on the patients ability and the intensity and duration of training was not preset the same for every patient.

Another factor that was involved in this investigation was resistance training and that could have been performed differently as well. Circuit weight training (CWT) format could have been used in this investigation where a combination of aerobic and resistance weight training exist in which seven resistance exercises are alternated with seven aerobic exercise stations. Following a CWT format, each exercise to be performed for 45 s, with 15-s intervals, signalled by a timer, for the purpose of moving to the next station. A trial examined the effect of circuit weight training (CWT) program on cardiorespiratory fitness, muscular strength, and body composition in patients with chronic heart failure (CHF), showed an increase in peak exercise oxygen uptake ($VO_{2\,peak}$), functional capacity and muscular strength after the 8-wk CWT program, since this way the peripheral abnormalities in CHF were specifically targeted (38). Improvement in skeletal muscle strength is important for patient capacity to perform tasks of daily living, many of which are dependent on muscular strength, and supports that CWT could have been an effective modality for improving peripheral muscle function in addition to $VO_{2\,peak}$. Besides the possibility of changing the format of the program in an attempt to see a more significant improvement in the outcome, it is not believed that the patients could have been pushed any harder or performed more exercise more frequently. The method of training performed in the current study was supported by many studies (14, 42, 50, 51) and therefore proved to be safe as well as effective. Most patients with heart failure have many other existing comorbid factors such as breathing difficulties caused by pulmonary dysfunction, musculoskeletal problems, diabetes that may cause episodes as a result of drop in the blood sugar and etc. and thus training these individuals any harder or more than what was proposed can be problematic.

Chapter 6:

Summary, Conclusion, Recommendations & limitation

6.1. Summary

The main purpose of this study was to develop an appropriate means of home-based exercise training by including monitoring, education and follow-ups for patients with congestive heart failure. A combination of interval and resistance training was used for the purpose of this investigation. The intent was to improve the VO_2 max, which is considered to be the main measure of survival for heart failure patients, as well as other cardiopulmonary parameters, exercise tolerance and quality of life. It was believed that a home based program that results in such significant improvements could lower the associated costs with heart failure by improving survival and therefore lessen the economical burden.

Forty patients with chronic heart failure were recruited after a screening process. They were stratified based on their age, aerobic capacity, body mass index and New York Heart Association functional class and randomized to two groups of experimental (n=20) and control group (n= 20). Due to complications, 11 patients dropped out and a total of 29 patients completed the study. The experimental group (n=15) underwent interval and resistance training. They followed a very structured exercise program tailored to each individual by following the heart rate training zone. They kept record of their heart rate, their walking distances by pedometers as well as a diary of duration and frequency of the exercise they performed. Besides they received weekly follow-ups via phone or email by an exercise specialist. The control group (n= 14) maintained their habitual activity level, but no formal instruction on exercise was given to them and also no follow ups were provided.

Results indicated that the individualized home based program resulted in a significant improvement in vo_2 max (assessed by cardiopulmonary bike test), exercise capacity (assessed by

6 minute walk test) and quality of life (assessed by Minnesota Living with Heart Failure Questionnaire) in experimental group. There was also significant improvement in metabolic responses (relative and absolute VO_2 max, work and VCO_2) at anaerobic threshold in the experimental group after the intervention. However, other measures such as ventilatory, gas-exchange and cardiovascular responses did not improve significantly at peak anaerobic threshold after 12 weeks. There were no significant changes in the control group and no significant improvement in other cardiopulmonary parameters at peak as a result of 12 weeks intervention.

6.2. Conclusion

Reflecting back to the hypothesis set forth prior to the execution of this research, the following assumptions are supported:

1. The prescribed exercise and follow-ups did result in significant improvement ($p<0.05$) in quality of life, walking ability and VO_2 max; thus the hypothesis that predicted improvement in these variables is accepted. However, no significant improvement was evident in other cardiopulmonary parameters at peak.
2. The intervention did result in significant improvement ($p<0.05$) in metabolic responses at anaerobic threshold in the experimental group; therefore the hypothesis suggesting such improvement is accepted. However, there was no significant improvement in ventilatory, gas-exchange and cardiovascular responses at anaerobic threshold; thus the hypothesis suggesting such improvement will be rejected.

