AUTONOMIC NERVOUS SYSTEM ADAPTATIONS TO PHYSICAL TRAINING IN CONGESTIVE HEART FAILURE

AUTONOMIC NERVOUS SYSTEM ADAPTATIONS TO PHYSICAL TRAINING IN CONGESTIVE HEART FAILURE

By

TODD C. BENTLEY, B.Sc. (KIN)

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Master of Science

McMaster University

MASTER OF SCIENCE (1996) McMaster University
(Kinesiology) Hamilton, Ontario

TITLE: Autonomic Nervous System Adaptations to Physical Training in Congestive Heart Failure

AUTHOR: Todd C. Bentley, B.Sc. (KIN) (University of Waterloo)

SUPERVISOR: Dr. Neil McCartney, Ph.D.

SUPERVISORY COMMITTEE: Dr. Markad V. Kamath, Ph.D., P.Eng.
Dr. Ernest L. Fallen, M.D.
Dr. Tim Lee, Ph.D.

NUMBER OF PAGES: xiv, 176

ABSTRACT

The purpose of this investigation was to examine the potential differences in autonomic nervous system adaptations, as assessed by heart rate variability techniques, between a group of stabilized CHF patients randomized to either a training group (aerobic+resistance) or a control group (usual care). In a single-blind, randomized controlled trial of 3-months of supervised exercise training and a further 3-months of home-based exercise, 28 stabilized CHF patients (NYHA I-III) were randomized to either a training (AERWT) (n=16;11M,5F; age, 64.9±2.3; LVEF, 29.4±1.7%) or usual care (UC) (n=12; 10M,2F; age, 58.0±2.8; LVEF, 24.4±2.0%) group. Upon completion of the supervised exercise program, the AERWT group increased peak oxygen uptake ($\dot{V}O_2$) (13.2±0.5 to 15.5±0.84 ml/kg/min, $p<0.05$), and single-arm curl scores (16.2±2.8 to 19.2±3.3 kg, $p<0.05$) significantly compared to the UC group, without any deleterious effect upon clinical status or left-ventricular function (LVEF: 31.3±1.7 to 33.2±1.9%, $p=0.99$). Physical training reduced expired ventilation and carbon dioxide based on successive workloads during symptom-limited incremental cycle ergometry in the AERWT group; however, this was found to be non-significant, in addition to changes in resting heart rate, anaerobic threshold, maximal exercise duration, maximal power output, and double product following training.

Supine, resting power spectral indices remained unchanged from baseline to 6-months in both groups, as did the recovery of power spectral indices during supine rest following a

symptom-limited incremental cycle ergometry test. A qualitative comparison of the power spectral changes from supine to standing revealed no significant differences between groups with respect to improvements in the baroreceptor response to orthostatic stress. Time domain parameters, derived from 24-hour ambulatory holter monitoring, were also obtained at baseline, 3-months, and 6-months. The indices believed to be largely representative of vagal modulation, SDNN-Index, r-MSSD, and pNN50, tended to increase in the AERWT group with increased participation in the training program; however, the results did not obtain statistical significance ($p=0.07$). In addition, there were no significant changes in mean 24-hour heart rate or NN-interval, SDNN, or SDANN in the AERWT group ($p=0.21$).

The present investigation revealed some evidence to suggest that exercise training in selected populations of CHF patients results in favourable changes in vagal modulation and baroreceptor sensitivity; however, unlike Coats et al. (1992), the present investigation failed to note any significant alterations in HRV frequency domain indices as a result of exercise training despite identical improvements in peak $\dot{V}O_2$. The lack of significant findings in both the frequency and time domain HRV data could indicate that the autonomic dysfunction is so widespread and rampant in CHF that we cannot induce alterations through training as would be demonstrated in normal, healthy controls. In effect, these findings reinforce the hypothesis that in CHF the heart is the 'slave' of the periphery, and that due to the progressive lack of neural control of both the heart and circulation, in addition to an impairment in pump function, that the only effective means of improving physiological variables is through changes at the peripheral level.

A journey of a thousand miles begins with little steps...

Mao-Tse Tung

Dedication

This thesis is dedicated to.....

my parents, Douglas and Mary Bentley, for demonstrating to me that dreams certainly can come true with a little bit of work, integrity, faith, and help from the prayer hotline in the 'Holy Land;'

the heart failure patients lost to their illness during the course of the EXERT trial;

and finally, my grandparents Raymond and Erleen Brash, who succumbed to cardiovascular disease in my youth. Thank-you for starting me on my journey.....

Health is not just the absence of a disease.
It's an inner joyfulness that should be ours all the time-
a state of positive well-being...

Deepak Chopra

Acknowledgements

I would like to extend my gratitude to all those involved in the completion of this project. Special thanks to Katie Hendrican, Dianne Tomson, and Anne Page at Dr. McKelvie's office for their patience, organizational skills, and numerous favours. Thanks to Bob and Jane at Hamilton General MDU and the technicians in the Holter lab at MUMC.

I want to express my appreciation to my fellow graduate students for their friendship over the last two-years. In particular, I want to thank the 'Gary Boys,' Jonathon, Dan, and Matt for endless nights of laughter. I would also like to thank my friends Wade, Kevin, and Holly for their support during the ups and downs. In addition, I must not forget 'mother' Mary Cleland for her excellent advice and endless support!

Thanks a million to Drs. Tim Lee and Digby Elliott for sharing their statistical wisdom.

Special thanks to my friend Dr. Markad Kamath for giving me the 'reins' and trusting in my abilities. Your lessons and patience have been greatly appreciated.

Thanks to Dr. Fallen for his sense of humour, direction, and softball invitation!

Above all, I want to thank my mentor and friend Dr. Neil McCartney. Your guidance, respect, and faith in my abilities has empowered me from the beginning.

Cheers!

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

1.0 REVIEW OF LITERATURE

1.1 Introduction

Congestive heart failure is defined by Braunwald (1992) as a "pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or to be able to do so only from an elevated filling pressure." Congestive heart failure occurs as a final common pathway in a number of cardiac disorders (Deedwania, 1994; Braunwald, 1992), and has been described as "the most important public health problem in cardiovascular medicine" (Garg et al., 1993). From an epidemiologic perspective, congestive heart failure has been reported to affect an estimated 250 000 individuals in Canada, and accounts for an estimated 100 000 hospitalizations each year (Brophy, 1989). The statistics from the United States are proportionately similar, with approximately 2.3 million people suffering from CHF, and between 400 000 and 500 000 new cases being reported each year (Smith, 1985). The prognosis for patients afflicted by CHF has been reported to be between 4 and 5 years (Kannel et al., 1988); however, evidence from the Framingham Study demonstrated a 62% and 42% mortality rate for males and females respectively within five years following the development of CHF, and a cumulative mortality rate of 75% by nine years of CHF diagnosis (McKee et al., 1971). Despite a 31% decline in age-adjusted mortality rates from ischemic heart disease, the incidence and prevalence of CHF has been on the rise (Kannel et al., 1991).

a decrease in mortality following acute myocardial infarction results in more patients developing CHF; improved management of hypertension postpones, but does not prevent the development of CHF; and, the aging of the population inflates the incidence of CHF (Deedwania, 1994). The prevalence of CHF has been found to increase with advancing age; and has been reported to be 0.8% and 9.1% for individuals between the ages of 50 and 59 years, and between 80 and 89 years respectively (Kannel et al., 1991).

Both systolic and diastolic dysfunction are hallmarks of congestive heart failure, although the former is more common; however, in many patients both conditions are found to coexist (Braunwald, 1992). Systolic dysfunction is highlighted by the inability of the ventricle to expel its contents due to a reduced inotropic state, whereas diastolic dysfunction is an impairment in ventricular filling due to an accumulation of non-distensible fibrous scar tissue. Individuals with congestive heart failure, depending upon severity, demonstrate the characteristic symptoms of muscle fatigue, systemic edema, dyspnea, and exercise intolerance, along with poor subjective reports of quality-of-life (Hanson, 1994; Braunwald, 1992; Minotti et al., 1992; Rossi, 1992; Uren et al., 1992). The etiology of the underlying cardiac failure can be due to a number of mechanisms: hypertensive, ischemic, viral, or idiopathic (Braunwald, 1992). Clinical manifestations of heart failure have been found to vary enormously across individuals, and are dependent upon a number of factors including the age of the patient, the extent and rate at which cardiac performance becomes impaired, the etiology of heart disease, the precipitating cause of failure, and the specific ventricle involved in the disease process (Guyton & Hall, 1996; Braunwald, 1992). Thus, this clinical syndrome

proceeds on somewhat of a continuum. A number of physiological limitations have been identified in congestive heart failure and are classified according to central, peripheral, or ventilatory factors (McKelvie et al., 1995; Myers et al., 1991); among these include elevated catecholamine levels, increased resting heart rate, systemic vasoconstriction, decreased parasympathetic modulation of heart rate, selective atrophy of Type I muscle fibers, altered skeletal muscle oxidative metabolism, and increased pulmonary capillary wedge pressures.

It has been observed that congestive heart failure represents a clinical syndrome in which there is significant derangement in one or both limbs of the autonomic nervous system (Ferguson et al., 1990; Porter et al., 1990; Francis et al., 1985; Levine et al., 1982; Goldstein et al., 1975; Eckberg et al., 1971). Examples of autonomic dysfunction include a deregulation of the SA node and subsequent loss of automaticity, an impairment in baroreceptor sensitivity, a reduction in myocardial norepinephrine stores, and marked neurohormonal activation. Recently, heart rate variability (HRV) techniques have been developed as a non-invasive means by which to assess underlying neurocardiac function through changes in sympathovagal balance (Kamath et al., 1993; Saul, 1990; Fallen et al., 1988; Akselrod et al., 1985, 1981). Both time domain statistics and frequency domain indices are derived from a heart rate tachogram which is based upon the differences between successive RR-intervals in the electrocardiographic signal (Kamath et al., 1993; Kleiger et al., 1992; Ori et al., 1992). A significant reduction in heart rate variability, as is observed following acute myocardial infarction, has been associated with an increased risk of sudden cardiac death and increased morbidity and mortality (Kleiger et al., 1987). Significant reductions in heart rate variability

(Gang et al., 1993; Casolo et al., 1991, 1989) and increased incidence of sudden cardiac death (Packer, 1985) have also been reported in patients suffering from CHF; results from the Framingham study reported that 25% and 13% of males and females with CHF, respectively, died of sudden cardiac death (Deedwania, 1994). However, Packer (1985) reported that 50% of patients with myocardial failure die of lethal arrhythmias. This is largely attributable to the reduction in vagal modulation of heart rate which has been identified in CHF patients and in early post-infarction patients, and has been implicated in lowering of the fibrillation threshold (Bigger et al., 1988). Clinical investigations of CHF patients have also reported reductions in baroreceptor sensitivity (BRS) in response to orthostatic stress (Fallen et al., 1996; Grassi et al., 1993; Binkley et al., 1991; Goldstein et al., 1975), as well as pronounced neurohormonal activation (Packer, 1988; Francis et al., 1984) including the renin-angiotensin-aldosterone axis.

The improvements in CHF patient management can largely be attributed to the development of effective pharmacological interventions, such as angiotensin converting enzyme inhibitors which have been commercially available since 1983 (Deedwania, 1994). However, in contrast to normal cardiac patients, congestive heart failure has been described as an absolute contraindication to participation in cardiac rehabilitation (American College of Sports Medicine, 1993; Braunwald, 1992). Historically, the recommended course of treatment for these individuals has been to refrain from physical activity and overexertion for fear of further compromising left ventricular function and increasing symptoms (Arvan, 1988; Conn et al., 1982; Klassen et al., 1972; Burch et al., 1966). However, congestive heart

failure, with the interpolated effects of physical deconditioning, could precipitate further disability and complications in clinical status. Recently, a number of studies in the literature have explored the safety, efficacy, and outcome of exercise training in congestive heart failure (Bellardinelli et al., 1995; Hambrecht et al., 1995; McKelvie et al., 1995; Adamopoulos et al., 1992; Baigrie et al., 1992; Coats et al., 1992, 1990; Jetté et al., 1991; Arvan, 1988; Jugdutt et al., 1988; Sullivan et al., 1988; Conn et al., 1982; Lee et al., 1979). The consensus from these investigations is that patients can achieve significant training effects without any deleterious effects upon cardiac function and subjective reports of symptoms. However, some findings are subject to speculation due to lack of randomized controlled designs, questionable statistical analysis, and heterogeneous follow-up and training periods. Nonetheless, the improvements noted in exercise capacity have been hypothesized to be a result of changes in the periphery, highlighted by positive alterations in skeletal muscle metabolism and blood flow. Improvements in muscle strength have been demonstrated in training studies with selected cardiac patients (McCartney et al., 1993, 1991; McKelvie et al., 1990; Haslam et al., 1988) and the elderly (Benn et al., 1996; McCartney et al., 1995; Brown et al., 1990); however, no study of its kind has been reported in congestive heart failure. Recently, the safety of resistance training in congestive heart failure patients has been documented (McKelvie et al., 1995) and may represent a viable means by which to improve the symptoms of skeletal muscle fatigue in these individuals. Improvements in muscular strength have the potential to facilitate the performance of activities-of-daily living (ADL) which were previously taxing. Exercise training consisting of both aerobic and resistance

training, therefore, represents a possible medium by which to improve patient autonomy, psychological well-being, and clinical status in patients with CHF.

Thus, congestive heart failure represents an enormous burden not only upon the patient, but also the health care system. If there existed a viable means by which further patient encounters could be reduced and improvements in symptoms, quality-of-life, and functional capacity could be attained, this would have a marked impact from both a patient and health-care economics perspective. Exercise training consisting of both aerobic and resistive exercise may represent an approach to help attain the above goals. One such investigation in the literature reported an increase in both maximal oxygen uptake and anaerobic threshold, an increase in leg arteriovenous oxygen difference, leg blood flow, and a reduction in systemic vascular resistance as a result of an 8-week home cycling program; this was coupled with a significant reduction in sympathetic overexcitation and a marked return of vagal modulation of heart rate (Coats et al., 1992). A return of vagal modulation, and subsequent increase in heart rate variability, has been reported to be associated with a decrease in the risk of sudden cardiac death, via an increase in the fibrillation threshold, and a re-organization of sympathovagal balance may induce a cardioprotective effect via a decrease in the chronic sympathetic overexcitation which is typical of this disorder. Chronic sympathetic stimulation, as a result of compensatory mechanisms, has been attributed to deleterious consequences found in end-stage CHF such as reduced baroreceptor sensitivity and marked neurohormonal activation (Braunwald, 1992; Packer, 1992). Heart rate variability represents one strategy with which the underlying sympathovagal balance of the

autonomic nervous system may be observed, as the various HRV indices, in both the time and frequency domain, represent sympathetic and vagal activity occurring at physiological levels at which they can respond to regulatory mechanisms (Malik et al., 1993). These indicators, in turn, can be monitored for further follow-up investigations in order to assess the progression of the underlying failure, in addition to the effects of a therapeutic intervention such as exercise training.

The following review will discuss the relevant literature concerning the above topics. In addition, the review will address some of the inadequacies and methodological errors of previous reports in the literature concerned with exercise training of congestive heart failure patients, as well as heart rate variability assessment, in an effort to provide a rationale for the methodology of the current investigation.

1.2 EXERCISE TRAINING IN CONGESTIVE HEART FAILURE

1.2.1 Limitations to Exercise Performance in Congestive Heart Failure

Congestive heart failure represents a clinical syndrome in which the characteristic symptoms of dyspnea, and both muscle weakness and fatigue limit patient activity (Hanson, 1994; Braunwald, 1992; Minotti et al., 1992; Rossi, 1992; Uren et al., 1992). While an individual may appear to be asymptomatic at rest, upon mild exertion, the previously dormant symptoms may become exacerbated (Guyton & Hall, 1996). It has been suggested in the literature that the impaired exercise tolerance of CHF patients can be explained in terms of central, peripheral, and ventilatory limitations (McKelvie et al., 1995; Myers et al., 1991).

Both systolic and diastolic dysfunction are hallmarks of congestive heart failure and may occur either alone, or in combination; although the former is more common (Braunwald, 1992) . As a result of CHF due to a large anterior infarction, the left ventricle during systole is characterized by systolic stretch which impairs the ability of the ventricle to eject its entire contents. In addition, regional hypokinesis of the infarcted area and surroundings limit the ability of the ventricular musculature to forcefully eject its contents. The impairment in contractility, therefore, is a key determinant of the level of systolic function (Braunwald, 1992). With diastolic dysfunction there are a number of architectural modifications to the venticular wall including: increased ventricular stiffness as a result of an increase in non-distensible fibrous tissue; impaired relaxation; and, an impaired contribution of the atria to late diastolic filling due to a change in the V_1 fast atrial isoform to the V_3 slow isoform (Bonow et al., 1992; Braunwald, 1992). In addition, the increase in intraventricular pressure precipitates eccentric hypertrophy and subsequent thinning of the ventricular wall which increases myocardial oxygen demand (Braunwald, 1992). The typical reduction in left ventricular ejection fraction (LVEF) noted in CHF patients, however, has not been found to correlate with exercise tolerance either at rest (Massie et al., 1988; Szlachcic et al., 1985; Higginbotham et al., 1983; Weber et al., 1982; Franciosa et al., 1979) or during maximal exercise (Higginbotham et al., 1983; Port et al., 1981). Central abnormalities which are noted, in conjunction with a reduction in maximal cardiac output, and hence cardiac reserve include: increased sympathetic activity as indicated by increased plasma norepinephrine spillover (Ferguson et al., 1990; Packer, 1988; Pierpoint et al., 1987; Cohn et al., 1984;

Levine et al., 1982); reduced myocardial norepinephrine uptake (Bohm et al., 1995); organ malperfusion (Guyton & Hall, 1996; Braunwald, 1992); decreased venous return as a result of an edematous periphery (Guyton & Hall, 1996; Braunwald, 1992); alterations in intracardiac calcium homeostasis (Braunwald, 1992); decreased parasympathetic activity (Nolan et al., 1992; Porter et al., 1990; Eckberg et al., 1971); an impaired chronotropic response to physical activity (Francis et al., 1985); activation of the renal angiotensin aldosterone axis (Packer, 1988; Francis et al., 1984); reduced baroreceptor sensitivity (BRS) (Fallen et al., 1996; Grassi et al., 1993; Binkley et al., 1991; Goldstein et al., 1975); and marked reductions in heart rate variability (Gang et al., 1993; Casolo et al., 1991, 1989).

An enormous amount of work in the literature has focused its attention upon abnormalities at the skeletal muscle level in CHF patients. Indeed there are several mechanisms by which abnormalities in skeletal muscle morphology and metabolism may in fact explain the exercise intolerance experienced by this population. Much of the impaired exercise tolerance in congestive heart failure is believed to be due to adverse changes in the periphery, and may in fact be due to adaptations as a result of decreased cardiac reserve and the impaired delivery of blood to skeletal muscle. For instance, it is noted that in CHF patients that there is an impaired vasodilatory capacity in skeletal muscle due to decreases in endothelial-derived relaxing factor (EDRF) (Nakamura et al., 1994), as well as increases in endothelin levels and sympathetic mediated vasoconstriction (Wei et al., 1994; Katz et al., 1993). A selective muscle atrophy of Type I slow-oxidative fibers has also been observed (Sullivan et al., 1990; Lipkin et al., 1988), although deconditioning due to inactivity has been

implicated in causing this abnormality (Minotti et al., 1992). Abnormalities of skeletal muscle metabolism include an impaired oxidative metabolism via altered mitochondrial density and V_{max} (Drexler et al., 1992), and an early depletion of high energy phosphate stores, as evidenced by a greater Pi/PCr ratio and lower muscle pH (Sullivan et al., 1991, 1990; Massie et al., 1987) and early lactate accumulation (Weber et al., 1985) at the onset of physical activity. In addition, skeletal muscle afferents, via Type III and Type IV fibers, have been reported to evoke an exaggerated response in CHF patients (Piepoli et al., 1996). The reported overactivation of this ergoreflex has been implicated as the 'missing link' in the heightened ventilatory response, diastolic pressure, leg vascular resistance, and sympathetic activation observed in this population as a result of moderate activity (Piepoli et al., 1996). The reported increases in insulin-like growth factors (IGFs) and tumor necrosis factor (TNF) in the skeletal muscle of CHF patients has led to speculation whether CHF, coupled with inactivity, result in a net catabolic state (Hurst, 1994).

There is some disagreement in the literature that additional limitations to exercise tolerance in CHF may be linked to certain respiratory variables. Increased pulmonary capillary wedge pressures (PWP) (Braunwald, 1992; Sullivan et al., 1988), a heightened ventilatory drive ($\dot{V}E/\dot{V}CO_2$) (Buller et al., 1990; Sullivan et al., 1988; Fink et al., 1986), and an increase in ventilatory dead space to tidal volume ratio ($\dot{V}D/\dot{V}T$) (Sullivan et al., 1988; Weber et al., 1982) have been observed in CHF; however, it has been found that CHF patients are able to maintain normal levels of arterial oxygen saturation during progressive incremental exercise testing despite these noted abnormalities (Franciosa et al., 1988; Sullivan et al.,

1988). As such, it is argued by investigators in the literature that these ventilatory variables do not represent limiting factors of exercise performance.

Although a number of potential limiting factors to exercise performance have been identified in the literature, researchers have nonetheless explored the safety, efficacy, and tolerance of physical activity in CHF populations. These investigations have challenged current dogma which do not advocate exercise training in CHF patients due to concerns with eliciting a further impairment in ventricular function and increasing symptoms. The results of these investigations are summarized in the following section.

1.2.2 Historical Perspectives

Historically, exercise training of the congestive heart failure patient has not been advocated due to concerns with eliciting a further impairment in left ventricular function and clinical status (Arvan, 1988; Conn et al., 1982; Klassen et al., 1972; Burch et al., 1966). Major textbooks of cardiovascular medicine, as well as the ACSM position stand on exercise training of the coronary patient, list congestive heart failure as an absolute contraindication to participation in exercise training (American College of Sports Medicine, 1993; Braunwald, 1992). The lives of these individuals can be mildly or severely limited by the symptoms of breathlessness and skeletal muscle fatigue. Undoubtedly, if there existed a viable way with which to improve their clinical status, this would impact their quality-of-life enormously. Until recently, there have only been a small number of studies in the literature which focused specifically on exercise training of the congestive heart failure patient and those with severe left ventricular dysfunction. Out of the 12 studies in this area, only 5 investigations

(Hambrecht et al., 1995; Adamopoulos et al., 1992; Coats et al., 1992, 1990; Jetté et al., 1991) have used randomized controlled designs. Although the remaining 7 studies (Belardinelli et al., 1995; Baigrie et al., 1992; Arvan, 1988; Jugdutt et al., 1988; Sullivan et al., 1988; Conn et al., 1982; Lee et al., 1979) reported significant gains in functional capacity and other physiological measures, the lack of randomization and control groups, insufficient stratification of medication use, as well as unequal periods of training and follow-up in these investigations limit the external validity of their findings. In addition, the majority of the studies conducted have used a population in which the congestive heart failure, or left ventricular dysfunction was due entirely to an ischemic etiology. This may not reflect the typical population of CHF patients, as it has been demonstrated that this disorder can also be due to idiopathic, viral, or hypertensive origins (Braunwald, 1992). Of additional concern in these investigations has been the heterogeneity of the intensity, duration, frequency, and type of exercise stimuli used during the respective training periods. While some investigations have utilized an intensity based upon a percentage of maximal heart rate (MHR) achieved during a baseline exercise test, others have used a percentage of peak oxygen uptake ($\dot{V}O_2$ peak); in addition, some of the studies in the literature have been supervised training programs, whereas others have been exclusively home-based exercise programs. These findings make it difficult to compare and contrast between studies in the literature.

The intensity of the aerobic training stimulus used in CHF studies in the literature has ranged between 40% to 85% peak $\dot{V}O_2$ and 70% to 80% MHR, and patients have trained for between 4- weeks and 42-months. However, regardless of randomization, intensity, or

duration of training, the investigations concerning exercise training of the CHF and LV-dysfunction patient have reported improvements in peak $\dot{V}O_2$ in the range of 9% to 44%. It is believed that these improvements in oxygen uptake have been a direct result of adaptations taking place in the periphery, as the central hemodynamics, as well as left ventricular function and architecture are not altered appreciatively as a result of exercise training in this population. Although not every study in the literature has assessed left-ventricular function following exercise training, those investigations which have, have reported that these improvements in functional capacity have occurred without any adverse changes in LVEF. One report in the literature, however, did report that in a group of patients with LV-dysfunction participating in 12-weeks of exercise training, when patients were subdivided into those with >18% asynergy compared to those with <18% asynergy of the left ventricle, patients with >18% asynergy experienced a further increase in asynergy from 32.2% to 40%, a decline in LVEF from 43% to 30%, and a deterioration in their functional class score (Jugdutt et al., 1988). An additional study by Jetté et al. (1991) also reported that in a group of patients with LVEF <30%, following 4-weeks of cycling training at an intensity of 70-80% MHR, there were significant increases in exercise capacity compared to controls at the expense of elevations in pulmonary wedge pressures. In addition, the LVEF<30% training and control groups realized significant increases in LVEF following training; however, this was believed to be a result of spontaneous recovery of ventricular function due to the time elapsed (10-weeks) since their large anterior myocardial infarction.

Studies in the literature have also reported significant improvements in exercise

duration, maximal workload achieved, ventilatory threshold, oxygen pulse, systemic and peripheral arterial-venous oxygen difference, leg blood flow, and volume density of mitochondria and cytochrome-c in CHF/LV-dysfunction patients. In addition, the literature has also reported reductions in phosphocreatine half-life, ADP-formation during exercise, systemic vascular resistance, resting and submaximal heart rates during incremental exercise, and ergoreflex overactivation following a regimen of physical activity. Thus, it is clear that CHF patients can demonstrate positive adaptations as a result of following a course of physical activity. These improvements, which are believed to be largely due to peripheral adaptations, would noticeably impact patient autonomy and quality-of-life (QOL) by increasing their functional capacity and tolerance for activities-of-daily living (ADL).

1.2.3 Uncontrolled or Non-Randomized Trials of Exercise Training in Congestive Heart Failure

Lee et al. (1979) provided the first study in the literature of the effects of physical training in coronary patients with impaired ventricular function. A total of 18 patients with LV-dysfunction (LVEF<40%) of ischemic etiology participated in the study. Exercise testing and cardiac catheterization were performed at baseline and during a 12-42 month ($\bar{x}$=18.5 months) follow-up period during which patients performed walking, jogging, or stationary cycling at an intensity of 70-85% MHR, 2-6 times/week, for 20-45 minutes/session. Following the supervised 8-weeks of training, patients were given a home exercise program and returned for exercise supervision only once a week. The authors discovered that there was no deterioration in ventricular function as a result of the training period, and there were

no changes in ejection fraction, stroke index, cardiac index, pulmonary artery pressure, and left-ventricular end-diastolic pressure (LVEDP) or volume (LVEDV). There was, however, a significant increase in exercise test duration, a decrease from 32.1% to 23.4% in the functional aerobic impairment of the CHF patients, in addition to a reduction in resting and submaximal heart rates during maximal, symptom-limited exercise testing. This investigation can be criticized, however, due to lack of a control group, in addition to lack of a standardized period of training and follow-up.

A study by Conn et al. (1982) investigated the response of 10 patients with severe left ventricular dysfunction (LVEF<27%, $\bar{x}$=20) of ischemic origin to a 4-37 month ($\bar{x}$=12.7 months) period of physical conditioning. Patients performed stationary cycling (5-15min), as well as walking and/or jogging (30min) 3-5 days/week at an intensity of 70-80% MHR. At the time of the follow-up investigation, it was found that patients increased their O_2 pulse by 22.7% (12.8 to 15.7 ml/beat); in addition, patients increased their maximum METS by 21.4% (7.0 to 8.5 METS). The authors found that there was no correlation between resting left ventricular function and exercise capacity in this group of patients. A follow-up radionuclide ventriculography test was not perfomed in this investigation and precludes any statement on the effects of training on LV-function in this group of patients. There was no indication as to the NYHA functional class in this group of patients, although 6 of 10 patients reported symptoms of CHF; the initial average exercise capacity of 7 METS seems reasonably high, and could represent higher functioning patients. Once again, the absence of a control group, and lack of a defined follow-up and training period jeopardizes the external validity

of these findings.

Jugdutt et al. (1988) investigated the effects of 12-weeks of exercise training in a group of 37 patients (NYHA I-II) an average of 15-weeks following an anterior Q-wave infarction. The 37 patients were subdivided into 24 controls, and the 13 training patients were further classified into those with <18% (n=7, GP 1), and those with >18% (n=6, GP 2) asynergy of the left ventricle. The training stimulus included the RCAF 5BX/XBX program, consisting of calisthenics and a stationary run for 11-minutes/day. The frequency of each exercise was increased accordingly as patients progressed throughout the training period, and patient supervision was attenuated following the initial 2-weeks of training. Following the 12-weeks of training, GP2 patients experienced a significant further increase in asynergy and functional class score, coupled with a decrease in LVEF; this was also accompanied by increased stretching and thinning of the infarcted zone. Caution should be exercised in the extrapolation of these results to patients with CHF, as the average LVEF for GP1 and GP2 were 59 ± 4% and 43 ± 7% respectively, and do not reflect patients with severe limitations in left ventricular function. This investigation failed to report any objective measure of increased exercise capacity (i.e. peak $\dot{V}O_2$), although both groups improved their total work during exercise by 350 W; in addition, there were no observed improvements in any of the hemodynamic indices. Additional concerns with this investigation include the failure to randomize patients to the respective training and control groups, and the use of an exercise stimulus without a defined exercise intensity. The hemodynamic and metabolic effects of 4 to 6-months of exercise training in a group of 12 CHF patients (NYHA I-III; LVEF $\bar{x}$=24 ±

10%) of both ischemic and idiopathic etiology was investigated by Sullivan et al. (1988). The supervised exercise sessions included activities such as cycling, walking, jogging, and stair climbing at an intensity of 75% peak $\dot{V}O_2$ for one hour, at a frequency of 3-5 times/week. This detailed study demonstrated a 23% increase in peak $\dot{V}O_2$, an increase in systemic and leg arteriovenous oxygen difference of 1.6 ml/dl, and an improvement in peak exercise leg blood flow of 0.5 L/min. In addition, patients realized significant reductions in both arterial and femoral venous lactate levels during submaximal exertion, along with reductions in resting and submaximal heart rates during the exercise test. Once again, these investigators reported no alterations in ventricular function as a result of the exercise training: LVEDV, LVESV, right atrial pressure (RAP), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressures (PCWP), and systemic arterial pressures remained unchanged. Although this investigation demonstrated impressive hemodynamic and metabolic adaptations to training in CHF patients, it is subject to some methodological criticism. Once again, a control group was absent from this investigation, and there was not a defined training or follow-up period.

Arvan (1988) investigated the effects of 12-weeks of exercise training in patients with a history of recent acute myocardial infarction (AMI). A total of 65 patients (NYHA I-III) within 12-weeks of their AMI were subdivided into two groups: Group 1- LVEF>40%($\bar{x}$=56%) (n=40); and, Group 2- LVEF<40% ($\bar{x}$=28%) (n=25). These groups were subdivided further into those with (B) and without (A) exercise test evidence of myocardial ischemia: Group 1A (n=22), Group 1B (n=18), Group 2A (n=14), and Group 2B (n=11). The supervised training program included activities such as stationary cycling,

treadmill walking, or arm cycling for a duration of 30 to 45-minutes an average of 3-days/week. The training intensity was 50-75% of peak $\dot{V}O_2$ for the first 2-weeks of training, and was increased to 75-85% of peak $\dot{V}O_2$ for the remainder of the study. At the conclusion of the study, groups 1A, 1B, and 2A demonstrated similar improvements in exercise duration and peak $\dot{V}O_2$, as well as reductions in submaximal heart rates during exercise testing. As a group, the subjects in group 2 (LVEF<40%) increased their peak $\dot{V}O_2$ by 31.8%, and exercise duration by 60%; however, the subgroup without evidence of exercise induced ischemia (2A) demonstrated improvements of 44% and 66.7% respectively. The group 2B patients, however, were unable to achieve a significant training effect during the 12-week phase II cardiac rehabilitation program. These investigators suggested that patients with both left ventricular dysfunction and myocardial ischemia could not achieve a significant training effect due to chronotropic incompetence. The findings in this investigation are subject to scrutiny due to the lack of a control group, and the questionable sensitivity of ST-segment changes on treadmill testing to identify CHF patients with exercise induced ischemia, as well as the possiblility of spontaneous improvement in ventricular function following acute myocardial infarction.

The effects of a 16-week supervised walking program in 17 CHF patients (LVEF 21 ± 2%) was conducted by Baigrie et al. (1992). The etiology of CHF and functional class of the patients were not reported, nor was the distance travelled, frequency, intensity, or duration of the walking program. Following the training regimen, the investigators reported a 9% increase in peak $\dot{V}O_2$, an 11.6% increase in peak workload, a 10.9% increase in

ventilatory threshold, and an 11.3% increase in O_2 pulse. In addition, the CHF patients realized a significant 7.6% reduction in resting heart rate, and an 8.4% reduction in double product at a workload of 200 kpm/min. This investigation also reported a 17.6% increase in distance travelled during the 6-Minute Walk test, and significant improvements in quality-of-life scores as assessed by the Standard Gamble questionaire. The findings of this investigation are difficult to interpret based upon the lack of a control group, and the insufficient information concerning the exercise stimulus and patient demographics.

Belardinelli et al. (1995) investigated the effects of an 8-week low intensity exercise training program upon 27 CHF patients (NYHA II-III; LVEF 19%-38%) of either ischemic or idiopathic origin. The patients were matched according to clinical and functional characteristics and were then allocated to a training (n=18) or control group (n=9). The supervised training sessions consisted of stationary cycling at an intensity of 40% peak $\dot{V}O_2$ for 30-minutes at a frequency of 3 days/week. At the conclusion of the 8-week training period, the trained patients had increased their peak $\dot{V}O_2$ by 17%, their ventilatory threshold by 20%, and the peak workload achieved by 21%; however, in accordance with other studies in the literature, there were no differences in cardiac output or stroke volume. Skeletal muscle biopsies of vastus lateralis revealed an increase in the volume density of mitochondria in the trained group versus the control group upon completion of training, as well as an increase in size of both type I and II skeletal muscle fibers. This investigation can be criticized due to its lack of randomization of patients to groups. In addition, if patients were apparently matched between groups, why was there such a marked difference in group size? The

matching process was obviously not based upon etiology of CHF, for the ischemic etiology of the control group was 55.5%, whereas in the exercise group it was 72%.

1.2.4 Randomized Controlled Trials of Exercise Training in Congestive Heart Failure

The first randomized trial of exercise training in congestive heart failure was performed by Coats et al. (1990). Their design consisted of a physician-blind, random-order, crossover trial of 8-weeks of home-based stationary cycling and 8-weeks of activity restriction. A total of 11 CHF patients (NYHA II-III; LVEF 19 ± 8%) of ischemic etiology participated in the training study. The CHF patients performed 20-minutes of cycle ergometry at an intensity of 70-80% MHR with a frequency of 5 days/week. Upon conclusion of the study, the CHF patients demonstrated an increase of 18.7% in peak $\dot{V}O_2$, as well as an increase in exercise duration of 18.2%. In addition, submaximal heart rates and double product values were significantly reduced along with patient symptom scores. Identical results were also reported in a slightly larger group of CHF patients by Coats et al. (1992) (n=17) and Adamopoulos et al. (1992) (n=25); however, they also found significant reductions in systemic vascular resistance (SVR), as well as ventilatory drive as indicated by a reduced slope in the ratio of ventilation ($\dot{V}E$) to carbon dioxide production ($\dot{V}CO_2$). Cardiac output at submaximal and maximal levels was enhanced post-training as a result of an increase in peak exercise heart rate. In addition to the hemodynamic and ventilatory indices, there were also improvements in autonomic function as assessed by whole body radiolabeled norepinephrine (NE) spillover and heart rate variability (HRV) techniques. Despite the impressive design and results of these investigations, there are a few

methodological concerns. The frequency, intensity, and duration of the stimulus is of concern, for it could have produced a significant volume load on an already enlarged left ventricle and could have produced deleterious effects. Echocardiographic measures of left ventricular function were performed only at baseline, and as a result, no inference can be made as to the safety of the particular stimulus. Although a cross-over study controls for order of treatment and carry-over effects, there may be some ethical difficulties in using such a design in an exercise study of this type. The CHF subjects who exercised first may have been reluctant to undergo an 8-week period of total activity restriction if they felt that they had improved their function, and as such could have influenced the results of the study. Also, from a historical perspective, there has been greater compliance with supervised exercise training programs compared to home-based programs (Hamm et al., 1992); however, compliance with the home cycling program was reported to be 75% (range 26-110%), as assessed by the expected number of bicycle wheel revolutions for the duration of the training period. Perhaps the results could have been even more impressive if the training had been performed in a supervised setting.

Jetté et al. (1991) conducted a randomized 4-week exercise trial in patients with impaired left ventricular function (NYHA I-III). All of the 39 male patients' ventricular dysfunction was due to a large anterior myocardial infarction that was less than 10-weeks old. Subjects were randomly assigned to either one of two training or control groups based upon their resting LVEF: 1) training-LVEF<30% (n=7), control-LVEF<30% (n=8), and 2) training-LVEF 31-50% (n=11), control- LVEF 31-50% (n=10). The morning exercise

training sessions consisted of jogging (5-minutes), calisthenics (30-minutes), relaxation training (20-minutes), and stationary cycling (15-minutes), whereas the afternoon sessions consisted of 30-60 minutes of walking. Patients performed the above activities 5-days/week, and the intensity of the jogging and cycling was designed to elicit 70-80% of the MHR achieved during their previous stress test. There were no changes in any of the resting, submaximal, or maximal hemodynamic indices in any of the groups upon the post-training follow-up, nor were there any changes in the mean work capacity and peak $\dot{V}O_2$ in the training-LVEF 31-50% group. The training-LVEF<30% group realized a 22% increase in peak $\dot{V}O_2$ and a 17% increase in work capacity as a result of the training regimen; however, these improvements were accompanied by an increase in mean pulmonary wedge pressure. The echocardiographic indices remained unchanged in all groups, and suggested that there were no deteriorations in ventricular function as a result of the physical training. However, in both the training-LVEF <30% and control-LVEF<30% groups there was an improvement in LVEF, but this was believed to be due to spontaneous recovery of ventricular function due to the relatively short time since the initial infarction.

Hambrecht and colleagues (1995) examined the effects of a 6-month cycling program in CHF patients (NYHA II-III) randomized to either a training group (n=12) (LVEF 26 ± 9%) or control group (n=10) (LVEF 27 ± 10%). The origin of CHF was dilated cardiomyopathy and ischemic heart disease. The cycling program was supervised for the first 3-weeks and then patients were given a home-based cycling program. During the first 3-weeks, the patients cycled six times daily for 10-minutes at an intensity of 70% peak $\dot{V}O_2$;

then, upon beginning the home program, the patients cycled twice daily for a minimum of 40-minutes total at the same exercise intensity. In addition, patients were also required to participate twice a week in supervised 60-minute group exercise sessions consisting of walking, calisthenics, and ball games. At the conclusion of the 6-month training period, the trained group had increased their peak $\dot{V}O_2$, ventilatory threshold, and peak leg oxygen consumption by 31%, 23%, and 45% respectively; biopsies of the vastus lateralis revealed that the trained group had increased the volume density of mitochondria by 19%, as well as the volume density of cytochrome-c by 41%. All of these adaptations occurred without any changes in cardiac output at rest or submaximal activity. Of particular interest in this investigation was its lack of information concerning compliance with the training regimen. Perhaps if the supervised sessions had been of a longer duration, rather than only 3-weeks, patients would have performed even better.

1.2.5 Recent Advances in Exercise Training of Congestive Heart Failure Patients

Peripheral muscle weakness is a common complaint of CHF patients, and recently McKelvie et al. (1995) explored the safety and efficacy of resistance training as an adjunct to aerobic training in CHF patients. Previous reports by this group of investigators have demonstrated the applicability and suitability of resistance training among cardiac patients without CHF symptoms (McCartney et al., 1993, 1991; McKelvie et al., 1990; Haslam et al., 1988), and in healthy elderly subjects (Benn et al., 1996; McCartney et al., 1995; Brown et al., 1990). In their most recent report, they compared the hemodynamic responses of 5-minutes of cycling at 70% of peak power output, and 2 sets of 10 repetitions of single leg

press at 70% 1RM in a group of 10 male CHF patients (NYHA I-III; LVEF 27 ± 2%). There were no differences in maximal systolic blood pressure or cardiac volumes during the cycling and resistance exercise; however, the resistance exercise elicited a greater diastolic blood pressure, and a lower maximal heart rate and rate-pressure product compared to cycling. These results suggested that resistance exercise in this group of patients created a situation in which there was better myocardial perfusion, coupled with less of a myocardial oxygen demand. All of the reports in the literature which have examined the effects of exercise training in CHF patients have included aerobic exercise exclusively. There are no reports in the literature which examine the effectiveness of resistance training in this population. From a simplistic point-of-view, if CHF patients could increase peripheral muscle strength, perhaps this would allow patients to increase their tolerance in strength-related activities-of-daily living.