In conclusion, it is now widely acknowledged that exercise training is an important component of the management of CHF that can improve functional capacity, quality of life, and prognosis. The results of this study suggest that an exercise training modality that specifically targets the peripheral limitations to exercise tolerance evident in patients with CHF, improves cardiorespiratory fitness and skeletal muscle strength. Although our program was formal and structured, a simplified program combining aerobic and resistance components should provide similar benefits that could be associated with improved prognosis and an increased capacity to perform tasks of daily living. This confirms that a properly selected exercise program that is tailored to each patient's individual's need, will result in significant improvement in cardiopulmonary measures that could result in reduction in hospitalization and mortality and reduces the costs significantly.

6.3. Recommendations

The findings of the current study strongly support that an individualized home- based exercise program is an effective means of functionally rehabilitating chronic heart failure. The exercise intervention significantly increased quality of life and exercise capacity by improving the walking ability. Most importantly, there was a significant improvement in VO_2 max, which predicts survival.

Most current heart function clinics in BC generally advice patients to exercise but no specific guidance and follow-ups, specifically on exercise, are provided. Finding how significantly a home based exercise program can improve the current condition of individuals with heart failure and as a result lower the cost for the hospital and the health care system, more similar programs should be implemented for those who do not have accessibility to hospital based exercise program. Long term follow-ups on heart failure patients should be implemented in BC in order to increase compliance and therefore lower hospitalization, morbidity and mortality.

6.4. Limitations

The study can have some limitations. Concomitant disease is common in patients with heart failure and limits the patient exercise capacity as a result. Due to the nature of the disease, patients with heart failure do not always have a stable condition and their functionality can change from day to day. Even though, a lot of variables were controlled before starting this study, factors still remain to be controlled. Dropouts and withdrawal from the study affected the finding by lowering the number of patients and therefore reducing the power. Larger sample sizes are less affected by this but the problem remains in the recruitment of these individuals as they all have other limitations or diseases that either caused their heart failure or happened concurrently and therefore makes it harder to find two people with the exact same background. This would explain the reason why there is such a large standard error for cardiac population and specifically for patients with heart failure. Also, majority of the patients in this study are male and below 75 years old, therefore the finding cannot be generalized to both genders and all age groups.

References

1. Adamopoulos S, Coats A, Brunoote F. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. Journal of American College of Cardiology 1993; 21: 1101-6.
2. AHA Science Advisory: Assessment of Functional Capacity in Clinical and Research Applications, 71-0190. Circulation 2000;102:1591-1597
3. Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, and Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. Journal of Cardiopulmonary Rehabilitation 2001; 21(3): 164-166.
4. American College of Sports and Medicine. ACSM's guidelines for exercise testing and prescription. Williams & Wilkings. Baltimore. (1995).
5. Barlow CW, Quayyum MS, Davey PP. Effect of physical training on exercise-induced hyperkalemia in chronic heart failure: relation with ventilation and catecholamines. Circulation 1994; 89: 1144-52.
6. Belardinelli R, Georgiou D, Cianci G, and Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure. Circulation 1999; 99: 1173-1182.
7. Belardinelli R, Georgiou D, Scocco V, Barstow T J, and Purcaro A. Low intensity exercise training in patients with chronic heart failure. Journal of the American College of Cardiology 1995; 26(4): 975-82.
8. Brilla CA. The cardiac structure-function relationship and the renin-angiotensin-aldosterone system in hypertension and heart failure. Current Opinion of Cardiology 1994; 9(Suppl 1): S2-S11.
9. Brubaker C, Witta L, Angelopoulos TJ. Maintaining exercise tolerance and quality of life by long-term participation in a hospital-based wellness program for individuals with congestive heart failure. Journal of Cardiopulmonary Rehabilitation 2003; 23(5): 352-356.
10. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, and DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest 1996; 110: 325-332.
11. Cline C, Willenheimer R, Erhardt L, Wikiund I, and Israelsson B. Health-related quality of life in elderly patients with heart failure. Scandanavian Cardiovascular Journal 1999; 33: 278-285.
12. Coats AL, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, Solda PL, Davey P, Ormerod O, Forfar C, Conway J, and Sleight P. Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation, and autonomic function. Circulation 1992; 85: 2119- 2131.
13. Cohn-Solal A, Chabernaud JM, Gourgon R. Comparison of oxygen uptake during bicycle exercise in patients with chronic heart failure and in normal subjects. Journal of American College of Cardiology 1990; 16: 80-5.
14. Collins E, Langbein W, Dilan-Koetje J, Maloney C, Williams K, Edwards L, and Hines E. Exercise training improves QOL in older patients with heart failure. Journal of Cardiopulmonary Rehabilitation, 2000; 20(5): 291.
15. Corvera-Tindel T, Doering LV, Woo MA, Khan S, Dracup K. Effects of a Home Walking Exercise Program on Functional Status and Symptoms in Heart Failure. American Heart Journal 2004; 147(2):339-346.
16. Costs JB, Rosen RC, Cosgrove NM. Non-pharmacologic therapy improves functional and emotional status in congestive heart failure. Chest 1994; 106: 996-1001.