1.2.6 Summary

The majority of exercise trials in populations of CHF patients have reported positive physiological adaptations as a result of aerobic training without any further complications in ventricular function and clinical symptoms. It is believed that these improvements are a result of peripheral, rather than central adaptations. These findings have challenged current dogma concerning the rehabilitation of the CHF patient; where inactivity and pharmacological management prevailed in recent years, more evidence in the literature has suggested that exercise rehabilitation, using aerobic exercise, represents a safe and effective means by which CHF patients can increase their functional capacity and tolerance of ADL tasks. However,

some of the studies in the literature can be criticized due to certain methodological problems such as inconsistent periods of training, non-randomization to groups, lack of suitable follow-up procedures, and use of patients that do not represent a normal population of CHF patients with respect to etiology of failure, medication use, and NYHA functional class. These observations, in addition to the heterogeneity of training stimuli, jeopardize the external validity of their findings to the CHF population at large. Recently, resistance exercise has been shown to exert less of a myocardial oxygen demand and greater myocardial perfusion than aerobic exercise in a group of CHF patients. Resistance exercise may represent a medium with which to combat the symptoms of skeletal muscle weakness reported by this population. One way to evaluate the effectiveness of a therapeutic intervention includes the use of heart rate variability techniques. Heart rate variability has been used in a number of studies in the literature in both clinical and normal populations; it represents a reliable, non-invasive means in which the underlying sympathovagal balance of an individual can be assessed in order to evaluate the impact of a particular intervention, such as exercise training, upon the autonomic nervous system.

1.3 HEART RATE VARIABILITY

1.3.1 Historical Perspectives

Heart rate variability (HRV) has struggled to gain acceptance as a viable prognostic indicator and diagnostic tool within mainstream cardiology and neurology. The use of heart rate variability as a measurement tool is rooted in the early observations of Hon et al. (1965) in obstetrics during the monitoring of fetal heart rate; it was demonstrated that birth

complications and fetal distress parallelled the loss of variability in the fetal heart rate signal. The early observation by Hales (1733) of 'beat-to-beat' changes in heart rate as a result of changing respiratory inputs, has also led to the current movement in the literature to characterize autonomic control of the heart (Akselrod et al., 1981). Since then, it has been confirmed that heart rate, in addition to arterial blood pressure, stroke volume, and the morphology of the ECG signal, all demonstrate 'beat-to-beat' fluctuations (Malik et al., 1993; Saul, 1990; Appel et al., 1989; Akselrod et al., 1985). The variability of these cardiovascular signals is believed to reflect a 'homeodynamic' interplay between both exogenous and endogenous perturbations to cardiovascular function and cardiovascular regulatory mechanisms (Appel et al., 1989). Heart rate variability, in recent years, has demonstrated to be a viable, non-invasive measurement tool able to assess underlying neurocardiac function through changes in sympathovagal balance (Task Force of the European Society of Cardiology and NASPE, 1996; Kamath et al., 1993; Fallen et al., 1988). Heart rate variability has been used to study autonomic dysfunction in conditions such as congestive heart failure (Geng et al., 1993; Mortara et al., 1993; Stefenelli et al., 1992; Casolo et al., 1991, 1989), diabetic autonomic neuropathy (Bellavere et al., 1992; Ewing et al., 1991), myocardial ischemia (Kamath et al., 1996; vanBoven et al., 1995; Goseki et al., 1994; Marchant et al., 1994), and acute myocardial infarction (Bigger et al., 1992, 1991, 1988; Cripps et al., 1991; Ewing et al., 1991; Kamath et al., 1991; Pipilis et al., 1991; Malik et al., 1990; Kleiger et al., 1987). In addition, HRV has been used to assess the effects of pharmacological (Pomeranz et al., 1985) and exercise interventions (Furlan et al., 1993; Coats et al., 1992, 1990; Dixon

et al., 1992; LaRovere et al., 1992; Rimoldi et al., 1992; Kamath et al., 1991; Arai et al., 1989; Seals et al., 1989), as well as physiologic manoeuvres such as tilt (Kamath et al., 1993; LaRovere et al., 1992; Fallen et al., 1988) and lower-body negative pressure (LBNP) (Seals et al., 1989).

Both microneurographic recordings and denervation studies have confirmed that the efferent divisions of the autonomic nervous system are continually active (Kulbertus & Franck, 1988) . These basal rates of activity are referred to as sympathetic and parasympathetic *'tone'* respectively. The value of tone is thought to allow a single nervous system to increase or decrease the activity of a stimulated organ (Braunwald, 1992). The overall tone of the sympathetic nervous system is the result of two complementary mechanisms: both the tone from the direct stimulation of sympathetic efferents, in addition to the tone exerted by the basal secretion of both epinephrine (0.2ug/kg/min) and norepinephrine (0.05ug/kg/min) (Braunwald, 1992; Guyton & Hall, 1996). Alternatively, the tone exerted by the parasympathetic efferents is only under phasic control, and is without humoral regulation by circulating catecholamines (Guyton & Hall, 1996). It should be noted, that heart rate variability techniques are used to identify the ability and integrity of the autonomic limbs to modulate cardiovascular regulatory mechanisms, rather than providing specific information regarding the inherent tone of either division (Malik et al., 1993).

1.3.2 Frequency Domain Analysis of Heart Rate Variability

It is impossible to estimate the state of sympathovagal balance and autonomic tone solely on the basis of mean heart rate, for there are far too many control mechanisms and

underlying pathophysiologic phenomena at work (Malik et al., 1995, 1993; Kamath et al., 1993; Saul, 1990; Akselrod et al., 1985). Instead, the use of spectral analysis to examine heart rate variability, in the frequency domain, involves the decomposition of the heart rate RR-interval tachogram into the sum of its component sine waves of varying amplitudes and frequencies during a given recording period. This is performed using either a fast-Fourier transform or autoregressive modelling procedure upon the raw ECG signal (Task Force, 1996; Cerutti et al., 1995; Kamath et al., 1993). The resultant power spectrum displays the squared amplitude of the sine waves as a function of frequency captured during a fixed recording period of 2.2 minutes (Kamath et al., 1993). Figure 1 demonstrates a simplistic illustration of heart rate variability assessment in both the frequency and time domain. In order to ensure optimal reliability and reproducibility within a frequency domain recording period, it is essential that the heart rate signal meets certain criteria: the signal must be random, and insists upon the inability of a mathematical expression to define the heart rate sequence; the signal must also be stationary, whereby the probability function of the signal remains constant over time; and finally, a sufficiently long sampling period must be used in order to obtain a consistent collection of power spectra (Task Force, 1996; Cerutti et al., 1995; Kamath et al., 1993). In addition, the ECG beat data must be as ectopic-free as possible in order to discount the effects of a compensatory pause as an increase in vagal modulation, and its subsequent contribution to an increase in high-frequency (HF) power (Kamath et al., 1995, 1993; Ori et al., 1992).

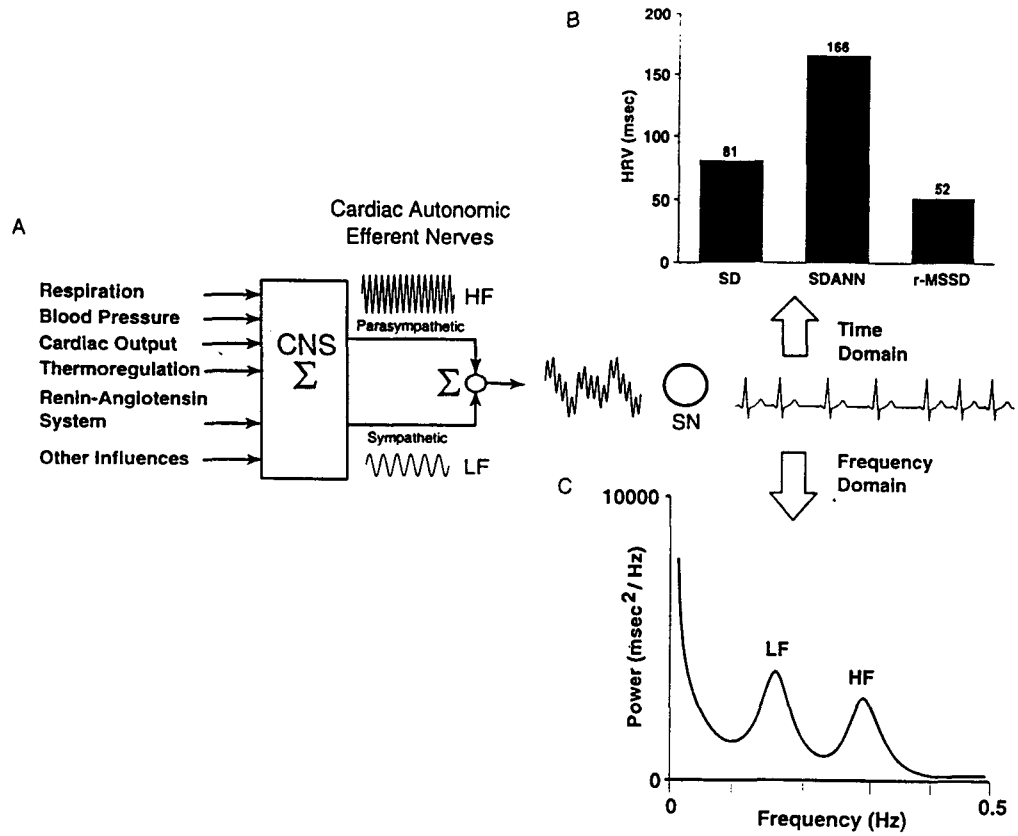


Figure 1: Neuroregulatory influences on sinus rate and rhythm, heart rate variability (HRV), and differences between time and frequency domain analysis of HRV (from Ori et al., 1992).

Akselrod et al. (1981), in a classic study, revealed the existence of three distinct spectral peaks in the frequency domain ranging from 0 to 1Hz. A high frequency (HF) peak occurred between 0.20Hz and 0.35Hz which was shown to be a result of both vagal modulation and the respiratory sinus arrhythmia. A low frequency (LF) peak was observed at approximately 0.1Hz, and was believed to be under both sympathetic and parasympathetic control in the modulation of the baroreceptor reflex. A very low frequency (VLF) peak at 0.02Hz-0.05Hz, although not always evident, was thought to reflect thermoregulatory activity

and activity of the renin-angiotensin-aldosterone system; however, the DC frequency band lies within this very low frequency range, and it is typically filtered out to avoid contamination of the signal due to a low signal to noise ratio (Task Force, 1996; Cerutti et al., 1995; Kamath et al., 1993; Ori et al., 1992). More recently, however, the spectral band of interest used in most investigations of HRV is in the range of 0.05Hz-0.5Hz. The co-existence of both sympathetic and parasympathetic inputs within the LF-peak was confirmed by Pomeranz et al. (1985), who demonstrated a decrease in the low frequency peak of the power spectrum during supine recordings in normal patients undergoing cholinergic blockade. These findings were later confirmed by Akselrod et al. (1985) and Kamath et al. (1993).

A number of variables appear to influence the resultant signal of the power spectrum. Increasing age has been found to decrease both the absolute LF and HF-power, however, the LF:HF ratio appears to be maintained, resembling that of younger, healthy controls (Odemuyiwa, 1995; Pagani et al., 1986). A supine, semi-recumbent posture in healthy subjects is characterized by a predominance of the HF component, whereas upon standing there is a resultant decrease of the HF- peak, followed by a sharp increase in the LF-peak (Malik et al., 1995; Kamath et al., 1993; Fallen et al., 1988); in addition, investigators in the literature have demonstrated a leftward shift of the LF-central frequency (cf) upon standing, and have validated this phenomenon using atropine to prevent the shift. These observations confirmed that there was modulation by both limbs of the ANS in the LF region. The circadian rhythm of heart rate variability may also influence data collection; in normal controls a bimodal peak in heart rate variability exists during REM sleep and in the waking hours

(Fallen et al., 1995; Kleiger et al., 1992). Training status may also influence the spectral pattern; it was demonstrated by Furlan et al. (1993), in a group of Olympic swimmers in their peak season, that supine semi-recumbent spectral recordings were characterized by an increased LF-peak at rest, in addition to a lower HF-peak and concurrent training bradycardia. When recordings were performed during the off-season, the detrained subjects also had a training bradycardia and their spectral profile revealed a predominant HF-peak along with a lower LF-peak. The findings in the former group of athletes were in contrast to Dixon et al. (1992) who identified that endurance trained athletes had a significantly lower LF:HF ratio compared to sedentary controls when subjects were observed in the supine state.

There appears to be some disagreement in the literature as to the physiologic origin of the various spectral components. Some investigators have inferred that the spectral patterns demonstrated by studies in the frequency domain reflect the prevailing tone of both the sympathetic and parasympathetic autonomic divisions. Caution should be used in the interpretation of spectral patterns, however, for as described by Malik et al. (1993), there is no solid basis for the relationship between tone and both the LF and HF spectral components; the impulses and effects of parasympathetic tone are very short and discrete, and are much faster than the HF components of the power spectra (Task Force, 1996; Malik et al., 1993; Kamath et al., 1993). Therefore, it has been suggested by Malik et al. (1993), that the presence of both LF and HF spectral components are to be interpreted as sympathetic and vagal activity occurring at physiological levels at which they can respond to regulatory mechanisms. Therefore, the LF:HF ratio has been used as a reliable indicator of

sympathovagal balance, rather than treating either one of the individual components as mutually exclusive.

The loss of HRV, as assessed by both decreased LF and HF power in the power spectra, or predominance of LF power, has been linked to increasing morbidity and mortality (Odemuyiwa et al., 1991; Kleiger et al., 1987). Excluding pathology, modulated vagal and sympathetic activity have been demonstrated to decrease in two situations: 1) either vagal or sympathetic blockade, and 2) saturating overstimulation of the respective autonomic division (Malik et al., 1993). Saturating overstimulation leading to decreased HF power, for example, could be due to chronic stimulation of the baroreceptors using phenylephrine infusion, whereas saturating overstimulation leading to a decrease in LF power could be due to the effects of maximal exercise on adrenergic stimulation. At maximum exercise it has been noted by certain investigators (Kamath et al., 1991; Arai et al., 1989) that there is an overall loss of power in the HRV spectra, and the sustained levels of increased catecholamines, which possess a greater temporal latency, are modulating heart rate more so than direct sympathetic stimulation (Furlan et al., 1993).

1.3.3 Time Domain Analysis of HRV

The analysis of HRV in the time domain is assessed primarily through collection of heart rate data using 24-hour ambulatory holter monitoring (Task Force, 1996; Kleiger et al., 1995, 1992); it is within these longer recording periods where the most reliable variables are found which predict mortality following myocardial infarction (Kleiger et al., 1987). The human heart beats approximately 100 000 times during a 24-hr period, and it is from the raw

ECG holter data, a time point series, which a number of useful descriptive statistics can be calculated (Kleiger et al., 1995, 1987; Kamath et al., 1993). The holter recordings are scanned using commercially available software for the occurrence of QRS intervals; movement artifact, ectopic beats, and normal RR-intervals are then annotated and recorded (Kleiger et al., 1995; Kamath et al., 1993). The algorithm used to calculate the time domain indices is designed to exclude non-normal intervals such as premature ventricular beats, as the compensatory pause typical of these beats increases the RR-interval and appears to resemble vagal modulation (Kamath et al., 1993).

The time domain descriptive statistics which are obtained from the holter data can be classified into two distinct categories: 1) those variables which are derived *directly from the intervals* themselves, such as the mean HR, mean RR-interval, SDNN, and SDANN, and 2) those variables which reflect *differences between adjacent cycles*, such as the SDNN-index, r-MSSD, and pNN50 (Kleiger et al., 1995, 1992). The variables derived directly from the intervals are thought to reflect more broadly based measures of HRV, whereas those derived from differences between adjacent cycles reflect very short-term HRV measured over a much longer period of time and are believed to be almost entirely mediated by parasympathetic activity (Kleiger et al., 1995, 1992). For an explanation of the above time domain statistics, refer to Table 1 below.

Kleiger et al. (1991) attempted to correlate time domain statistics with frequency domain indices and found that the differencing methods such as the pNN50 and the r-MSSD, observed to be largely representative of short-term vagal modulation, were highly correlated

Table 1: *Definitions of Time Domain Variables*

VARIABLE	DEFINITION
SDNN (msec)	Standard deviation of normal RR-intervals during the entire 24-hour recording.
SDANN (msec)	Standard deviation of the mean of adjacent normal RR-intervals for each 5 minute period of the entire 24-hour recording.
SDNN-Index (msec)	Mean of the standard deviations of all normal RR-intervals for all 5 minute segments over the entire 24-hour recording.
r-MSSD (msec)	Root mean square of successive differences: the square root of the mean of the sum of the squared differences between adjacent normal RR-intervals over the entire 24-hr recording.
pNN50 (%)	The percent difference between adjacent normal RR-intervals which are greater than 50msec, computed over the entire 24-hr recording

(r=0.98, r=0.92 respectively) with the HF-power in the frequency domain. In addition, the pNN50 and the r-MSSD were found to be highly correlated with each other (r=0.90). It was noted by these investigators, however, that it was impossible for time domain indices to separate the autonomic input signals which influence the sinoatrial node despite significant correlations with frequency domain variables.

Additional time domain statistics derived from the 24-hour holter data include a plot of circadian variation in both mean and standard deviation of heart rate, as well as a frequency distribution or histogram of the occurrence of specific RR-interval durations (Task Force, 1996; Fallen et al., 1995; Malik et al., 1995); armed with this information, it is possible to

observe the response of the heart rate during ambulation and activities-of-daily living, which is a better representation of actual neurocardiac control compared to the artificial conditions created during short-term stationary laboratory recordings of frequency domain indices.

Although time domain recordings have proven to be reproducible (Kautzner, 1995; VanHoogenhuyze et al., 1991), and advantageous for both the recording of circadian variations and long term follow-up effects of therapeutic interventions, they are subject to some methodological controversy (Kleiger et al., 1995, 1992; Kamath et al., 1993). There is question as to the lack of control of the patient's dynamic state during the recording period, and its subsequent bias upon the time domain statistics (Kamath et al., 1993). For an illustration of the various approaches to HRV signal processing and their respective uses, please refer to Figure 2.

1.3.4 Impact of Respiratory Sinus Arrhythmia Upon HRV

At rest, the average respiratory rate of the human is between 10 and 20 breaths/min (Astrand & Rodahl, 1986), which corresponds to a frequency range of 0.17 to 0.33Hz. The effect of the resulting respiratory cycle on cardiovascular variables has been well documented in the literature (Novak et al., 1993; Seals et al., 1990; Eckberg et al., 1983, 1985; Hirsch et al., 1981). The fluctuations noted between consecutive QRS complexes, as a result of respiration, are called the *respiratory sinus arrhythmia*, and are generated by the intimate communication between both the respiratory and cardiac centres within the medulla (Berne & Levy, 1992). In addition, the effects of respiration on heart rate are mediated by pulmonary reflexes, the Bainbridge reflex, and baroreceptor reflexes (Novak et al., 1993;

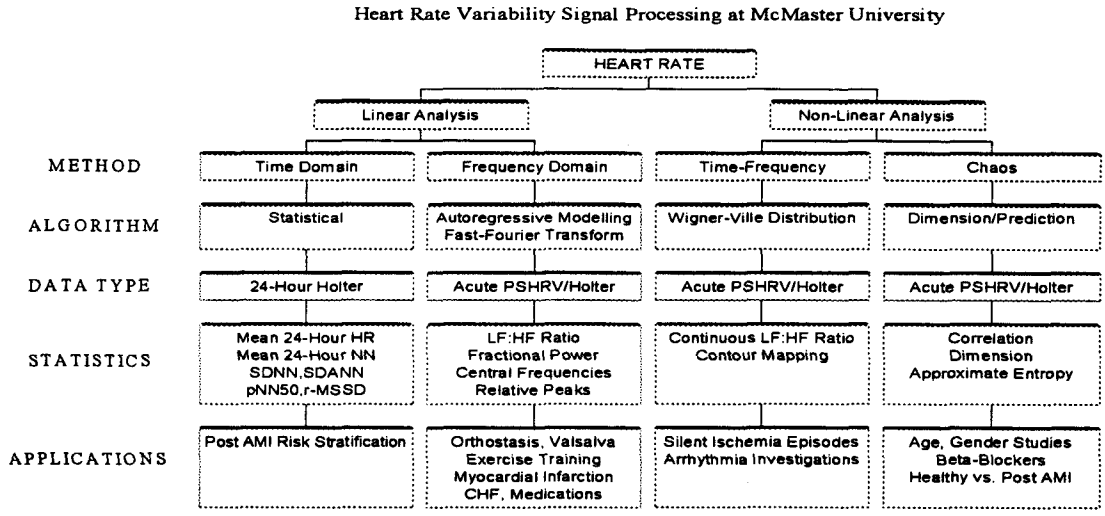


Figure 2: Approaches to Heart Rate Variability Signal Processing at McMaster University and Their Respective Roles

Berne & Levy, 1992; Akselrod et al., 1985; Hirsch et al., 1981). With each inspiration there is a resulting increase in heart rate and blood pressure due to a decreased intrathoracic pressure which leads to an accelerated venous return to the right atrium. The resulting increase in right atrial pressure stimulates atrial receptors located at the venoatrial junctions, and is manifested by the Bainbridge reflex which increases heart rate (Berne & Levy, 1992). Paradoxically, there is a simultaneous cardioinhibitory effect exerted by the baroreceptor reflex due to the increase in arterial pressure. Upon expiration, there is a corresponding decrease in heart rate as the atria are unloaded, and arterial pressure is decreased (Novak et

al., 1993; Berne & Levy, 1992).

Katona et al. (1970) explored the effects of cardiac vagal efferent (CVE) activity and heart period in the carotid sinus reflex in anaesthetized dogs under a variety of conditions. During the inspiratory phase of spontaneous respiration, it was found that the activity of CVE fibres always stopped or greatly decreased regardless of the blood pressure level. When blood pressure was increased, their data revealed a delay of 55-140msec between the beginning of the systolic pressure rise and the onset of increased firing in the cervical vagus. These results are similar to those of Kollai et al. (1979), who demonstrated in anaesthetized dogs the temporal similarity in nerve discharges between cardiac sympathetic efferents and the phrenic nerve which initiates diaphragmatic contraction; alternatively, the cardiac vagal efferent nerve traffic occurred between the phrenic nerve discharges. The differences in neurotransmitter latency periods between acetylcholine and norepinephrine are believed to be responsible for the rhythmic oscillations exerted upon the heart rate; the delayed re-uptake of norepinephrine precludes sympathetic activity from exerting rhythmic changes on heart rate, and it is widely supported that 'beat-to-beat' modulation of heart rate is mediated almost entirely by vagal activity (Murakawa et al., 1993; Saul, 1990; Eckberg et al., 1983, 1985; Kollai et al., 1979).

Brown et al. (1993) demonstrated that the amplitude of the RR-interval tachogram at respiratory (0.17-0.33) and low (0.06-0.14Hz) frequencies decreased significantly as breathing frequency increased to 24 breaths/min (0.4Hz). Power spectral analysis of HRV revealed that, for a given frequency of respiration, the RR-interval spectral power was higher

at a larger tidal volume, although neither breathing frequency nor tidal volume influenced average RR-intervals significantly. Similarly, using time-frequency analysis of HRV, Novak et al. (1993) demonstrated a reduction in the high frequency respiratory component with increasing frequency of respiration. In addition, Eckberg et al. (1983), using controlled respiration, identified that the amplitudes of RR-fluctuations were proportional to the tidal volume, and for a given tidal volume, the RR-interval fluctuations increased as breathing frequency decreased.

Hirsch et al. (1981) quantified the effects of breathing frequency and tidal volume on the magnitude of the respiratory sinus arrhythmia. They found that there was a direct relationship between tidal volume and respiratory sinus arrhythmia; in terms of breathing frequency, it was observed that for a given tidal volume, increases in breathing frequency up to 7 breaths/min exerted an increase in the magnitude of the RSA (beats/min); however, past this critical frequency the RSA decreased in magnitude. The observed relationship between tidal volume and RSA magnitude is explained with respect to pulmonary mechanoreceptors; with increasing expansion of the chest wall there would be a correspondingly larger stretch stimulus, which would then provide greater afferent feedback to the respiratory centres in the medulla resulting in an increase in sympathetic activation (Seals et al., 1990). In addition, respiratory rates of less than 7 breaths/min have been implicated in causing entrainment, or fusion of the high and low frequency peaks of the spectral signal into one powerful oscillation, as the respiratory frequency impinges upon the Mayer wave (0.1Hz) and low frequency bandwidth (Malliani et al., 1991). In this situation it is difficult to tease out the power in the

HF bandwidth and the subsequent vagal modulation upon heart rate.

In a more lucrative study, Saul et al. (1989) investigated the transfer function between respiration and heart rate. It was demonstrated that at breathing frequencies greater than 0.15Hz, there was an immediate increase in heart rate upon inspiration; however, at breathing frequencies less than 0.15Hz, the increase in heart rate took place only slightly before the onset of inspiration.

In summary, the previous investigations demonstrate the importance of accounting for the contribution of the respiratory sinus arrythmia when performing any recording of heart rate variability. It was documented by Brown et al. (1993) that breathing rate is probably more important than tidal volume in the contribution to the power spectra, as breathing frequencies at the upper limit of the physiological range (i.e. tachypnea) result in a decrease in the HF autospectral power, and can be implicated in the lack of vagal modulation of neurocardiac control. The rationale for conducting these studies was due to the increased use of spectral indices in the clinical setting, and the lack of respiration recordings in some HRV studies in the literature. If the information from the power spectrum is to be interpreted accurately, the influence of respiratory inputs upon the resulting signal must be addressed.

1.4 HEART RATE VARIABILITY IN CONGESTIVE HEART FAILURE

1.4.1 Relationship with Etiology of Failure, Left Ventricular Function, and Severity of Disease

Congestive heart failure is characterized by a derangement of one or both limbs of the autonomic nervous system (Ferguson et al., 1990; Porter et al., 1990; Francis et al., 1985;

Levine et al., 1982; Goldstein et al., 1975; Eckberg et al., 1971). Typically, it is has been reported that CHF patients have an absence of parasympathetic modulation of heart rate which is concurrent with an augmented sympathetic drive; a result of compensatory mechanisms attempting to preserve cardiac function in spite of the underlying failure (Braunwald, 1992). A number of abnormalities of adrenergic control exist in congestive heart failure. It has been demonstrated that there is a marked reduction in the chronotropic response to orthostatic stress (Fallen et al., 1996; Grassi et al., 1993; Binkley et al., 1991; Goldstein et al., 1975), as well as during exercise (Francis et al., 1985; Goldstein et al., 1975); it is believed that this may in fact be due to post-synaptic down-regulation of beta-receptors in the SA-node. A reduction in beta-receptor density has also been noted in ventricular myocardium (Pierpoint et al., 1987; Bristow et al., 1986), in addition to decreases in contractility and adenylate cyclase activity. This down-regulation of beta-receptors may have a deleterious effect upon cyclic-AMP concentrations indirectly through increases in the G_i-protein subunit (Vatner et al., 1985). In addition, both atrial and ventricular norepinephrine stores have been found to be reduced (Pierpoint et al., 1987). Similarly, dysfunction of the parasympathetic nervous system has also been observed in congestive heart failure. A decrease in the sensitivity of the arterial baroreflex, in addition to a reduction in vagal restraint of SA-node automaticity have been found to be related to a decrease in the density of high-affinity muscarinic receptors in the heart (Wells et al., 1981).

The above findings have fostered the current research direction using heart rate variability techniques in order to investigate the changes in sympathovagal balance in patients

with congestive heart failure. It has been found consistently in the literature that both time and frequency domain indices of HRV are significantly lower than those of normal, age-matched controls. In addition, impaired physiological reactions have been observed in response to orthostatic stress, lower-body negative pressure, and both phenylephrine and nitroprusside blood pressure challenges. The reported decrease in baroreceptor sensitivity (BRS), and loss of SA-node modulation in these patients results in an attenuated response of the heart rate to the above challenges. Patients with CHF demonstrate a markedly reduced 24-hour standard deviation of the RR-interval, an altered circadian profile, less diurnal variation of heart rate, a higher resting heart rate, and an altered morphology of the RR-interval histogram compared to age-matched controls. An attempt has been made by some investigators in the literature to correlate heart rate variability indices with CHF disease severity, etiology of failure, left ventricular function, muscle sympathetic nerve activity, neurohormonal status, and exercise capacity; the results of which will be highlighted herein.

The reproducibility of HRV time domain indices, and their relation to mean heart rate, was investigated by VanHoogenhuyze et al. (1991) in a group of 22 CHF patients (NYHA II-III) of ischemic origin taking both diuretics and digoxin, and a group of 33 non-age or gender matched normal controls. It was reported that CHF patients had a higher mean heart rate and a lower HRV than the control subjects. The mean group values for heart rate and HRV for the controls and CHF patients respectively, demonstrated the following correlations between days 1 and 2: 1) mean RR-interval, r=0.89, 0.97; 2) SDANN, r=0.87, r=0.87; 3) SDNN-index, 0.93, 0.97; and, 4) CV, r=0.95, 0.97. A similar amount of individual day-to-

day variation occurred in both groups (0 to 51%), but low HRV values were found to be more reproducible and resulted in less day-to-day variation compared to subjects with high HRV values. Therefore, it was concluded that time domain HRV indices were more likely to be reproducible in CHF patients versus normal control subjects with high HRV indices; however, there was no mention as to the reproducibility of frequency domain indices.

Stefenelli et al. (1992) examined the heart rate behaviour at different stages of CHF in a group of 21 patients (NYHA II-IV; LVEF 18 ± 11%) at baseline and after 6-months of oral therapy. Their results demonstrated marked differences in the morphology of the RR-histogram between NYHA functional classes: NYHA-II was characterized by a bimodal, broad based pattern; the NYHA-III histogram was unimodal and narrow based; and, the histogram for NYHA-IV had an attenuated amplitude, compared to the other classes, and was unimodal and narrow based. It was also found that the higher the NYHA functional class, the smaller was the RR-interval variability and standard deviation of RR-intervals. Completion of the oral treatment regimen at 6-months yielded interesting results. Those patients who remained stable or improved their clinical status did so without any changes in heart rate variability indices, whereas those with a deterioration in clinical status demonstrated a further shortening of the mean RR-interval variability.

Kienzle and colleagues (1992) examined clinical, hemodynamic, and sympathetic neural correlates of HRV in a group of 23 CHF patients (NYHA II-IV; LVEF 21 ± 7%), mainly of idiopathic origin, without their cardiac medications. Both time (mean RR-interval, SDNN) and frequency domain (LF, HF-power) HRV indices were obtained from 24-hour

holter monitoring; in addition, the protocol involved radionuclide ventriculography, right-sided heart catheterization, peroneal microneurography, and plasma norepinephrine determination. The investigators found that there were no relationships between HRV indices and age, LVEF, cardiac output, or NYHA functional class. However, modestly strong negative correlations were found between the spectral and non-spectral HRV indices and muscle sympathetic nerve activity, as well as plasma norepinephrine levels. Therefore, the authors concluded that the spectral and non-spectral measures of HRV were not indicative of the severity of disease, rather, they were indicators of sympathoexcitation.

Mortara et al. (1993) also examined the ability of power spectral analysis to identify CHF patients with more pronounced neurohormonal activation. Among the group of 72 CHF patients (NYHA II-IV; LVEF 22 ± 1%) of ischemic (n=41) and idiopathic (n=31) etiology, two distinct patterns of HRV were revealed during supine rest: 1) an absence of LF-power with the total power concentrated in the HF-band (30 $msec^2$, 61nu) (n=20); and, 2) an increased LF-power and reduced HF-power (n=52) compared to a group of 15 age-matched controls. In those patients found to have an undetectable LF-power, they also had a significantly lower mean RR-interval (745 ± 25 vs. 864 ± 36msec) and total power (126 ± 12 vs. 975 ± 71$msec^2$), in addition to elevated plasma NE levels (635 ± 75 vs. 329 ± 54pg/ml) compared to other patients with preseved LF-power. The investigators concluded that in patients with advanced heart failure, the marked neurohormonal activation was accompanied by a reduction in the neural modulation of heart rate; however, the presence of the HF-power was described as a phenomenon due to the mechanical effects of ventilation.

A similar study was preformed by Gibelin et al. (1993) which included 63 CHF patients (NYHA II-IV) of ischemic (n=37) and idiopathic (n=25) etiology; however, these investigators derived their power spectral measures from 24-hour holter monitors. Their results identified a correlation between the degree of heart rate variability, both spectral and non-spectral, and the NYHA functional class, as well as between HRV and plasma norepinephrine levels ($r=0.85$, $p<0.01$). Therefore, those patients with more severe heart failure were found to have a lower LF-power, SDNN, and LVEF along with an elevation in plasma NE levels.

Recently, Fallen and colleagues (1996) discovered three different spectral patterns in a group of 26 CHF patients (NYHA II-III) in response to orthostatic stress, and related them to the patients' neurohormonal status (NE, ANP) and left ventricular ejection fraction. Upon assuming an upright posture following 20-minutes of supine rest, comparisons of supine and standing heart rate autospectrum yielded the following three patterns: 1) a normal increase in the LF-power from supine to standing; 2) a decrease in the LF-power on standing; and 3) a flat power spectrum, highlighted by an absence of both LF and HF-power. The CHF patients with the lowest LVEFs ($18.2 \pm 3.4\%$) and greatest ANP levels (51.5 ± 6.7 pg/ml) comprised the group with the flattened autospectral profile; however, the other two groups were not significantly different from each other with respect to left ventricular function and both NE and ANP concentrations. Their results suggested that neurohormonal activation in CHF patients may not be elicited despite a depressed baroreceptor gain as interpreted by changes in the heart rate autospectrum in response to orthostatic stress. Rather, the

progression of CHF is believed to exist upon a temporal continuum in which decreased baroreceptor activity precedes the onset of catecholamine overstimulation, which precedes the reduction in HRV indices and subsequent changes to the ANS. These results can probably be explained as a result of different levels of compensatory measures across patients as noted by other investigators in the literature (Casolo, 1995; Odemuyiwa, 1995).

Geng et al. (1993) investigated the ability of both time and frequency domain indices of HRV derived from 24-hour holter monitoring to identify CHF patients based upon age and etiology of failure. The 73 CHF patients (n=38 ischemic, n=35 idiopathic), as a group, had significantly lower HRV in all indices compared to a group of 24 non-age matched, normal controls; however, there were no observable differences between CHF patients of different etiology of failure, and HRV indices were found to be independent of age in this population, in accordance with the earlier findings of Kienzle et al. (1992). Of additional note in this investigation was the absence of CHF patient demographics such as LV function and NYHA functional class. Perhaps this additional information could have improved the results from their stepwise regression analysis which revealed, that in CHF patients, HRV was influenced by left ventricular systolic function (shortening fraction) and maximal oxygen consumption. Their results are confusing, for the authors reported that there were significant differences in the time domain indices SDNN and SDANN between the CHF-ischemia group and the CHF-idiopathic group; however, in their conclusions they stated that there were no differences in HRV observed between groups when using analysis of covariance.

Casolo et al. (1989) identified differences in HRV indices between 20 CHF patients

(NYHA II-IV; LVEF 25 ± 5%) and 20 age-matched controls. The control subjects demonstrated significantly higher heart rate variability at all hours of the day versus the CHF patients as indicated by the standard deviation of the 24-hour heart rate. In addition, the control subjects had a significantly greater mean hourly standard deviation of the RR-interval (232 ms vs. 97.5ms), a lower 24-hour heart rate (73.1 b/min vs. 84.2 b/min), and a lower night-day heart rate ratio (0.77 vs. 0.91) versus the CHF patients. A significant difference was also found between groups in the shape of the 24-hour RR-interval histogram. In a similar investigation, Casolo et al. (1991) reproduced their earlier findings and provided information on spectral indices of heart rate variability. The CHF patients were found to have a significant reduction in both absolute LF and HF-power, as well as a reduced fractional HF-power; however, there were no significant differences in LF-fractional power between groups. The finding of a reduced HF absolute and fractional power served to confirm earlier reports of an impairment in parasympathetic function in CHF patients.

Saul et al. (1988) investigated both time domain and frequency domain indices, derived from 24-hour holter monitoring, in a group of 25 CHF patients (NYHA III-IV; LVEF 29 ± 16%) of various etiologies (n=16 ischemic; n=8 idiopathic; n=1 viral) and a group of 21 normal, age-matched controls. In accordance with other investigations in the literature (vanHoogenhuyze et al., 1991), it was found that CHF patients demonstrated an increased mean heart rate and respiratory rate, as well as a markedly reduced standard deviation of heart rate, mean RR-interval, and standard deviation of RR-intervals. In addition, the CHF patients had lower heart rate power in all frequency bands versus their control counterparts.

However, contrary to Casolo et al. (1991), there were no significant differences in fractional LF or HF-power between the CHF patients and the controls. Significant negative correlations were reported between age and HRV indices in the control group, the highest of which was between age and HF-power ($r=-0.783$, $p<0.0001$); however, there were no significant correlations between spectral data and age or survival in the CHF patients.

Panina et al. (1995) assessed sympathovagal balance, using both time and frequency domain indices, over a 24-hour period in a group of 20 CHF patients (NYHA II-III; LVEF 9%-32%). The group consisted of 5 patients with ischemic cardiomyopathy and 15 patients with dilated cardiomyopathy. When the HRV indices were calculated from 24-hour holter monitoring, the results revealed a preservation of the normal heart rate circadian pattern; however, HRV indices remained unchanged over the 24-hour period. Further analysis of their results demonstrated no significant correlations between heart rate and frequency domain indices. Therefore, the authors concluded that the relative independence of heart rate and HRV implied that these two measures were governed by different mechanisms which remain at large.

Circadian variations of heart rate variability in congestive heart failure were also investigated by Tani et al. (1991). They compared a group of 11 CHF patients (LVEF 37 ± 6%) with dilated cardiomyopathy to 12 normal, age-matched controls using spectral analysis of HRV derived from 24-hour holter recordings. The CHF patients demonstrated a significant reduction in both LF and HF power over the entire 24-hour period compared to the control subjects. In addition, the CHF patients' LF-power demonstrated an absence of

circadian variation, whereas the HF-power, although reduced, displayed relative preservation of the diurnal variation. These results are in contrast to those of Casolo et al. (1991) and Panina et al. (1995), who found an absence of circadian variation in both LF and HF-power in their group of 15 and 20 CHF patients respectively. Of note, however, is that Tani et al. (1991) failed to report the functional classes of their CHF patients; as well, the mean LVEF appears quite high, compared to the patients in the aforementioned investigations with LVEF<30%.

Nolan and colleagues (1992) investigated cardiac parasympathetic activity and its relation to left ventricular function in a group of 43 CHF patients (NYHA II-III; $\bar{x}$ LVEF=17.8%). The etiology of failure was ischemic cardiomyopathy in all CHF patients, and the only medications being taken during the investigation period were diuretics. From the 24-hour holter monitor data, the investigators counted the number of times that each RR-interval exceeded the preceding RR-interval by more than 50 ms (i.e. pNN50). The authors reported that the 'counts' for the CHF patients were significantly lower than a group of normal, age-matched controls investigated previously, and a significant correlation was found between the number of 'counts' and LVEF. The latter finding is subject to criticism, for the reported correlation coefficient was $r=0.49$ ($p<0.05$); although significant statistically, the number of 'counts' in 24-hours explains approximately 25% of the variance in LVEF. This group of investigators should have been a little more cautions in making the conclusion that the degree of parasympathetic dysfunction was related to the severity of left ventricular dysfunction.

Adamopoulos et al. (1992) compared different methods of assessing sympathovagal

balance in a group of 25 CHF patients (NYHA II-III; LVEF 21.6 ± 2%) secondary to coronary artery disease. They examined the possible relationships between time domain (SDNN), frequency domain (LF,HF,LF:HF), 24-hour day/night heart rate, submaximal heart rate during upright cycle ergometry, and radiolabelled norepinephrine spillover measures. There were no significant correlations found between any of the above variables, and none of the measures were found to correlate with LVEF, maximal oxygen uptake, or duration of the exercise test. In addition, there were no significant correlations between plasma norepinephrine levels and either of absolute or relative LF-power. The conclusions offerred by this group of investigators was that in patients with CHF, the individual parameters of autonomic control refect different aspects of circulatory control.

1.4.2 Summary

In summary, the aforementioned investigations have demonstrated that no consistent relationship has been found between HRV indices and left ventricular function. This proves to be somewhat of a paradox, as it was demonstrated by Kleiger et al. (1987) that in the early stages following myocardial infarction, HRV measures and left ventricular function have shown a modest relationship. In contrast, Casolo et al. (1995) reported that given the same level of left ventricular dysfunction, two patients can have two markedly different exercise capacities due to differences in the expressions of compensatory mechanisms, previous level of function, as well as their temporal onset. Similarly, Odemuyiwa (1995) added that hemodynamic variables and neurohormonal activity vary widely in patients with the same left-ventricular ejection fraction as a result of different compensatory mechanisms. As for

possible associations between HRV and etiology of congestive heart failure, the consensus of the limited number of investigations in the literature is that there is no relationship between the HRV indices and the actual precipitating cause of failure (i.e. idiopathic, ischemic cardiomyopathy). Therefore, the degree of impairment of HRV measures that has been found in patients following acute myocardial infarction is most likely to approximate those of patients of idiopathic, viral, or hypertensive origin of ventricular failure. It has, however, been demonstrated by studies in the literature that both spectral and non-spepctral HRV indices decrease progressively with increasing severity of symptoms, as indicated by the NYHA functional class. The results of some previous investigations in the literature, however, are subject to some methodological criticism and limits the external validity of their finding due to the use of 24-hour holter data to derive frequency domain indices, lack of controlled variables, as well as a lack of randomized controlled designs.

Heart rate variability techniques have been utilized in order to examine the effects of steady-state exercise and training interventions on the spectral profiles of selected clinical populations and normal controls. To date, there is only one study in the literature which has investigated the effects of exercise training on HRV indices in CHF patients (Coats et al., 1992). The results of the former, as well as other investigations concerning exercise and HRV will be summarized in the following section.

1.5 EXERCISE, THE AUTONOMIC NERVOUS SYSTEM, AND HEART RATE VARIABILITY

1.5.1 Historical Perspectives

An exercise stimulus imparts a unique challenge upon the autonomic nervous system and has been the subject of a considerable number of investigations in the literature (Furlan et al., 1993; Kamath et al., 1993; Nakamura et al., 1993; Adamopoulos et al., 1992; Coats et al., 1992, 1990; Dixon et al., 1992; LaRovere et al., 1992; Rimoldi et al., 1992; Somers et al., 1991; Yamamoto et al., 1991; Bernardi et al., 1990; Meredith et al., 1990; Arai et al., 1989; Seals et al., 1989; Pagani et al., 1988; Victor et al., 1987; Maciel et al., 1986; Stone et al., 1985; Savin et al., 1982; Fagraeus et al., 1976; Robinson et al., 1966); the phenomenon of athlete/training bradycardia has received additional attention as well (Katona et al., 1982; Ekblom et al., 1973). The premise of these studies has been to identify the contributions made by both the sympathetic and parasympathetic divisions of the ANS to cardioacceleration at the onset of physical activity, autonomic modulation and vasomotor control during exercise, and cardiodeceleration during post-exercise recovery. The earliest studies in the literature utilized pharmacological blockade of the respective autonomic limbs in order to identify their individual roles (Maciel et al., 1986; Katona et al., 1982; Savin et al., 1982; Fagraeus et al., 1976; Ekblom et al., 1973; Robinson et al., 1966). Attempts to elucidate the individual contributions have produced conflicting results. For example, a consensus remains elusive as to the exact contributions of each ANS division during the onset of physical activity. Some investigators ascribe to a monophasic response in which rapid vagal withdrawal is the sole mechanism of cardioacceleration (Victor et al., 1987); a biphasic mechanism at the onset of exercise in which there is a rapid vagal withdrawal followed by an increase in sympathetic discharge (Maciel et al., 1986); and a triphasic response in which there

is a rapid vagal withdrawal, an increase in sympathetic drive, followed by a subsequent brief surge of vagal activity (Fagraeus et al., 1976). One of the problems with investigations using pharmacological blockade, however, is whether or not it is indeed possible to effectively block all receptor sites. Additional substances such as neuropeptide-Y, which is co-secreted with norepinephrine at the synaptic level, could invariably lead to an increased chronotropic response despite adequate blockade of adrenergic beta receptors.

Investigations in the literature which have attempted to elucidate the origin of training bradycardia have suggested four potential mechanisms to explain this phenomenon: 1) an increase in vagal modulation; 2) a decrease in sympathetic activity concurrent with a down-regulation of beta-receptor sites; 3) a resetting of arterial baroreceptors; and, 4) a decrease in the intrinsic heart rate of the individual. However, there is much disagreement and speculation in the literature whether these mechanisms occur concurrently, or act independently. A number of investigations in the literature have utilized HRV techniques to examine changes in the respective ANS divisions at the onset of physical activity, during dynamic exercise, and also during post-exercise recovery in normals and in selected clinical populations. In addition, some studies in the literature have used HRV techniques to investigate the cumulative effects of a prolonged training regimen upon underlying sympathovagal balance. The findings of these investigations will be summarized herein.

1.5.2 Exercise and Heart Rate Variability

The differences between the neural regulation of heart rate variability in endurance athletes (long distance runners) and sedentary controls at rest, during standing, and during 15-

minutes of steady-state exercise at 50% of maximum workload was investigated by Dixon et al. (1992). Their results identified two very contrasting spectral profiles between athletes and controls during supine rest. The athletes demonstrated a greater HF-peak and lower LF-peak versus their control counterparts, along with a significant supine resting bradycardia (52 ± 4.9 b/min vs. 67 ± 8.7 b/min). Of particular interest, was that during standing and steady-state exercise there were no observable differences in spectral indices between the groups; however, supine recovery values following the exercise bout revealed that the athletes' LF:HF ratio had returned to their pre-exercise supine values within 5-minutes, whereas the control subjects' LF:HF ratio remained elevated following 15-minutes of post-exercise recording. The differences between the groups during recovery were explained in terms of circulating catecholamines. It was believed that the trained group had less spillover of catecholamines as a result of the exercise stress compared to the control group; this hypothesis would explain the sustained tachycardia of exercise and elevation of the LF:HF ratio observed in the latter group.

Furlan et al. (1993) studied 29 healthy controls, 15 detrained athletes, and 21 trained athletes at rest, during tilt, and during graded treadmill exercise using power spectral analysis of heart rate variability. Their results were in contrast to Dixon et al. (1992), and demonstrated two markedly different spectral profiles between the groups of athletes during the resting supine recordings despite both having a concurrent training bradycardia. The detrained athletes had a prevailing HF component and the trained athletes had a high LF component at rest. It was also found that both groups of athletes responded more favourably

to the orthostatic stress induced by tilting compared to the controls; in addition, the controls demonstrated an elevated LF component for 24-hours following the exercise bout. Other researchers attempted to explain the apparent disparity between the resting spectral profiles of both groups of athletes as an effect of overtraining by the trained group (Piepoli et al., 1993), and the effects of accumulated muscle fatigue inducing an increase in the central drive to the musculature of the body via type III and IV skeletal muscle afferents (Fallen, 1993). Piepoli et al. (1994) also speculated that the supposed selective location of type III-IV afferents to fast twitch muscle fibres could also explain the results of Furlan et al. (1993). Due to the inherent stimulation of slow twitch fibres by endurance training, this would account for the decreased LF component in detrained endurance athletes and endurance athletes who were not overtraining.

Yamamoto et al. (1991) examined the autonomic control of heart rate during exercise in 8 healthy subjects using power spectral analysis. Subjects performed six 17-minute bicycle tests at intensities corresponding to 20 W, as well as 30, 60, 90, 100, and 110% of their predetermined ventilatory threshold (VT). Their results demonstrated that HF power decreased progressively from rest to 60% VT and that LF power increased only when the intensity exceeded 100% VT. The LF:HF ratio remained unchanged up to 100% VT, but increased markedly when greater than 100%.

In contrast, Kamath et al. (1991) examined the effects of steady-state exercise on the power spectrum of HRV in 19 healthy subjects. Subjects were observed during 15-minutes of supine rest, 10-minutes of standing, 10-minutes of steady-state exercise at 50% of the

predetermined maximal power output during cycle ergometry, and 15-minutes of post-exercise supine recovery. Steady-state exercise was found to suppress both the LF and HF components, and there was a leftward shift in the LF-central frequency (cf) which was interpreted as a withdrawal of vagal modulation of the LF-peak. During the 15-minute post-exercise recovery period, the LF-peak remained elevated for 15-minutes post-exercise and there was a rightward shift in the LF-cf which suggested a return of vagal modulation of the LF-peak. In addition, the HF-power was attenuated for up to 10-minutes of recovery, despite a return of heart rate to pre-exercise supine levels.

Cardiac autonomic activity during and immediately after exercise was compared between a group of 43 healthy subjects, 8 CHF (NYHA III(n=4), IV(n=4)) patients, and 6 heart transplant patients by Arai et al. (1989) using power spectral analysis of HRV. They found that prior to exercise, during a supine rest recording, both the LF and HF power were greater in normals versus both groups of patients, with no detectable differences between the groups of patients. However, similar to Kamath et al. (1991), they noted a progressive decrease in spectral power during the exercise recordings in the normal subjects, and interestingly, there were no differences in the exercise spectral profiles between normals and patients at peak exercise.

LaRovere et al. (1992) examined the adaptations of the autonomic nervous system to short-term exercise training in a group of 22 male patients with a first or recent myocardial infarction. Subjects randomized to the exercise group completed 4-weeks of in-hospital training, 4 to 8-weeks following the event, using light calisthenics and cycle ergometry at an

intensity of 75% of patients' ventilatory threshold (VT). In later weeks, the intensity was increased to 85% and 95% of VT; however, there was no mention of the duration and frequency of the exercise sessions. Upon completion of the training, the exercise group demonstrated a significant increase in exercise duration from 13.7 to 17.1-minutes, as well as an increase in the anaerobic threshold from 9.5 to 12.0-minutes; however, there were no significant changes in resting spectral components and heart rate between groups. Alternatively, the post-training autonomic response to 70-degrees of head-up tilt in the exercise group produced an increase in LF and decrease in HF power compared to controls, in addition to greater increases in the LF:HF ratio following the response to this orthostatic stress. It was hypothesized that the unaltered response to tilt in the untrained group was a result of maximum LF activation due to the underlying infarction; however, due to the relatively short period since the infarction, their results may be biased due to spontaneous recovery of autonomic indices.

In a group of patients with uncomplicated mild hypertension without target organ damage, Pagani et al. (1988) investigated the effects of a 6-month training program on autonomic regulation. The supervised training sessions included 22-minutes of calisthenics followed by 20-minutes of jogging at least five times per week. Physical training was found to reduce mean arterial pressure, increase average heart period, and result in a reduction in LF power and increased HF power at rest. In addition, using cross spectral analysis, it was found that the gain of the relationship between heart period and systolic arterial pressure was improved as a result of the training regimen. These authors concluded that, as a result of

physical training, there was a readjustment of sympathovagal balance at rest which included an increase in the gain of the baroreflex and enhanced vagal modulation.

The effects of endurance training on autonomic measures in 16 borderline hypertensives (140/90) was investigated by Somers et al. (1991). Both RR-variability and blood pressure variability (BPV) were measured in these patients before and after a 6-month training program consisting of the RCAF 5BX/XBX program performed twice daily, and jogging for 20-minutes 3-4 times per week. The investigators inferred increased fitness as a result of a lower resting heart rate and blood pressure, although no objective measure of increased fitness was performed following the training program. Baroreflex sensitivity (BRS), assessed using phenylephrine injection, was shown to increase following the training period; however, BPV changed very little, and RR-variability was shown to be higher with increased fitness. The authors found that there was no correlation between changes in BRS and changes in RR-variability, or between either of these measures and the observed reductions in blood pressure. These results suggested that BRS and BPV are independent entities, similar to the relationship observed between heart rate and HRV.

Seals et al. (1989) examined the influence of 14-weeks of physical training on heart rate variability and baroreflex circulatory control in a group of 19 normotensive, healthy males. A total of 11 subjects volunteered to participate in the exercise group, whereas the remaining 8 volunteered for the control group. Their training stimulus consisted of walking or jogging 3 to 4 days/week, for 30 to 40 minutes/day, at an intensity of 70 to 80% of heart rate reserve (HRR). Heart rate variability was recorded in the supine position and was

defined as the standard deviation (SD) of RR-intervals over a 5-minute period. The chronotropic response as a result of baroreflex stimulation was assessed via neck suction, and the forearm vasoconstriction response was investigated using 3 levels of lower-body negative pressure (LBNP@-10, -20, -30 mmHg). The exercise group improved their exercise capacity following training, and had a small decrease in resting heart rate. In addition, HRV at rest was found to be greater, and the magnitude of the increase in forearm vasoconstriction in response to LBNP was attenuated post-training. However, the chronotropic response to baroreflex stimulation via neck suction was unchanged following the training period. The results of this study could be biased due to the lack of randomization of subjects to groups. It could very well be that there was an inception cohort in terms of activity pattern; where those subjects who were more active would have a tendency to exercise more than those subjects who were typically sedentary. In addition, using a time-domain statistic such as the standard deviation of RR-intervals over a 5-minute period to express HRV may not reflect the true state of sympathovagal balance and has questionable reproducibility. Short-term recording periods are typically represented using frequency domain parameters such as the LF and HF peaks, LF and HF fractional power, or the LF:HF ratio.

The autonomic control of heart rate and fractal dimension of heart rate variability during physical exercise was examined in 10 healthy subjects by Nakamura et al. (1993). The non-harmonic, or fractal component (i.e. < 0.05Hz), was assessed using the parameter D_f which is believed to be representative of the complexity of a time series, and more specifically, the number of independent oscillators responsible for the generation of a time series. The

harmonic component of HRV, on the other hand, in the range of 0.05Hz to 0.5Hz, was examined using frequency domain parameters. The exercise stimulus used in this investigation was not steady state, and HRV monitoring was continuous as the subjects performed progressive cycle ergometry to exhaustion. The HF power significantly decreased at intensities greater than 50% of peak VO_2, and the LF power increased between 50% and 60% peak VO_2, with a further increase at intensities greater than 60%. These findings are in opposition with those investigations noting a supression of autospectral power during steady-state physical exercise (Kamath et al., 1991; Arai et al., 1989). The parameter D_f, was found to approximate 3 during mild exercise, whereas moderate to high intensity exercise resulted in a D_f approaching unity. Therefore, if D_f reflects the number of dominant ANS inputs and their subsequent interactions, moderate to high physical activity ($D_f \sim 1$) could represent a situation in which the ANS is overtaken by humoral regulation of the circulation during exercise. Alternatively, mild exercise ($D_f \sim 3$) may be a situation in which autonomic control of HRV is preserved in both divisions, in addition to the contribution made as a result of humoral regulation of the circulation. However, caution should be used in the interpretation of these results, as the non-harmonic or fractal component has been criticized for having a low signal-to-noise ratio (Kamath et al., 1993).

Bernardi et al. (1990) compared HRV between the transplanted and intact heart during submaximal exercise. Three groups of subjects participated in this study: 9 sedentary healthy males aged 21-28; 6 semi-pro cyclists aged 16-23; and 6 heart transplant patients aged 40-62, between 6 and 18-months post-transplant. Frequency domain indices of LF and HF-

power were recorded at rest during 20-minutes of sitting on the cycle ergometer, then during each stage of graded exercise to exhaustion. Recording periods occurred during 4 to 5-minutes of steady state exercise achieved between successive increments in workload. Following the exercise test, subjects were observed for a period of 15-minutes of recovery. In both the sedentary and athlete groups during peak exercise, the LF-power was found to be significantly decreased, whereas the HF-power had increased compared to pre-exercise values. In the transplant patients during peak exercise, the variance and HF power increased from the beginning of exercise and directly correlated with ventilatory variables; however, there was no measureable LF-power in these patients. The results from the 15-minute recovery period demonstrated an increase in the LF-power with decreased HF-power in both the sedentary and athletic groups, whereas the spectral profile of the transplant patients had a reduction in HF-power. In both the sedentary and patient groups, the recovery values were significantly different from baseline; however, the athletic subjects' power spectral indices had returned to their resting values following the recovery period in accordance with other investigations (e.g. Dixon et al., 1992). In the normal subjects, the LF and HF spectral indices were presumed to represent the sympathetic and parasympathetic ANS limbs respectively, whereas the HF-power identified during peak exercise in the transplant patients was believed to be due to the respiratory modulation of the intrinsic heart rate. The authors proposed an intrinsic, non-autonomic mechanism to explain this phenomenon in the denervated heart. This mechanism was proposed to be responsible for heart rate fluctuations in synchrony with ventilation in both the intact and denervated heart. This non-autonomic

component was believed to occur as a result of increased stretch of the atrial wall concurrent with increased changes in intrathoracic pressure and venous return during exercise. Although it was not mentioned, the athletes in this study demonstrated a predominant LF-peak at rest which was similar to the results of Furlan et al. (1993) in their group of trained athletes.

Rimoldi et al. (1992) also investigated the contribution of neural mechanisms accompanying different intensities of dynamic exercise in a group of 12 champion swimmers aged 14 to 18-years, and 8 conscious dogs. In the group of athletes, moderate levels of exercise and the early stages of recovery were accompanied by an increased LF-power, whereas at peak exercise the LF-power was reduced from control levels. The investigators used a modified Bruce protocol with 5-minute stages in order to reach a steady-state level during each workload. These findings are concurrent with other reports in the literature concerning exercise recovery and the prevailing LF component which outlasts the exercise stimulus (e.g. Kamath et al., 1993; Dixon et al., 1992). In the group of dogs, the LF power of the RR-interval and systolic BPV increased significantly during the treadmill run; however, when the protocol was repeated following intravenous administration of prazosin, an alpha-adrenergic antagonist, the LF of the RR-interval was maintained and the LF of BPV was reduced. The dogs' systolic blood pressure at rest and during the treadmill run was also significantly reduced. The authors concluded that peripheral vasodilation and metabolic changes which occur during dynamic exercise could interfere with sympathetic vasomotor control. The changes noted in the spectral profiles during steady-state dynamic exercise are in contrast to the flattened spectral profiles observed during exercise by Kamath et al. (1993)

and Arai et al. (1989).

In the only study of its kind, Coats et al. (1992) used a controlled crossover design to evaluate changes in autonomic function as a result of an 8-week home exercise program in 17 patients with congestive heart failure (NYHA II-III; LVEF 19.6 ± 2.3%). Patients performed cycle ergometry at an intensity of 50 RPM at 60-80% of their maximum heart rate (MHR) for a duration of 20-minutes at a frequency of 5-days per week. Following the exercise program, the trained patients had significantly increased their exercise tolerance from 13.9 to 16.5 minutes, their peak $\dot{V}O_2$ from 13.2 to 15.6 ml/kg/min, and their cardiac output at submaximal and maximal exercise. In addition, the trained patients demonstrated a decrease in systemic vascular resistance (SVR), and a reduction in the slope of relationship between ventilation ($\dot{V}E$) and carbon dioxide production ($\dot{V}CO_2$) upon follow-up examination. In terms of autonomic measures, resting spectral profiles of HRV demonstrated a reduction in LF power of 21.2%, an increase in HF power of 51.3%, as well as increased RR-variability of 19.2%. Similar results were also reported in a related study using a group of 25 CHF patients (NYHA II-III; LVEF 21.6 ± 2%) by Adamopoulos et al. (1992), although time domain statistics were also provided. They reported increases in SDNN and HF-power of 21% and 41% respectively, in addition to significant reductions in LF-power, LF:HF ratio, and radiolabelled norepinephrine spillover by 19%, 48%, and 28.9% respectively. These investigations failed to examine the effects of the exercise training on the baroreceptor response to an orthostatic stress, as well as the spectral profiles of patients during post-exercise recovery.

1.5.3 Summary

In summary, the autonomic control of heart rate during dynamic exercise, and following a regimen of physical activity have been investigated in both normal and clinical populations. Essentially, those individuals who are highly trained exhibit a typical supine resting spectral pattern of increased HF-power and decreased LF-power with a concurrent training bradycardia. However, it has also been observed that in those individuals believed to be overtrained, there is a training bradycardia together with a heightened LF-power and moderate HF-power. As for clinical populations, the results have been less conclusive; this is probably dependent upon target organ damage, time since the primary event, and duration of pathology. Nonetheless, clinical populations have demonstrated improvements in HRV indices both at rest and in response to physiological manoeuvers, although results from some investigations in the literature are subject to criticism due to questionable statistical analysis of their data. Heart rate variability techniques have been used during dynamic exercise, and several investigators have reported a suppression of both the HF and LF components resulting in a flattened spectral profile, whereas others have identified either or both HF and LF-peaks during the recording period. What is of key importance is the nature of the exercise stimulus in terms of intensity, duration, and stationarity. One of the key assumptions underlying the use of heart rate variability techniques, specifically in the frequency domain, is the stationarity of the recording period (Kamath et al., 1993). While investigators attempt to utilize a steady-state exercise stimulus, the progressive and cumulative humoral, metabolic, and thermoregulatory effects associated with sustained exercise may violate the stationarity

principle.

At the present time, only two studies in the literature have reported changes in autospectral profiles in CHF patients as a result of a physical training regimen. There remains no study in the literature which has examined in detail both frequency and time domain HRV indices in a population of CHF patients in response to participation in an exercise intervention including both aerobic and resistive exercise. In addition, there have been no investigations in this clinical population which have examined the effects of physical training on baroreceptor sensitivity, as observed through changes in HRV in response to an orthostatic stress.

1.6 STATEMENT OF PURPOSE

The purpose of this thesis investigation was to examine potential differences in autonomic nervous system adaptations, as assessed by heart rate variability techniques, between a group of stabilized CHF patients randomized to a training program (AERWT) consisting of aerobic and resistance exercise, and another group of CHF patients randomized to a 'usual care' (UC) control group. The substantive hypothesis is that the autonomic response to the training protocol will induce: 1) an increase in vagal modulation of heart rate; 2) an improvement in baroreceptor sensitivity, as assessed by the changes in power spectral profiles from supine to standing; and, 3) an improvement in the recovery of post-exercise spectral indices versus the control subjects. Additional secondary hypotheses include: 1) that CHF patients will demonstrate positive adaptations in peak $\dot{V}O_2$, anaerobic threshold, dynamic muscle strength, and Six-Minute Walk distance versus their UC counterparts; 2) these increases in exercise performance will occur without any adverse changes in cardiac

size, LVEF, or clinical status; and, 3) the increases in exercise performance will occur as a result of peripheral adaptations in skeletal muscle metabolism and blood flow, and will not be a result of changes in central hemodynamics.

2.0 METHODS

2.1 Subjects

2.1.1 Patient Demographics

A total of 28 stabilized CHF patients were recruited for participation in the current investigation. Following a 2-week period of drug stabilization and baseline assessments, patients meeting eligibility criteria were randomly assigned to either a usual care (UC) or aerobic-resistance training (AERWT) group. The randomization process resulted in 12 patients (10 male:2 female) aged 58 ± 2.8 (X ± SEM) years being assigned to the UC group, whereas 16 patients (11 male: 5 female) aged 64.9 ± 2.3 years served as subjects in the AERWT group. At the initial screening visit, the purpose, procedures, and risks were described in detail and informed consent (Appendix 1) was freely obtained by those patients meeting eligibility criteria. This study was approved by the Hamilton General Hospital's ethics committee. The reader is referred to Table 3 in the Results section for further information concerning patient demographics.

2.1.2 Inclusion Criteria

Patients with documented clinical evidence of CHF and left-ventricular dysfunction (i.e.LVEF<0.40), based upon radionuclide ventriculography (RNV) or echocardiographic assessment, were screened as potential candidates for the present study. Additional inclusion criteria included stable pharmaceutical management of CHF using one or more of the usual

"triple-therapy;" an ACE inhibitor, diuretic, and digoxin. A NYHA functional class of I-III, and a screening Six Minute Walk (SMW) test distance of less than 500 metres were also necessary for inclusion in the present investigation.

2.1.3 Exclusion Criteria

The inability to attend regular training sessions, an exercise test limited by angina or leg claudication, or an abnormal blood pressure response to exercise testing (decrease in SBP below resting level during exercise; or, a decrease in SBP greater than 20mmHg after the normal increase during exercise; or, a rise in DBP of greater than 15mmHg; or, a maximal SBP greater than 250mmHg: American College of Sports Medicine, 1993) precluded patients from participation in the study. In addition, any cerebrovascular or musculoskeletal disease which limited the patient's ability to partake in formal exercise testing or training, or the presence of any respiratory limitation (FEV_1 and/or VC less than 60% predicted) served as exclusion criteria. Poorly controlled cardiac arrhythmias (i.e. multifocal or runs of PVCs, runs of SVT, and AFIB), and any other non-cardiac disorder that would contraindicate participation in exercise training, or result in an increase in morbidity/mortality were grounds for exclusion.

2.1.4 Recruitment of Subjects

Patients were recruited from hospitals in Hamilton and the surrounding Hamilton-Wentworth health region. Cardiologists and internists in this region were contacted through correspondence notifying them of the purpose and inclusion/exclusion criteria of the present study, and were asked to contact the research office with the names of potential candidates.

The log book and patient files of Hamilton General Hospital's Nuclear Medicine and Medical Diagnostic departments were screened for potential candidates based upon the ejection fraction noted after RNV or echocardiographic testing. In addition, hospital in-patient discharge summaries from both the Henderson and Hamilton General were reviewed over the course of the preceding year for those patients with a discharge diagnosis of CHF. All potentially eligible patients were contacted for a screening visit only after obtaining approval from their family physician.

2.2 Design and Intervention

2.2.1 Screening Visit

The purpose of the screening visit was to allow a more detailed disclosure of the study protocol, purpose, and time committment to potential patients; in addition to providing an opportunity to confirm inclusion/exclusion criteria. The initial screening SMW test was administered at this time. Upon confirmation of eligibility, patients agreeing to participate provided informed consent. It was made clear to patients that participation in the study did not preclude them from being followed by their regular cardiologist; however, it did provide an opportunity for their condition to be monitored more frequently in addition to their regular care. Patients were not coerced to participate in any way.

2.2.2 Experimental Design

The design of the present investigation was a single-blind, randomized-control group design with repeated measures on several factors. Following both the two-week drug stabilization period and the pre-randomization evaluation of dynamic muscle strength (single

arm curl (SAC), single-leg press (SLP), single-leg knee extension (SKE)), Six Minute Walk (SMW), RNV, and symptom-limited incremental exercise test, patients were randomly assigned to either the UC or AERWT group. Follow-up observations were performed at three and six-months in order to evaluate changes in heart rate variability (HRV) time and frequency domain indices, as well as functional capacity by way of patients' performance on the SMW test. The three-month follow up of dynamic muscle strength (SAC, SLP, SKE) and symptom-limited incremental exercise test provided additional information as to potential physiological adaptations as a result of the exercise training regimen.

2.2.3 Intervention

A detailed outline of the testing protocol is documented in Table 2. The supervised exercise training sessions for the AERWT group were held in the gym of the Cardiac Care Clinic at Hamilton General Hospital twice-a-week for a period of three-months. Following the supervised exercise training, the patients in the AERWT group were prescribed a home exercise training program with which to continue training for a period of one year. Patients continued their aerobic portion with the cycle ergometer provided, in addition to arm and leg weights to continue strength training on their own. The exercise regimen for the strength training portion was modified at this time and included: 1) biceps curls, 2) triceps extensions, 3) arm raises, 4) pull ups, 5) side bending, 6) lying side leg raises, 7) leg extensions, 8) hamstring curls, and 9) calf raises. The proper use of this equipment and training technique were demonstrated to the patient in their home, and they were encouraged to continue with their exercise prescription at their prescribed exercise intensity.

The aerobic element of the supervised training program consisted of leg and cycle ergometry, and treadmill walking. The training intensity for the exercise prescription was based upon patients' initial performance on their symptom-limited incremental exercise test. The initial intensity for the aerobic component was 40% of their maximal power output; this was maintained for the first week of training and was increased to 70% over three to four weeks depending upon tolerance for these activities. Patients were taught how to monitor their heart rate, through palpation of either radial or carotid pulse, in order to stay within their prescribed target heart rate zone. The initial intensity for the weight-training component was based upon patients' pre-randomization 1RM performance on each of the single-arm curl (SAC), single-leg press (SLP), and single-knee extension (SKE); one set of 40% 1RM for each exercise, with a progression to 3 sets of 60-80% 1RM over a period of four weeks. When the desired training loads were achieved, patients were reassessed every four weeks in order to ensure that they remained in the prescribed intensity range. Following the supervised exercise rehabilitation program, patients were reassessed during their home-based program every three months in order to evaluate exercise intensity, and to monitor exercise tolerance and compliance with the training regimen. It should be noted that the use of 70% as the intensity in the current investigation parallels other investigations in the literature, and thereby permits comparisons with other studies. In addition, the rationale for employing single limb activity follows the observation that studies examining the cardiovascular response of cardiac patients to weightlifting and isometric exercise have typically used single-limb exercises (Haslam et al., 1988), and it has been recommended that weight training protocols of cardiac

rehabilitation programs include only single limb exercises (McKelvie et al., 1990).

Table 2: Protocol Flow Chart

Identification of Eligible Patients
(LVEF<40%, NYHA I-III, SMW<500m, Informed Consent)

Drug Stabilization (2 weeks)

Baseline Assessments (2 weeks)
(RNV, SMW (2), GXT, DMS, PSHRV-Supine, Standing, Post-Ex, 24-HR Holter)

RANDOMIZATION

Usual Care (n=12)

AERWT (n=16)
Supervised Training (3 months)

3-Month Follow-Up
(RNV, SMW (2), GXT, DMS, PSHRV-Supine, Standing, Post-Ex, 24-HR Holter)

Home Based Training (3-months)

6-Month Follow-Up
(SMW (1), PSHRV-Supine, Standing, 24-HR Holter)

2.3 Testing Protocol

2.3.1 Symptom-Limited Incremental Cycle Ergometer Test

The determination of both groups' peak exercise oxygen uptake (peak $\dot{V}O_2$) was performed using a symptom-limited incremental upright cycle ergometry test. Tests were performed in the Medical Diagnostics Unit of Hamilton General Hospital both at pre-randomization and at the three-month follow-up assessment. The protocol for the cycle test

began with an initial workload of 100 kpm/min, and was increased by 100 kpm/min every two minutes in order to allow patients to achieve a steady-state level with each increment in workload. Patients' heart rate and ECG were monitored using a standard 12-lead electrode placement, and blood pressure was monitored using auscultation during the last minute of each stage. Expired gas was monitored using a Sensor Medics 2900 metabolic cart, which permitted the evaluation of respiratory rate (RR), peak $\dot{V}O_2$ (relative/absolute), expired ventilation ($\dot{V}E$), expired carbon dioxide ($\dot{V}CO_2$), and respiratory exchange ratio (RER). From this metabolic information, the anaerobic threshold (ANT) for each patient was determined, defined as the inflection point at which a rise in oxygen uptake was accompanied by a marked increase in expired ventilation; this was confirmed by inspection of expired carbon dioxide for abrupt increases, as well as the respiratory exchange ratio (RER) for values approaching unity. Dependent measures of the exercise test included: 1) total exercise time (TEX), 2) maximum heart rate (MHR), 3) maximum blood pressure (MBP), 4) maximum workload achieved (MWL), 5) anaerobic threshold (ANT [$\%\dot{V}O_2$; ml/min]), 6) rate-pressure product (RPP) at stages 1 & 2, of the modified Bruce protocol, and 7) the expired ventilation ($\dot{V}E$) to expired carbon dioxide ($\dot{V}CO_2$) ratio per workload, an indicator of ventilatory drive.

2.3.2 Dynamic Muscle Strength

The measurement of dynamic muscle strength (DMS) was performed at the Cardiac Care Clinic at Hamilton General Hospital. Assessments of DMS were performed by all patients twice at pre-randomization to ensure reproducibility of testing, and once again at

three-months. The exercises used for the determination of dynamic muscle strength included single-arm curl (SAC), single-leg press (SLP), and the single-knee extension (SKE) using universal-type, global gym multi-station training equipment. The objective measure of dynamic muscle strength in this context is the patient's one repetition maximum, or 1RM; this is defined as the maximal amount of weight which can be lifted once through the entire range about a particular joint (Astrand & Rodahl, 1986). The 1RM evaluation has been demonstrated previously to be a simple, valid, and reproducible (±10%) index of dynamic muscle strength (Sale, 1991). Following appropriate demonstration of the exercise task, and adequate warm-up with three-to-five repetitions of minimal weight, patients performed unilateral single repetitions with progressively heavier weights. Patients rested for two to three minutes following each repetition in order to prevent the onset of fatigue, and to let the heart rate return toward resting levels. The order of exercises was SAC, SKE, and SLP; this prevented accumulated symptoms of fatigue by performing the larger muscle group exercises towards the end. The dependent measures from the dynamic muscle strength assessment included: 1) the greatest of the unilateral scores combined as a total score for each exercise task at pre-randomization, and 2) the unilateral scores combined as a total score for each exercise task at three-months.

2.3.3 Six-Minute Walk Test

The Six Minute Walk (SMW) test served as an objective measure of functional capacity, as it has been demonstrated in CHF patients to be highly predictive of mortality and hospitalizations, in addition to relating more closely to quality-of-life (QOL) and acitivities-of-

daily-living (ADL) than standard parameters of peak exercise performance (Bittner et al., 1993; Guyatt et al., 1985). The SMW test was performed at the screening visit, two additional times prior to randomization, twice at 3-months, and once at six months. A long, quiet corridor in the basement of the Hamilton General Hospital served as the venue for the SMW test. Two chairs were placed 33 m apart to mark the distance of the test, and 1.5 m sections were indicated on the ceiling using red markers. Patients sat on a chair prior to their performance of the SMW and received standardized instructions. They were instructed to walk from one chair to the other as many times as they could in a six-minute period. If symptoms necessitiated that they take rests throughout the test, they were encouraged to do so, and they were allowed to proceed when they were able to continue. Patients were given standardized encouragement throughout the test, and were told the time remaining after two and four-minutes had elapsed. At the end of the test, subjective reports of patients' maximal breathing effort, chest pain, and leg fatigue were recorded using a 10-point BORG rating of perceived exertion (RPE) scale. The total distance travelled served as the only dependent measure in the current investigation.

2.3.4 Resting Radionuclide Ventriculography

The radionuclide ventriculography (RNV) testing was performed in the Nuclear Medicine department of the Hamilton General Hospital. Patients underwent this procedure both at baseline and 3-months in order to assess end-diastolic and end-systolic volumes, ejection fractions, and wall motion abnormalities. The procedure was performed in a standardized fashion, using an invitro method for the labelling of red blood cells. The red

cells were pretreated with stannous pyrophosphate, and labelled using 1 Gbq of TC^{99m} pertechnitate. A camera with a small field of view was then positioned in order to maximize the resolution of the LV blood pool images. Images were then formatted to correspond to cardiac cycles of 32 frames/cycle, as determined by ECG morphology and RR-interval. A non-geometric count based method was then employed for volumetric analysis of the heart. Images were recorded on computer diskettes and were analyzed by a trained technician at the Hamilton General Hospital. The RNV reports were then forwarded to the research office for further review. The left ventricular ejection fraction (LVEF) served as the only dependent measure from this analysis. The coefficient of variation of this technique has been found to be ±10%.

2.4 Heart Rate Variability Techniques

2.4.1 Frequency Domain Analysis of HRV

2.4.1.1 Protocol and Signal Processing

The power spectral analysis of HRV was performed in an examination room in the Medical Diagnostics Unit of Hamilton General Hospital. During both the baseline and 3-month power spectrum visits, all patients were monitored in three conditions: 1) during 20-minutes of supine rest; 2) during 10-minutes of standing; and, 3) during 20-minutes of supine rest following a symptom-limited incremental cycle ergometer test. The six-month visits, however, were restricted to only the supine and standing conditions. Comparison of the supine and standing conditions allowed the response of HRV to an orthostatic stress to be observed (Kamath et al., 1993; Pomeranz et al., 1985), in addition to providing information

as to resting values of sympathovagal balance. The purpose of the post-exercise recordings was to observe the recovery of power spectrum indices towards supine values following a bout of physical activity. The recordings all took place between the hours of 09:00 and 12:00 in order to discount influences of circadian variation on HRV. Power spectral analysis of HRV in these acute studies permitted exploration of sympathovagal modulation of neurocardiac control in the frequency domain.

Prior to the onset of power spectrum monitoring, patients were given a hospital gown and were instructed to remove upper body garments in order to apply the monitoring electrodes. The examination room was quiet, in semi-darkness, and maintained at a constant temperature of 18 to 20°C in order to maximize the comfort of patients during the monitoring. Patients then assumed a semi-recumbent position on a hospital bed and were encouraged to remain awake and relaxed during the recording period. The skin was prepared in the appropriate areas by abrading the skin surface, followed by cleansing of the surface epidermis and skin oils with an alcohol preparation. The lead placement for all three conditions was identical, and consisted of a bipolar lead II arrangement, with the ground electrode positioned inferior to the proximal end of the left clavicle; care was taken to avoid DC interference and to ensure adequate R-wave signals for data processing. The electrode arrangement also permitted monitoring of the respiratory signal through impedence plethysmography; a 1kHz signal was passed between reference electrodes and responded to the rise and fall of the chest during inspiration and expiration. The recording of HRV necessitates that the respiration frequency is monitored, as well as heart rate, due to the

observed effects of the respiratory sinus arrhythmia (RSA) on HRV (Brown et al., 1993; Malliani et al., 1991; Saul et al., 1989).

Both the ECG and the respiratory signals were input into their respective analog recorders, were amplified using an HP 7087C amplifier, digitized using a 12 bit analog to digital converter at 1 kHz, and processed using an IBM pentium computer (Gateway 2000). The resulting signals were displayed continuously on a computer monitor using CODAS commercial data acquisition software. The gain and morphology of the ECG signal were adjusted accordingly prior to recording the data in order to maximize the resolution of successive RR-intervals; a robust R-wave facilitates detection by the HRV algorithms when computing HRV data (Kamath et al., 1993). The two-channels were displayed simultaneously using CODAS data acquisition software, and were each recorded at a sampling frequency of 500-samples/sec. The file size for both the supine and post-exercise recordings was 2400kB, and 1440kB for the standing condition.

Supine Condition

Prior to the onset of recording the data, patients were asked to relax as much as possible during the recording period and to keep talking and movement to a minimum; these instructions were important in order to prevent movement artifact upon the ECG signal and to minimize RSA effects due to talking. Blood pressure via auscultation, in addition to heart rate were measured both pre- and post-recording in the semi-recumbent position.

Standing Condition

Following the supine condition, patients were asked to sit up slowly and hang their

legs over the side of the hospital bed prior to standing up; this protected against syncope that may have occurred due to sudden changes in orthostatic stress. Once the patient was ready, they were asked to stand and assume a relaxed stance and were encouraged to shift their weight from side-to-side as necessary. At one-minute post-standing, both blood pressure and heart rate were recorded, at which time the 10-minutes of data acquistion began. Patients were allowed to talk freely during this period, as RSA effects due to talking are assumed to be negligible during standing. At the end of the recording period, the patient was disconnected from the monitoring devices and either proceeded to the exercise lab for their symptom-limited, incremental exercise test (baseline and 3-month visits), or was outfitted with a 24-hour ambulatory ECG monitor and permitted to leave (6-month visit).

Post-Exercise Condition

In the early stages of recovery (i.e. 6-8 minutes), following the symptom-limited, incremental exercise test (baseline, 3-month visits), patients were transferred as quickly as possible to a semi-recumbent hospital bed waiting directly outside the exercise test laboratory. Patients were then returned to the original examination room in the Medical Diagnostics Unit for a further 20-minutes of post-exercise recording. Following the 20-minute recording session, patients were outfitted with a 24-hour ambulatory ECG monitor and were permitted to leave (baseline, 3-month visits).

2.4.1.2 Power Spectral Analysis

The raw data patient files from the CODAS subdirectory on the 486-pentium computer at Hamilton General Hospital were downloaded to digital tape using Colorado

Backup software, and were transferred to the Clinical Neurocardiology Laboratory at MUMC for power spectral analysis of HRV . Files from the digital tape were uploaded to the CODAS subdirectory on the hard drive of an IBM 80486-33 computer using Colorado Backup software. Individual raw data files were analyzed in DOS in order separate the ECG and respiration data for individual analyses.

Using a QRS detection algorithm, an RR-interval series was formed from the continuous ECG data. Prior to spectral analysis, the RR-interval tachogram was inspected for evidence of ectopic beats. Ectopics were corrected using the algorithms found within the autoregressive modelling program in order to discount the compensatory pause characteristic to ectopic beats as an increase in vagal modulation and subsequent increase in HF power (Kamath et al., 1995). In situations where data files were contaminated by a great deal of ectopics, an attempt was made to manually extract a portion of the data file that was ectopic free in order to subject to spectral analysis. Patient files which were unable to be salvaged were excluded from statistical analysis. A beat-to-beat heart rate variability signal was computed from the ectopic-corrected tachogram, which was resampled at 2 Hz using linear interpolation to obtain an equally sampled time series. A record length of 256 points from the resampled signal (128 seconds) was selected for power spectral analysis. The mean value of the signal was subtracted and the equally sampled HRV signals were fed through a second order high pass Butterworth filter with a cut-off of 0.02 Hz. A 9th order autoregressive model was then applied to the demeaned, filtered

heart rate variability data (Kay et al., 1981). In the autoregressive (AR) approach, the signal x[n], at any instant 'n', is described as an output sequence from a black-box in response to an input driving white noise sequence u[n],

$$x[n] = -\sum_{k=1}^{p} a[k]\, x[n-k] + u[n] \quad \ldots(1)$$

where k={1,2..p} are the autoregressive parameters used to describe the signal. These parameters are then used to compute the AR power spectrum:

$$P_{AR}(f) = \frac{\sigma^2 \Delta t}{\left[1 + \sum_{k=1}^{p} a[k] \exp(-j2\pi f k \Delta t)\right]^2} \quad .. (2)$$

where σ^2 is the variance of the input noise sequence and Δt is the sampling interval. The computational details of the algorithm for estimating the AR parameters have been previously described in the literature (Kay et al., 1981).