17. Delagardelle C, Feiereisa P, Autier P, Shita R, Krecke R, and Beissel J. Strength/endurance training versus endurance training in congestive heart failure. Medicine & Science in Sports & Exercise 2002; 34 (12): 1868-1872.
18. Demopoulos L, Bijou R, Fergus I, Jones M, Strom J, and LeJemtel T. Exercise training in patients with severe congestive heart failure: enhancing peak aerobic capacity while minimizing the increase in ventricular wall stress. Journal of American College of Cardiology 1997; 29: 597-603.
19. Dubach P, Myers J, Dziekan G. Effect of high intensity exercise training on central hemodynamic responses to exercise in men with reduced left ventricular function. Journal of American College of Cardiology 1997; 29: 1591-8.
20. European Heart Failure Training Group. Experience from controlled trials of physical training in chronic heart failure: protocol and patient factors in effectiveness in the improvement in exercise tolerance. European Heart Journal 1998; 19: 466-75.
21. European Working Group Report. Recommendations for exercise training in chronic heart failure patients. European Heart Journal 2001; 22: 125-135.
22. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure, British Medical Journal 2004; 328(7433):189.
23. Francis GS. Neurohormonal responses to exercise in heart failure. In McCall, D. and S.H. Rahimtoola (Ed). pp. 90-106.Heart Failure. Futura Publishing Company. Armonk, New York. (1997).
24. Franklin BA, Pamtmat A, Johnson S. Metabolic cost of extremely slow walking in cardiac patients: Implications for exercise testing and training. Achieves Physical Medicine Rehabilitation 1983; 64: 564-7.
25. Hambrecht R, Niebauer J, Fiehn E. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultra-structural abnormalities of leg muscles. Journal of American College of Cardiology 1995; 25: 1239-49.
26. Heart and Stroke Foundation of Canada: The Changing Face of Heart Disease and Stroke in Canada, Ottawa. (1999).
27. HF-ACTION for Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training. Sponsor: National Institutes of Health. (2003).
28. Jaski BE. Basics of Heart Failure: In A problem Solving Approach. Kluwer Academic Publishers. Norwell, Massachussets. (2000).
29. Katz, AM. Heart Failure: Pathophysiology, Molecular Biology, and Clinical Management. Lippincott Williams & Wilkins. Philladelphia, PA. (2000).
30. Kavanagh T, Myers MG, Baigrie RS. Quality of life and cardiorespiratoy function in chronic heart failure: effects of 12 month's aerobic training. Heart 1996; 75: 42-9.
31. Keteyian SJ. How hard should we exercise the failing human heart? Journal of Cardiopulmonary Rehabilitation 2001; 21(3): 164 -166.
32. Keteyian SJ, Levine AB, Brawner CA. Exercise training in patients with heart failure. A randomized, controlled trial. Annual International Medicine 1996; 124: 1051-7.
33. Kiilavuori K, Sovijarvi A, Naveri H, Ikonen T, Leinonen H. Effect of physical training on exercise capacity and gas exchange in patients with chronic heart failure. Chest 1996; 110: 985-91.
34. Kushner PR, Smith SY.Collaboration and compliance: Improving outcomes in older women. Women's Health in Primary Care 1996; 2: 288-300.
35. Lars G, Swedberg K, Clark AL, Witte KK and Cleland JG. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. European Heart Journal 2005; 26 (8): 778-793.