The following dependent measures are computed in order to characterize the information contained in the power spectrum: the maximum value of the peak power in the both the low (0.02-0.15 Hz) and high frequency bands (0.15-0.5 Hz); the central frequency (cf) at which the peak power occurred within both bandwidths; the total area in each band, computed by numerically integrating the power under each frequency band; a percentage measure of the area under each peak, and therefore the frequency band, was obtained by dividing the power under each band by the total power contained in the whole

spectrum (i.e. fractional power); and finally, a ratio of the percentage power contained in the low frequency band to that in the high frequency band (LF:HF area ratio), as well as a ratio of the low frequency peak to that of the high frequency peak (LF:HF peak ratio).

2.4.2 Time Domain Analysis of HRV

At the conclusion of each of the power spectral analysis visits at baseline, three-months, and six-months, patients were asked to wear an ambulatory electrocardiographic (ECG) "holter" monitor for a 24-hour period (Medilog 4500, Oxford Medical Ltd., Oxon, UK). The beat data from the holter monitor permitted heart rate variability to be explored in the time domain. The lead placement for the holter consisted of a two-lead (V_1,V_5) precordial arrangement, with the ground electrode positioned in the lower right abdominal region approximating the suprailliac region, and two reference electrodes in the regular limb lead placement, inferior to the proximal portion of both claviculae. The skin in these regions abraded appropriately with a small coarse pad, followed by cleaning of the skin with an alcohol pad in order to remove surface epidermis and skin oils. After connecting the patient and turning the holter on, the holter required confirmation of the date and time, and patient status; when confirmation was given, the holter began an ECG signal test prior to calibrating the instrument. The sampling rate of the holter was 125/second. Following the calibration period, the electrodes were then taped in position in order to minimize movement artefact, and to prevent disconnection of the leads. Patients were instructed to dispose of the electrodes and tape following the recording period and to return the monitor at their earliest convenience.

The 24-hour holter tapes were collected and analyzed using the commercial software of the holter scanner in the Cardiorespiratory Department of MUMC (Medilog Excel, Oxford Medical Ltd., Oxon, UK). Upon confirmation of the tape calibration, as well as the time and date of recording, the tapes were analyzed using the automatic mode. The software digitised and recorrelated the raw beat data, and subjected the data to arrhythmia analysis. Full printouts of holter reports were obtained, and the beat data was exported to 3 1/2" diskette for further analysis of HRV time domain indices using software in the Clinical Neurocardiology Laboratory at MUMC.

The time domain indices derived from the 24-hour holter data included a plot of circadian variation of both the mean and standard deviation of heart rate, in addition to several statistics based upon the individual intervals. Dependent measures derived directly from the intervals themselves over the 24-hours include the mean HR, mean RR-interval, SDNN, and SDANN; in addition, the r-MSSD, pNN50, and SDNN-index are derived from differences between adjacent cycles over the 24-hour period.

2.5 Data Analysis

2.5.1 Supine Power Spectral Profiles

In order to assess the effect of exercise training upon resting supine spectral profiles, a quantitative assessment was made between groups using the baseline, 3-month, and 6-month supine recordings. The following frequency domain indices were carefully observed: 1) the HF-central frequency (cf) for changes in respiratory frequency; 2) the LF-cf for shifts in vagal modulation of the LF peak; 3) the LF:HF area ratio, indicating changes in resting

sympathovagal balance; and 4) the resting HR for indications of a training bradycardia.

2.5.2 Response to Orthostatic Stress

In order to assess the effect of exercise training upon baroreceptor sensitivity, a qualitative inspection of the response to orthostatic stress in both the AERWT and UC groups was performed at baseline. Patients were stratified according to the responses (i.e. normal, abnormal) of their respective spectral profiles. An improvement in the response to orthostatic stress was defined as: 1) an accentuated increase in LF-power upon standing where there was a normal response previously; 2) an increase in LF-power upon standing where there was attenuated response or no change at baseline; and, 3) an increase in LF-power where there was a flattened spectral profile previously. These changes were assessed through comparison of only the baseline and 3-month data in order to directly assess the effects of the 3-month supervised training intervention.

2.5.3 Post-Exercise Recovery of Power Spectral Profiles

In order to investigate the effect of exercise training upon post-exercise recovery, the post-exercise recording session was compared with the previous supine recording in order to quantitatively assess whether spectral profiles had returned to supine resting values following the exercise stimulus. The specific indices compared between the two conditions included: 1) the HF-central frequency (cf) for changes in respiratory frequency; 2) the LF-cf for shifts in vagal modulation of the LF peak; 3) the LF:HF area ratio, indicating differences in resting sympathovagal balance; and 4) the mean HR.

2.5.4 Time Domain Indices

All time domain parameters were compared between the baseline, 3-month, and 6-month visits in order to track the changes made in these indices as a result of the training intervention. Change scores were calculated for each parameter between baseline and the 3-month and 6-month assessments respectively.

2.6 Statistical Analysis

All data are presented as means and standard errors ($X \pm S.E.M$) unless otherwise indicated. Comparisons of baseline patient demographics and successive observations of exercise indices, left ventricular function, dynamic muscle strength, and Six-Minute Walk data within and between groups were performed using one-, two-, or three-way fixed effects, repeated measures multivariate analyses of variance (MANOVA). Post-hoc analysis of main effects or interactions were performed on individual dependent variables using two-, or three-way fixed effects ANOVAs; a Tukey HSD test was then used in order to assess differences in group means where significance was found. Where baseline variation precluded analysis using ANOVA, comparisons of successive observations were made within and between groups using either two- or three-way repeated measures analysis of covariance (ANCOVA). Qualitative assessment of patient demographics and improvements in orthostatic responses necessitated the use of a Chi-Square (χ^2) non-parametric test with Yates correction factor. Statistical significance was identified at $p<0.05$.

3.0 RESULTS

3.1 Subject Characteristics

A one-way fixed effects MANOVA revealed that the patients in both the AERWT and UC groups were comparable with respect to age, left-ventricular ejection fraction (LVEF), height, weight, BMI, and duration of CHF (Rao R=1.48 (6,21); p=0.234). Chi-square analysis of group gender, using Yates's correction factor, failed to detect any significant differences among the AERWT and UC groups (χ^2=0.19, df=1; p=0.659). Individual non-parametric assessments of both NYHA class and etiology of CHF were performed using a Chi-square observed-expected contingency table; this analysis indicated that the groups were comparable, with χ^2=0.781 (df=5; p=0.978), and $\hat{\chi}^2$ =4.95 (df=7; p=0.666) respectively. Inspection of patients' previous medical history and medication use also appeared to be similar. Please refer to Table 3 for further details concerning patient demographics. None of the patients in the AERWT group developed any significant symptoms as a result of the training regimen which precluded them from further participation in the current investigation. One of the patients in the UC group voluntarily withdrew from the study following his 3-month follow-up examination, and another in order to assess his candidacy for cardiac transplantation. Compliance with the training regimen was defined as the successful completion of 11 out of the 24 sessions during the 12-week supervised training period. The data from subjects who did not fulfil this criterion were excluded from group analysis. Two

male patients and one female patient in the training group were thereby termed non-compliant. Student's t-tests for independent samples were performed on the baseline data of the respective groups in order to assess homogeneity of the sample, and to provide direction for statistical analysis.

Table 3: Patient Demographics for AERWT and UC Groups

DEMOGRAPHIC	AERWT (n=16)	UC (n=12)
AGE (yrs)	64.9 ± 2.3	58 ± 2.8
GENDER	11 male, 5 female	10 male, 2 female
HEIGHT(cm)	167 ± 2.3	168 ± 2.3
WEIGHT(kg)	79.3 ± 5.2	86 ± 5.0
BMI	28.3 ± 1.6	30.6 ± 1.7
LVEF (%)	29.4 ± 1.7	24.4 ± 2.0
NYHA CLASS **-I** **-II** **-III**	 n=1 (6%) n=9 (56%) n=6 (38%)	 n=0 (0%) n=7 (58%) n=5 (42%)
ETIOLOGY OF FAILURE **-Ischemic** **-Idiopathic** **-Hypertensive** **-Viral**	 n=12 (75%) n=1 (6%) n=3 (19%) n=0 (0%)	 n=9 (75%) n=1 (8%) n=0 (0%) n=2 (17%)
CHF DURATION (mos.)	36.6 ± 9.7	16.1 ± 5.2
PREVIOUS HISTORY **-ANGINA** **-DIABETES** **-HYPERTENSION** **-INFARCTION** **-CABG**	 n=4 (25%) n=4 (25%) n=7 (44%) n=13 (81%) n=4 (25%)	 n=4 (33%) n=3 (25%) n=3 (25%) n=8 (67%) n=2 (17%)

DEMOGRAPHIC	AERWT (n=16)	UC (n=12)
MEDICATION USE		
-ACE INHIBITOR	n=14 (88%)	n=11 (92%)
-DIURETIC	n=13 (81%)	n=9 (75%)
-DIGOXIN	n=10 (63%)	n=6 (50%)
-"TRIPLE THERAPY"	n=6 (38%)	n=4 (33%)
-NITRATES	n=10 (63%)	n=6 (50%)
-ANTI-COAGULANTS	n=6 (38%)	n=7 (58%)
-ASA	n=9 (56%)	n=4 (33%)
-ANTI-ARRHYTHMICS	n=6 (38%)	n=1 (8%)
-BETA-BLOCKER	n=0 (0%)	n=2 (17%)

3.2 Effects of Exercise Training Regimen

3.2.1 Symptom Limited Incremental Cycle Ergometer Test

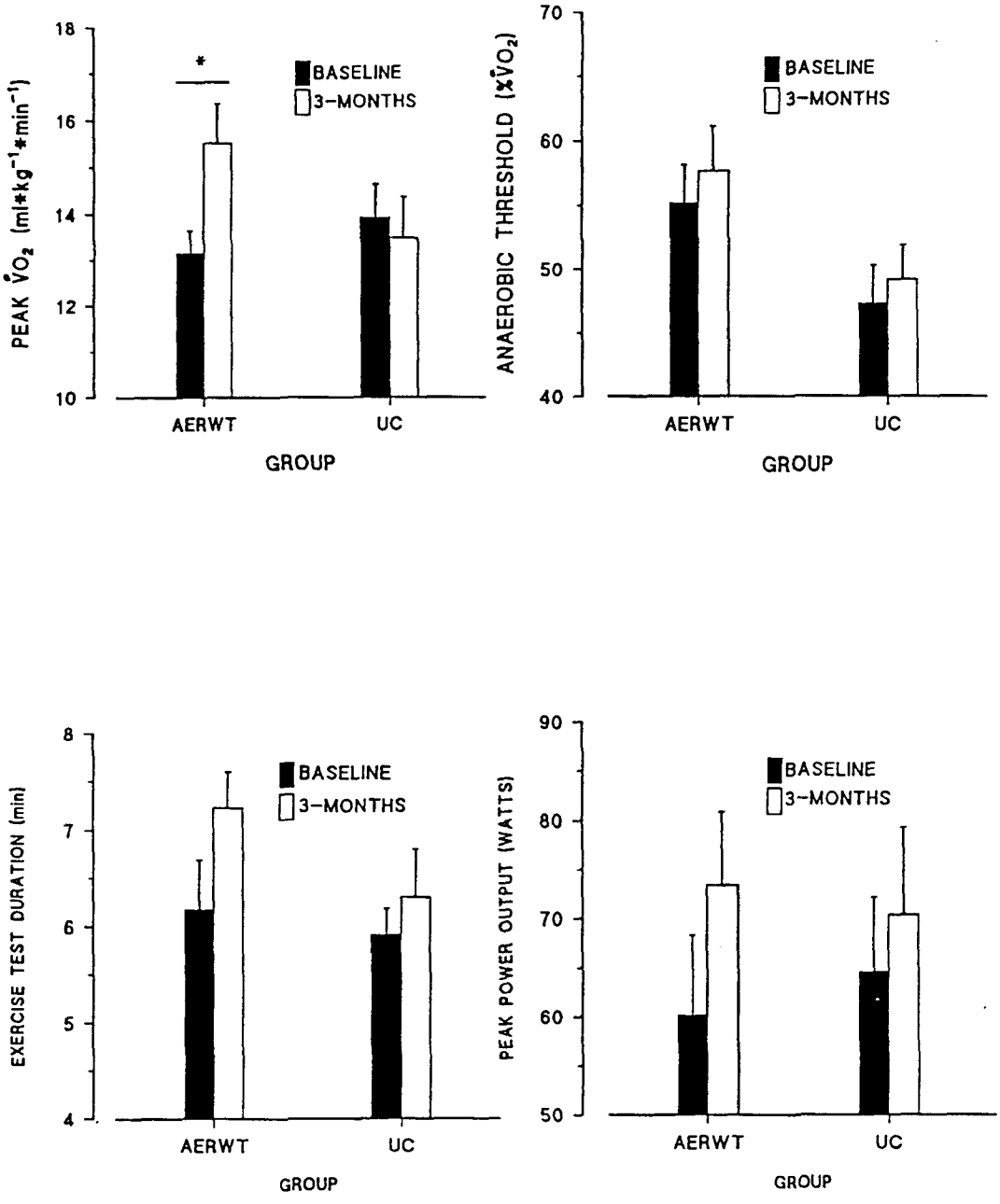
A symptom-limited incremental cycle ergometer test was performed by all patients at the baseline and 3-month evaluations in order to assess possible physiological adaptations and changes in maximal power output as a result of the training intervention. A two-way fixed effects MANOVA was performed and revealed a significant GROUP X TIME interaction, Rao R (10, 13)=4.00; $p<0.011$. Post-hoc analysis of the following dependent variables were performed using two-way ANOVAs, followed by Tukey HSD tests in order to assess differences in group means where significance was found: 1) peak relative $\dot{V}O_2$ (ml/kg/min); 2) peak absolute $\dot{V}O_2$ (L/min); 3) maximum exercise duration (MED; min); 4) maximum power output (MPO; Watts); 5) anaerobic threshold (%$\dot{V}O_2$); and, 6) anaerobic threshold (ml/min).

As demonstrated in Figure 3, the AERWT group significantly increased their peak relative $\dot{V}O_2$ by 19.2 ± 7.7% (13.2 ± 0.5 to 15.5 ± 0.84 ml/kg/min, $p<0.05$), compared to a

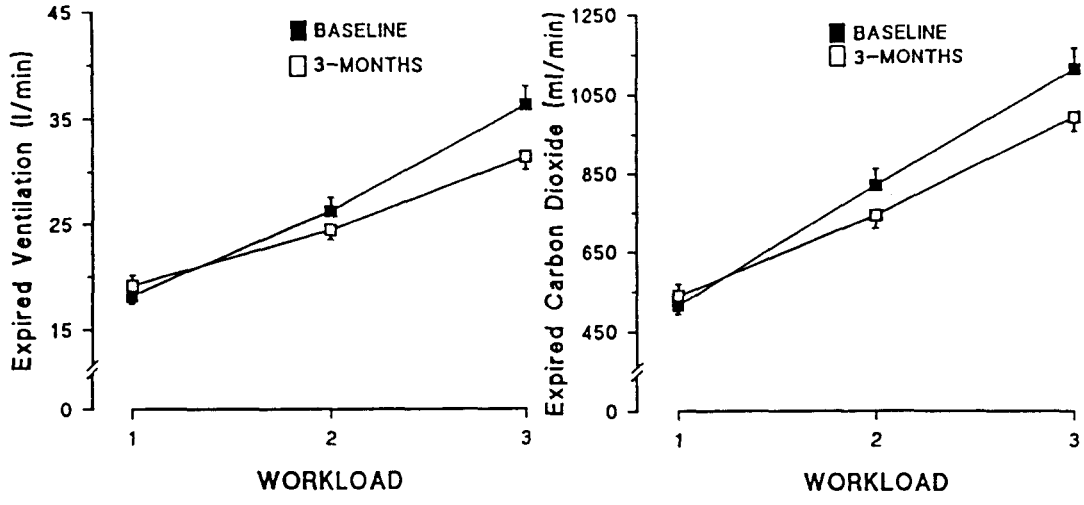
0.30 ± 5.1% decrease (13.9 ± 0.7 to 13.5 ± 0.9 ml/kg/min, N.S.) in the UC group. In peak absolute $\dot{V}O_2$, however, both groups demonstrated non-significant gains of 11.7 ± 4.5% (1.11 ± 0.096 to 1.23 ± 0.094 L/min, N.S.) and 2.9 ± 2.8% (1.14 ± 0.066 to 1.20 ± 0.087 L/min, N.S.) in the AERWT and UC groups respectively. With respect to maximum exercise duration (MED), the AERWT group demonstrated a 20.6 ± 5.9% increase in MED (6.18 ± 0.51 to 7.23 ± 0.37 min, N.S.) compared to an increase of only 5.2 ± 6.1% (5.92 ± 0.26 to 6.31 ± 0.50 min, N.S.) by the UC group (see Figure 3). As displayed in Figure 3, the maximal power output (MPO) achieved during the exercise test increased by 25.4 ± 5.5% (60.2 ± 8.2 to 73.4 ± 7.5 W, N.S.) in the AERWT group, and 8.79 ± 5.8% (64.6 ± 7.5 to 70.4 ± 8.9 W, N.S.) in the UC group.

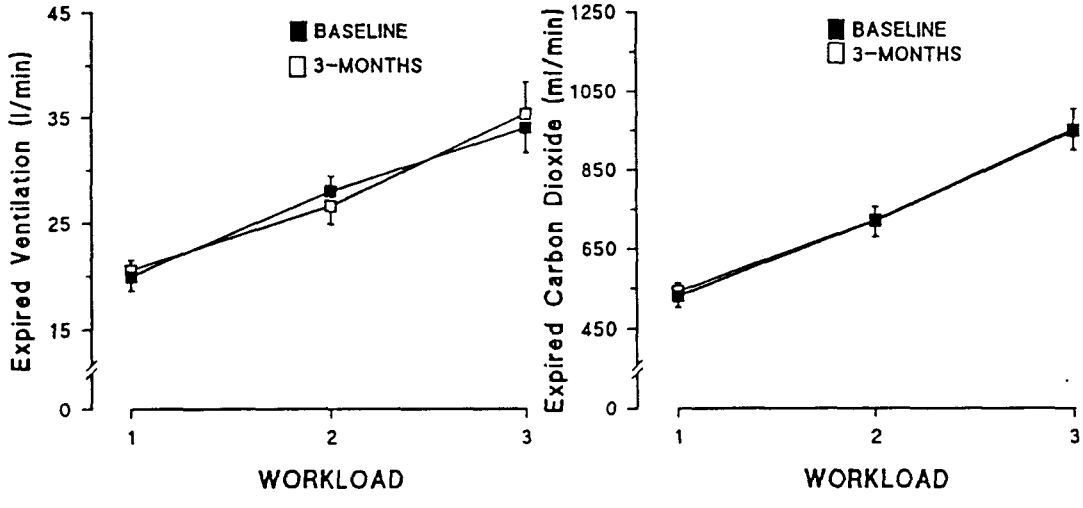
Anaerobic threshold was calculated and expressed in both absolute terms (ml/min) and as a percentage of the predicted maximal $\dot{V}O_2$ based on a healthy population. Both the AERWT and UC groups realized similar increases in anaerobic threshold of 4.9 ± 3.7% (55.2 ± 2.9 to 57.7 ± 3.4 %$\dot{V}O_2$, N.S.) and 5.8 ± 5.1% (47.4 ± 2.7 to 49.2 ± 2.9%$\dot{V}O_2$, N.S.) respectively (see Figure 3). Alternatively, when expressed in absolute terms, the AERWT group increased their anaerobic threshold by 10 ± 3.7% (926.9 ± 64.5 to 1014 ± 73.3 ml/min, N.S.) versus a 6.0 ± 5.2% increase (937.6 ± 50.3 to 1003 ± 78.7 ml/min, N.S.) by the UC group.

Expired ventilation ($\dot{V}E$), expired carbon dioxide ($\dot{V}CO_2$), and the $\dot{V}E$:$\dot{V}CO_2$ ratio were calculated for the three initial workloads (WL1, WL2, WL3) of the symptom limited incremental cycle ergometer test. A three-way, fixed effects MANOVA was performed on


PEAK $\dot{V}O_2$ (ml*kg^{-1}*min^{-1})
18
16
14
12
10
*
BASELINE
3-MONTHS
AERWT
UC
GROUP
ANAEROBIC THRESHOLD (%$\dot{V}O_2$)
70
60
50
40
BASELINE
3-MONTHS
AERWT
UC
GROUP
EXERCISE TEST DURATION (min)
8
7
6
5
4
BASELINE
3-MONTHS
AERWT
UC
GROUP
PEAK POWER OUTPUT (WATTS)
90
80
70
60
50
BASELINE
3-MONTHS
AERWT
UC
GROUP

the ventilation data from both the baseline and 3-month assessments. The analysis revealed a main effect for WORKLOAD (Rao R(6,14)=78.7, p<0.001), and a significant WORK X TIME interaction (Rao R(6,14)=2.97, p=0.044). The GROUP X WORKLOAD X TIME interaction, however, only approached statistical significance (Rao R(6,14)=2.48, p=0.075). Post-hoc analysis of the WORKLOAD main effect, using three-way ANOVAs, was significant for $\dot{V}E$ (p<0.001), $\dot{V}CO_2$ (p<0.001), and $\dot{V}E$:$\dot{V}CO_2$ (p<0.001); however, the WORKLOAD X TIME interaction was only significant for $\dot{V}CO_2$ (p<0.05). As demonstrated in Figure 4, although statistically non-significant, the AERWT group decreased their WL2 $\dot{V}E$ by an average of 5.12 ± 4.64% (26.2 ± 1.31 to 24.4 ± 0.93 L/min, N.S), and their WL3 $\dot{V}E$ by an average of 12.8 ± 2.92% (36.3 ± 1.72 to 31.4 ± 1.25 L/min, N.S.). Alternatively, the UC group increased their $\dot{V}E$ for the corresponding workloads by 3.50 ± 6.18% (26.0 ± 1.45 to 26.6 ± 1.73L/min, N.S.) and 5.92 ± 8.05% (34.0 ± 2.37 to 35.3 ± 3.07L/min, N.S.). The $\dot{V}CO_2$ levels of the AERWT group demonstrated a reduction of 8.36 ± 4.73% (816.7 ± 41.7 to 740.7 ± 34.4 ml/min, N.S.) during WL2, and a 10.7 ± 2.84% reduction in $\dot{V}CO_2$ during WL3 (1110 ± 52.9 to 989.5 ± 35.7 ml/min, N.S.). In contrast, the UC group increased their $\dot{V}CO_2$ levels by 1.40 ± 4.28% (718.3 ± 40.1 to 720.6 ± 32.9ml/min, N.S.) and 1.52 ± 5.74% (943.8 ± 46.5 to 948.5 ± 52.8ml/min, N.S.) for WL2 and WL3 respectively (see Figure 4). As for changes in the $\dot{V}E$:$\dot{V}CO_2$ ratio, the AERWT group increased from 3.19 ± 0.08 to 3.31 ± 0.09 (N.S.) at WL2, and decreased their ratio from 3.31 ± 0.08 to 3.21 ± 0.09 (N.S.) at WL3. The UC group, however, increased their ratios at the corresponding workloads from 3.66 ± 0.21 to 3.71 ± 0.21 (N.S.), and from 3.61 ± 0.22 to 3.74 ± 0.26 (N.S.) respectively.

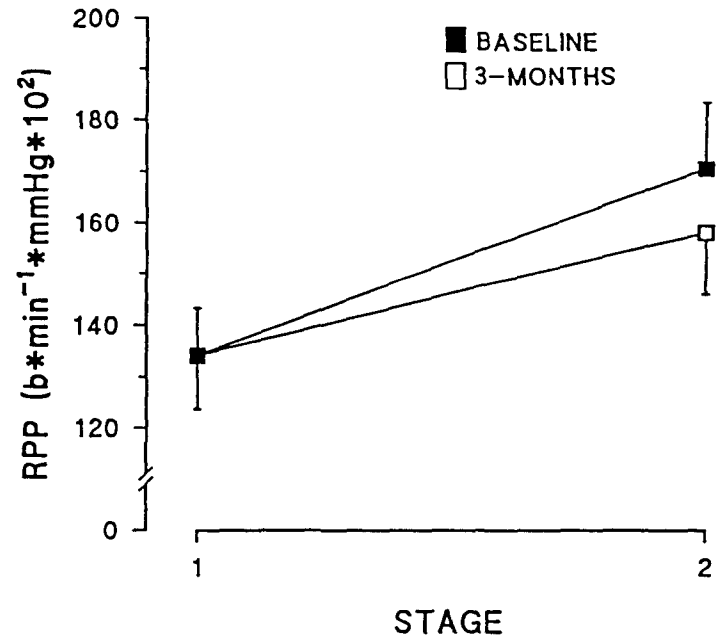

Expired Ventilation (l/min)
45
35
25
15
0
BASELINE
3-MONTHS
1
2
3
WORKLOAD
Expired Carbon Dioxide (ml/min)
1250
1050
850
650
450
0
BASELINE
3-MONTHS
1
2
3
WORKLOAD

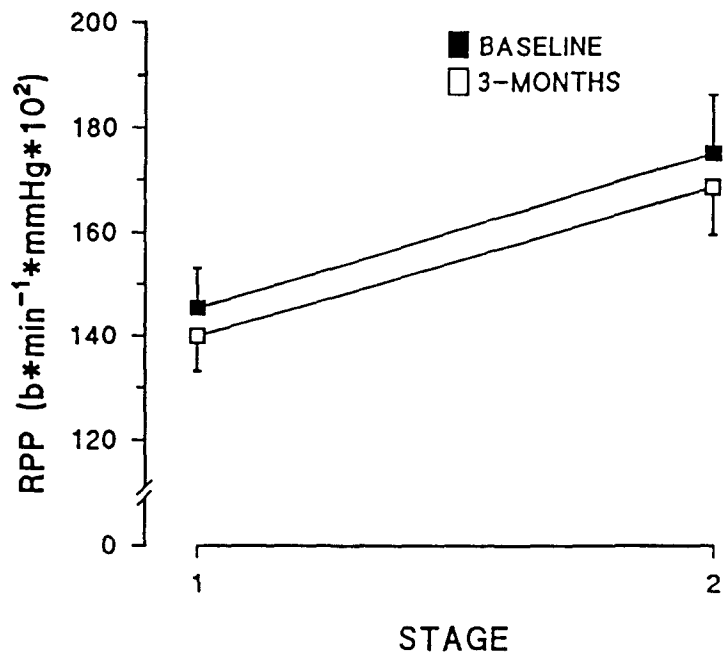

Expired Ventilation (l/min)
45
35
25
15
0
BASELINE
3-MONTHS
1
2
3
WORKLOAD
Expired Carbon Dioxide (ml/min)
1250
1050
850
650
450
0
BASELINE
3-MONTHS
1
2
3
WORKLOAD

The double products (RPP=(HR x SBP) from stages 1 and 2 of the modified Bruce protocol were derived from the symptom-limited incremental cycle ergometry data in order to investigate possible changes in myocardial oxygen demand as a result of the training intervention. A three-way fixed effects MANOVA was performed on the heart rate, systolic blood pressure, and double product data; the analysis only revealed a main effect for STAGE (Rao $R(3,20)=73.03$; $p<0.001$). This main effect was significant for all dependent variables. The GROUP X STAGE X TIME interaction reached a value of Rao $R(3,20)=1.63$ ($p=0.214$). Therefore, neither the heart rate, systolic pressure, nor double product at each respective stage were found to be different at the 3-month follow-up investigation. On an individual basis, the AERWT group increased their WL1-RPP by 0.102 ± 3.35% (134.2 ± 9.12 to 134.2 ± 10.5 b/min *mmHg*10^2, N.S.) and decreased their WL2-RPP by 6.90 ± 2.78% (170.6 ± 13.0 to 158.0 ± 12.1 b/min*mmHg*10^2, N.S.) following the training intervention, whereas the UC group reduced their WL1 and WL2 double products by 3.09 ± 2.76% (145.4 ± 7.75 to 140.0 ± 6.83 b/min*mmHg*10^2, N.S.) and 2.40 ± 3.63% (175.1 ± 11.2 to 168.7 ± 9.04 b/min*mmHg*10^2, N.S.) respectively (see Figure 5).

3.2.2 Dynamic Muscle Strength

The one-repetition maximum (1RM) strength test was performed by all patients twice at baseline, and during the 3-month follow-up evaluation in each of the single-arm curl (SAC), single-leg press (SLP), and single-knee extension (SKE) exercises. The tests were performed bilaterally, and the 1RM scores for each limb were combined for a total score on each task. The average increase in 1RM test scores in the AERWT group for the SAC, SLP, and SKE

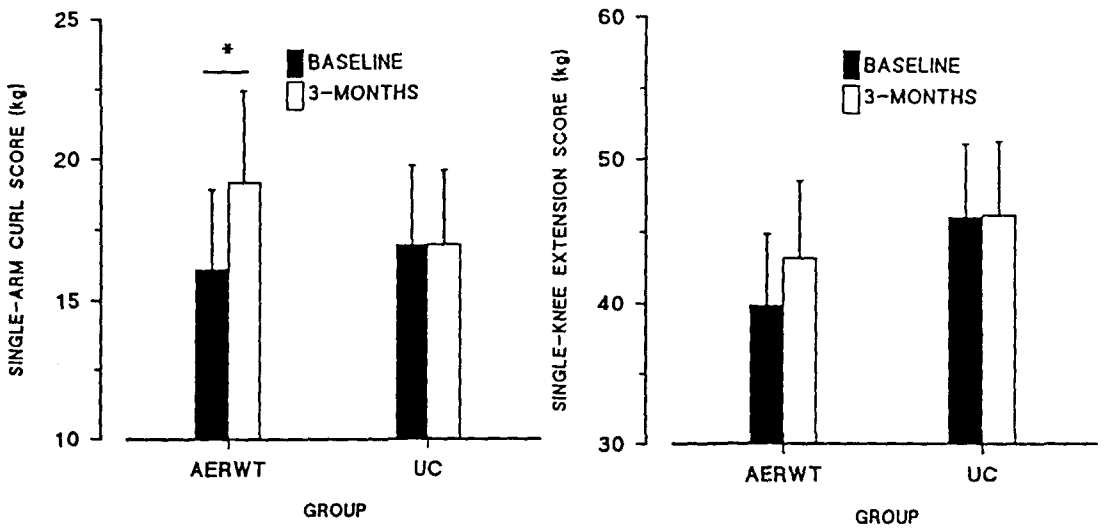

200
180
160
140
120
0
RPP (b*min⁻¹*mmHg*10²)
BASELINE
3-MONTHS
1
2
STAGE

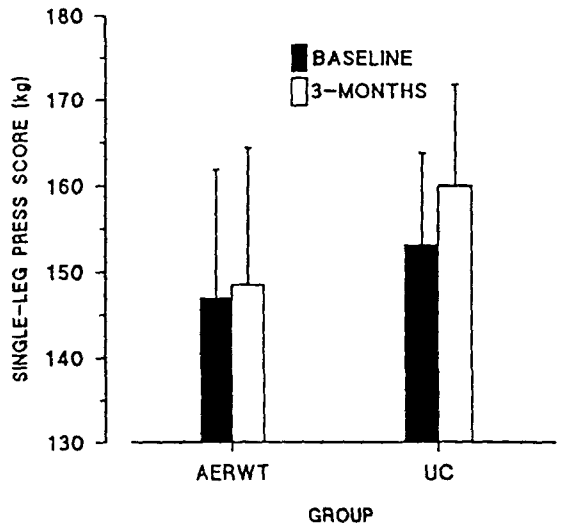

200
180
160
140
120
0
RPP (b*min⁻¹*mmHg*10²)
BASELINE
3-MONTHS
1
2
STAGE

was 9.5%, compared to an average increase of 5.2% in the UC group. A two-way fixed effects MANOVA revealed a significant GROUP X TIME interaction for the dependent variables investigated (Rao R (10, 13)=4.00; $p<0.001$). Post-hoc analysis using individual two-way ANOVAs for the dependent variables SAC, SLP, and SKE demonstrated a significant 19.6 ± 6% increase in SAC (16.2 ± 2.75 to 19.2 ± 3.29 kg, $p<0.05$) in the AERWT group, compared to a non-significant 12.0 ± 9.4% increase in SAC strength (17.0 ± 2.75 kg to 17.2 ± 2.58 kg, N.S.) by the UC group; there were also non-significant increases by the AERWT group in both SLP and SKE of 0.78 ± 2.2% (146.9 ± 14.9 to 148.5 ± 15.9 kg, N.S.) and 8.1 ± 5.0% (39.8 ± 4.96 to 43.2 ±5.29 kg, N.S.) respectively, compared to a non-significant gains of 3.8 ± 2.2% (153.2 ± 10.6 to 160.0 ± 11.7 kg, N.S.) and decrease of 0.85 ± 2.5% (46.0 ±5.0 to 45.7 ± 5.2 kg, N.S.) by the UC group respectively (see Figure 6).

3.2.3 Six-Minute Walk Test

The Six-Minute Walk (SMW) test was administered twice at both the baseline and 3-month assessments, in order to control for reproducibility, and once at the 6-month assessment. A two-way, fixed effects MANOVA was performed on the SMW distance, SMW work, and body weight data for all patients at baseline, 3-months, and 6-months. The analysis did not reveal any significant main effects or interactions; the GROUP X TIME interaction resulted in Rao R (6,14)=0.9405; $p=0.497$. The AERWT group increased their SMW distance 3.95 ± 1.94% (459.2 ± 12.5 to 478.0 ± 18.1m, N.S.) from baseline to 3-months; however, there was a 0.18 ± 3.31% decrease (459.2 ± 12.5 to 459.7 ± 23.1m, N.S.) in SMW distance from baseline to 6-months. The UC group demonstrated a 0.32 ± 4.02%

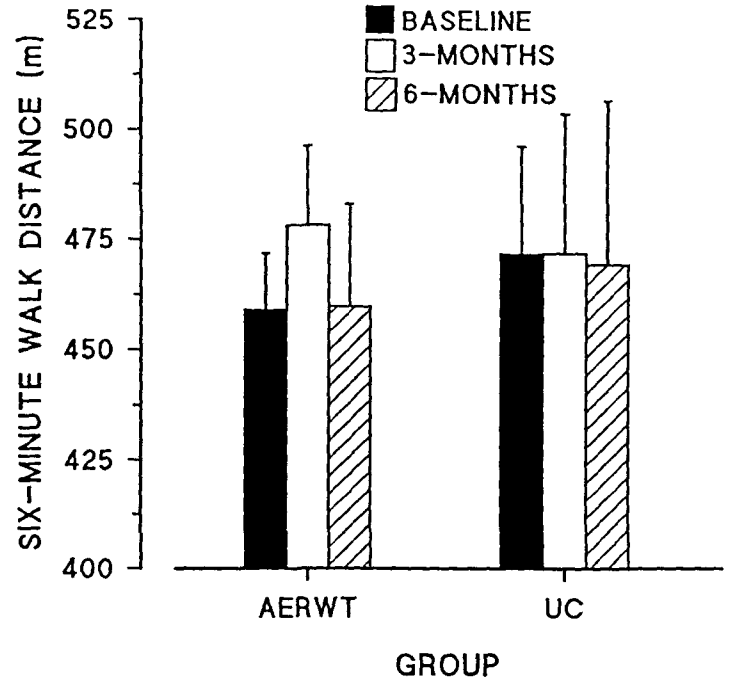

SINGLE-ARM CURL SCORE (kg)
25
20
15
10
*
BASELINE
3-MONTHS
AERWT
UC
GROUP
SINGLE-KNEE EXTENSION SCORE (kg)
60
50
40
30
BASELINE
3-MONTHS
AERWT
UC
GROUP

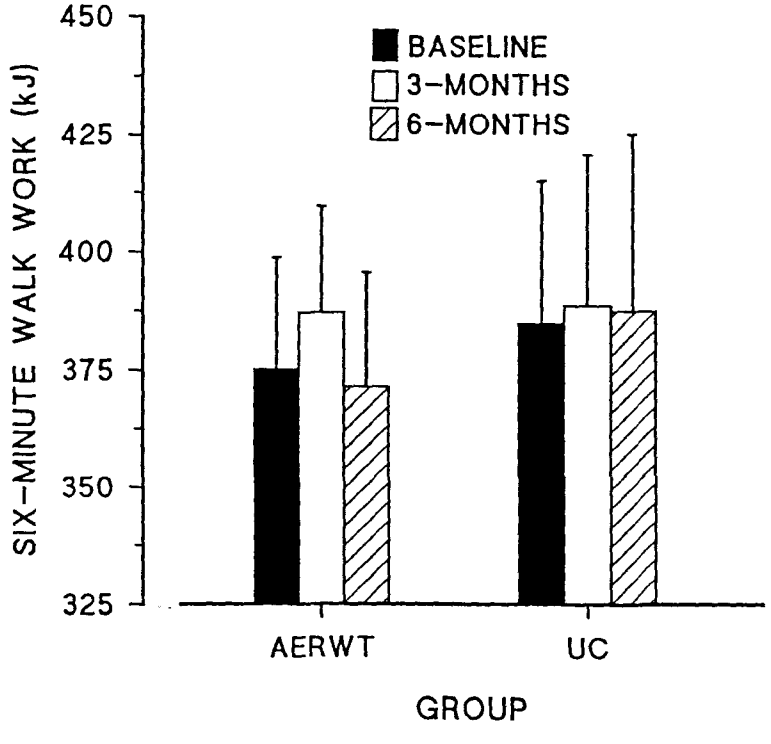

SINGLE-LEG PRESS SCORE (kg)
180
170
160
150
140
130
BASELINE
3-MONTHS
AERWT
UC
GROUP

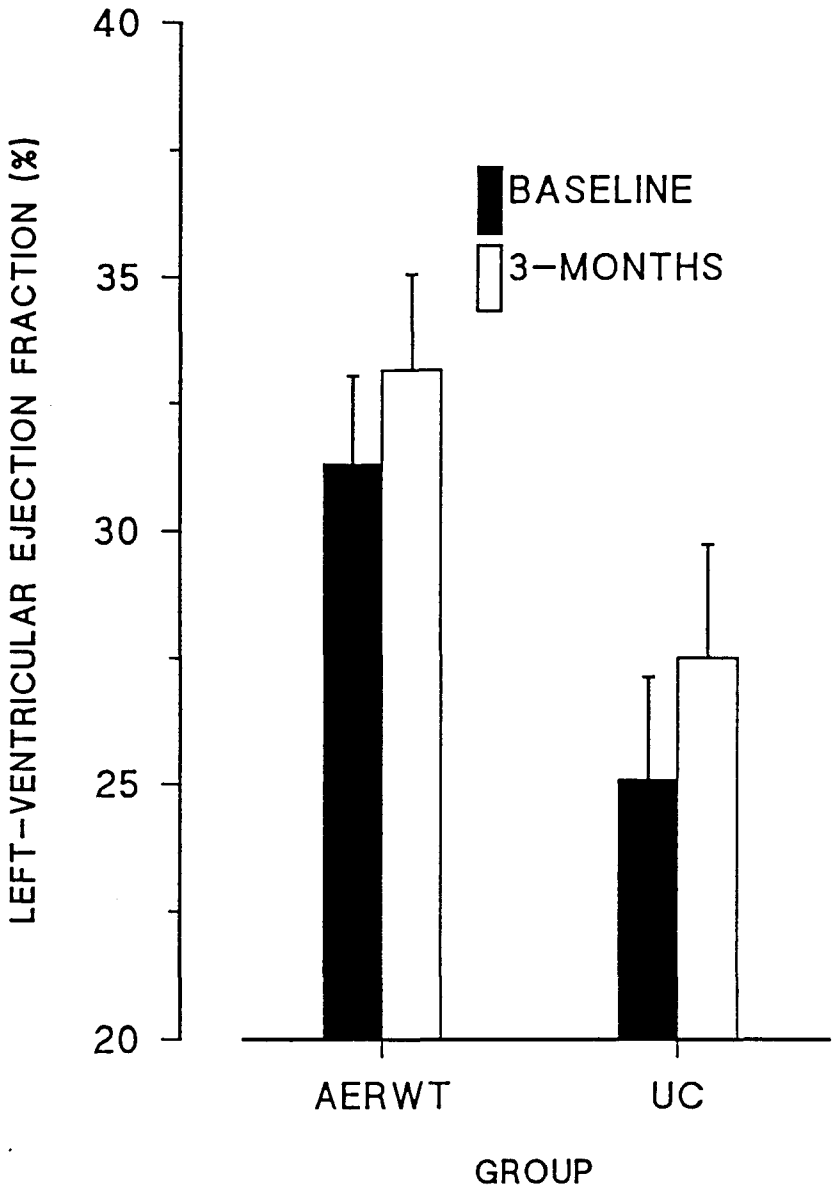
(471.7 ± 24.2 to 471.1 ± 31.8m, N.S.) and 1.10 ± 5.49% decrease (471.7 ± 24.2 to 469.2 ± 37.3m, N.S.) between the baseline/3-month and baseline/6-month assessments respectively. As for SMW walk-work, calculated by the formula WW(J)=SMW(m) * mass(kg) * 9.81 m/s^2, the AERWT group increased WW by an average of 3.60 ± 2.11% (375.4 ± 23.4 to 387.1 ±22.4 kJ, N.S.) from baseline to 3-months, followed by a 0.54 ± 3.37% decrease (375.4 ± 23.4 to 371.4 ± 24.2 kJ, N.S.) in WW from baseline to 6-months. The UC group, however, increased WW by 1.29 ± 4.18% (385.0 ± 30.0 to 388.7 ± 31.9 kJ, N.S.) and 0.25 ± 5.60% (385.0 ± 30.0 to 387.4 ± 37.6 kJ, N.S.) during the baseline/3-month and baseline/6-month periods respectively. The body weight of the patients in the AERWT group demonstrated little change from baseline to 3-months (84.3 ± 5.86 to 84.1 ± 6.02kg, N.S) and from baseline to 6-months (84.3 ± 5.86 to 84.1 ± 6.05kg, N.S.). In contrast, the body weight of the UC group changed modestlly during the baseline/3-month (83.6 ± 5.41 to 85.1 ± 5.82kg, N.S.) and baseline/6-month (83.6 ± 5.41 to 84.9 ± 5.80kg, N.S.) follow-up periods.