36. Lehmann M, Sodar H, Durr H. Behaviour of heart rate, blood pressure, lactate, glucose, noradrenaline and adrenaline level in coronary heart disease patients in the course of tight swimming stress. Z Kadio 1988; 77: 508-14.
37. Levinson W, Roter DL, Mullooly J. Physician-patient communication: the relationship with malpractice claims among primary care physicians and surgeons. JAMA 1997; 277: 553-559.
38. Maiorana A,O'Driscoll G, Cheetham C, Collis J, Goodman C, Rankin S, Taylor R, and Green D. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. Journal of Physiology 2000; 88(5): 1565-1570.
39. Mancini DM, Walter G, Reichek N. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992; 85: 1364-73.
40. McCartney N. Role of resistance training in heart disease. Medicine & Science in Sports & Exercise 1998; 30: S396-S402.
41. McConnell TR., Mandan JS, Sykes JS, Finial H, Disrupt H. Exercise training for heart failure patients improves respiratory muscle endurance, exercise tolerance, breathlessness, and quality of life. Journal of Cardiopulmonary Rehabilitation 2003; 23(1): 10-16.
42. McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T, Hendrican K, and Salim Y. Effects of exercise training in patients with heart failure: The exercise rehabilitation trial (Exert). American Heart Journal 2002; 144: 23-30.
43. McKelvie RS, McCartney N, Tomlinson C, Bauer R, and MacDougall JD. Comparison of hemodynamic responses to cycling and resistance exercise in congestive heart failure secondary to ischemic cardiomyopathy. American Journal of Cardiology 1995; 76: 977-979.
44. Metra M, Nodari S, Raccagni D *et al.* Maximal and submaximal exercise testing in heart failure. Journal of Cardiovascular Pharmacology 1998; 32(Suppl. 1): S36–S45.
45. Meyer K, Foster C, Georgeakopoulos N, Hayrick R. Comparison of left ventricular function during interval versus steady state exercise training in patients with chronic heart failure. American Journal of Cardiology 1998; 82: 1382-87.
46. Meyer K, Same L, Schwa bold M. Physical responses to different modes of interval exercise in patients with chronic heart failure- application to exercise training. European Heart Journal 1996; 17: 1040-7.
47. Meyer K, Same L, Schwa bold M. Interval training in patients with severe chronic heart failure; analysis and recommendations for exercise procedures. Medicine & Science in Sports & Exercise 1997; 29: 306-12.
48. Meyer K, Schwa bold M, Westbrook S. Effects of short-term exercise training and activity restriction on functional capacity in patients with severe chronic congestive heart failure. American Journal of Cardiology 1996; 78:1017-22.
49. Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, and Fowler MB. Cardiopulmonary Exercise Testing and Prognosis in Severe Heart Failure: 14 mL/kg/min Revisited. American Heart Journal 2000; 139(1):78-84.
50. Oka RK, De Marco T, Haskell WL, Botvinick E, Dae MW, Bolen K, and Chatterjee K. Impact of a home based walking and resistance training program on quality of life in patients with heart failure. American Journal of Cardiology 2000; 85(3): 365-369.
51. Owen, A. & Croucher, L. (2000). Effect of an exercise program for elderly patients with heart failure. European Journal of Heart Failure, 2, 65-70.
52. Packer M, Colucci WS, Sackner-Bernstein et al.Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. Circulation 1996; 94: 2793–2799.
53. Patterson JH and Adams KF. (1996). Pathophysiology of heart failure: Changing perceptions. Pharmacotherapy 1996; 16(2 Pt 2): 27S-36S.
54. Piepoli MF, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004; 328 (7441):711.

55. Public Health Agency of Canada, Economic Burden of Illness in Canada, 1998. Released 2002.
56. Reddy HK, Weber KT, Janicki JS. Hemodynamic, ventilatory and metabolic effects of tight isometric exercise in patients with chronic heart failure. Journal of American College of Cardiology 1988; 12: 353-8.
57. Selig SE, Carey MF, Menzies DG, et al.Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability, and forearm blood flow. Journal of Cardiology Failure 2004; 10: 21-30.
58. Sheppard R, Behlouli H, Richard H, Pilote L. Effect of gender on treatment, resource utilization, and outcomes in congestive heart failure in Quebec, Canada. American Journal of Cardiology 2005; 95(8): 955-9.
59. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. American Journal of Medicine 2004; 116(10):693-706.
60. Smith TW, Braunwald E, Kelly RA. The management of heart failure. In Braunwald E, (Ed.) Heart disease. 1st Edition, pp. 485-543. W. B. Saunder. Philadelphia. (1988).
61. Stevenson LW, Steimle AE, Fonarow G, Kermani M, Kermani D, Hamilton MA, Moriguchi, JD, walden J, Tillisch JH, Drinkwater DC, and Laks H. Improvement in exercise capacity of candidates awaiting heart transplantation. Journal of the American College of Cardiology 1995; 25(1):163-70.
62. Stewart S, Vandenbroek A, Pearson S, and Horowitz J. Prolonged beneficial effects of a home-based intervention on unplanned readmissions and mortality among patients with congestive heart failure. Archives of Internal Medicine 1999; 159: 257-261.
63. Sullivan M J, Higginbotham MB, Cobb FR. Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. Circulation 1989; 79(2): 324-9.
64. Sullivan MJ, Knight D, Higginbotham MB. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation 1989; 80: 769-81.
65. Warburton ER, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, and Chan SY. Effectiveness of high intensity interval training for the rehabilitation of patients with coronary artery disease. American journal of Cardiology 2005; 95: 1080-1084.
66. Wielenga RP, Huisveld IA, Bol E, Dunselman PH, Erdman RA, Baselier MR, and Mosters WL. Safety and effects of physical training in chronic heart failure: results of the chronic heart failure and graded exercise study. European Heart Journal 1999; 20(12): 872-9.
67. Willenheimer R, Erhardt L, Chine C, Rydberg E and Israelsson B. Exercise training in heart failure improves quality of life and exercise capacity. European Heart Journal 1998; 19: 774-781.
68. Willenheimer R, Rydberg E, Cline C, Broms K, Hillberger B, Öberg L, and Erhardt L. Effects on quality of life, symptoms and daily activity 6 months after termination of an exercise training program in heart failure patients. International Journal of Cardiology 2001; 77(1): 25-31.
69. Wilson JR, Groves JR, Rayos G. Circulatory status and response to cardiac rehabilitation in patients with heart failure. Circulation 1996; 94: 1567-72.
70. World Health Organization (WHO). The World Health Report. Geneva: World Health Organization. (1999).
71. Young JB and Mills RM. Practical approaches to the treatment of heart failure. In Young, J. B. (Ed.) Circulatory and physiologic responses in heart failure. 1st Edition, pp. 31-40. Williams & Wilkins. Baltimore, Maryland. (1998).