3.2.4 Resting Radionuclide Ventriculography

The RNV examinations were performed at baseline and at 3-months in order to assess potential alterations in left ventricular ejection fraction as a result of the training regimen. A Student's t-test for independent samples was performed on the baseline data of the respective groups following the exclusion of the three subjects in the AERWT group due to non-compliance with the training regimen. The test revealed a significant baseline difference in LVEF (t=2.60 (0.05, 23), p=0.016) between groups. Therefore, the data from the baseline and 3-month follow-up examinations were subjected to a one-way ANCOVA to control for


BASELINE
3-MONTHS
6-MONTHS
SIX-MINUTE WALK DISTANCE (m)
525
500
475
450
425
400
AERWT
UC
GROUP


BASELINE
3-MONTHS
6-MONTHS
SIX-MINUTE WALK WORK (kJ)
450
425
400
375
350
325
AERWT
UC
GROUP


40
35
30
25
20
LEFT-VENTRICULAR EJECTION FRACTION (%)
BASELINE
3-MONTHS
AERWT
UC
GROUP

this baseline variation. The AERWT group demonstrated a non-significant 6.3 ± 3.0% increase in LVEF (31.3 ± 1.73% to 33.2 ± 1.90%, N.S.) following the training program, and the UC group realized a 10.1 ± 4.9% increase in LVEF (25. 1 ±2.02% to 27.5 ± 2.23%, N.S.) (see Figure 8).

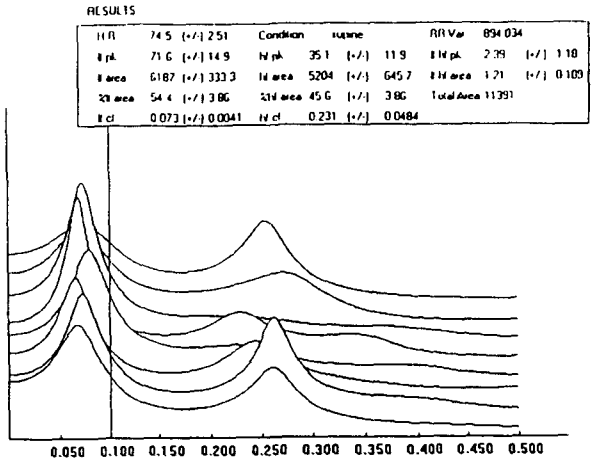
3.3 Heart Rate Variability Indices

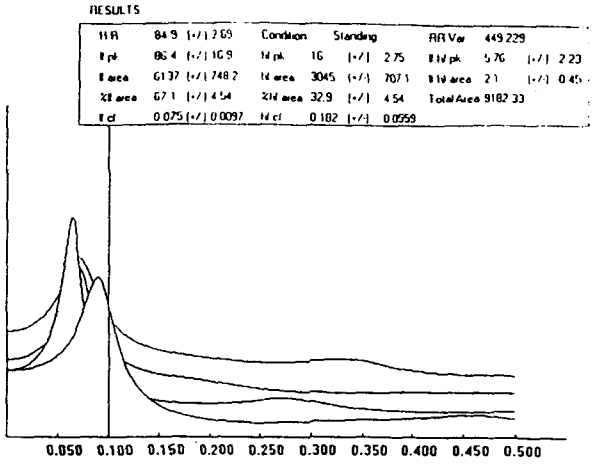
3.3.1 Frequency Domain-Acute Studies

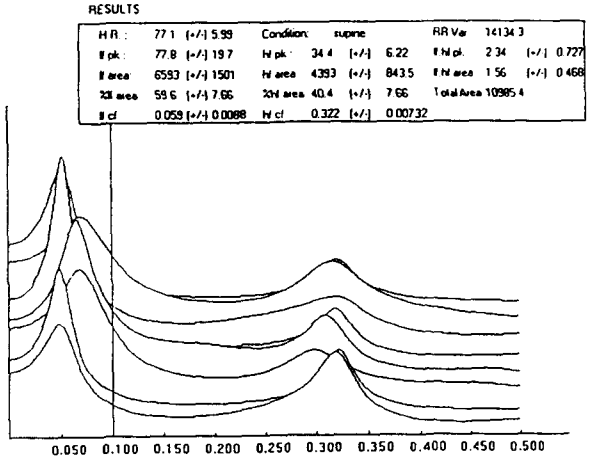
As mentioned previously, the power spectrum of HRV insists that the heart rate signal is as ectopic-free as possible in order to discount the effects of a compensatory pause as an increase in vagal modulation, and its subsequent contribution to an increase in HF-power. Each patient recording was reviewed for the presence of excess ectopic beats, and those recordings which were contaminated by numerous ectopics were excluded from group analysis. A total of 4 patients in the AERWT group and 5 patients in the UC group were excluded from statistical analysis. In the AERWT group, exclusion of patient recordings were due to excess ectopics in two individuals, atrial fibrillation in one patient, and lack of a 6-month recording in one patient due to hospitalization. In the UC group, there were three individuals with poor data due to contamination by ectopics, and two patients did not participate in the 6-month follow-up due to dropout and assessment for cardiac transplantation respectively.

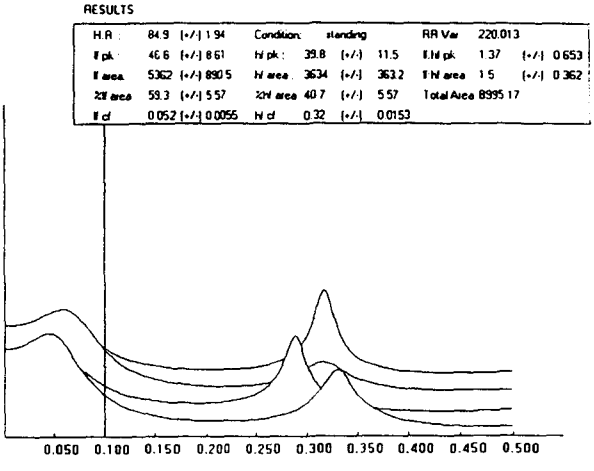
At baseline, 3-months, and 6-months, the response of the CHF patients to an orthostatic stress was assessed through changes in the power spectral indices from the 20-minute supine condition to the 10-minute standing condition. Upon inspection of the baseline

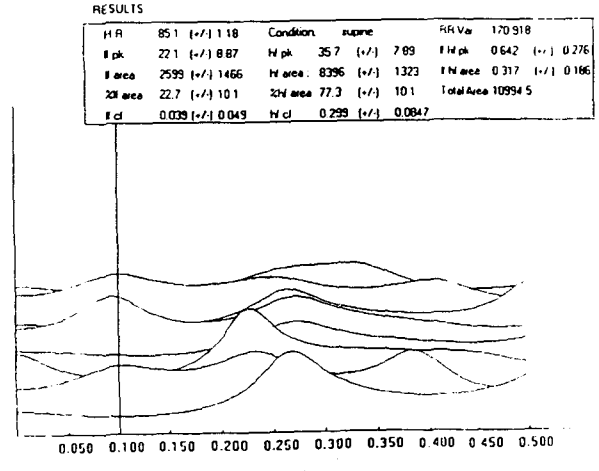
responses of all patients to orthostatic stress, three distinct patterns emerged in the power spectral profiles. In some of the patients there was a normal increase in the LF-power from supine to standing; however, in another group, the LF-power remained unchanged or was attenuated upon standing, and in yet another group there was a flattened spectral profile upon standing. These patterns of patient responses to orthostatic stress are demonstrated in Figure 9. These baseline differences precluded accurate quantitative analysis of the power spectral dependent variables for these two conditions, and instead, a qualitative analysis which assessed improvements in orthostatic response was undertaken by two independent, blinded evaluators. An improvement in the response to orthostatic stress was defined as: 1) an accentuated increase in LF-power upon standing where there was a normal response previously; 2) an increase in LF-power upon standing where there was attenuated response or no change at baseline; and, 3) an increase in autospectral power where there was a flattened spectral profile previously during the supine or standing conditions. These changes were assessed through comparison of only the baseline and 3-month data in order to directly assess the effects of the 3-month supervised training intervention. The qualitative analysis performed by one evaluator (T.C.B.) found that 6 patients in the AERWT group and 2 in the UC had improved their response to orthostatic stress, whereas another evaluator (E.L.F.) identified 7 AERWT patients and 2 UC patients with improvements in the response to orthostatic stress. Chi-square analysis, using Yates correction factor, resulted in $\chi^2 = 1.39$ (df=1; p=0.239) and $\chi^2 = 2.49$ (df=1; p=0.115) for the two independent evaluations respectively. In order to calculate the coherence between the independent evaluations of

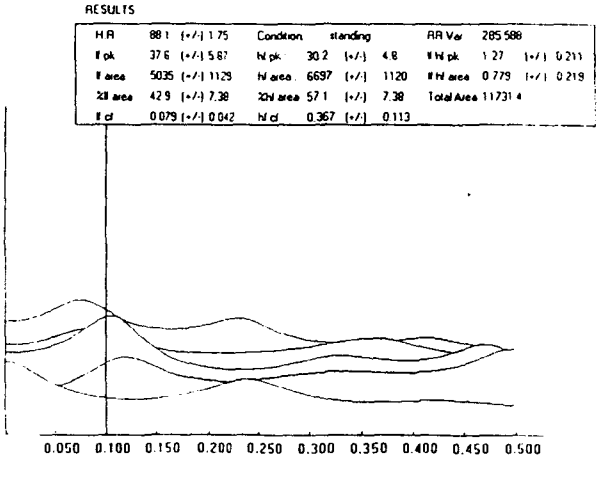

RESULTS
H R 74 5 (+/-) 2 51 Condition supine RR Var 894 034
ll pk 71 6 (+/-) 14 9 hl pk 35 1 (+/-) 11 9 ll hl pk 2 39 (+/-) 1 10
ll area 6187 (+/-) 333 3 hl area 5204 (+/-) 645 7 ll hl area 1 71 (+/-) 0 109
%ll area 54 4 (+/-) 3 86 %hl area 45 6 (+/-) 3 86 Total Area 11391
ll cl 0 073 (+/-) 0 0041 hl cl 0 231 (+/-) 0 0484
0.050 0.100 0.150 0.200 0.250 0.300 0.350 0.400 0.450 0.500


RESULTS
H R 84 9 (+/-) 2 69 Condition Standing RR Var 449 229
ll pk 86 4 (+/-) 16 9 hl pk 16 (+/-) 2 75 ll hl pk 5 76 (+/-) 2 23
ll area 6137 (+/-) 748 2 hl area 3045 (+/-) 707 1 ll hl area 2 1 (+/-) 0 45
%ll area 67 1 (+/-) 4 54 %hl area 32 9 (+/-) 4 54 Total Area 9182 33
ll cl 0 075 (+/-) 0 0097 hl cl 0 182 (+/-) 0 0559
0.050 0.100 0.150 0.200 0.250 0.300 0.350 0.400 0.450 0.500


RESULTS
H R 77 1 (+/-) 5 99 Condition supine RR Var 141343
ll pk 77 8 (+/-) 19 7 hl pk 34 4 (+/-) 6 22 ll hl pk 2 34 (+/-) 0 727
ll area 6593 (+/-) 1501 hl area 4393 (+/-) 843 5 ll hl area 1 56 (+/-) 0 468
%ll area 59 6 (+/-) 7 66 %hl area 40 4 (+/-) 7 66 Total Area 10985 4
ll cl 0 059 (+/-) 0 0088 hl cl 0 322 (+/-) 0 00732
0.050 0.100 0.150 0.200 0.250 0.300 0.350 0.400 0.450 0.500


RESULTS
H R 84 9 (+/-) 1 94 Condition standing RR Var 220 013
ll pk 46 6 (+/-) 8 61 hl pk 39 8 (+/-) 11 5 ll hl pk 1 37 (+/-) 0 653
ll area 5362 (+/-) 890 5 hl area 3634 (+/-) 363 2 ll hl area 1 5 (+/-) 0 362
%ll area 59 3 (+/-) 5 57 %hl area 40 7 (+/-) 5 57 Total Area 8995 17
ll cl 0 052 (+/-) 0 0055 hl cl 0 32 (+/-) 0 0153
0.050 0.100 0.150 0.200 0.250 0.300 0.350 0.400 0.450 0.500


RESULTS
H R 85 1 (+/-) 1 18 Condition supine RR Var 170 918
ll pk 22 1 (+/-) 8 87 hl pk 35 7 (+/-) 7 89 ll hl pk 0 642 (+/-) 0 276
ll area 2599 (+/-) 1466 hl area 8396 (+/-) 1323 ll hl area 0 317 (+/-) 0 186
%ll area 22 7 (+/-) 10 1 %hl area 77 3 (+/-) 10 1 Total Area 10994 5
ll cl 0 039 (+/-) 0 049 hl cl 0 299 (+/-) 0 0847
0.050 0.100 0.150 0.200 0.250 0.300 0.350 0.400 0.450 0.500


RESULTS
H R 88 1 (+/-) 1 75 Condition standing RR Var 285 588
ll pk 37 6 (+/-) 5 87 hl pk 30 2 (+/-) 4 8 ll hl pk 1 27 (+/-) 0 211
ll area 5035 (+/-) 1129 hl area 6697 (+/-) 1120 ll hl area 0 779 (+/-) 0 219
%ll area 42 9 (+/-) 7 38 %hl area 57 1 (+/-) 7 38 Total Area 11731 4
ll cl 0 079 (+/-) 0 042 hl cl 0 367 (+/-) 0 113
0.050 0.100 0.150 0.200 0.250 0.300 0.350 0.400 0.450 0.500

improvements in the response to orthostatic stress, the phi coefficient was calculated for these nominal data and resulted in $\phi = 0.71$.

The 20-minute supine power spectral recordings were compared with the 20-minute post-exercise supine recordings at baseline and 3-months in order to assess how participation in physical training might affect the recovery of the power spectral indices following the symptom-limited incremental cycle ergometer test. A total of 11 dependent variables were obtained from each spectral profile, and included: 1) average heart rate (HR); 2) low-frequency peak power (LP); 3) low-frequency area (LA); 4) low-frequency fractional power (PL); 5) low-frequency power central frequency (LC); 6) high-frequency peak power (HP); 7) high-frequency area (HA); 8) high-frequency fractional power (PH); 9) high-frequency power central frequency (HC); 10) LF:HF peak ratio (RP); and, 11) LF:HF area ratio (RA). The size of the subsequent design necessitated the use of two separate MANOVAs for statistical analysis; therefore, a three-way fixed effects MANOVA (GROUP X CONDITION X TIME) was used for the analysis of the HR, LP, LA, PL, and LC dependent variables, and another for the HP, HA, PH, HC, RP, and RA dependent variables. The first MANOVA revealed a main effect for CONDITION ($RaoR(5,13)=7.40$; $p<0.01$); however, post-hoc analysis of this main effect using a three-way ANOVA was significant for only the HR ($p<0.001$) and PL ($p<0.01$) variables. There were no further main effects or interactions for the HR, LP, LA, PL, and LC data; the GROUP X CONDITION X TIME interaction was non-significant at $Rao\ R(5,13)=0.131$; $p=0.982$. The second MANOVA used to identify differences in the HP, HA, PH, HC, RP, and RA variables, however, did not reveal any

significant main effects or interactions; the GROUP X CONDITION X TIME interaction for these dependent variables was non-significant at Rao R(6,12)=0.651; p=0.689.

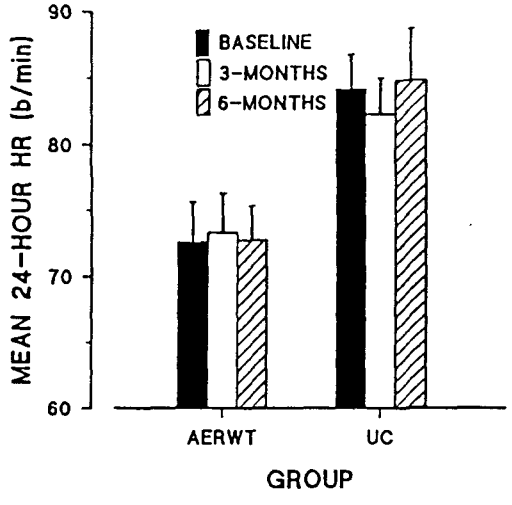
3.3.2 Time Domain 24-hour Ambulatory Holter Monitoring

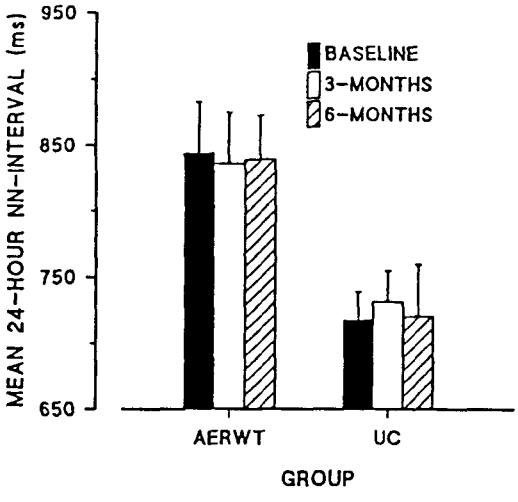
Ambulatory ECG monitoring was performed at baseline, 3-months, and 6-months in order to assess time domain parameters of HRV. As described previously, time domain statistics of HRV derived from an ambulatory ECG monitor can be classified into two distinct categories: 1) those which are derived from the differences between adjacent RR-intervals such as the SDNN-index, pNN50, and r-MSSD; and, 2) those derived directly from the intervals themselves such as the mean 24-hour heart rate and NN-interval, as well as the SDNN and SDANN. In the AERWT group, 24-hour holter monitoring was not performed at 3-months and 6-months in one patient due to hospitalization. In the UC group, one patient refused 24-hour holter monitoring on each occasion, and three patients did not participate at 6-months due to hospitalization, dropout, and assessment for cardiac transplantation respectively.

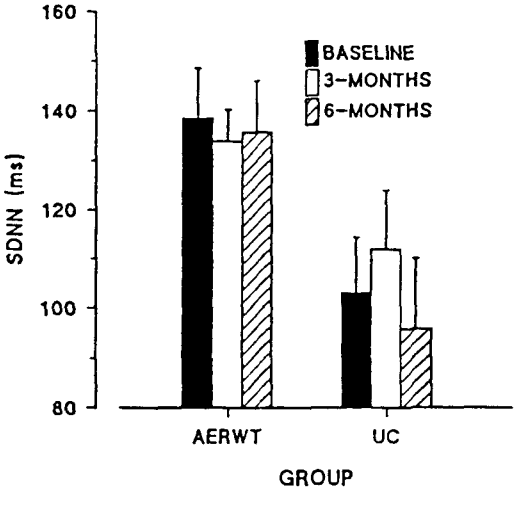
A two-way, fixed effects MANOVA was performed on the SDNN-index, pNN50, and r-MSSD change scores from baseline to 3-months, and from baseline to 6-months; the analysis revealed no significant main effects or interactions, although the GROUP X TIME interaction for this group of dependent measures approached statistical significance, Rao R (3,16)=2.79, p=0.074. These dependent measures are presented graphically in Figure 10. On an individual basis, the SDNN-index increased 22.9 ± 10% from baseline to 3-months (49.3 ± 4.31 to 58.3 ± 4.96 ms, N.S.), and 42.1 ± 23.4% from baseline to 6-months (49.3 ± 4.31

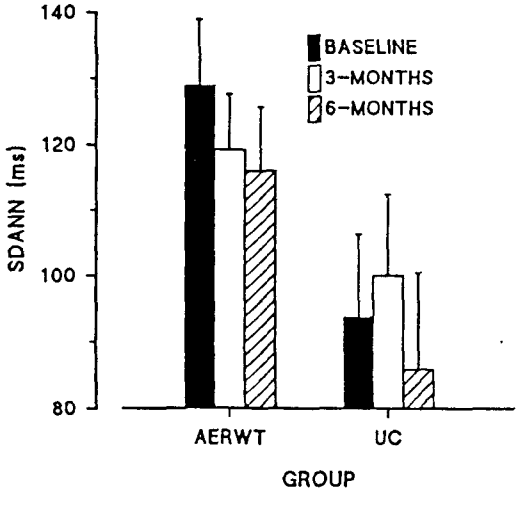
to 65.8 ± 9.33 ms, N.S.) in the AERWT group, compared to a 20.7 ± 13.1% increase (41.5 ± 3.75 to 50.2 ± 7.25ms, N.S.) and a 3.43 ± 5.03% decrease (41.5 ± 3.75 to 39.9 ± 3.87ms, N.S.) during the same time periods respectively in the UC group. In the AERWT group, the pNN50 increased by 44.4 ± 28.2% (9.27 ± 1.78 to 10.2 ± 2.56%, N.S.) between baseline and 3-months, and by 71.2 ± 50.3% (9.27 ± 1.71 to 14.6 ± 4.14%, N.S.) between baseline and 6-months. Alternatively, the UC group pNN50 values for the corresponding time periods revealed a 6.37 ± 17.6% increase (8.33 ± 1.87 to 8.94 ± 2.96%, N.S.) and 1.59 ± 17.1% increase (8.33 ± 1.87 to 6.51 ± 1.10%, N.S.) respectively. The r-MSSD increased 23.4 ± 13.8% (37.6 ± 3.56 to 46.5 ± 7.63ms, N.S.) and 35.9 ± 24.8% (37.6 ± 3.56 to 52.6 ± 11.9 ms, N.S.) in the AERWT group between the baseline/3-month, and baseline/6-month assessments respectively, contrasted to the UC group which demonstrated a 4.02 ± 9.1% increase (35.0 ± 4.54 to 37.6 ± 7.60ms, N.S.) and 2.73 ± 8.0% decrease (35.0 ± 4.54 to 32.6 ± 3.53ms, N.S.) during the same time periods.

A two-way fixed effects MANOVA was performed on the 24-hour mean HR, 24-hour mean NN-interval, SDNN, and SDANN change scores between baseline and 3-months, and between baseline and 6-months. The analysis revealed no significant main effects or interactions; the GROUP X TIME interaction was Rao R(4,15)=1.67, p=0.210. These dependent measures are presented in Figure 11. The 24-hour mean heart rate in the AERWT group increased 1.30 ± 1.98% (72.6 ± 3.02 to 73.3 ± 2.96 b/min, N.S.) between baseline and 3-months, and increased 0.79 ± 2.81% (72.6 ± 3.02 to 72.7 ± 2.61b/min, N.S) between baseline and 6-months. In the UC group, there was a 1.79 ± 1.01% decrease (84.2 ± 2.55 to

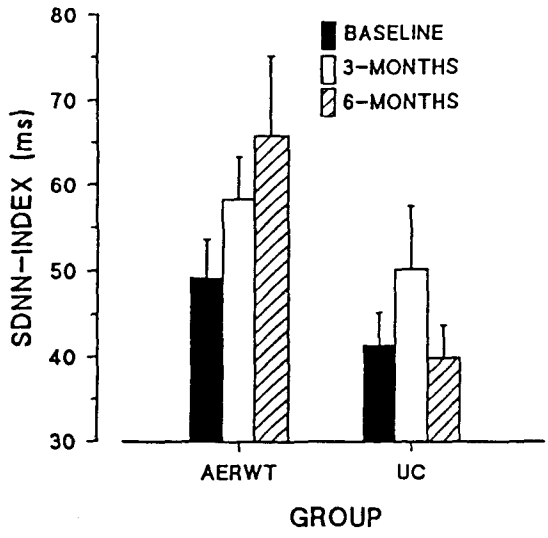

MEAN 24-HOUR HR (b/min)
90
80
70
60
BASELINE
3-MONTHS
6-MONTHS
AERWT
UC
GROUP

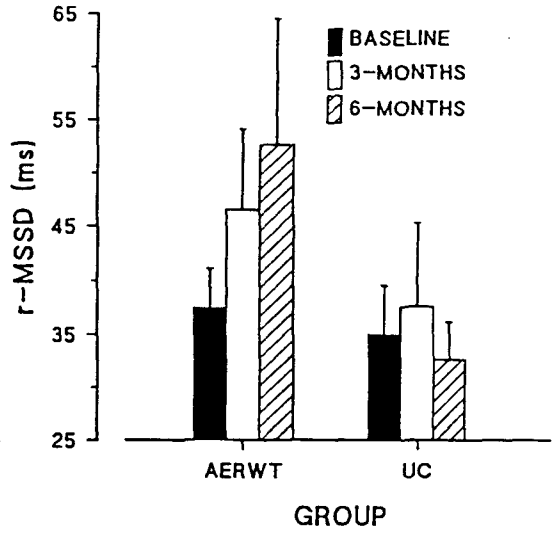

MEAN 24-HOUR NN-INTERVAL (ms)
950
850
750
650
BASELINE
3-MONTHS
6-MONTHS
AERWT
UC
GROUP

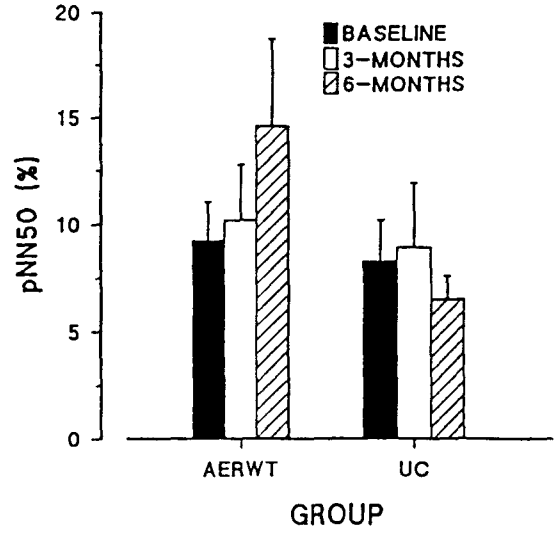

SDNN (ms)
160
140
120
100
80
BASELINE
3-MONTHS
6-MONTHS
AERWT
UC
GROUP


SDANN (ms)
140
120
100
80
BASELINE
3-MONTHS
6-MONTHS
AERWT
UC
GROUP

82.3 ± 2.69b/min, N.S.) in 24-hour mean heart rate from baseline to 3-months, and a 0.69 ± 3.58% increase (84.2 ± 2.55 to 84.8 ± 3.90b/min, N.S.) from baseline to 6-months. The AERWT group demonstrated a 0.87 ± 1.94% (844.1 ± 38.4 to 835.3 ± 39.3ms, N.S.) and a 0.011 ± 2.55% decrease (844.1 ± 38.4 to 838.8 ± 33.6ms, N.S.) in mean 24-hour NN-interval during the baseline/3-month and baseline/6-month assessments respectively. In contrast, the UC group realized a 1.90 ± 1.04% increase (717.4 ± 21.5 to 731.1 ± 23.4ms, N.S.) and a 0.23 ± 3.76% increase (717.4 ± 21.5 to 720.0 ± 39.0ms, N.S.) in mean 24-hour NN-interval during the baseline/3-month and baseline/6-month follow-up investigations. The SDNN of the AERWT group increased 0.59 ± 6.54% (138.6 ± 10.0 to 133.8 ± 6.35ms, N.S.) from baseline to 3-months, and 3.12 ± 10.5% (138.6 ± 10.0 to 135.6 ± 10.4, N.S.) from baseline to 6-months. This is contrasted to an 11.5 ± 11.5% increase (103.1 ± 11.3 to 111.8 ± 12.2ms, N.S.) in the UC group from baseline to 3-months, and a 6.93 ± 10.4% decrease (103.1 ± 11.3 to 95.8 ± 14.2ms, N.S.) in SDNN from baseline to 6-months. In the AERWT group, the SDANN decreased 3.50 ± 7.50% (128.9 ± 9.97 to 119.2 ± 8.38ms, N.S.) and 5.20 ± 9.30% (128.9 ± 9.97 to 116.0 ± 9.62ms, N.S.) between the baseline/3-month and baseline/6-month assessments respectively. Alternatively, in the UC group, there was a 10.6 ± 11.5% increase (93.8 ± 12.5 to 100.0 ± 12.4ms, N.S.) in SDANN from baseline to 3-months, and a 7.69 ± 11.4% reduction (93.8 ± 12.5 to 85.9 ± 14.5ms, N.S.) in SDANN from baseline to 6-months.


80
70
60
50
40
30
SDNN-INDEX (ms)
BASELINE
3-MONTHS
6-MONTHS
AERWT
UC
GROUP


65
55
45
35
25
r-MSSD (ms)
BASELINE
3-MONTHS
6-MONTHS
AERWT
UC
GROUP


20
15
10
5
0
pNN50 (%)
BASELINE
3-MONTHS
6-MONTHS
AERWT
UC
GROUP

4.0 DISCUSSION

4.1 Introduction

Congestive heart failure represents a clinical syndrome of staggering epidemiologic prevalence in the western world. Traditionally, the use of physical training as a means of improving functional status in populations of CHF patients has been contraindicated, but in recent years has received increasing attention (Bellardinelli et al., 1995; Hambrecht et al., 1995; McKelvie et al., 1995; Adamopoulos et al., 1992; Baigrie et al., 1992; Coats et al., 1992, 1990; Jetté et al., 1991; Arvan, 1988; Jugdutt et al., 1988; Sullivan et al., 1988; Conn et al., 1982; Lee et al., 1979). The rationale behind these investigations is that CHF, with the interpolated effects of physical deconditioning, could precipitate further disability and complications in clinical status. The consensus from both randomized and non-randomized studies in the literature is that patients can realize significant training effects without any deleterious effects upon cardiac function and subjective reports of symptoms. However, some findings are subect to speculation due to lack of randomized controlled designs, questionable statistical analysis, suitable follow-up procedures, and defined training periods.

It has been observed that congestive heart failure represents a clinical syndrome in which there is significant derangement in one or both limbs of the autonomic nervous system (Ferguson et al., 1990; Porter et al., 1990; Francis et al., 1985; Levine et al., 1982; Goldstein et al., 1975; Eckberg et al., 1971). Clinical evaluations of CHF patients have reported

reductions in baroreceptor sensitivity (BRS) in response to orthostatic stress, pronounced neurohumoral activation, and marked reductions in heart rate variability (HRV). A significant reduction in HRV, as is observed following acute myocardial infarction, has been associated with an increased risk of sudden cardiac death and increased morbidity and mortality (Kleiger et al., 1987). A return of vagal modulation, and subsequent increase in HRV, has been associated with a decrease of sudden cardiac death, via an increase in the fibrillation threshold (Bigger et al., 1988), and a re-organization of sympathovagal balance may indeed induce a cardioprotective effect by initiating a reduction in the sympathetic overexcitation which is typical of this disorder.

It has been demonstrated in the literature in normal healthy controls, and selected clinical populations, that physical training involving aerobic exercise represents an intervention which elicits favourable changes in sympathovagal balance via an increase in vagal modulation (Furlan et al., 1993; Coats et al., 1992; Dixon et al., 1992; Seals et al., 1989; Pagani et al., 1988). Despite these findings, the study by Coats et al. (1992) remains to be the only investigation in the literature to have observed aerobic training in CHF and its subsequent effects upon HRV indices. They found that participation in an 8-week home based cycling program induced a 19.2% and 51.3% increase in RR-variation and high-frequency power respectively, in addition to reducing low-frequency power by 21.2% and norepinephrine spillover by 16%. Although impressive results, there are some methodological concerns with this investigation which will be highlighted in an upcoming section.

Improvements in physiological variables, in addition to HRV indices, have the

potential to exert an enormous impact upon the life of the CHF patient. Increases in both functional capacity and muscular strength have the potential to increase their tolerance for strength-related ADL taks which previously were taxing, and translates into greater patient autonomy and quality-of-life. From the perspective of the autonomic nervous system, a return of vagal modulation in these patients has the potential to decrease morbidity and mortality.

4.2 Purpose

The purpose of this investigation was to examine the potential differences in autonomic nervous system adaptations, as assessed by heart rate variability techniques, between a group of stabilized CHF patients randomized to either a training group (aerobic+resistance) or a control group (usual care). In addition, the present investigation was undertaken in order to supplement the limited amount of literature in this area, and to improve upon methodological concerns inherent in their respective designs.

4.3 Symptom-Limited Incremental Cycle Ergometry Tests

4.3.1 Peak Relative Oxygen Uptake

The significant 19.2% increase in peak $\dot{V}O_2$ (ml/kg/min) demonstrated by the AERWT group is curiously similar to the improvements reported by the related investigations of Coats et al. (1990;1992) and Adamopoulos et al. (1992). Their patients increased peak oxygen uptake from 13.2 ± 0.9 to 15.6 ± 1.0 ml/kg/min ($p<0.001$), whereas the training group in the current investigation improved from 13.2 ± 0.5 to 15.5 ± 0.84 ml/kg/min ($p<0.05$). The increase of 19.2%, in comparison to other randomized investigations in the literature, is lower

than both the 22% and 31% increase in peak oxygen uptake by the patients of Jetté et al. (1991), and Hambrecht et al. (1995) respectively; however, as mentioned previously, the improvements noted in the 4-week trial of Jetté et al. (1991) could have been due to spontaneous recovery of ventricular function , and the results of Hambrecht and colleagues were reported after 6-months of physical training. Although there were no measurements of cardiac output, systemic vascular resistance, or peripheral blood flow, it is believed that the improvements made in peak oxygen uptake are a result of peripheral mechanisms; more definitive proof, however, is warranted in order to substantiate this claim and represents a further research direction..

4.3.2 Maximal Exercise Duration and Maximal Power Output

The significant increases in peak oxygen uptake realized by the AERWT group were coupled with non-significant gains of 20.6 ± 5.9% (N.S.) and 25.4 ± 5.5% (N.S.) in exercise test duration and maximal power output respectively, compared to corresponding increases of 5.2 ± 6.1% (N.S.) and 8.79 ± 5.8% (N.S.) respectively by the UC group. The increases noted in the AERWT group, although non-significant, are in accordance with results from other investigations in the literature which have reported improvements in exercise duration between 18.5% and 26% (Hambrecht et al., 1995; Coats et al., 1990; 1992), and improvements of between 11.6 and 21% in maximal power output (Belardinelli et al., 1995; Baigrie et al., 1992; Jetté et al., 1991). Interestingly, in comparison to other studies in the literature involving populations of normal cardiac patients, the baseline maximal power output demonstrated by the CHF patients in the present investigation is only 34% of the maximal

power output demonstrated by the cardiac patients of McCartney et al. (1991) (62 Watts vs. 180 Watts); however, it is likely that this discrepancy is due to the fact that the training group in the latter investigation was comprised exclusively of male subjects.

4.3.3 Anaerobic Threshold

Perhaps the most surprising result was the lack of improvement in anaerobic threshold in the training group. It was hypothesized that the training stimulus used in this investigation would approximate that of interval training, and would therefore be more ADL specific where short bouts of activity were required. Nonetheless, the training group realized non-significant gains of 4.9 ± 3.7% (55.2 ± 2.9 to 57.7 ± 3.4% $\dot{V}O_2$, N.S), as did the control group with an increase of 5.8 ± 5.1% (47.4 ± 2.7 to 49.2 ± 2.9% $\dot{V}O_2$). In comparison to other studies in the literature, the CHF patients in the randomized study of Hambrecht et al. (1995) demonstrated a 23% increase in anaerobic threshold following 6-months participation in a cycling program; in addition, the non-randomized training studies of both Baigrie et al. (1992) and Belardinelli et al. (1995) demonstrated increases of 10.9% and 20% respectively in their groups of CHF patients. It is unclear why similar, but non-significant increases in anaerobic threshold were noted in both groups in the present investigation.

4.3.4 Expired Ventilation, Expired Carbon Dioxide, and $\dot{V}E:\dot{V}CO_2$ Ratio

The ventilatory indices of expired ventilation, expired carbon dioxide, and the ratio of $\dot{V}E:\dot{V}CO_2$ were assessed in order to track improvements as a result of participation in the physical training regimen. The reductions noted in these ventilatory indices by the training group, however, only approached statistical significance ($p=0.075$). Although non-significant,

the training group demonstrated reductions in both expired ventilation and expired carbon dioxide at submaximal and maximal workloads during symptom-limited incremental cycle ergometry, whereas the control group either remained unchanged, or realized slight increases in these ventilatory indices. The reductions in expired ventilation of 5.12 ± 4.64% (N.S.) and 12.8 ± 2.92% (N.S.) during WL2 and WL3 respectively in the AERWT group, can be compared to the 10.5% reduction in maximal expired ventilation realized by the CHF subjects of Coats et al. (1992). Interestingly, in the current investigation, the reductions in expired carbon dioxide paralleled those of expired ventilation, with reductions of 8.36 ± 4.73% and 10.7 ± 2.84% for WL2 and WL3 respectively. The trend in these indices, although statistically non-significant, has practical implications for the CHF patient. A reduction in the perceived ventilatory stress of a particular workload has the potential to translate into a greater tolerance for an activity of similar intensity.

4.3.5 Double Product During Progressive Stages of Modified Bruce Protocol

The results from the present investigation failed to demonstrate any statistically significant alterations in heart rate, systolic pressure, or double product as a result of participation in the training intervention. The lack of changes in these indices would suggest that the adaptations noted in the AERWT group were likely due to changes taking place at the peripheral level. There have been conflicting reports in the literature with respect to changes in double product following exercise training in CHF patients. Both Belardinelli et al. (1995) and Jetté et al. (1991) found that following their respective training periods that the double products during both submaximal and maximal workloads remained unchanged. In

contrast, the results of Baigrie et al. (1992) and Coats et al. (1990) demonstrated that the double products during maximal and submaximal workloads respectively, were significantly reduced following their training regimens.

4.4 Dynamic Muscle Strength

In comparison to other studies in the literature concerned with resistance training in populations of normal cardiac patients, the current investigation provides some interesting contrasts. An investigation conducted by McCartney et al. (1991) closely approximates the testing protocol of the present study. They randomized 10 patients to a combined aerobic and resistance training regimen, and another 8 patients to an aerobic training only group. Although their results could be somewhat inflated due to the fact that the patients were all males, the baseline strength measure of the patients in the current investigation approximated 47%, 74%, and 76% of the baseline results of McCartney et al. (1991) for the SAC, SKE, and SLP respectively. In terms of improvements in dynamic muscle strength noted by the combined training group of McCartney et al. (1991), they increased SAC, SKE, and SLP by 42%, 25%, and 21% respectively.

In the present investigation, the training group realized a significant 19.6 ± 6% increase in single-arm curl following the 3-month supervised training period; this finding is the first reported increase in muscle strength demonstrated by this population as a result of a resistance training program. The implications of this finding are equally as important, as it has been demonstrated that CHF patients can increase peripheral muscle strength without any increases in symptoms or deleterious effects in left-ventricular function. Of major

disappointment were the results from both the single-leg press and single-knee extension exercises. It was hypothesized that the leg press would be a more useful indicator of improvement since it is a closed-chain kinetic exercise and more closely resembles functional activity (i.e. stair climbing). The inability of SLP to demonstrate significance could be due to two reasons: 1) the fact that the original testing apparatus had to be replaced due to damage, and follow-up assessments would be affected due to the new testing device; and, 2) improper control of seat distance and knee joint angle, thereby giving a more mechanically advantageous lever position to some moreso than others. Perhaps another reason why the SLP failed to attain significance is the failure to stratify patients according to their baseline strength measures; those with high pre-test values, therefore, would have less to gain than individuals with lower pre-test measures. The SKE scores of the AERWT group did increase by 8.1 ± 5.0% (39.8 ± 4.96 to 43.2 ± 5.29 kg, N.S); although this did not achieve statistical significance, it appears to be clinically significant when compared to the decrease of 0.85 ± 2.5% (46.0 ± 5.0 to 45.7 ± 5.2 kg, N.S.) demonstrated by the UC group.

4.5 Six-Minute Walk Test

The baseline, 3-month, and 6-month evaluations of Six-Minute Walk distance and walk work, although non-significant, demonstrated an interesting pattern. These indices remained relatively unchanged between baseline and 6-months in the UC group; however, the AERWT group realized an initial improvement in both maximal distance and walk-work at the conclusion of the 3-month supervised training period, whereas the 6-month values had returned to baseline levels. This pattern may be due to lack of compliance with the desired

training intensity of the home-exercise training program, and lends support to evidence that supervised training programs demonstrate larger gains in physiological indices. The only investigation in the literature to use the Six-Minute Walk test to assess the efficacy of physical training in CHF was performed by Baigrie et al. (1992); although they reported a 17.6% increase in walk distance following 16-weeks of a supervised walking program, it was unclear from the report whether this result reached statistical significance, and the intensity, frequency, and duration of the training stimulus was not mentioned.