72. Young JB and Mills RM. Practical approaches to the treatment of heart failure. In Cross Jr. A.M. and Mills Jr. R.M. (Ed.) Altered loading in heart failure. 1st Edition, pp. 41-47. Williams & Wilkins. Baltimore, Maryland. (1998).

Appendix A

New York Heart Association Functional Classes

Functional Capacity
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. 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.

* AHA Science Advisory (2000)

Appendix B

Relative and absolute contraindications to exercise training among patients with stable chronic heart failure

Relative contraindications

1. > 1.8 kg increase in body mass over previous 1 to 3 days
2. Concurrent continuous or intermittent dobutamine therapy
3. Decrease in systolic blood pressure with exercise
4. New York Heart Association functional class IV
5. Complex ventricular arrhythmia at rest or appearing with exertion
6. Supine resting heart rate > 100 beats/min
7. Pre-existing comorbilities

Absolute contraindication

1. Progressive worsening of exercise tolerance or dyspnoea at rest or on exertion over previous 3 to 5 days
2. Significant ischaemia at low rates (<2 METS)
3. Uncontrolled diabetes
4. Acute systemic illness or fever
5. Recent embolism
6. Thrombophlebitis
7. Active pericarditis or myocarditis
8. Moderate to severe aortic stenosis
9. Regurgitant valvular heart disease requiring surgery
10. Myocardial infarction within previous 3 weeks
11. New onset atrial fibrillation

Appendix C

Relative criteria necessary for the initiation of an aerobic exercise training program

- Compensated heart failure for at least 3 weeks
- Ability to speak without dyspnoea (with a respiratory rate of < 30 breaths /min)
- Resting HR of < 110 beats/min
- Less than moderate fatigue
- Cardiac index of > 21. Min-1.m-2 (for invasively monitored patients)
- Central venous pressure of < 12 mmHg (for invasively monitored patients)

Relative criteria indicating the need to modify or terminate the training program

- Marked dypnoea or fatigue (> 14 on Borg scale)
- Respiratory rate of > 40 breaths/min during exercise
- Development of an S3 or pulmonary rates
- Increase in pulmonary rates
- Increase in the second component of the second sound (p2)
- Poor pulse pressure (< 10 mmHg difference between systolic and diastolic BP)
- Decrease in BP (of > 10 mmHg) during progressive exercise
- Increased supraventricular or ventricular ectopy during exercise
- Diaphoresis, pallor or confusion

Appendix D

LIVING WITH HEART FAILURE QUESTIONNAIRE

These questions concern how your heart failure (heart condition) has prevented you from living as you wanted during the last month. The items listed below describe different ways some people are affected. If you are sure an item does not apply to you or is not related to your heart failure, then circle 0 (No) and go on to the next item. If an item does apply to you, then circle the number rating how much it prevented you from living as you wanted.

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 family or friends 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, fatigues, 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 all night difficult?	0	1	2	3	4	5
10. Making you eat less of the food you like?	0	1	2	3	4	5
11. Making your 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