4.6 Radionuclide Ventriculography Assessment

The results from the resting radionuclide ventriculography assessements are inconclusive, and do not provide much information regarding changes in central function. It was not anticipated that there would be any changes in LVEF, however, both the AERWT and UC groups realized similar increases in LVEF of 6.3 ± 3.0% and 10.1 ± 4.9% respectively. What is of particular concern is the coefficient of variation of the measurement tool (± 10%) which probably influenced the results of this dependent variable. Despite the baseline variation in LVEF between the AERWT and UC groups, it was hypothesized that these indices would remain unchanged, or show modest increases in the intervention group rather than demonstrating spontaneous improvement in the group of controls.

4.7 Heart Rate Variability Indices

4.7.1 Frequency Domain

The evaluation of HRV using power spectral analysis in acute studies of supine, standing, and post-exercise conditions failed to demonstrate any conclusive evidence that,

similar to healthy normal controls, there is an increase in vagal modulation of the HRV power spectrum, and improvements in baroreceptor sensitivity (BRS) following a regimen of physical training undertaken by CHF patients. The results from the orthostatic evaluations were interesting, as baroreceptor sensitivity appeared to be improved in several patients in the AERWT group upon qualitative evaluation by two independent investigators; however, these results were not statistically significant. In contrast, there were only two individuals (N.S.) in the UC group that demonstrated improvements in their response to orthostatic stress.

In the current investigation, comparisons of the power spectra from supine to standing were performed in order to identify the baroreceptor response to an orthostatic stress. While blood pressure was recorded via auscultation, it really did not provide any useful information concerning the status of the baroreceptor probably as a result of chronic dehydration due to medication use. Of particular concern, of course, was the small sample size used in these evaluations; rhythm disturbances plagued the data of some individuals and prevented them from being assessed statistically. In addition, the different patterns which emerged at baseline between the supine and standing spectral profiles proved costly in terms of accurate analysis using parametric statistics. These observations are, undoubtedly, a phenomenon of working with this particular population. In some individuals there was a relatively normal power spectral response to standing, whereas in others there were abnormal responses of the LF-power to orthostasis and even a flattening of the autospectrum in yet another smaller group.

It was interesting to note there were some individuals with a flattened power spectrum during the resting supine condition. The question remains, however, as to the etiology of this

observation. Could this phenomenon be a factor of the heart operating on the descending limb of the Starling curve and that the inotropic state of the heart is being supported by circulating catecholamines due to the loss of neural control? The HRV spectral profile of patients with severe CHF have been found by some investigators to be similar to those of patients with diabetic autonomic neuropathy (DAN) and heart transplantation; a progressive autonomic denervation has been suggested by these authors to explain the reductions in HRV observed in CHF patients. The flattened autospectral profiles observed in some of the patients during the resting supine conditions are also similar to those observed during steady-state exercise in both normal healthy individuals, and in various clinical populations; it has been forwarded by some investigators that this phenomenon is due to the support of the heart and circulation by circulating catecholamines during physical activity (Dixon et al., 1992). In addition, this attenuated spectral profile could be due to a small signal to noise ratio, as a barely detectable efferent signal could be driving the heart. Also, the advancing age of the patients, coupled with a progressive underlying autonomic neuropathy could be affecting the quality of the data. Nonetheless, the differences found in the resting supine power spectra, and the response to orthostatic stress, reinforce the fact that CHF is a complex clinical syndrome which proceeds on somewhat of a continuum. The observation of these abnormal responses would be interpreted by Fallen et al. (1996) to represent those individuals with the greatest decrement in ventricular function and more pronounced neurohumoral activation.

As for the comparison of HRV frequency domain indices' between the resting supine and post-exercise supine conditions, there was no evidence to suggest that there were

improvements in the recovery of these indices as a result of training, which has been demonstrated previously in other investigations involving normal healthy controls (Dixon et al., 1992). None of the 11 dependent variables from the power spectra demonstrated any significant differences between the baseline and 3-month assessments for either group. It was hypothesized that the high-frequency indices would return to their pre-exercise supine levels within a shorter duration of time as a result of participation in the exercise training regimen; it was also expected that there would be corresponding changes in the low-frequency indices as a result of the combined modulation of this region. In addition, it was believed that significant alterations in the exercise test ventilation indices would be able to be detected by changes in the high-frequency variables of the resting supine condition via alterations in the contribution of the respiratory sinus arrhythmia to the power spectrum. The results from the ventilation indices suggested a reduction in ventilatory drive for the same relative workload in the AERWT group, although this was not reflected at resting levels in the spectral profiles, as the HF-power central frequency remained relatively constant.

4.7.2 Time Domain

None of the time domain HRV indices in the AERWT group demonstrated significant changes from baseline to 6-months; although the indices derived from differences between intervals (i.e. SDNN-Index, pNN50, and r-MSSD) displayed a progressively increasing trend which approached statistical significance ($p=0.074$), whereas the indices derived from the intervals themselves (24-hr HR, 24-hr NN-interval, SDNN, and SDANN) remained relatively fixed for the duration of the present investigation. It is this similar increasing trend of the

former indices which is of particular interest. The SDNN-index, pNN50, and r-MSSD reflect vagal modulation of the heart rate and are highly correlated with HF- power. The SDNN, an indicator of total power, however, manages to stay relatively fixed throughout the follow-up period in both groups. Therefore, while vagal modulation may gradually be returning, sympathetic activity may remain unchanged. This may have certain application to the 'saturating overstimulation' hypothesis offerred by Malik et al. (1993); despite a return of vagal modulation, as suggested by the increases in SDNN-index, pNN50, and r-MSSD, the underlying 'sympathetic binge' of CHF prevented the manifestation of vagal effects. Perhaps the conclusions of Malik et al. (1993) could be applicable to the reduced HRV observed in CHF; the 'saturating' chronic stimulation of the sympathetic branch could lead to a progressive loss in heart rate and baroreceptor modulation, and would explain the sympathetic derangement characteristic to CHF, and the inability to be effectively modulated through various therapeutic interventions.

In effect, what is being demonstrated in the results of the present investigation is a contrast of two specific theories; the 'saturating overstimulation' hypothesis offered by Malik et al. (1993), juxtaposed with the 'accentuated antagonism' hypothesis of Levy et al. (1969). The 'accentuated antagonism' hypothesis would suggest that any amount of vagal stimulation elicited in the midst of a predominant sympathetic signal would result in marked reductions in heart rate. However, the inability to demonstrate a training bradycardia in the AERWT group lends support to the notion that perhaps not enough of the vagal signal was allowed to be expressed due to the degree of background sympathetic stimulation in this population.

The lack of training bradycardia was surprising, as certain investigations in the literature have identified significant reductions in resting heart rate following exercise training in groups of CHF patients (Belardinelli et al., 1995; Hambrecht et al., 1995; Baigrie et al., 1992; Sullivan et al., 1988; Lee et al., 1979).

4.8 Proposed Mechanisms for Reduced HRV in CHF

As mentioned previously, investigations in the literature which have addressed HRV measures, autonomic function, neurohormonal status, and baroreceptor sensitivity, all agree that there is both parasympathetic and sympathetic derangement in congestive heart failure. However, the mechanism(s) by which this cascade of autonomic dysfunction proceeds is speculative at best. There are, however, several proposed mechanisms for the chronology of events on the heart failure continuum. To implicate a central, neurohormonal, or neural mechanism in isolation is probably simplistic, for this complex clinical syndrome is most likely multifactorial in origin. The augmented sympathetic drive, which is elicited as a result of compensatory mechanisms in the acute stages of heart failure, serves to support the inotropic state of the heart, as well as the circulation. However, this chronic adrenergic stimulation has been suggested to exert deleterious effects upon long-term neural control of the heart; it has been demonstrated that the neural drive to the SA-node is greatly reduced and potentially lost, which would result in the heart behaving like somewhat of a metronome. Therefore, the inhibition of vagal modulation of heart rate due to increased sympathetic stimulation, in addition to a progressive loss in neural drive to the SA-node, has the potential to reduce HRV substantially. In addition, it has been suggested that the reduction in myocardial

norepinephrine content in CHF is associated with a decrease in sympathetic neural endings, coupled with an impaired reuptake of norepinephrine by synaptic endings. A chronic increase in norepinephrine spillover, therefore, has been implicated in causing primary organ damage.

The fact that some investigators have identified similarities between the spectral profiles of patients with diabetic autonomic neuropathy, heart transplantation, and severe CHF have led these investigators to implicate a progressive autonomic denervation to explain the reduction in HRV observed in CHF patients. It has been proposed that with the loss of neural control of the heart that circulating catecholamines support the heart and circulation. Fallen (1996) (personal communication) hypothesizes that the progression of diminished HRV in CHF is a function of three distinct events: 1) a loss of baroreceptor sensitivity precipitates; 2) an increase in circulating catecholamines; which, 3) results in changes to the autonomic nervous system as expressed by a reduction in HRV indices. Simplistically, the theory offerred by Fallen (1996) has been incorporated into the rationale of the present investigation, although working in reverse. It was hypothesized that by trying to induce autonomic changes, using a physical training stimulus, that the amount of circulating catecholamines would be altered and there would be improvements in baroreceptor sensitivity.

Another theory to explain the reduced HRV in CHF concerns the actual architecture and orientation of the vagal inputs to SA-node, and the nodal region itself. It is proposed by this investigator that the chronic increases in right-atrial pressure characteristic to CHF could be responsible for the desensitization of vagal inputs, since the vagal autonomic inputs are localized to this region; it could very well be that chronic pressure overload of the right atrium

leads to a permanent deformation of the nodal region which is unable to be reversed. This hypothesis, however, remains to be investigated and represents a further area of research.

4.9 Present Investigation vs. Coats et al. (1992)

The relative intensity of the aerobic exercise stimulus used in the current investigation is in accordance with other investigations in the literature involving CHF patients; however, the addition of a resistance training component and its subsequent effects upon sympathovagal balance represents a new direction in the rehabilitation of the CHF patient. The only investigations of exercise training in CHF to measure changes in sympathovagal balance have been the related works of Coats et al. (1992) and Adamopoulos et al. (1992). In comparison, the present investigation has demonstrated identical significant gains in peak oxygen uptake as the patients of Coats et al. (1992), and improvements in exercise duration of similar magnitude, despite being non-significant. The ventilation indices in the current study suggested a decrease in relative ventilatory effort per workload in accordance with the results of Coats et al. (1992); however, the results only approached statistical significance ($p=0.075$). In addition, the present investigation failed to demonstrate significant changes in double product during progressive cycle ergometry, whereas the patients of Coats et al. (1992) realized significant reductions in submaximal double products during similar activity. Some apparent differences between this investigation and that of Coats et al. (1992) and Adamopoulos et al. (1992) include: 1) their program consisted of 8-weeks of home based training; 2) their design was a controlled-crossover design; 3) they did not measure left-ventricular function post-training to evaluate the safety of the training stimulus, despite a high

volume of training; 4) there was no assessment of changes in baroreceptor sensitivity in response to orthostatic stress as a result of training; 5) the LF and HF frequency domain indices were derived from approximately 8-minutes of supine recording; and, 6) although 24-hour holter monitoring was performed by Coats et al. (1992), they did not report any time domain statistics; however, the related study by Adamopoulos et al. (1992) revealed a 21% increase in SDNN following participation in the exercise training program. The investigation conducted by Coats et al. (1992) did, however, measure norepinephrine spillover kinetics in order to supplement the information provide by the HRV indices, as well as both cardiac output and peripheral vascular resistance in order to distinguish between central and peripheral adaptations to physical training. Of particular interest is the fact that despite the significant shifts away from sympathetic predominance toward enhanced vagal activity after training in these investigations, that the resting heart rate of patients remained unchanged.

Although similar increases in peak oxygen uptake were realized between the current investigation and that of Coats et al. (1990; 1992) and Adamopoulos et al. (1992), there is some question as to whether the combined training stimulus of aerobic and resistance training had any deleterious outcome on the HRV parameters. It has been suggested that both Type-III and Type-IV muscle afferents are preferentially localized to fast-twitch mucle fibres (Piepoli et al., 1996;1994). Due to the combined aerobic and resistance stimuli in the present investigation, we are stimulating changes in the areas of both fast-twitch (resistance) and slow-twitch (aerobic) fibres. Therefore, it could be that the increase in FT fibre area, as a result of resistance training, potentiates sympathetic feedback and hence contributes to the

modulation of LF-power; whereas aerobically trained normals and the CHF patients of Coats et al. (1990; 1992) and Adamopoulos et al. (1992), increase the area of slow-twitch fibres, increase HF-power, and reduce LF-power. Did the addition of resistance training in the present investigation take away from the potential increases in vagal modulation as a result of this selective localization of muscle afferents? While increases in muscle cross-sectional area, as a result of resistance training, provide increases in skeletal muscle blood-flow, reductions in peripheral resistance, and increased contribution of the muscle pump to venous return, this could have had deleterious consequences upon HRV via a potentiation of the ergoreflex via Type III and IV muscle afferents; this hypothesis, however, remains to be investigated.

4.10 Possible Influence of Medications on HRV Indices

A potential confounding variable of the studies which have attempted to relate HRV measures to the level of autonomic activity in CHF has been the use of medications by these patients. Investigations in the literature have attempted to control for study medications by either a wash-out period prior to the investigation, or controlling for the effects of a single medication across subjects. The pharmacological management of CHF typically includes an angiotensin-converting enzyme inhibitor (ACE-I), digoxin, and a diuretic either alone or in combination. Unfortunately, these medications have been found to impart significant effects upon the autonomic nervous system, and have been found to favourably influence heart rate variability (Brouwer et al., 1995; Krum et al., 1995; Binkley et al., 1993; Flapan et al., 1992). However, witholding necessary medications, despite being in a controlled environment, raises

ethical concerns.

5.0 SUMMARY AND RECOMMENDATIONS

5.1 Summary

Historically, exercise rehabilitation of the CHF patient has been contraindicated due to concerns with eliciting an increase in symptoms and adverse effects in ventricular function. Recently, there have been a number of investigations which have challenged current dogma and have reported increases in physiological variables without any deleterious effects. The rationale behind these investigations is that inactivity, coupled with deconditioning could potentiate both morbidity and mortality in this population.

The effects of exercise training upon the autonomic nervous system, and more specifically, heart rate variability indices have been well documented in populations of normal healthy individuals. Only two related studies, however, have examined the effects of exercise training upon the heart rate variability indices of CHF patients. Therefore, it was the purpose of this investigation to further the information in this area, and to improve upon some of the methodological concerns of other studies in the literature.

Selected heart failure patients are able to achieve significant improvements in both peak oxygen uptake and muscle strength without any untoward changes in ventricular function, symptoms, or heart rate variability indices. The present investigation is the first of its kind to demonstrate that CHF patients can increase peripheral muscle strength as a result of an exercise training regimen consisting of both aerobic and resistive exercise, and is likely

to have beneficial effects upon the performance of strength-related ADL tasks. The ventilation indices of the training group demonstrated powerful trends, however, the reductions noted in this group were non-significant. The implications of a reduction in ventilatory drive and therefore perceived effort, allow CHF patients to tolerate activities previously found to be taxing.

The present investigation revealed some evidence to suggest that exercise training in selected populations of CHF patients results in favourable changes in vagal modulation and baroreceptor sensitivity; however, unike previous studies in the literature using normal healthy populations and CHF populations, the present investigation failed to note any significant alterations in HRV as a result of exercise training. The lack of significant findings in both the frequency and time domain HRV data could indicate that perhaps the autonomic dysfunction is so widespread and rampant in CHF that we cannot induce alterations through training as would be demonstrated in normal, healthy controls; however, it could also mean that the investigation was underpowered. In effect, these findings reinforce the hypothesis that the heart is the 'slave' of the periphery, and that due to the progressive lack of neural control of both the heart and circulation, in addition to an impairment in pump function, that the only effective means of improving physiological variables is through changes at the peripheral level.

The results of the current investigation have brought forth a number of questions: 1) was the intensity of the exercise stimulus indeed sufficient to induce the anticipated changes in sympathovagal balance?; 2) did the addition of the resistance training component take

anything away from the autonomic adaptations demonstrated in other investigations consisting of only aerobic exercise?; and, 3) was the supervised training period of sufficient duration in order to elicit the required stimulus?

5.2 Recommendations

A number of things could be done to improve future investigations of this nature. First of all, a power analysis may reveal that an additional number of patients would be required in order to demonstrate significant findings in the HRV and physiological variables. In terms of the assessment of dynamic muscle strength in this population, follow-up assessments of dynamic muscle strength should include the performance of successive repetitions to failure using baseline 1-RMs for each of the SAC, SLP, and SKE in order to observe improvements in muscular endurance. Although it has never been done in any previous investigation involving this population, perhaps CHF patients can be matched according to a time domain HRV variable such as SDNN or r-MSSD prior to randomization in order to control for homogeneity of groups. In addition, the use of a 'gold standard' in terms of autonomic testing such as neck suction, muscle sympathetic nerve activity (MSNA), or a phenylephrine blood pressure challenge could be used in order to quantify the autonomic response of the patients and substantiate the HRV findings. The inference of improvements in baroreceptor sensitivity to orthostatic stress using HRV was interesting; however, if the HRV indices were coupled with blood-pressure variability (BPV) measures via 'cross spectral analysis,' the sympathovagal interactions in these patients could be more accurately observed and assessed and could be monitored upon follow-up investigations. Finally, in order to

substantiate the central versus peripheral hypotheses explaining adaptations to physical training in CHF, both central and peripheral hemodynamic variables should be measured in order to elucidate the origin of these changes.

REFERENCES

Adamopoulos, S., Coats, A.J.S., Brunotte, F., Arnolda, L., et al. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. Journal of the American College of Cardiology, 21: 1101-6, 1993.

Adamopoulos, S., Piepoli, M., McCance, A., Bernardi, L., et al. Comparison of different methods for assessing sympathovagal balance in chronic congestive heart failure secondary to coronary artery disease. American Journal of Cardiology, 70: 1576-1582, 1992.

Akselrod, S., Gordon, D., Ubel, F.A., Barger, A., and R.J. Cohen. Power spectrum analysis of heart rate fluctuations: a quantitative probe of beat-to-beat cardiovascular control. Science, 213: 220-222, 1981.

Akselrod, S., Gordon, D., Madwed, J.B., Snidman, N.C., et al. Hemodynamic regulation: investigation by spectral analysis. American Journal of Physiology, 249: H867-H875, 1985.

American College of Sports Medicine. Resource Manual for Guidelines for Exercise Testing and Prescription (2nd ed.). Philadelphia: Lea & Febiger, 1993.

Appel, M.L., Berger, R. Saul, J.P., Smith, J.M., et al. Beat to beat variability in cardiovascular variables: noise or music? Journal of American College of Cardiology, 14: 1139-48, 1989.

Arai, Y., Saul, J.P., Albrecht, P., Hartley, L.H., et al. Modulation of cardiac autonomic activity during and immediately after exercise. American Journal of Physiology, 256: H132-H141, 1989.

Arvan, S. Exercise performance of the high risk acute myocardial infarction patient after cardiac rehabilitation. American Journal of Cardiology, 62: 197-201, 1988.

Astrand, P.O., and K. Rodahl. Textbook of Work Physiology: Physiological Bases of Exercise (3rd ed.): Ch. 5. McGraw-Hill: New York, 1986.

Baigrie, R.S., Myers, M.G., Kavanagh, T., and G. Guyatt. Benefits of physical training in patients with heart failure. (Abstract) Canadian Journal of Cardiology, 8 (Suppl.B): 107B, 1992.

Belardinelli, R., Georgiou, D., Scocco, V., Barstow, T.J., et al. Low intensity exercise training in patients with chronic heart failure. Journal of the American College of Cardiology, 26: 975-82, 1995.

Bellavere, F., Balzani, I., DeMasi, G., Carraro, M., et al. Power spectral analysis of HRV improves assessment of diabetic cardiac autonomic neuropathy. Diabetes, 41: 633-640, 1992.

Benn, S.J., McCartney, N., and R.S. McKelvie. Circulatory responses to weight lifting, walking, and stair climbing in older males. Journal of the American Geriatrics Society, 44: 121-125, 1996.

Bernardi, L., Salvucci, F., Suardi, R., Solda, P.L., et al. Evidence for an intrinsic mechanism regulating heart rate variability in the transplanted and the intact heart during submaximal dynamic exercise? Cardiovascular Research, 24: 969-981, 1990.

Berne, R.M., and M.N. Levy. Cardiovascular Physiology (6th ed.): Ch. 4, 10, 12. Mosby: St. Louis, 1992.

Bigger, J.T., Kleiger, R.E., Fleiss, J.L., Rolnitzky, L.M., et al. Components of heart rate variability measured during healing of acute myocardial infarction. American Journal of Cardiology, 61:208-215, 1988.

Bigger J.T., Fleiss, J.L., Steinman, R.C., Rolnitzky L.M., et al. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation, 85: 164-171, 1992.

Bigger, J.T., Fleiss, J.L., Rolnitzky, L.M., Steinman, R.C., et al. Time course of recovery of heart period variability after myocardial infarction. Journal of American College of Cardiology, 18: 1643-1649, 1991.

Binkley, P.F., Haas, G.J., Starling, R.C., et al. Sustained augmentation of parasympathetic tone with angiotensin converting enzyme inhibition in patients with congestive heart failure. Journal of the American College of Cardiology, 21: 655-661, 1993.

Binkley, P.F., Nunziatta, E., Haas, G.J., Wadwa, P., et al. Autonomic response to baroreceptor unloading vs. loading in congestive heart failure: definition by analysis of heart rate variability. (Abstract). Clinical Research, 39: 231A, 1991.

Bittner, V., Weiner, D.H., Yusuf, S., Rogers, W.J., et al. Prediction of mortality and morbidity with a Six Minute Walk Test in patients with left ventricular dysfunction. JAMA, 270: 1702-1707,1993.

Bohm, M., LaRosee, K., Schwinger, R.H., and E. Erdmann. Evidence for reduction of norepinephrine uptake sites in the failing human heart. Journal of the American College of Cardiology, 25: 146-153, 1995.

Bonow, R.O., and J.E. Udelson. Left ventricular diastolic dysfunction as a cause of congestive heart failure: mechanisms and management. Annals of Internal Medicine, 117: 502-510, 1992.

Braunwald, E.G. (ed.). Heart Disease: A Textbook of Cardiovascular Medicine (4th ed.): Ch 13, 38. W.B. Saunders: Philadelphia, 1992.

Bristow, M.R., et al. ß1 and ß2 adrenergic-receptor subpopulations in non-failing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective ß1 receptor down-regulation in heart failure. Circulation Research, 59: 297, 1986.

Brophy, J.M. Epidemiology of congestive heart failure: Canadian data from 1970 to 1989. Canadian Journal of Cardiology, 8: 495-498, 1992.

Brouwer, J., vanVeldhuisen, D.J., Man, A.J., Dunselman, P.H., et al. Heart rate variability in patients with mild to moderate heart failure: effects of neurohumoral modulation by digoxin and ibopamine. Journal of the American College of Cardiology, 26: 983-90, 1995.

Brown, A.B., McCartney, N., and D.G. Sale. Positive adaptations to weightlifting training in the elderly. Journal of Applied Physiology, 69: 1725-1733, 1990.

Brown, T.E., Beightol, L.A., Koh, J., and D.L. Eckberg. Important influence of respiration on human RR-interval power spectra is largely ignored. Journal of Applied Physiology, 75: 2310-2317, 1993.

Buller, N.P., and P.A. Poole-Wilson. Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. British Heart Journal, 63: 281-283, 1990.

Burch, G.E., and N.P. DePasquale. Potentials and limitations of patients after myocardial infarction. American Heart Journal, 72: 830, 1966.

Casolo, G., Balli, E., Taddei, T., Amuhasi, J., et al. Decreased spontaneous heart rate variability in congestive heart failure. American Journal of Cardiology, 64: 1162-1167, 1990.

Casolo, G., Balli, E., Fazi, A., Gori, C., et al. Twenty-four-hour spectral analysis of heart rate variability in congestive heart failure secondary to coronary artery disease. American Journal of Cardiology, 67: 1154-1158, 1991.

Cerutti, S., Bianchi, A.M., and L.T. Mainardi. Spectral Analysis of the Heart Rate Variability Signal. *In Heart Rate Variability, M.Malik & A.J. Camm (eds.).* Armonk: Futura, 1995. Ch.5, pp.63-74.

Coats, A.J.S., Adamopoulos, S., Radaelli, A., McCance, A., et al. Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation, and autonomic function. Circulation, 85: 2119-2131, 1992.

Coats, A.J.S., Adamopoulos, S., Meyer, T.E., Conway, J., et al. Effects of physical training in chronic heart failure. Lancet, 335: 63-66, 1990.

Cohn, J.N., Levine, T.B., Olivari, M.T., Garberg, V., et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. New England Journal of Medicine, 311: 819-823, 1984.

Conn, E.H., Williams, R.S., and A.G. Wallace. Exercise responses before and after physical conditioning in patients with severely depressed left ventricular function. American Journal of Cardiology, 49: 296-300, 1982.

Cripps, T.R., Malik, M., Farrell, T.G., and A.J. Camm. Prognostic value of reduced heart rate variability after myocardial infarction: clinical evaluation of a new analysis method. British Heart Journal, 65: 14-19, 1991.

Deedwania, P.C. Prevalence and prognosis of heart failure. Cardiology Clinics, 12: 1-8, 1994.

Dixon, E.M., Kamath, M.V., McCartney, N., and E.L. Fallen. Neural regulation of heart rate variability in endurance athletes and sedentary controls. Cardiovascular Research, 26: 713-719, 1992.

Drexler, H., Riede, U., Munzel, T., Konig, H., et al. Alterations of skeletal muscle in chronic heart failure. Circulation, 85: 1751-1759, 1992.

Eckberg, D.L. Human sinus arrythmia as an index of vagal cardiac outflow. Journal of Applied Physiology, 54, 961-966, 1983.

Eckberg, D.L., Drabinsky, M., and E. Braunwald. Defective cardiac parasympathetic control in patients with heart disease. New England Journal of Medicine, 285: 877-883, 1971.

Eckberg, D.L., Nerhed, C., and B.G. Wallin. Respiratory modulation of muscle sympathetic and vagal cardiac outflow in man. Journal of Physiology, 365: 181-196, 1985.

Ekblom, B., Kilbom, A., and J. Soltysiak. Physical training, bradycardia, and autonomic nervous system. Scandinavian Journal of Clinical and Laboratory Investigation, 32: 251-256, 1973.

Ewing, D.J., Boland, O., Neilson, J.M., Cho, C.G., et al. Autonomic neuropathy, QT-lengthening, and unexpected deaths in male diabetic patients. Diabetologia, 34: 182-185, 1991.

Ewing, D.J. Heart rate variability: an important new risk factor in patients following myocardial infarction. Clinics in Cardiology, 14: 683-685, 1991.

Fagraeus, L., and D. Linnarsson. Autonomic origin of heart rate fluctuations at the onset of muscular exercise. Journal of Applied Physiology, 40: 679-682, 1976.

Fallen, E.L. Heart Rate and Athletic Training (letter). Cardiovascular Research, 27: 1383-1384, 1993.

Fallen, E.L., Kamath, M.V., and D.N. Ghista. Power spectrum of heart rate variability: a non-invasive test of integrated neurocardiac function. Clinical and Investigative Medicine, 2: 331-340, 1988.

Fallen, E.L., Bentley, T.C., Kamath, M.V., Moe, G., et al. Patterns of autonomic dysregulation in congestive heart failure: relationship with LV function and neurohormonal activation. Abstract submitted to the 49th Annual Meeting of the Canadian Cardiovascular Society, October 29-November 2, 1996-Montreal, Quebec.

Fallen, E.L., and M.V. Kamath. Circadian Rhythms of Heart Rate Variability. *In Heart Rate Variability, M.Malik & A.J. Camm (eds.)*. Armonk: Futura, 1995. Ch.23, pp.293-310.

Ferguson, D.W., Berg, W.J., and J.S. Sanders. Clinical and hemodynamic correlates of sympathetic nerve activity in normal humans and patients with heart failure: evidence from direct microneurographic recordings. Journal of the American College of Cardiology, 16: 1125-1134, 1990.

Fink, L.I., Wilson, J.R., and N. Ferraro. Exercise ventilation and pulmonary artery wedge pressure in chronic stable congestive heart failure. American Journal of Cardiology, 57: 249-253, 1986.

Flapan, A.D., Nolan, J., Neilson, J.M., et al. Effect of captopril on cardiac parasympathetic activity in chronic cardiac failure secondary to coronary artery disease. American Journal of Cardiology, 69, 532-535, 1992.

Franciosa, J.A., Ziesche, S.A., and M. Wilen. Functional capacity of patients with chronic left ventricular failure: relationship of bicycle exercise performance to clinical and hemodynamic characterization. American Journal of Medicine, 67: 460-466, 1979.

Franciosa, J.A., Leddy, C.L., Wilen, M., and D.E. Schwartz. Relation between hemodynamic and ventilatory responses in determining exercise capacity in severe congestive heart failure. American Journal of Cardiology, 53: 127-134, 1984.

Francis, G.S., Goldsmith, S.R., Ziesche, S., Nakajima, H., et al. Relative attenuation of sympathetic drive during exercise in patients with congestive heart failure. Journal of the American College of Cardiology, 5: 832-839, 1985.

Francis, G.S., Goldsmith, S.R., Levine, T.B., Olivari, M.T., et al. The neurohormonal axis in congestive heart failure. Annals of Internal Medicine, 101: 370-377, 1984.

Furlan, R., Piazza, S., Dell'Orto, S., Gentile, E., et al. Early and late effects of exercise and athletic training on neural mechanisms controlling heart rate. Cardiovascular Research, 27: 482-488,1993.

Gang, Y., Keeling, P.J., Fei, L., Bashir, Y., et al. An analysis of heart rate variability in patients with chronic congestive heart failure (Abstract). British Heart Journal, 69: 72, 1993.

Garg, R., Packer, M., Pitt, B., and S. Yusuf. Heart failure in the 1990's: evolution of major public health problem in cardiovascular medicine. Journal of the American College of Cardiology, 22 (Suppl. A): 3A-5A, 1993.

Gibelin, P., Dybal-Dadoun, M., and P. Morand. Is heart rate variability a good marker of the severity of chronic heart failure?(Abstract). European Heart Journal, 14: 90, 1993.

Goldstein, R.E., Beiser, G.D., Stampfer, M., and S.E. Epstein. Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction. Circulation Research, 36: 571-578, 1975.

Goseki, Y., Matsubara, T., Takahashi, N., Takeuchi, T., et al. Heart rate variability before the occurrence of silent myocardial ischemia during ambulatory monitoring. American Journal of Cardiology, 73: 845-849, 1994.

Grassi, G., Seravalle, G., Cattaneo, B.M., Lanfranchi, A., et al. Sympathetic nearve traffic and baroreflex control of circulation in moderate and severe congestive heart failure. (Abstract) European Heart Journal, 14: 9, 1993.

Guyatt, G.H., Sullivan, M.J., Thompson, P.J., Fallen, E.L., et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Canadian Medical Association Journal, 132: 919-923, 1985.

Guyton, A.C., and J.E. Hall. Textbook of Medical Physiology (9th ed.): Ch. 9, 10, 41, 60. W.B Saunders: Philadelphia, 1996.

Hambrecht, R., Niebauer, J., Fiehn, E., Kälberer, B., et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. Journal of the American College of Cardiology, 25: 1239-49, 1995.

Hamm, L.F., and A.S. Leon. Exercise Training for the Coronary Patient. In *Rehabilitation of the Coronary Patient (3rd ed.), N.K. Wenger and H.K. Hellerstein (eds.).* New York: Churchill Livingstone, 1992.

Hanson, P. Exercise testing and training in patients with chronic heart failure. Medicine and Science in Sports and Exercise, 26: 527-537, 1994.

Haslam, D.R., McCartney, N., McKelvie, R.S., and J.D. MacDougall. Direct measurements of arterial blood pressure during formal weightlifting in cardiac patients. Journal of Cardiopulmonary Rehabilitation, 8: 213-225, 1988.

Higginbotham, M.B., Morris, K.G., Conn, E.H., Coleman, R.E., et al. Determinants of variable exercise performance among patients with severe left ventricular dysfunction. American Journal of Cardiology, 51: 52-60, 1983.

Hirsch, J.A., and B. Bishop. Respiratory sinus arrythmia in humans: how breathing patterns modulate heart rate. American Journal of Physiology, 241: H620-H629, 1981.

Hon, E.H., and S.T. Lee. Electronic evaluation of the fetal heart rate patterns preceding fetal death, further observations. American Journal of Obstetrics and Gynecology, 87: 814-826, 1965.

Jetté, M., Heller, R., Landry, F., and G. Blümchen. Randomized 4-week exercise program in patients with impaired left ventricular function. Circulation, 84: 1561-1567, 1991.

Jugdutt, B.I., Michorowski, B.L., and C.T. Kappagoda. Exercise training after anterior Q-wave myocardial infarction: importance of regional left ventricular function and topography. Journal of the American College of Cardiology, 12: 362-72, 1992.

Kamath, M.V, Fallen, E.L., and R. McKelvie. Effects of steady state exercise on the power spectrum of heart rate variability. Medicine and Science in Sports and Exercise, 23: 428-4334, 1991.

Kamath, M.V., and E.L. Fallen. Power spectral analysis of heart rate variability: a noninvasive signature of cardiac autonomic function. Critical Reviews in Biomedical Engineering, 21(3): 245-311, 1993.

Kamath, M.V., and E.L. Fallen. Correction of the Heart Rate Variability Signal for Ectopics and Missing Beats. *In Heart Rate Variability, M.Malik & A.J. Camm (eds.).* Armonk: Futura, 1995. Ch.6, pp.75-86.

Kamath, M.V., Fallen, E.L, McArthur, A., and J. Runions. Detection of silent myocardial ischemia during ambulatory monitoring by time-frequency power spectral analysis. Journal of Non-Invasive Electrocardiology, 1: 63-69, 1996.

Kamath, M.V., and E.L. Fallen. Diurnal variations of neurocardiac rhythms in acute myocardial infarction. American Journal of Cardiology, 68: 155-160, 1991.

Kannel, W.B., Belanger, A.J. Epidemiology of heart failure. American Heart Journal, 121: 951, 1991.

Kannel, W.B., Plehn, J.F., and L.A. Cupples. Cardiac failure and sudden death in the Framingham Study. American Heart Journal, 115: 869-875, 1988.

Katona, P.G., McLean, M., Dighton, D.H., and A. Guz. Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest. Journal of Applied Physiology, 52: 1652-1657, 1982.

Katona, P.G., Poitras, J.W., Barnett, G.O., and B.S. Terry. Cardiac vagal efferent activity and heart period in the carotid sinus reflex. American Journal of Physiology, 218: 1030:1037, 1970.

Katona, P.G., and F. Jih. Respiratory sinus arrythmia: noninvasive measure of parasympathetic cardiac control. Journal of Applied Physiology, 39: 801-805, 1975.

Katz, S.D., Schwarz, M., Yuen, J., and T.H. LeJemtel. Impaired acetylcholine-mediated vasodilation in patients with congestive heart failure: role of endothelium-derived vasodilating and vasoconstricting factors. Circulation, 88: 55-61, 1993.

Kienzle, M.G., Ferguson, D.W., Birkett, C.L., Myers, G.A., et al. Clinical, hemodynamic and sympathetic neural correlates of heart rate variability in congestive heart failure. American Journal of Cardiology 69: 761-767, 1992.

Klassen, G.A., Woodhouse, S.P., Hathirat, S.P., and A.L. Johnson. The effects of physical training of post-myocardial patients: a controlled study. (Abstract). Canadian Medical Association Journal, 107: 632, 1972.

Kleiger, R.E., Stein, P.K., Bosner, M.S., and J.N. Rottman. Time domain measurements of heart rate variability. Cardiology Clinics, 10: 487-498, 1992.

Kleiger, R.E., Miller, J.P., Bigger, J.T., and A.J. Moss. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. American Journal of Cardiology, 59: 256-262, 1987.

Kleiger, R.E., Stein, P.K., Bosner, M.S., and J.N. Rottman. Time-Domain Measurements of Heart Rate Variability. *In Heart Rate Variability, M.Malik & A.J. Camm (eds.).* Armonk: Futura, 1995. Ch.3, pp.33-46.

Kollai, M., and K. Koizumi. Cardiac vagal and sympathetic nerve responses to baroreceptor stimulation in the dog. Journal of the Autonomic Nervous System, 1: 33-37, 1979.

Kollai, M., and G. Mizsei. Respiratory sinus arrhythmia is a limited measure of cardiac parasympathetic control in man. Journal of Physiology, 424: 329-342, 1990.

Krum, H., Bigger, J.T., Goldsmith, R.L., and M. Packer. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. Journal of the American College of Cardiology, 25: 289-294, 1995.

Kulbertus, H.E., and G. Franck. (eds.). Neurocardiology: Ch. 1-7, 10. Futura: New York, 1988.

LaRovere, M.T., Mortara, A., Sandrone, G., and F. Lombardi. Autonomic nervous system adaptations to short-term exercise training. Chest, 101: 299S-303S, 1992.

Lee, A.P., Ice, R., Blessey, R., and M.E. Sanmarco. Long-term effects of physical training on coronary patients with impaired ventricular function. Circulation, 60: 1519-1526, 1979.

Levine, T.B., Francis, G.S., Goldsmith, S.R., Simon, A.B., et al. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. American Journal of Cardiology, 49: 1659-1666, 1982.

Lipkin, D.P., Jones, D.A., Round, J.M., and P.A. Poole-Wilson. Abnormalities of skeletal muscle in patients with chronic heart failure. International Journal of Cardiology, 18: 187-195, 1988.

Lombardi, F., Sandrone, Gl, Pernpruner, S., Sala, R., et al. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. American Journal of Cardiology, 60: 1239-1245, 1987.

Maciel, B.C., Gallo, L., Marin-Etto, J.A., Filho, E.C., et al. Autonomic nervous control of the heart rate during dynamic exercise in normal man. Clinical Science, 71: 457-460, 1986.

Malik, M., and A.J. Camm. Components of heart rate variability-what they really mean and what we really measure. American Journal of Cardiology, 72: 821-822, 1993.

Malik, M., Farrell, T., and A.J. Camm. Circadian rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. American Journal of Cardiology, 66: 1049-1054, 1990.

Malik, M. Geometrical Methods for Heart Rate Variability Assessment. *In Heart Rate Variability, M.Malik & A.J. Camm (eds.).* Armonk: Futura, 1995. Ch.4, pp.47-62.

Malliani, A., Pagani, M., Lombardi, F., and S. Cerutti. Cardiovascular neural regulation explored in the frequency domain. Circulation, 84: 482-492, 1991.

Marchant, B., Stevenson, R., Vaishnav, S., Wilkinson, P., et al. Influence of the autonomic nervous system on circadian patterns of myocardial ischaemia: comparison of stable angina with the early postinfarction period. British Heart Journal, 71: 329-333, 1994.

Massie, B.M. Exercise tolerance in congestive heart failure: role of cardiac function, peripheral blood flow, and muscle metabolism and effect of treatment. American Journal of Medicine, 84 (Suppl.3A):75-82, 1988.

Massie, B.M., Conway, M., Yonge, R., Frostick, S., et al. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. Circulation, 76: 1009-1019, 1987.

McCartney, N., Hicks, A.L., Martin, J.E., and C.E. Webber. Long-term strenth training in the elderly: Effects on dynamic strength, exercise capacity, muscle, and bone. Journal of Gerontology, 50 A: B97-104, 1995.

McCartney, N., McKelvie, R.S., Martin, J., Sale, D.G., et al. Weight-training-induced attentuation of the circulatory response of older males to weight lifting. Journal of Applied Physiology, 74: 1056-1060, 1993.

McCartney, N., McKelvie, R.S., Haslam, D.R., and N.L. Jones. Usefulness of Weightlifting Training in Improving Strength and Maximal Power Output in Coronary Artery Disease. American Journal of Cardiology, 67: 939-945, 1991.

McKee, P.A., Castelli, W.P., McNamara, P.M., et al. The natural history of congestive heart failure: The Framingham study. New England Journal of Medicine, 285: 1442-1446, 1971.

McKelvie, R.S., McCartney, N., Tomlinson, C., Bauer, R., et al. Comparison of hemodynamic responses to cycling and resistance exercise in congestive heart failure secondary to ischemic cardiomyopathy. American Journal of Cardiology, 76: 977-979, 1995.

McKelvie, R.S., Teo, K.K., McCartney, N., Humen, D., et al. Effects of exercise training in patients with congestive heart failure: a critical review. Journal of the American College of Cardiology, 25: 789-96, 1995.

McKelvie, R.S., and N. McCartney. Weightlifting Training in Cardiac Patients: Considerations. Sports Medicine, 10: 355-364, 1990.

Meredith, I.T., Jennings, G.L., Esler, M.D., Dewar, E.M., et al. Time-course of the antihypertensive and autonomic effects of regular endurance exercise in human subjects. Journal of Hypertension, 8: 859-866, 1990.

Minotti, J.R., and B.M. Massie. Exercise training in heart failure patients: does reversing the perippheral abnormalities protect the heart? Circulation, 85: 2323-2325, 1992.

Mortara, A., LaRovere, M.T., Pantaleo, P., Cobelli, F., et al. Can spectral analysis of heart rate variability identify congestive heart failure patients with more pronounced neurohormonal activation? (Abstract). European Heart Journal, 14: 9, 1993.

Murakawa, Y, Ajiki, K., Usui, M., Yamashita, T., et al. Parasympathetic activity is a major modulator of the circadian variability of heart rate in healthy subjects and in patients with coronary artery disease or diabetes mellitus. American Heart Journal, 126: 108-114, 1993.

Myers, J., and V.F. Froelicher. Hemodynamic determinants of exercise capacity in chronic heart failure. Annals of Internal Medicine, 115: 377-386, 1991.

Nakamura, M., Ishikawa, M., Funakoshi, T., Hashimoto, K., et al. Attenuated endothelium-dependent peripheral vasodilation and clinical characteristics in patients with chronic heart failure. American Heart Journal, 128: 1164-1169, 1994.

Nakamura, Y., Yamamoto, Y., and I. Muraoka. Autonomic control of heart rate during physical exercise and fractal dimension of heart rate variability. Journal of Applied Physiology, 74: 875-881, 1993.

Nolan, J., Flapan, A.D., Capewell, S., MacDonald, T.M., et al. Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. British Heart Journal, 67: 482-485, 1992.

Novak, V., Novak, P., DeChamplain, J., LeBlanc, R., et al. Influence of respiration on heart rate and blood pressure fluctuations. Journal of Applied Physiology, 74: 617-626, 1993.

Odemuyiwa, O. Effect of Age on Heart Rate Variability. *In Heart Rate Variability, M.Malik & A.J. Camm (eds.).* Armonk, NY: Futura, 1995. Ch.5, pp.63-74.

Ori, Z., Monir, G., Weiss, J., Sayhouni, X., and D.H. Singer. Heart rate variability: frequency domain analysis. Cardiology Clinics, 10(3): 499-533, 1992.

Packer, M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. Journal of the American College of Cardiology, 20: 248-254, 1992.

Packer, M. Neurohormonal interactions and adaptations in congestive heart failure. Circulation, 77: 721-730, 1988.

Packer, M. Sudden unexpected death in patients with congestive heart failure: a second frontier. Circulation, 72: 681, 1985.

Pagani, M., Somers, V., Furlan, R., Dell'Orto, S., et al. Changes in autonomic regulation induced by physical training in mild hypertension. Hypertension, 12: 600-610, 1988.

Pagani, M., Lombardi, F., Guzzetti, S., et al. Power spectral analysis of heart rate and arterial pressure variables as a marker of sympathovagal interaction in man and the conscious dog. Circulation Research, 59: 178-193, 1986.

Panina, G., Khot, U., Nunziata, E., Cody, R.J., et al. Assessment of autonomic tone over a 24-hour period in patients with congestive heart failure: relation between mean heart rate and measures of heart rate variability. American Heart Journal, 129: 748-753, 1995.

Piepoli, M., and A.J.S. Coats. Effects of exercise on the autonomic control of the heart: training or overtraining?(letter). Cardiovascular Research, 28: 141-143, 1994.

Piepoli, M., Clark, A.L., Volterrani, M., Adamopoulos, S., et al. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of exercise training. Circulation, 93: 940-952, 1996.

Pierpoint, G.L., Francis, G.S., DeMaster, E.G., Olivari, M.T., et al. Heterogeneous myocardial catecholamine concentrations in patients with congestive heart failure. American Journal of Cardiology, 60: 316-321, 1987.

Piplis, A., Flather, M., Ormerod, O., and P. Sleight. Heart rate variability in acute myocardial infarction and its association with infarct site and clinical course. American Journal of Cardiology, 67: 1137-1139, 1991.

Pomeranz, B, MacAulay, R.J., Caudill, M.A., Kutz, I., et al. Assessment of autonomic function in humans by heart rate spectral analysis. American Journal of Physiology, 248: H151-H153, 1985.

Port, S., McEwan, P., and F.R. Cobb. Influence of resting ventricular function on left ventricular response to exercise in patients with coronary artery disease. Circulation, 63: 856-863, 1981.

Porter, T.R., Eckberg, D.L., Fritsch, J.M., Rea, R.F., et al. Autonomic pathophysiology in heart failure patients: sympathetic-cholinergic interrelations. Journal of Clinical Investigatioin, 85: 1362-1371, 1990.

Rimoldi, O., Furlan, R., Pagani, M., Piazza, S., et al. Analysis of neural mechanisms accompanying different intensities of dynamic exercise. Chest, 101: 226S-230S, 1992.

Robinson, B.F., Epstein, S.E., Beiser, G.D., and E. Braunwald. Control of heart rate by the autonomic nervous system: studies in man on the interrelation between baroreceptor mechanisms and exercise. Circulation Research, 19: 400-411, 1966.

Rossi, P. Physical training in patients with congestive heart failure. Chest, 101: 350S-353S, 1992.

Sale, D. Testing strength and power. *In Physiologic Testing of the High Performance Athlete (2nd ed.)., J.D. MacDougall, H. Wenger, and H.J. Green (eds.).* Champaigne: Human Kinetics, 1991, pp.21-106.

Saul, J.P., Arai, Y., Berger, R.D., Lilly, L.S., et al. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. American Journal of Cardiology, 61: 1292-1299, 1988.

Saul, J.P., Berger, R.D., Chen, M.H., and R.J. Cohen. Transfer function analysis of autonomic regulation: II Respiratory sinus arrythmia. American Journal of Physiology, 25: H153-H161, 1989.

Saul, J.P. Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. NIPS, 5: 32-37, 1990.

Savin, W.M., Davidson, D.M., and W.L. Haskell. Autonomic contribution to heart rate recovery from exercise in humans. Journal of Applied Physiology, 53: 1572-1575, 1982.

Seals, D.R., Suwarno, N.O., and J.A. Dempsey. Influence of lung volume on sympathetic nerve discharge in normal humans. Circulation Research, 67: 130-141, 1990.

Seals, D.R., and P.B. Chase. Influence of physical training on heart rate variability and baroreflex circulatory control. Journal of Applied Physiology, 66: 1886-1895, 1989.

Smith, W.M. Epidemiology of congestive heart failure. American Journal of Cardiology, 55: 3A-5A, 1985.

Somers, V.K., Conway, J., Johnston, J., and P. Sleight. Effects of endurance training on baroreflex sensitivity and blood pressure in borderline hypertension. Lancet, 337: 1363-68, 1991.

Stefenelli, T., Bergler-Klein, J., Globits, S., Pacher, R., et al. Heart rate behaviour at different stages of congestive heart failure. European Heart Journal, 13: 902-907, 1992.

Stone, H.L., Dormer, K.J., Foreman, R.D., Thies, R., et al. Neural regulation of the cardiovascular system during exercise. Federation Proceedings, 44: 2271-2278, 1985.

Sullivan, M.J., Green, H.J., and F.R. Cobb. Altered skeletal muscle metabolic response to exercise in chronic heart failure: relation to skeletal muscle aerobic enzyme activity. Circulation, 84: 1597-1607, 1991.

Sullivan, M.J., Green, H.J., and F.R. Cobb. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. Circulation, 81: 518-527, 1990.

Sullivan, M.J., Higginbotham, M.B., and F.R. Cobb. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. Circulation, 78: 506-515, 1988.

Sullivan, M.J., Higginbotham, M.B., and F.R. Cobb. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. Circulation, 77: 552-559, 1988.

Szlachcic, J., Massie, B.M., Kramer, B.L., Topic, N., et al. Correlates and prognostic implications of exercise capacity in chronic congestive heart failure. American Journal of Cardiology, 55: 1037-1042, 1985.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use. Circulation, 93: 1043-1065, 1996.

Uren, N.G., and D.P. Lipkin. Exercise training as therapy for chronic heart failure. British Heart Journal, 67: 430-433, 1992.

vanBoven, A.J., Brouwer, J., Crijns, H.J., Haaksma, J., et al. Differential autonomic mechanisms underlying early morning and daytime transient myocardial ischaemia in patients with stable coronary artery disease. British Heart Journal, 73: 134-138, 1995.

VanHoogenhuyze, D., Weinstein, N., Martin, B.J., Weiss, J.S., et al. Reproducibility and relation to mean heart rate of heart rate variability in normal subjects and in patients with congestive heart failure secondary to coronary artery disease. American Journal of Cardiology, 68: 1668-1676, 1991.

Vatner, D.E., et al. Loss of high affinity cardiac beta-adrenergic receptors in dogs with heart failure. Journal of Clinical Investigation, 76: 2259, 1985.

Victor, R.G., Seals, D.R., and A.L. Mark. Differential control of heart rate and sympathetic nerve activity during dynamic exercise: insight from intraneural recordings in humans. Journal of Clinical Investigation, 79: 508-516, 1987.

Weber, K.T., and J.S. Janicki. Lactate production during maximal and submaximal exercise in patients with chronic heart failure. Journal of the American College of Cardiology, 6: 717-724, 1985.

Weber, K.T., Kinasewitz, G.T., Janicki, J.S., and A.P. Fishman. Oxygen utilisation and ventilation during exercise in patients with chronic cardiac failure. Circulation, 65: 1213-1223, 1982.

Wei, C.M., Lerman, A., Rodeheffer, R.J., McGregor, C.G., et al. Endothelin in human congestive heart failure. Circulation, 89: 1580-1586, 1994.

Wells, J.W., Wong, H.M., and M.J. Sole. Muscarinic receptors in heart failure. (Abstract). Proceedings of the Society of Neuroscience, 7, 1981.

Yamamoto, Y., Hughson, R.L., and J.C. Peterson. Autonomic control of heart rate during exercise studied by heart rate variability spectral analysis. Journal of Applied Physiology, 71: 1136-1142, 1991.

SECTION 6.0:

APPENDICES

APPENDIX A:

Consent Forms

EXERT Substudy
Power Spectrum Analysis

You are particpating in the EXERT study which evaluates the effects of exercise on functional status, quality of life and safety in patients with congestive heart failure. In this context, we wish to find out more about how exercise affects changes in the levels of neurohormones (naturally occurring body chemicals) in people who have congestive heart failure.

In order to obtain this information you will have your heart rate monitored for 35 minutes prior to the exercise test, and 20 minutes after the exercise test. You will then wear an ambulatory heart monitor home for 24 hours after the test. This will occur at the time your regularly scheduled exercise tests are performed for the EXERT study. In addition to the exercise tests required for the EXERT study you will be asked to come in for an exercise test 6 months following entrance into the study.

Your participation in this study is voluntary. Refusal to participate or withdrawal from the study will result in no penalty or loss of benefits to which you would otherwise be entitled. All information obtained in this study will be confidential and only used for research purposes.

I agree to participate in the EXERT substudy which evaluates how exercise affects neurohormone levels and I have been given a copy of this form.

_____ _____
Patient's Signature Date

_____ _____
Witness' Signature Date

A RANDOMIZED CONTROLLED TRIAL OF EXERCISE TRAINING IN PATIENTS WITH CONGESTIVE HEART FAILURE

CONSENT FORM 1

Orientation Period: Baseline Drug Stabilization, Pre-Randomization and Baseline Assessment (6 min walk test, Quality of Life Questionnaire, Muscle Strength Assessment), Peak Exercise VO_2, RNV

You have been found to have heart failure which means that the heart does not pump blood adequately. The symptoms of heart failure include fatigue, shortness of breath and a decrease in exercise capacity. Some preliminary studies suggest that regular exercise may improve these symptoms, but this has not been conclusively proven. McMaster University and the University of Alberta are conducting a research study in Canada to clarify this. The aim of the study is to find out whether or not regular exercise reduces the symptoms associated with heart failure, improves your ability to carry out your usual activities and your sense of well being.

For this first phase of the study you will be seen by one of the physicians (Dr. Yusuf/Montague) involved in the study to have the doses of the medications that you are receiving optimized. During this time you will perform the 6 minute walk test (involves walking in a corridor for 6 minutes) twice on two separate days, have your muscle strength assessed and complete a quality of life questionnaire. There is an extremely small risk of having a heart attack or collapsing while performing the 6 minute walk test or muscle strength assessment. However, this test will be performed under supervision in hospital, and emergency equipment will be available at all times. If you experience any untoward symptom (eg. chest pain, shortness of breath, fatigue or dizziness) the tests may be stopped.

You will be assessed with a radionuclide ventriculogram, to determine the ability of the heart to pump blood, before the study starts and after being in the study for 3 months. There is no risk associated with this test. You will perform an exercise test on a cycle ergometer before the study starts; and 3 months and 12 months later. There is a 1 in 10,000 risk of having a heart attack or dying during this test. However, this risk is no higher than it would be for anyone else who has heart disease. The tests will be supervised by a physician trained in exercise testing. Your heart rate, blood pressure, electrocardiogram and symptoms will be continuously monitored throughout the exercise test. The 6 minute walk test will be done at 3 months and every 6 months to the end of the study, muscle strength assessment at 3 months and 12 months, and quality of life questionnaires will be performed at 3 months, 12 months and at the end of the study. There is a small risk of having a heart attack or collapsing while performing the 6 minute walk test or muscle strength assessment, but this risk is very small. Emergency equipment is available at all times in the laboratory and a study physician will always be present should such an event occur.

You will be carefully followed in the Heart Function Clinic every month. If your clinical condition changes, a study physician will re-assess your treatment. There will also be regular communication with the physician that normally is responsible for taking care of your heart failure condition. You will always be offered any treatment that your clinical condition requires and participating in this study will not affect that.

Your participation in the study is entirely voluntary and will not affect any medical care to which you are entitled. You are free to refuse to participate or withdraw from the study at any time without penalty. All information obtained as part of the study will be confidential and only used for research purposes. Before starting the exercise period of the study you will have the objectives reviewed again and be requested to sign another consent form.

I agree to participate in the study of exercise training in patients with heart failure and I have been given a copy of this form.

Patient's Signature	Date
Witness' Signature	Date
Participating Investigator's Signature	Date

A RANDOMIZED CONTROLLED TRIAL OF EXERCISE TRAINING IN PATIENTS WITH CONGESTIVE HEART FAILURE

CONSENT FORM 2

Exercise Training and Follow Up Period: Supervised and home exercise training, all outcome assessments

As described previously you have been found to have heart failure which means that the heart does not pump blood adequately. Regular exercise is felt to improve these symptoms, but this has not been proven. McMaster University and the University of Alberta are conducting a research study to find out whether or not regular exercise reduces the symptoms associated with heart failure and increases your functional ability.

For the exercise training and follow up period of the study you have an equal chance of entering either the regular care or exercise training group. The people performing the assessments of your exercise capacity will not know to which group you have been assigned, nor do they need to know. Furthermore, it is very important that you do not, in any way, indicate to anyone performing your assessments to which group you have been assigned. If you are entered into the exercise group, you will have regular contact with a specially designated member of the research team.

If you are in the exercise group, you will attend exercise sessions 2 times a week for month at the medically supervised cardiac rehabilitation program. Following this period of time you will continue to exercise at home for the remainder of the study. During the period of home training the appropriate exercise equipment will be provided. A study staff member will call you monthly to insure you are not having difficulties with the exercise equipment or the training program. Also you will be asked to return to the cardiac rehabilitation program every month to review your training program. If you are in the group that receives regular care you will be encouraged to walk regularly and be called once per month for the first 3 months. You will be called once per month for the remainder of the study.

You will be reviewed every 3 months in the Heart Function Clinic by a study cardiologist to carefully review your symptoms. At that time the physician will make any necessary alterations to your medical treatment.

Your participation in the study is entirely voluntary and will not affect any medical care to which you are entitled. You are free to refuse to participate or withdraw from the study at any time without penalty. All information obtained as part of the study will be confidential and only used for research purposes.

I agree to participate in the study of exercise training in patients with heart failure and I have been given a copy of this form.

_____ _____

Patient's Signature Date

_____ _____

Witness' Signature Date

_____ _____

Participating Investigator's Signature Date

APPENDIX B:

Raw Data

i) Baseline patient demographics

Patient	GROUP	AGE	LVEF1	NYHA	CHF ET	NITRATES	ACE	DIURETIC	DIG	BETA-B	ANTI-COAG	OTHER
1	1	74	34	2	ID	Nitrospray	EN 20mg	FU (40mg)	0.250 mg	N	COU 5mg	mevacor
2	1	71	28	1	IS	N	EN 10mg	N	0.125mg	N	ASA 325mg	amiodarone
3	1	57	28	2	IS	Nitropatch	CA 150mg	N	0.125mg	N	ASA 325mg	Cordarone,Dilantin,Thyroxin,Atrovent
4	1	65	22	2	IS	N	CA 75mg	FU (40mg)	N	N	ASA 325mg	slowk, simvestatin
5	1	78	31	3	IS	Nitrospray	LI 10mg	FU (40mg)	0.375mg	N	ASA 325mg	slowk,amiodarone,oxazepam
6	1	67	22	2	IS	IS 60mg	N	FU (80mg)	N	N	COU	cordarone, lorazepam, hydralazine
7	1	59	32	2	IS	Nitrospray	EN 10mg	FU(40mg)	N	N	ASA 325mg	amiodarone,ventolin,tyl#3,ativan,glyburide
8	1	61	19	3	ID	Nitropaste	CA 112.5mg	F 100mg,HCT 25mg	0.250mg	N	COU 5mg	Trimetrene(kspar),slowk,mexilitine,lovastatin
9	1	64	39	3	IS	N	CA 75mg	FU (40mg)	0.125mg	N	ASA 325mg	colace, glyburide
10	1	59	36	3	IS	N	EN 20mg	FU (20mg)	0.125mg	N	ASA 325mg	allopurinol,lanoxin
11	1	58	39	3	HYP	N	EN 20mg	FU (20mg)	N	N	N	vitE,stress tab
12	1	76	36	2	HYP	Nitropaste	CA 75mg	FU (80mg)	0.125mg	N	COU 2.5mg	calmicort, ventolin,nitrospray,KDir
13	1	72	23	2	IS	Nitrospray	CA 25mg	N	0.125mg	N	COU 5/2.5mg	amiodarone,novasen,tapazole,ranitidine
14	1	41	23	2	IS	IS 90mg	EN 20mg	FU (80mg)	N	N	ASA 2600mg	oxazepam
15	1	64	37	2	IS	N	EN 10 mg	FU (80mg)	N	N	ASA 325 mg	diltiazem, glyburide, allopurinol, vitE, ibuprofen
16	1	73	22	3	HYP	IS 135mg	N	FU (80mg)	0.250mg	N	COU	adalat,glyburide
17	2	46	32	2	VIR	N	LI 10mg	FU (40mg)	0.125mg	N	COU 5/2.5mg	slowk,gemfibrozil,famotidine
18	2	64	15	3	IS	IS 60mg	N	FU (40mg)	0.250mg	N	N	Zoloft,VitE,Tyl#2,hydrazine,amiloride
19	2	45	26	3	IS	N	EN 20mg	FU (40mg)	0.250mg	N	COU 5mg	none
20	2	58	17	3	IS	Nitrospray	EN 40mg	N	N	N	COU 5mg	tetracycline, surgam
21	2	61	30	2	ID	N	LI 20mg	FU (40mg)	0.250mg	N	COU 2.5mg	estraconpatch
22	2	83	24	2	IS	Nitropaste	CA 150mg	N	0.250mg	N	N	glyburide
23	2	72	27	3	IS	Nitrospray	EN 20mg	FU (40mg)	N	MET 100mg	ASA 325mg, COU	glyburide
24	2	63	32	2	IS	N	EN 20mg	FU (20mg)	N	N	ASA 325mg	amiodarone,provachol
25	2	64	34	3	IS	Nitropaste/spray	CA 225 mg	F 160mg, HCT 25 mg	N	N	ASA 325 mg	spironolactone,glyburide,endomethacin,metformin
26	2	41	21	2	VIR	N	CA 150mg	FU (40mg)	0.250mg	N	COU	NONE
27	2	53	13	2	IS	Nitrospray	CA 37.5 mg	FU (20mg)	N	N	ASA 80mg, COU	serex, niacin
28	2	66	22	2	IS	N	EN 10mg	N	N	AT 25mg	COU 4mg	simvestatin

AERWT	MEAN	64.9	29.4
	STDEV	9.3	6.9
	SEM	2.3	1.7
UC	MEAN	58.0	24.4
	STDEV	9.8	7.0
	SEM	2.8	2.0

ii) Peak oxygen uptake ($\dot{V}O2$) expressed in relative (ml/kg/min) and absolute terms (L/min) following cycle ergometry at baseline and 3-months

Patient	GROUP	VO2R1	VO2R2	%DIFF	VO2A1	VO2A2	%DIFF
1	1	14.49	14.65	1.10	1.2	1.25	4.17
2	1	11.67	9.89	-15.25	1.3	1.12	-13.85
3	1	13.6	15.54	14.26	1.15	1.28	11.30
4	1	13.3	15.32	15.19	1.18	1.35	14.41
5	1	13.96	11.76	-15.76	1.33	1.12	-15.79
6	1	12.05	14.25	18.26	0.82	0.93	13.41
7	1	16.16	17.91	10.83	1.07	1.18	10.28
9	1	12.51	15.68	25.34	0.63	0.67	6.35
10	1	10.6	13.51	27.45	0.99	1.27	28.28
11	1	11.25	21.83	94.04	1.13	1.31	15.93
12	1	13.46	18.88	40.27	0.9	1.3	44.44
13	1	11.99	15.44	28.77	0.79	1.003	26.96
15	1	16.1	17	5.59	2.04	2.16	5.88
17	2	19.05	18.7	-1.84	1.54	1.57	1.95
18	2	14.05	12.9	-8.19	0.75	0.69	-8.00
19	2	13.31	12.9	-3.08	1.14	1.21	6.14
20	2	10.59	13.74	29.75	1.18	1.08	-8.47
21	2	15.22	9.41	-38.17	1.01	1.14	12.87
22	2	13.88	15.25	9.87	1.21	1.36	12.40
23	2	13.27	11.81	-11.00	1.15	1.2	4.35
24	2	11.34	10.47	-7.67	0.77	0.73	-5.19
25	2	9.93	11	10.78	1.14	1.19	4.39
26	2	15.88	19.4	22.17	1.45	1.77	22.07
27	2	13.62	12.24	-10.13	1.21	1.1	-9.09
28	2	13.66	14.2	3.95	1.23	1.25	1.63

AERWT	MEAN	13.16	15.51	19.24	1.12	1.23	11.68
	STD	1.73	3.05	27.80	0.35	0.34	16.17
	SEM	0.48	0.84	7.71	0.10	0.09	4.48
UC	MEAN	13.65	13.50	-0.30	1.15	1.19	2.92
	STD	2.44	3.06	17.64	0.23	0.30	9.69
	SEM	0.71	0.88	5.09	0.07	0.09	2.80

iii) Maximal power output (Watts) and maximal exercise test duration for symptom-limited incremental cycle ergometry at baseline and 3-months

Patient	GROUP	MPO1	MPO2	%DIFF	TIME1	TIME2	%DIFF
1	1	66.7	81.7	22.50	8.33	9.33	12.00
2	1	51.3	66.7	29.87	6.67	7.67	15.00
3	1	51.3	61.7	20.13	6.00	6.33	5.56
4	1	62.5	66.7	6.67	6.00	7.67	27.78
5	1	51.0	66.7	30.72	5.67	7.00	23.53
6	1	50.8	66.7	31.15	6.00	7.00	16.67
7	1	51.2	66.7	30.29	5.00	7.00	40.00
9	1	30.8	30.8	0.00	4.00	4.00	0.00
10	1	50.8	63.3	24.59	5.00	8.00	60.00
11	1	66.7	83.3	25.00	7.00	8.33	19.05
12	1	45.8	81.7	78.18	4.67	7.00	50.00
13	1	50.8	66.8	31.48	5.00	6.00	20.00
15	1	153.0	151.8	-0.76	11.00	8.67	-21.21
17	2	117.3	116.8	-0.43	7.00	7.00	0.00
18	2	35.5	30.8	-13.15	4.33	3.33	-23.08
19	2	66.7	66.7	0.00	6.67	5.33	-20.00
20	2	30.8	30.8	0.00	4.33	3.00	-30.77
21	2	62.5	81.7	30.67	6.00	7.33	22.22
22	2	66.7	84.0	26.00	6.00	8.00	33.33
23	2	46.0	66.8	45.29	6.67	7.67	15.00
24	2	50.8	48.3	-4.92	5.33	5.33	0.00
25	2	45.8	51.0	11.27	5.33	6.00	12.50
26	2	102.3	133.3	30.29	6.00	8.00	33.33
27	2	84.2	66.7	-20.79	6.67	7.00	5.00
28	2	66.7	67.5	1.25	6.67	7.67	15.00

AERWT	MEAN	60.22	73.42	25.37	6.18	7.23	20.64
	STD	29.38	26.94	19.68	1.83	1.34	21.17
	SEM	8.15	7.47	5.46	0.51	0.37	5.87
UC	MEAN	64.61	70.38	8.79	5.92	6.31	5.21
	STD	26.08	30.85	20.04	0.91	1.74	21.11
	SEM	7.53	8.91	5.78	0.26	0.50	6.09

iv) Anaerobic threshold expressed as a percentage of predicted maximal $\dot{V}O_2$ based on a healthy population,and in absolute terms for symptom-limited cycle ergometry at baseline and 3-months

Patient	GROUP	AT%1	AT%2	%DIFF	ATA1	ATA2	%DIFF
1	1	57	58	1.75	1050	1050	0
2	1	66	53	-19.70	1100	1000	-9.09
3	1	52	62	19.23	1000	1200	20.00
4	1	52	67	28.85	850	1100	29.41
5	1	45	43	-4.44	1000	950	-5.00
6	1	58	62	6.90	700	750	7.14
7	1	42	47	11.90	900	1000	11.11
9	1	54	54	0.00	600	600	0.00
10	1	70	76	8.57	900	987	9.67
11	1	65	65	0.00	1000	1000	0.00
12	1	51	43	-15.69	800	1100	37.50
13	1	36	41	13.89	650	750	15.38
15	1	70	79	12.86	1500	1700	13.33
17	2	50	53	6.00	1200	1200	0.00
18	2	62	40	-35.48	700	450	-35.71
19	2	35	41	17.14	900	1100	22.22
20	2	51					
21	2	56	62	10.71	900	1000	11.11
22	2	53	61	15.09	1000	1150	15.00
23	2	48	50	4.17	864	900	4.17
24	2	39	39	0.00	700	733	4.71
25	2	56	56	0.00	1050	1050	0.00
26	2	39	52	33.33	1100	1450	31.82
27	2	32	36	12.50	800	900	12.50
28	2	51	51	0.00	1100	1100	0.00

AERWT	MEAN	55.23	57.69	4.93	926.92	1014.38	9.96
	STD	10.60	12.34	13.43	232.39	264.18	13.45
	SEM	2.94	3.42	3.72	64.45	73.27	3.73
UC	MEAN	47.67	49.18	5.77	937.64	1003.00	5.98
	STD	9.33	8.98	16.88	166.80	261.00	17.12
	SEM	2.69	2.71	5.09	50.29	78.69	5.16

v) Expired ventilation ($\dot{V}E$) (L/min) based upon successive workloads of symptom-limited incremental cycle ergometry at baseline and 3-months

Patient	GROUPS	W1_1	W1_2	%DIFF	W2_1	W2_2	%DIFF	W3_1	W3_2	%DIFF
1	1	21.2	21.8	2.8	27.5	24.7	-10.2	32.7	28.2	-13.8
2	1	20.5	21.4	4.4	30.5	25.5	-16.4	43.0	31.1	-27.7
3	1	16.8	18.8	11.9	21.2	27.0	27.4	31.8	32.0	0.6
4	1	20.8	18.8	-9.6	30.3	27.5	-9.2	43.9	37.1	-15.5
5	1	21.9	16.4	-25.1	33.0	26.5	-19.7	44.9	35.2	-21.6
6	1	16.1	16.4	1.9	21.1	22.1	4.7	31.6	31.0	-1.9
7	1	17.4	17.4	0.0	29.4	22.1	-24.8	38.2	30.1	-21.2
9	1	15.9	18.6	17.0	22.4	28.7	28.1			
10	1	18.1	26.2	44.8	27.4	29.2	6.6	39.6	38.0	-4.0
11	1	16.0	15.7	-1.9	23.0	18.6	-19.1	29.7	23.7	-20.2
12	1	15.2	21.0	38.2	22.2	22.7	2.3	31.3	30.8	-1.6
13	1	16.0	17.2	7.5	22.1	22.6	2.3	33.0	28.4	-13.9
15	1	23.6			29.8	21.0	-29.5	31.1	33.5	7.7
17	2	17.3	18.3	5.8	24.6	24.5	-0.4	29.8	29.8	0.0
18	2	31.2	21.4	-31.4	44.1	39.9	-9.5	47.8		
19	2	13.1	21.6	64.9	17.7	26.8	51.4	25.0	35.4	41.6
20	2	27.6	21.8	-21.0	35.2	34.4	-2.3	39.3		
21	2	14.1	14.1	0.0	19.3	17.2	-10.9	23.7	22.9	-3.4
22	2	19.1	21.3	11.5	27.3	26.1	-4.4	45.5	30.7	-32.5
23	2	20.3	18.8	-7.4	24.9	24.3	-2.4	26.7	31.3	17.2
24	2	22.4	24.5	9.4	29.4	27.7	-5.8	39.0	36.8	-5.6
25	2	23.1	19.4	-16.0	31.3	28.9	-7.7	39.4	42.8	8.6
26	2	19.4	22.3	14.9	26.7	25.2	-5.6	32.3	30.4	-5.9
27	2	25.8	24.6	-4.7	31.4	39.3	25.2	38.4	58.6	52.6
28	2	24.5	19.9	-18.8	27.4	26.2	-4.4	40.1	34.7	-13.5

AERWT	MEAN	18.18	19.19	6.80	26.15	24.41	-5.12	36.34	31.42	-12.80
	STD	2.46	3.15	19.76	4.35	3.09	15.38	5.71	4.14	9.67
	SEM	0.74	0.95	5.96	1.31	0.93	4.64	1.72	1.25	2.92
UC	MEAN	19.91	20.48	5.97	26.00	26.62	3.50	33.99	35.34	5.92
	STD	4.22	3.13	23.61	4.59	5.46	19.55	7.48	9.70	25.46
	SEM	1.33	0.99	7.47	1.45	1.73	6.18	2.37	3.07	8.05

Expired carbon dioxide ($\dot{V}CO2$) (ml/min) based upon successive workloads of symptom-limited incremental cycle ergometry at baseline and 3-months

Patient	GROUPS	W1_1	W1_2	%DIFF	W2_1	W2_2	%DIFF	W3_1	W3_2	%DIFF
1	1	597	600	0.5	812	712	-12.3	1071	895	-16.4
2	1	680	655	-3.7	1040	826	-20.6	1422	1035	-27.2
3	1	473	613	29.6	720	943	31.0	1049	1124	7.1
4	1	564	503	-10.8	883	774	-12.3	1210	1068	-11.7
5	1	542	419	-22.7	926	785	-15.2	1236	1074	-13.1
6	1	448	452	0.9	605	654	8.1	894	885	-1.0
7	1	528	542	2.7	953	752	-21.1	1217	1068	-12.2
9	1	436	471	8.0	598	728	21.7			
10	1	513	706	37.6	812	805	-0.9	1169	1020	-12.7
11	1	494	470	-4.9	730	594	-18.6	964	775	-19.6
12	1	448	562	25.4	766	656	-14.4	1012	988	-2.4
13	1	455	459	0.9	732	618	-15.6	931	858	-7.8
15	1	668			857	584	-31.9	903	945	4.7
17	2	540	597	10.6	807	809	0.2	933	989	6.0
18	2	728	504	-30.8	825	819	-0.7	882		
19	2	408	586	43.6	569	717	26.0	808	992	22.8
20	2	759	579	-23.7	1061	1039	-2.1	1229		
21	2	467	417	-10.7	661	531	-19.7	867	714	-17.6
22	2	422	523	23.9	616	650	5.5	1060	825	-22.2
23	2	537	556	3.5	690	760	10.1	792	986	24.5
24	2	489	489	0.0	638	583	-8.6	822	710	-13.6
25	2	714	576	-19.3	1012	859	-15.1	1264	1253	-0.9
26	2	564	647	14.7	793	778	-1.9	1017	920	-9.5
27	2	594	501	-15.7	716	795	11.0	865	1102	27.4
28	2	565	519	-8.1	681	724	6.3	1010	994	-1.6

AERWT	MEAN	522.00	543.73	5.05	816.27	738.09	-6.36	1106.82	980.91	-10.85
	STD	71.76	92.34	18.27	125.00	103.71	15.68	159.03	110.85	9.43
	SEM	21.64	27.84	5.51	37.69	31.27	4.73	47.95	33.43	2.84
UC	MEAN	530.00	541.10	4.25	718.30	720.60	1.40	943.80	948.50	1.52
	STD	89.86	85.26	19.84	126.66	103.95	13.52	146.94	157.05	18.15
	SEM	28.42	20.64	6.18	40.05	32.87	4.28	46.47	52.83	5.74

vi) Expired ventilation to expired carbon dioxide ratio for successive workloads of symptom-limited incremental cycle ergometry at baseline and 3-months

Patient	GROUP	W1_1	W1_2	W2_1	W2_2	W3_1	W3_2
1	1	3.55	3.63	3.39	3.47	3.05	3.15
2	1	3.01	3.27	2.93	3.09	3.02	3.00
3	1	3.55	3.07	2.94	2.86	3.03	2.85
4	1	3.69	3.74	3.43	3.55	3.63	3.47
5	1	4.04	3.91	3.56	3.38	3.63	3.28
6	1	3.59	3.63	3.49	3.38	3.53	3.50
7	1	3.30	3.21	3.08	2.94	3.14	2.82
9	1	3.65	3.95	3.75	3.94		
10	1	3.53	3.71	3.37	3.63	3.39	3.73
11	1	3.24	3.34	3.15	3.13	3.08	3.06
12	1	3.39	3.74	2.90	3.46	3.09	3.12
13	1	3.52	3.75	3.02	3.66	3.54	3.31
15	1	3.53		3.48	3.60	3.44	3.54
17	2	3.20	3.07	3.05	3.03	3.19	3.01
18	2	4.29	4.25	5.35	4.87	5.42	
19	2	3.21	3.69	3.11	3.74	3.09	3.57
20	2	3.64	3.77	3.32	3.31	3.20	
21	2	3.02	3.38	2.92	3.24	2.73	3.21
22	2	4.53	4.07	4.43	4.02	4.29	3.72
23	2	3.78	3.38	3.61	3.20	3.37	3.17
24	2	4.58	5.01	4.61	4.75	4.74	5.18
25	2	3.24	3.37	3.09	3.36	3.12	3.42
26	2	3.44	3.45	3.37	3.24	3.18	3.30
27	2	4.34	4.91	4.39	4.94	4.44	5.32
28	2	4.34	3.83	4.02	3.62	3.97	3.49

	MEAN	3.49	3.54	3.19	3.31	3.31	3.21
AERWT	STD	0.28	0.29	0.25	0.28	0.26	0.30
	SEM	0.09	0.09	0.08	0.09	0.08	0.09
	MEAN	3.77	3.82	3.66	3.71	3.61	3.74
UC	STD	0.62	0.67	0.65	0.67	0.69	0.82
	SEM	0.20	0.21	0.21	0.21	0.22	0.26

vii) Heart rate, systolic blood pressure, and double products for successive stages of modified Bruce protocol during symptom-limited incremental cycle ergometry at baseline and 3-months

Patient	GROUPS	HR1_1	HR1_2	%DIFF	HR2_1	HR2_2	%DIFF	SP1_1	SP1_2	%DIFF	SP2_1	SP2_2	%DIFF	R1_1	R1_2	%DIFF1	R2_1	R2_2	%DIFF2
1	1	88	85	-3.41	93	88	-5.38	135	140	3.70	145	145	0.00	118.8	119	0.17	134.85	127.6	-5.38
2	1	99	94	-5.05	110	100	-9.09	140	150	7.14	170	160	-5.88	138.6	141	1.73	187	160	-14.44
3	1	91	106	16.48	106	118	11.32	170	180	5.88	195	190	-2.56	154.7	190.8	23.34	206.7	224.2	8.47
4	1	111	111	0.00	128	120	-6.25	170	170	0.00	180	180	0.00	188.7	188.7	0.00	230.4	216	-6.25
5	1	72	66	-8.33	80	70	-12.50	120	115	-4.17	130	130	0.00	86.4	75.9	-12.15	104	91	-12.50
6	1	62	64	3.23	69	70	1.45	130	130	0.00	140	140	0.00	80.6	83.2	3.23	96.6	98	1.45
7	1	123	107	-13.01	137	116	-15.33	120	145	20.83	170	160	-5.88	147.6	155.15	5.12	232.9	185.6	-20.31
9	1	85	89	4.71	94	98	4.26	150	120	-20.00	190	140	-26.32	127.5	106.8	-16.24	178.6	137.2	-23.16
10	1	99	120	21.21	117	127	8.55	130	120	-7.69	140	135	-3.57	128.7	144	11.89	163.8	171.45	4.67
11	1	102	93	-8.82	108	102	-5.56	140	145	3.57	150	150	0.00	142.8	134.85	-5.57	162	153	-5.56
12	1	98	97	-1.02	108	110	1.85	190	160	-15.79	190	170	-10.53	186.2	155.2	-16.65	205.2	187	-8.87
13	1	91	101	10.99	112	111	-0.89	120	115	-4.17	130	130	0.00	109.2	116.15	6.36	145.6	144.3	-0.89
15	1	NO DATA																	
17	2	123	119	-3.25	140	135	-3.57	135	130	-3.70	150	150	0.00	166.05	154.7	-6.84	210	202.5	-3.57
18	2	105	104	-0.95	119	113	-5.04	145	150	3.45	160	170	6.25	152.25	156	2.48	190.4	192.1	0.89
19	2	100	102	2.00	109	112	2.75	110	110	0.00	120	120	0.00	110	112.2	2.00	130.8	134.4	2.75
20	2	101	89	-11.88	108	99	-8.33	155	150	-3.23	160	155	-3.13	156.55	133.5	-14.72	172.8	153.45	-11.20
21	2	119	108	-9.24	137	120	-12.41	150	130	-13.33	165	140	-15.15	178.5	140.4	-21.34	226.05	168	-25.68
22	2	106	93	-12.26	113	100	-11.50	140	175	25.00	160	180	12.50	148.4	162.75	9.67	180.8	180	-0.44
23	2	84	83	-1.19	92	89	-3.26	135	130	-3.70	140	130	-7.14	113.4	107.9	-4.85	128.8	115.7	-10.17
24	2	74	74	0.00	79	81	2.53	170	150	-11.76	180	160	-11.11	125.8	111	-11.76	142.2	129.6	-8.86
25	2	122	117	-4.10	132	123	-6.82	160	155	-3.13	185	175	-5.41	195.2	181.35	-7.10	244.2	215.25	-11.88
26	2	118	116	-1.69	136	134	-1.47	130	140	7.69	140	150	7.14	153.4	162.4	5.87	190.4	201	5.57
27	2	111	115	3.60	123	145	17.89	110	110	0.00	110	115	4.55	122.1	126.5	3.60	135.3	166.75	23.24
28	2	103	97	-5.83	115	114	-0.87	120	135	12.50	130	145	11.54	123.6	130.95	5.95	149.5	165.3	10.57

AERWT	MEAN	93.42	94.42	1.41	105.17	102.50	-2.30	142.92	140.83	-0.89	160.83	152.50	-4.56	134.15	134.23	0.10	170.64	157.95	-6.90
	STD	16.23	16.85	10.47	19.01	18.60	8.12	22.81	21.72	10.79	24.39	19.71	7.64	33.66	36.31	11.62	44.95	41.77	9.62
	SEM	4.69	4.87	3.02	5.49	5.37	2.36	6.58	6.27	3.11	7.04	5.69	2.21	9.72	10.48	3.35	12.98	12.06	2.78
UC	MEAN	105.50	101.42	-3.73	116.92	113.75	-2.51	136.33	136.75	0.82	150.00	149.17	0.00	145.44	139.97	-3.09	175.10	168.67	-2.40
	STD	14.95	14.57	5.16	18.58	19.21	8.05	18.99	18.72	10.48	22.86	20.65	8.76	26.84	23.65	9.55	38.76	31.32	12.59
	SEM	4.32	4.21	1.49	5.36	5.54	2.32	5.48	5.40	3.03	6.60	5.96	2.53	7.75	6.83	2.76	11.19	9.04	3.63

viii) Dynamic muscle strength scores for single-arm curl (SAC), single-leg press (SLP), and single-knee extension (SKE) assessments at baseline and 3-months

Patient	GROUP	ARM1	ARM2	%DIFF	LEG1	LEG2	%DIFF	KNEE1	KNEE2	%DIFF
1	1	13	13	0.00	150	130	-13.33	42	41	-2.38
2	1	24	30	25.00	170	175	2.94	53	50	-5.66
3	1	26	28	7.69	185	197.5	6.76	67	62	-7.46
4	1	30	38	26.67	265	280	5.66	62	72	16.13
5	1	12	10	-16.67	75	80	6.67	15	11	-26.67
6	1	3	5	66.67	130	125	-3.85	39	40	2.56
7	1	16	23	43.75	135	150	11.11	36	46	27.78
9	1	1	1	0.00	70	65	-7.14	13	12	-7.69
10	1	13	18	38.46	130	145	11.54	27	36	33.33
11	1	8	9	12.50	110	110	0.00	22	29	31.82
12	1	14	16	14.29	140	125	-10.71	32	36	12.50
13	1	16	20	25.00	130	135	3.85	49	61	24.49
15	1	34	38	11.76	220	212.5	-3.41	61	65	6.56
17	2	21	18	-14.29	187.5	205	9.33	72	67	-6.94
18	2	0	0	0.00	85	85	0.00	13	12	-7.69
19	2	28	27	-3.57	190	204.5	7.63	64	68	6.25
20	2	17	19	11.76	155	150	-3.23	45	41	-8.89
21	2	2	4	100.00	115	120	4.35	40	42	5.00
22	2	22	24	9.09	120	130	8.33	28	28	0.00
23	2	26	24	-7.69	160	180	12.50	40	46	15.00
24	2	4	6	50.00	110	120	9.09	32	31	-3.13
25	2	22	20	-9.09	170	160	-5.88	52	44	-15.38
26	2	23	26	13.04	185	205	10.81	62	68	9.68
27	2	20	20	0.00	192.5	200	3.90	64	63	-1.56
28	2	19	18	-5.26	170	150	-11.76	39	38	-2.56

AERWT	MEAN	16.15	19.15	19.62	146.92	148.46	0.77	39.85	43.15	8.10
	STD	9.92	11.86	21.66	53.83	57.21	7.98	17.88	19.06	18.19
	SEM	2.75	3.29	6.01	14.93	15.87	2.21	4.96	5.29	5.05
UC	MEAN	17.00	17.17	12.00	153.33	159.13	3.76	45.92	45.67	-0.85
	STD	9.53	8.95	32.40	36.65	40.39	7.50	17.44	17.86	8.61
	SEM	2.75	2.58	9.35	10.58	11.66	2.17	5.04	5.16	2.49

ix) Six-minute walk distance (m), six-minute walk work (kJ), and body weight data (kg) for AERWT and UC groups at baseline, 3-months, and 6-months

Patient	GROUP	6MW1	6MW2	6MW3	%DIFF1	%DIFF2	WW (kJ)	WW (kJ)	WW (kJ)	%DIFF1	%DIFF2	WT (kg)	WT (kg)	WT (kg)	%DIFF1	%DIFF2
1	1	439	463.5	442.5	5.58	0.80	354.9	386.1	364.3	8.78	2.63	82.5	85	84	3.03	1.82
2	1	430.5	437.5	330	1.63	-23.34	470.4	484.5	368.7	2.99	-21.63	111.5	113	114	1.35	2.24
3	1	413	439	414	6.30	0.24	340.8	352.8	332.7	3.52	-2.38	84.2	82	82	-2.61	-2.61
4	1	472.5	462	466	-2.22	-1.38	412.1	398.4	401.9	-3.32	-2.48	89	88	88	-1.12	-1.12
5	1	420	385.5	396	-8.21	-5.71	391.0	358.9	368.7	-8.21	-5.71	95	95	95	0.00	0.00
6	1	477	480.5	396	0.73	-16.98	317.9	306.1	256.1	-3.71	-19.42	68	65	66	-4.41	-2.94
7	1	429	480	478	11.89	11.42	277.5	310.5	309.2	11.89	11.42	66	66	66	0.00	0.00
9	1	313	367.5		17.41		153.4	154.9		0.97		50	43		-14.00	
10	1	415.5	456	453	9.75	9.03	378.7	420.1	417.3	10.93	10.20	93	94	94	1.08	1.08
11	1	550.5	643.5	654	16.89	18.80	323.7	378.4	384.6	16.89	18.80	60	60	60	0.00	0.00
12	1	519.5	528	520.5	1.64	0.19	351.3	357.0	346.9	1.64	-1.26	69	69	68	0.00	-1.45
13	1	481.5	498	486	3.43	0.93	311.4	317.2	309.6	1.86	-0.59	66	65	65	-1.52	-1.52
15	1	462	462	480	0.00	3.90	575.0	575.0	597.4	0.00	3.90	127	127	127	0.00	0.00
17	2	508	541.5	520.5	6.59	2.46	403.3	445.8	428.5	10.54	6.26	81	84	84	3.70	3.70
18	2	481.5	489	445.5	1.56	-7.48	251.5	258.8	235.8	2.89	-6.26	53.3	54	54	1.31	1.31
19	2	559	554.5	562	-0.81	0.54	471.1	477.7	484.1	1.39	2.76	86	87.9	87.9	2.21	2.21
20	2	412.5	400	409	-3.03	-0.85	448.7	450.8	460.9	0.46	2.72	111	115	115	3.60	3.60
21	2	457.5	517	529.5	13.01	15.74	295.9	324.3	332.1	9.58	12.23	66	64	64	-3.03	-3.03
22	2	391.5	279	234.3	-28.74	-40.15	333.8	243.3	202.1	-27.10	-39.47	87	89	88	2.30	1.15
23	2	355.5	387	391.5	8.86	10.13	303.1	352.7	356.8	16.37	17.72	87	93	93	6.90	6.90
24	2	369	363		-1.63		245.9	249.0		1.27		68	70		2.94	
25	2	350.5	324.5		-7.42		395.0	365.7		-7.42		115	115		0.00	
26	2	528	549	592.5	3.98	12.22	470.9	489.6	522.6	3.98	10.98	91	91	90	0.00	-1.10
27	2	477	463.5		-2.83		416.0	408.8		-1.74		89	90		1.12	
28	2	552	528	538	-4.35	-2.54	486.9	455.3	464.0	-6.47	-4.70	90	88	88	-2.22	-2.22
	MEAN	459.17	477.96	459.67	3.95	-0.18	375.39	387.08	371.43	3.60	-0.54	84.27	84.08	84.08	-0.35	-0.38
AERWT	STD	43.37	62.69	79.94	6.71	11.48	81.09	77.62	83.90	7.31	11.67	20.31	20.84	20.96	1.92	1.62
	SEM	12.52	18.10	23.08	1.94	3.31	23.41	22.41	24.22	2.11	3.37	5.86	6.02	6.05	0.55	0.47
	MEAN	471.72	471.67	469.20	-0.32	-1.10	385.02	388.70	387.43	1.29	0.25	83.59	85.10	84.88	1.64	1.39
UC	STD	72.71	95.31	111.92	12.06	16.47	89.89	95.59	112.88	12.54	16.60	16.24	17.45	17.39	3.08	3.16
	SEM	24.24	31.77	37.31	4.02	5.49	29.96	31.86	37.63	4.18	5.60	5.41	5.82	5.80	1.03	1.05

x) Raw data for acute power spectrum investigations during 20-minutes supine(i), 10-minutes standing(ii), and 20-minutes post-exercise(iii) for both AERWT and UC groups at baseline

(i) Patient	Group	HR	lf peak	lf area	%lf area	lf cf	hf peak	hf area	%hf area	hf cf	lf:hf peak	lf:hf area	total area
1	1												
2	1	61	103	7030	62.1	0.071	21.8	4242	37.9	0.216	5.14	1.66	11271.2
3	1	60	51.5	4859	39.8	0.038	52.1	7279	60.2	0.198	1.01	0.689	12138.1
4	1	64.7	89.8	8312	68.2	0.067	25.6	3956	31.8	0.305	3.78	2.23	12267.3
5	1	52.4	81.9	6773	65.7	0.059	24.9	3521	34.3	0.257	3.52	2.1	10294.3
6	1	43.4	26.5	2966	27.4	0.11	77.5	7828	72.6	0.232	0.353	0.381	10794
7	1	75.7	78.2	6255	56.1	0.064	22.4	4891	43.9	0.21	3.85	1.33	11145.8
9	1	64	64.4	6059	51.7	0.06	31.8	5710	48.3	0.277	2.37	1.13	11769.2
10	1	61.4	37.7	4568	40.2	0.081	96.8	6824	59.8	0.297	0.466	0.678	11391.2
11	1	61.7	71.2	4983	49.6	0.14	77.7	5075	50.4	0.155	0.988	1.04	10058.2
12	1	60	74	6375	66.3	0.053	18.8	3309	33.7	0.161	4.3	2.07	9683.8
13	1	68.7	49.7	5431	45.6	0.06	48	6480	54.4	0.219	1.1	0.843	11910.6
15	1	77.1	77.8	6593	59.6	0.059	34.4	4393	40.4	0.322	2.34	1.56	10985.4
17	2	85.8	48.6	4781	47.4	0.071	66.4	5142	52.6	0.193	0.951	0.926	9922.79
18	2	72	48.5	6376	57.5	0.047	22.2	4714	42.5	0.296	2.27	1.45	11089.5
19	2	74.2	71.3	6844	58.6	0.077	34	4727	41.4	0.172	2.23	1.56	11571.2
20	2	74.5	71.6	6187	54.4	0.073	35.1	5204	45.6	0.231	2.39	1.21	11391
21	2	73.7	91.6	6394	60.8	0.07	45.3	4175	39.2	0.186	2.27	1.63	10568.7
22	2	84.7	55.2	6065	54.8	0.072	23.9	4953	45.2	0.223	2.39	1.25	11017.8
23	2	65.1	54.5	4743	43.8	0.068	97.9	6101	56.2	0.265	0.614	0.779	10844.4
24	2	58.5	36.5	4150	33.7	0.095	51.7	8139	66.3	0.226	0.705	0.513	12288.9
25	2												
26	2	86.4	75.8	5603	68.3	0.06	12.4	2586	31.7	0.221	6.16	2.18	8189.48
27	2	85.1	22.1	2599	22.7	0.039	35.7	8396	77.3	0.299	0.642	0.317	10994.5
28	2	72.3	58	5039	48.1	0.059	59.7	5370	51.9	0.302	1.07	1.01	10409.1

(ii) Patient	Group	HR	lf peak	lf area	%lf area	lf cf	hf peak	hf area	%hf area	hf cf	lf:hf peak	lf:hf area	total area
1	1												
2	1	63.3	106	6456	59.6	0.057	21.2	4420	40.4	0.191	5.11	1.49	10875.5
3	1	61.4	73.7	6115	49.4	0.061	43.5	6246	50.6	0.225	2.13	1.01	12361
4	1	78.4	72.9	6096	70.4	0.059	15.8	2643	29.6	0.204	5	2.47	8738.3
5	1	52.7	83.7	6009	65.5	0.058	16.5	3163	34.5	0.216	5.05	1.91	9172.16
6	1	50.2	37.5	4579	39.1	0.058	38.4	7154	60.9	0.233	0.982	0.663	11733.1
7	1	95.5	74.6	6199	63.9	0.069	15.2	3539	36.1	0.232	4.91	1.82	9737.65
9	1	71.9	85.1	7412	64.7	0.065	22.1	4062	35.3	0.279	4.35	1.84	11474.1
10	1	68.3	40	6769	53.8	0.094	51.2	6083	46.2	0.373	0.857	1.26	12851.8
11	1	82.6	85	6384	71.3	0.07	19.7	2572	28.7	0.15	4.69	2.52	8955.62
12	1	68.3	90.7	6545	72	0.054	16.7	2548	28	0.174	5.74	2.65	9092.72
13	1	67.1	41.3	5000	42.9	0.072	27.3	6647	57.1	0.511	1.51	0.752	11646.8
15	1	84.9	46.8	5362	59.3	0.052	39.8	36.34	40.7	0.32	1.37	1.5	8995.17
17	2	110	123	7607	66.1	0.069	25.6	3912	33.9	0.213	4.93	1.95	11519.5
18	2	73.9	36.2	4302	49.2	0.057	33.6	4540	50.8	0.38	1.08	1.02	8842.13
19	2	74.5	53.6	5313	58.2	0.084	49.5	3793	41.8	0.164	1.29	1.55	9106.55
20	2	84.9	86.4	6137	67.1	0.075	16	3045	32.9	0.182	5.76	2.1	9182.33
21	2	80.8	53.2	5920	58.4	0.083	32	4127	41.6	0.212	1.69	1.48	10047
22	2	92.3	54.3	5108	65.8	0.072	16.8	2963	34.2	0.257	3.33	2.14	8070.24
23	2	75.5	68	5736	62.9	0.079	18.1	3470	37.1	0.183	3.84	1.74	9206.05
24	2	57.7	42.9	5343	39.9	0.092	41.8	8008	60.1	0.208	1.14	0.697	13351.1
25	2												
26	2	103	83.9	6893	76.1	0.072	13.1	2138	23.9	0.17	6.82	3.31	9030.94
27	2	88.1	37.6	5035	42.9	0.079	30.2	6697	57.1	0.367	1.27	0.779	11731.4
28	2	73.4	88.6	6727	55.6	0.076	23.2	5368	44.4	0.28	3.8	1.27	12094.7

(iii) Patient	Group	HR	lf peak	lf area	%lf area	lf cf	hf peak	hf area	%hf area	hf cf	lf:hf peak	lf:hf area	total area
1	1												
2	1	67.7	58.8	5932	53.5	0.072	39.3	5241	46.5	0.293	1.7	1.24	11172.9
3	1	65	79.4	6835	51.7	0.099	34.5	6374	48.3	0.15	2.3	1.07	13209.6
4	1	72.7	68.3	6982	69	0.067	21.7	3187	31	0.23	3.21	2.28	10169.9
5	1	50.2	92.4	7103	71.5	0.059	20.3	2806	28.5	0.28	4.87	2.6	9909.57
6	1	44.7	30.5	3396	30.9	0.085	75.1	7522	69.1	0.243	0.409	0.449	10918.1
7	1	78.5	92.5	7063	71.4	0.063	16.1	2776	28.6	0.168	5.74	2.58	9839.03
9	1	69.5	70.6	5556	55.4	0.064	33.9	4513	44.6	0.306	2.5	1.28	10069.1
10	1	75.9	25.4	3389	30.8	0.1	97.7	7493	69.2	0.325	0.263	0.455	10881.4
11	1	72.9	93.3	9793	64.3	0.058	22	3742	35.7	0.173	4.31	1.81	10535
12	1	63.8	93.7	7374	71.2	0.055	19.5	2963	28.8	0.174	5.13	2.53	10337.2
13	1	71.9	39.2	3916	35.7	0.067	47.5	7027	64.3	0.201	0.842	0.598	10942.3
15	1	85.4	95.2	5889	54.4	0.069	27.1	4797	45.6	0.338	3.65	1.24	10686
17	2	97.1	78	6085	61.4	0.068	40.9	3718	38.6	0.224	2.65	1.67	9803.06
18	2	74.5	47.1	5615	56.3	0.062	35.4	4485	43.7	0.379	1.4	1.48	10100.2
19	2	76.2	59.4	5639	64.7	0.071	21	3090	35.3	0.179	3.32	1.93	8728.82
20	2	80.9	85.4	6430	66.5	0.081	21.2	3197	33.5	0.199	4.32	2.04	9626.61
21	2	79.2	93.5	7327	62.5	0.079	37.5	4418	37.5	0.217	3.13	1.75	11745.5
22	2	89.2	51.1	5708	53.8	0.064	31.8	4917	46.2	0.312	1.81	1.23	10625.2
23	2	60.6	48	5122	46.3	0.069	44.1	6000	53.7	0.255	1.33	0.871	11122.7
24	2	60.4	59.6	5781	49	0.06	31.5	5970	51	0.221	1.99	0.985	11751
25	2												
26	2	92.9	116	6996	77.3	0.052	11.1	2070	22.7	0.17	10.7	3.43	9066.53
27	2	95.9	25.8	3639	31.3	0.082	58.8	7974	68.7	0.303	0.542	0.461	11613
28	2	72.8	67.6	6249	59.9	0.064	54.1	4069	40.1	0.337	1.44	1.6	10317.7

xi) Raw data for acute power spectrum investigations during 20-minutes supine(i), 10-minutes standing(ii), and 20-minutes post-exercise(iii) for both AERWT and UC groups at 3-months

(i) Patient	Group	HR	lf peak	lf area	%lf area	lf cf	hf peak	hf area	%hf area	hf cf	lf:hf peak	lf:hf area	total area
1	1												
2	1	54.8	67.5	7452	69.4	0.067	26	3220	30.6	0.279	2.72	2.34	10672.3
3	1	61	82.2	6150	63.3	0.067	22.7	3546	36.7	0.154	3.65	1.75	9695.69
4	1	67.7	61.1	6240	66.7	0.065	18.6	3168	33.3	0.206	3.38	2.22	9408.04
5	1	50.6	69.6	6413	59.1	0.064	28.2	4421	40.9	0.182	2.58	1.47	10834.1
6	1	42.2	26.6	3267	27.3	0.12	87.1	8581	72.7	0.237	0.32	0.389	11847.8
7	1	66.4	68.5	5789	57.9	0.064	19.3	4167	42.1	0.198	3.59	1.43	9956.07
9	1	73	79.8	6165	63.6	0.062	24.4	3563	36.4	0.284	3.58	1.82	9728.55
10	1	71.8	34.8	4679	41.6	0.11	81.1	6500	58.4	0.326	0.487	0.727	11179
11	1	64.5	75.4	5710	50.3	0.066	46.5	5662	49.7	0.215	2.03	1.06	11372.1
12	1	69.6	64.1	6843	57.8	0.076	27.5	4868	42.2	0.261	2.41	1.44	11710.6
13	1												
15	1												
17	2	79.4	71.6	6779	58.3	0.064	39.5	4783	41.7	0.183	1.88	1.42	11561.8
18	2	76.3	72.3	6512	56.8	0.069	22.3	4823	43.2	0.181	3.24	1.34	11335.7
19	2	76.4	77.7	6959	63.3	0.058	25.9	4115	36.7	0.199	3.56	1.81	11074.4
20	2	72.3	93.8	6247	63.2	0.057	24.1	3644	36.8	0.207	4.11	1.79	9890.62
21	2	66.6	76	6030	54.5	0.061	36.8	4806	45.5	0.18	2.15	1.26	10836.9
22	2	79.1	59.3	6230	49.9	0.074	39.3	6257	50.1	0.288	1.52	1.01	12486.4
23	2	64.1											
24	2	67.2	40.1	4328	35.1	0.062	67.4	7932	64.9	0.275	0.618	0.546	12259.3
25	2												
26	2	73.8											
27	2	89.6	42.1	4301	40.8	0.073	32.4	5839	59.2	0.255	1.28	0.707	10139.8
28	2	70.2	55	5678	52.3	0.082	54.5	5220	47.7	0.277	1.16	1.15	10898.8

(ii) Patient	Group	HR	lf peak	lf area	%lf area	lf cf	hf peak	hf area	%hf area	hf cf	lf:hf peak	lf:hf area	total area
1	1												
2	1	59.6	79.9	6333	55.7	0.068	23.7	5062	44.3	0.174	3.41	1.26	11395
3	1	67.1	104	6866	59.3	0.065	24	4629	40.7	0.185	4.38	1.5	11494.7
4	1	78.2	85	6978	68.2	0.061	30.5	3295	31.8	0.376	2.77	2.17	10272.1
5	1	50.4	80.5	5920	63.3	0.068	18.9	3419	36.7	0.184	4.26	1.73	9339.28
6	1	50.2	104	6570	64.4	0.071	21.3	3654	35.6	0.181	4.91	1.84	10223.7
7	1	86.2	92.2	6741	65.5	0.074	16.9	3538	34.5	0.15	5.89	1.96	10279.1
9	1	81	75.1	5531	60.5	0.064	18	3520	39.5	0.31	4.09	1.56	9050.67
10	1	90.8	42.8	6832	58.4	0.098	31.7	4706	41.6	0.352	1.36	1.52	11538
11	1	79.3	68.6	5534	64.5	0.076	19	3031	35.5	0.174	3.61	1.82	8564.91
12	1	76	58.4	6294	56.1	0.062	22.5	5130	43.9	0.243	2.7	1.33	11424.6
13	1												
15	1												
17	2	103	67.9	6717	66	0.084	21.6	3463	34	0.15	3.15	1.94	10180.8
18	2	77.7	56	5951	51.2	0.038	43.2	5523	48.8	0.404	1.37	1.09	11474
19	2	76.9	85	6915	65.7	0.059	21.2	3560	34.3	0.277	4.18	2.19	10474.8
20	2	80.5	119	7248	72.3	0.074	13.9	2770	27.7	0.221	8.61	2.64	10018.3
21	2	83.3	88.8	7451	63.5	0.077	31	4286	36.5	0.18	3.05	1.77	11736.7
22	2	81.1	61.7	4803	56.2	0.067	17.4	3881	43.8	0.188	3.67	1.32	8683.98
23	2	74.8	93.3	6440	64.9	0.061	19.6	3542	35.1	0.15	5.91	1.87	9981.64
24	2	64.6	36.7	4413	32.4	0.13	39.6	9208	67.6	0.217	0.927	0.48	13621.2
25	2												
26	2												
27	2	92.4	49.6	5250	48.3	0.075	23.9	5998	51.7	0.292	2.16	0.983	11248.2
28	2	76.7	68.5	6459	64	0.064	21.2	3605	36	0.191	3.27	1.82	10064

(iii) Patient	Group	HR	lf peak	lf area	%lf area	lf cf	hf peak	hf area	%hf area	hf cf	lf:hf peak	lf:hf area	total area
1	1												
2	1	62.3	71.5	6328	56.4	0.059	34.4	4870	43.6	0.279	2.22	1.36	11197.8
3	1	71.2	69.8	6138	59	0.084	27.5	4251	41	0.159	2.67	1.49	10388.8
4	1	70.3	85	6991	66.6	0.067	20.4	3518	33.4	0.179	4.51	2.17	10509.3
5	1	48	82.1	6842	62.3	0.065	25.3	4080	37.7	0.203	3.47	1.71	10921.6
6	1	45	28	3065	27.4	0.098	84.3	8192	72.6	0.242	0.354	0.378	11256.8
7	1	71.9	84.6	7642	74	0.065	18.1	2527	26	0.221	4.69	3.64	10169.3
9	1	71.7	80.4	6508	69	0.054	16.5	2922	31	0.196	5.4	2.27	9430.38
10	1	92	27.3	4883	44.4	0.092	103	6038	55.6	0.35	0.355	0.805	10920.6
11	1	72.2	76.1	5843	56.8	0.07	34.5	4287	43.2	0.214	2.59	1.49	10130
12	1	74.6	71.2	6835	53.3	0.072	27.9	6541	46.7	0.185	3.21	1.25	13375.8
13	1												
15	1												
17	2	92.6	70.6	6486	61.1	0.064	36.7	4084	38.9	0.213	2.32	1.63	10569.6
18	2	77.3	71.4	6587	60.3	0.051	22	4300	39.7	0.356	3.32	1.55	10887
19	2	79.7	95.4	6725	71.9	0.064	16.1	2592	28.1	0.164	6.15	2.6	9317.42
20	2	72.2	83.6	6895	70.1	0.066	22.4	2941	29.9	0.206	4.27	2.38	9836.72
21	2	75	56.8	5610	57.3	0.079	32.2	4208	42.7	0.191	1.8	1.36	9817.92
22	2	77.8	49.7	5173	45.5	0.078	38.4	6163	54.5	0.188	1.52	0.85	11336.3
23	2	63.1	56.6	5902	45.9	0.085	49.1	6950	54.1	0.213	1.29	0.853	12852.7
24	2	66.7	33.2	3685	32.7	0.054	62.8	7665	67.3	0.315	0.615	0.499	11349.8
25	2												
26	2	94.1	93.8	7063	73.8	0.065	19.5	2496	26.2	0.156	5.03	3	9559.04
27	2	93.8	93.6	6811	62.5	0.07	20.8	4047	37.5	0.234	4.58	1.69	10858.1
28	2	78.3	84.1	6552	61.8	0.072	27.6	4157	38.2	0.242	4.09	1.69	10708.5

xii) Raw data for acute power spectrum investigations during 20-minutes supine(i), and 10-minutes standing(ii) for both AERWT and UC groups at 6-months

(i) Patient	Group	HR	lf peak	lf area	%lf area	lf cf	hf peak	hf area	%hf area	hf cf	lf:hf peak	lf:hf area	total area
1	1												
2	1	71.9	55.5	5104	46	0.061	68.5	5802	54	0.335	0.91	0.888	10906.1
3	1	56.7	79.5	6500	53.5	0.076	32.7	6183	47.5	0.205	2.63	1.15	12682.4
4	1	58.1	94.8	7035	66.6	0.058	23.5	3504	33.4	0.278	4.63	2.24	10539.3
5	1	53.8	90.4	7492	60.9	0.073	24.9	4898	39.1	0.192	4.11	1.58	12389.7
6	1	47.2	34	3675	28.6	0.034	68.8	8978	71.4	0.256	0.523	0.413	12653.2
7	1	64	120	7885	66.5	0.062	21.3	4000	33.5	0.182	6.35	2.01	11884.7
9	1												
10	1	74.2	40.1	6041	51.7	0.1	75.6	5634	48.3	0.326	0.568	1.09	11674.8
11	1	64.1	43.7	4792	43.7	0.096	74.5	6146	56.3	0.195	0.616	0.786	10938.1
12	1	64.1	50.9	5287	49.5	0.026	29	5526	50.5	0.22	2.14	1.04	10812.4
13	1												
15	1	64.5	92.5	6757	61	0.045	30.7	4441	39	0.327	3.2	1.73	11197.8
17	2	82.1	67.5	6036	57.3	0.054	36.8	4506	42.7	0.209	1.94	1.4	10542.9
18	2	76.7	45.2	5940	51.9	0.035	35.9	5540	48.1	0.39	1.41	1.24	11480.9
19	2	75.2	75.4	6606	57.3	0.086	26.4	4991	42.7	0.181	2.94	1.39	11596.5
20	2	65.9	87.7	6822	65.2	0.065	21.1	3619	34.8	0.215	4.25	1.93	10440.6
21	2	65	53.4	4154	47.6	0.063	50.1	4545	52.4	0.199	1.14	0.915	8698.97
22	2	80.7	53	5656	47.5	0.07	33.9	6318	52.5	0.236	1.63	0.913	11974.5
23	2	81.6	60.2	5322	44.2	0.066	57.4	6679	55.8	0.228	1.32	0.832	12001.8
24	2												
25	2												
26	2	88.9	75.6	6076	66.3	0.073	18.6	3069	33.7	0.183	4.04	2	9144.81
27	2												
28	2	86.6	69.3	6856	60.8	0.08	27	4375	39.2	0.225	2.79	1.63	11231.3

(ii) Patient	GROUP	HR	lf peak	lf area	%lf area	lf cf	hf peak	hf area	%hf area	hf cf	lf:hf peak	lf:hf area	total area
1	1												
2	1	73.2	76	6191	61.3	0.056	27.7	3840	38.7	0.403	2.69	1.67	10031.6
3	1	62	86	6241	56.4	0.064	23.4	4838	43.6	0.247	3.66	1.33	11078.8
4	1	66.6	82.4	7099	65.7	0.069	21.4	3744	34.3	0.32	3.9	1.99	10843.5
5	1	55.4	79.9	7265	64.6	0.06	23.4	4096	35.4	0.15	3.78	1.87	11360.7
6	1	55.7	57.3	5299	49.2	0.073	23.6	5565	50.8	0.212	2.57	1.02	10864.2
7	1	81.3	90.5	6812	63.1	0.072	19	3980	36.9	0.15	4.74	1.71	10792.6
9	1												
10	1	93.1	52.7	5230	46.5	0.091	28.1	6036	53.5	0.171	1.87	0.871	11266.4
11	1	77.7	58	5928	60.6	0.072	29.9	3867	39.4	0.174	1.99	1.55	9795.02
12	1	72.2	104	7506	57.5	0.069	21.9	5428	42.5	0.196	4.71	1.37	12933.2
13	1												
15	1	79.9	68.2	7317	61.4	0.073	31.3	4585	38.6	0.416	2.43	1.74	11901.2
17	2	107	76.5	5969	66.1	0.072	205	3109	33.9	0.178	3.79	1.96	9077.57
18	2	78.9	59.1	5871	43.3	0.064	33.9	7650	56.7	0.327	1.93	0.792	13521.7
19	2	85.2	68.7	6954	65.1	0.065	24.9	3601	34.9	0.221	2.77	1.95	10554.6
20	2	76.6	97	6544	68.4	0.074	19.1	3000	31.6	0.26	5.17	2.33	9544.17
21	2	78.7	61.2	6101	60.9	0.076	23.5	3922	39.1	0.15	2.6	1.56	10023.1
22	2	84.2	46.9	4881	47.9	0.1	27	5357	52.1	0.21	1.79	0.938	10237.8
23	2	68.2	65.9	7033	61.7	0.064	24.7	4356	38.3	0.244	2.68	1.97	11388.9
24	2												
25	2												
26	2	105	79.2	4909	68.3	0.067	11.7	2337	31.7	0.171	6.9	2.21	7246.74
27	2												
28	2	86.6	69.3	6856	60.8	0.08	27	4375	39.2	0.225	2.79	1.63	11231.3

xiii) Mean 24-hour heart rate and NN-interval, SDNN, and SDANN time domain HRV parameters derived from 24-hour ambulatory holter monitoring at baseline, 3-months, and 6-months

Patient	Group	HR_1	HR_2	HR_3	%DIFF1	%DIFF2	NN_1	NN_2	NN_3	%DIFF1	%DIFF2	SD_1	SD_2	SD_3	%DIFF1	%DIFF2	SA_1	SA_2	SA_3	%DIFF1	%DIFF2
1	1	86.9	82.1	80.6	-5.59	-7.25	690.3	731.2	744.3	5.92	7.82	163.8	126.5	96.6	-22.8	-41.0	170.4	126.9	73.0	-25.5	-57.1
2	1	68.0	62.0	72.9	-8.69	7.30	883.0	967.0	823.0	9.52	-6.80	108.4	123.0	71.7	13.5	-33.8	100.6	115.2	63.4	14.4	-37.0
3	1	70.0	72.1	67.2	3.09	-3.98	857.5	831.8	893.0	-3.00	4.14	83.5	110.5	126.1	32.4	51.0	73.6	92.6	94.1	25.9	27.8
4	1	70.8	74.3	66.1	5.04	-6.62	847.8	807.1	907.9	-4.80	7.09	166.5	173.6	149.6	4.2	-10.2	146.8	158.4	132.1	7.9	-10.0
5	1	56.8	57.3	60.5	0.90	6.45	1055.7	1046.3	991.7	-0.89	-6.06	144.5	151.4	204.2	4.8	41.3	138.5	153.8	163.3	11.1	17.9
6	1	53.4	53.2	54.3	-0.51	1.58	1122.7	1128.4	1105.2	0.51	-1.56	150.7	139.1	152.0	-7.7	0.8	138.6	120.9	138.0	-12.8	-0.5
7	1	84.7	81.8	76.0	-3.43	-10.25	708.3	733.5	789.2	3.55	11.42	108.7	154.9	156.3	42.4	43.8	98.5	134.5	144.9	35.2	45.6
9	1	73.3					818.1					86.3					80.2				
10	1	68.2	77.5	85.4	13.70	25.27	880.3	774.3	702.7	-12.05	-20.17	171.2	141.4	136.8	-17.4	-20.1	158.2	130.2	132.3	-17.7	-16.4
11	1	77.7	81.1	78.8	4.46	1.48	772.6	739.7	761.3	-4.27	-1.46	199.9	155.2	160.6	-22.4	-19.7	185.5	146.7	151.9	-20.9	-18.1
12	1	73.6	77.8	74.0	5.82	0.55	815.6	770.8	811.1	-5.50	-0.55	118.9	110.5	123.4	-7.1	3.8	105.7	84.0	96.7	-20.5	-8.4
13	1	76.4	83.1	79.3	8.77	3.80	785.2	721.9	756.5	-8.07	-3.66	148.4	104.7	93.7	-29.4	-36.8	138.8	62.8	79.5	-54.7	-42.7
15	1	84.4	77.7	77.0	-7.99	-8.81	710.5	772.2	779.2	8.69	9.66	98.9	115.3	156.6	16.6	58.4	90.4	104.7	123.3	15.8	36.5
17	2	96.5	95.4	93.0	-1.08	-3.66	621.8	628.6	645.4	1.10	3.80	159.8	112.7	99.5	-29.5	-37.7	157.2	111.7	92.2	-29.0	-41.4
18	2	76.0	78.1	80.6	2.83	6.15	790.0	768.2	744.4	-2.75	-5.77	77.1	50.9	42.1	-34.0	-45.4	67.2	41.9	34.0	-37.6	-49.4
19	2																				
20	2	78.5	78.0		-0.56		764.7	769.0		0.56		122.8	122.4		-0.3		104.7	103.6		-1.1	
21	2	85.8	81.1	77.0	-5.46	-10.16	699.6	740.0	778.8	5.77	11.31	111.2	142.3	161.8	28.0	45.6	107.4	136.2	156.6	26.8	45.7
22	2	85.3	83.2	89.0	-2.47	4.34	703.5	721.4	674.3	2.54	-4.16	80.1	99.6	58.8	24.3	-26.6	71.8	91.3	46.8	27.1	-34.8
23	2	75.0	71.4	62.4	-4.80	-16.72	800.5	840.9	961.2	5.04	20.07	142.4	165.4	142.8	16.2	0.3	132.6	155.7	128.1	17.4	-3.4
24	2	57.3	62.8		9.65		1047.6	955.4		-8.80		78.4	98.6		25.8		71.3	91.6		28.4	
25	2	85.1	82.3	94.0	-3.31	10.40	704.9	729.0	638.5	3.43	-9.42	75.9	126.9	76.5	67.2	0.9	56.7	92.9	61.0	63.6	7.6
26	2	90.0	91.3	94.5	1.42	4.93	666.3	657.0	635.1	-1.40	-4.69	86.3	90.4	96.5	4.8	11.8	78.3	77.6	89.4	-1.0	14.1
27	2	86.7	93.6		7.94		691.8	640.8		-7.36		74.9	59.0		-21.2		70.8	55.7		-21.4	
28	2	79.8	78.6	87.9	-1.46	10.24	752.3	763.5	682.4	1.49	-9.29	92.0	105.9	88.1	15.1	-4.2	79.1	82.8	79.1	17.3	0.0

AERWT	MEAN	72.57	73.35	72.67	1.30	0.79	844.13	835.34	838.76	-0.87	-0.01	138.62	133.83	135.83	0.59	3.13	128.87	119.23	116.05	-3.48	-9.20
	STD	10.45	10.24	9.03	6.85	9.73	133.06	136.08	116.51	6.72	8.85	34.80	21.99	36.00	22.64	36.45	34.54	29.01	33.34	25.91	32.20
	SEM	3.02	2.96	2.61	1.98	2.81	38.41	39.28	33.63	1.94	2.55	10.05	6.35	10.39	6.54	10.52	9.97	8.38	9.62	7.48	9.30
UC	MEAN	84.17	82.67	84.80	-1.78	0.69	717.36	731.07	719.99	1.90	0.23	103.09	111.75	95.76	11.51	-6.93	93.61	100.01	85.91	10.59	-7.69
	STD	7.20	7.82	11.02	2.87	9.90	80.71	86.16	110.28	2.95	10.64	32.01	34.60	40.11	32.43	29.37	35.33	35.05	40.90	32.65	32.18
	SEM	2.55	2.69	3.90	1.01	3.50	21.46	23.39	38.99	1.04	3.76	11.32	12.23	14.18	11.47	10.38	12.49	12.39	14.46	11.54	11.38

xiv) SDNN-Index, pNN50, and r-MSSD time domain HRV parameters derived from 24-hour ambulatory holter monitoring at baseline, 3-months, and 6-months

Patient	GROUP	SI_1	SI_2	SI_3	%DIFF1	%DIFF2	PN_1	PN_2	PN_3	%DIFF1	%DIFF2	RM_1	RM_2	RM_3	%DIFF1	%DIFF2
1	1	40.64	71.96	52.49	77.07	29.16	8.8	14	47.2	59.09	436.36	48.53	90.38	166.18	86.26	242.46
2	1	35.03	39.05	26.93	11.48	-23.12	1.35	2.7	0.464	100.00	-65.63	29.38	33.05	19.18	12.49	-34.72
3	1	35.49	37.57	106.2	5.86	199.24	7.73	6.81	15.2	-11.90	96.64	29.66	29.85	56.49	0.64	90.47
4	1	57.53	48.05	56.66	-16.48	-1.51	9.06	0.645	0.763	-92.88	-91.58	29.14	15.47	15.92	-46.90	-45.37
5	1	63.63	89.96	120.6	41.38	89.53	3.09	9.67	14.9	212.94	382.20	26.57	48.51	65.47	82.58	146.43
6	1	42.81	52.38	54.49	22.35	27.28	8.22	10.4	11.7	26.52	42.34	34.62	48.95	44.42	41.42	28.32
7	1	39.33	67.28	52.07	71.07	32.39	2.32	6.35	1.6	173.71	-31.03	19.88	34.97	19.41	75.94	-2.33
9	1	25.79					2.87					22.46				
10	1	38.75	37.95	30.22	-2.06	-22.01	6.72	6.53	1.93	-2.83	-71.28	29.83	28.53	20.23	-4.37	-32.20
11	1	81.47	48.25	51.16	-40.78	-37.20	14.9	6.33	7.8	-57.52	-47.65	43.84	27.97	29.47	-36.21	-32.77
12	1	48.61	68.04	72.55	39.97	49.25	11.2	19.5	22.8	74.11	103.57	47.12	58.18	66.14	23.48	40.37
13	1	67.82	79.03	46.51	16.53	-31.42	14.8	33.5	33.2	126.35	124.32	60.56	104.13	69.31	71.93	14.43
15	1	40.59	60.08	119.3	48.02	193.91	23.1	5.96	17.5	-74.20	-24.24	51.44	37.82	59.33	-26.47	15.33
17	2	48.93	41.21	40.95	-15.78	-16.31	13.9	4.56	4	-67.19	-71.22	38.56	23.69	23.61	-38.56	-38.77
18	2	29.85	23.26	22.76	-22.08	-23.75	2.84	2.43	4.05	-14.44	42.61	19.02	20.79	24.34	9.31	27.98
19	2															
20	2	56.67	57.35		1.20		4.17	2.88		-30.94		25.61	22.50		-12.17	
21	2	33.14	42.15	38.62	27.19	16.54	11.3	7.82	5.85	-30.80	-48.23	31.84	28.17	26.10	-11.54	-18.05
22	2	31.66	38.78	31.63	22.49	-0.09	7.35	8.21	9.42	11.70	28.16	33.94	36.45	40.98	7.39	20.72
23	2	60.71	60.6	61.23	-0.18	0.86	6.75	8.27	8.61	22.52	27.56	39.62	38.44	40.64	-2.99	2.58
24	2	31.17	28.06		-9.98		12.4	9.63		-22.34		37.03	30.70		-17.11	
25	2	48.52	91.91	42.16	89.43	-13.11	16.8	28	11.8	66.67	-29.76	59.63	82.87	45.42	38.96	-23.83
26	2	38.16	58.65	43.59	53.69	14.23	6.03	10.9	5.73	80.76	-4.98	38.21	52.75	39.82	38.05	4.22
27	2	22.04	18.17		-17.56		2.83	1.25		-55.83		20.08	14.00		-30.30	
28	2	40.9	45.22	38.52	10.56	-5.82	1.59	1.3	2.68	-18.24	68.55	19.54	17.89	20.19	-8.47	3.34
	MEAN	49.31	58.30	65.77	22.87	42.12	9.27	10.20	14.59	44.45	71.17	37.55	46.48	52.63	23.40	85.87
AERWT	STD	14.92	17.20	32.31	34.65	81.18	6.16	8.86	14.33	97.73	174.41	12.34	26.44	41.34	47.94	85.93
	SEM	4.31	4.96	9.33	10.00	23.43	1.78	2.56	4.14	28.21	50.35	3.56	7.63	11.94	13.84	24.81
	MEAN	41.48	50.22	39.93	20.67	-3.43	8.32	8.94	6.52	6.37	1.59	35.05	37.63	32.64	4.02	-2.73
UC	STD	10.61	20.51	10.96	36.95	14.23	5.29	8.36	3.14	49.70	48.34	12.85	21.49	9.98	25.85	22.63
	SEM	3.75	7.25	3.87	13.06	5.03	1.87	2.96	1.11	17.57	17.09	4.54	7.60	3.53	9.14	8.00

APPENDIX C:

Multivariate Analysis of Variance and Chi-Square Summary Tables

MANOVA Summary Tables

1. Baseline Patient Demographics of Age, Weight, Height, BMI, CHF Duration, and Left-Ventricular Ejection Fraction

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Group	0.703443	1.475527	6	21	0.234

Marked effects at $p<0.05$

2. Baseline and 3-month Follow-up Assessments of Left-Ventricular Ejection Fraction, Peak Relative Oxygen Uptake (ml/kg/min), Peak Absolute Oxygen Uptake (L/min), Anaerobic Threshold as a Percentage of the Predicted Maximal VO_2 Based on a Healthy Population, Anaerobic Threshold in Absolute Terms (ml/min), Maximal Power Output (Watts), Maximal Exercise Duration (min), and Dynamic Muscle Strength Scores (kg) of Single-Arm Curl (SAC), Single-Leg Press (SLP), and Single-Knee Extension (SKE)

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Group (G)	0.465972	1.489868	10	13	0.246
Time (T)	0.442588	1.637267	10	13	0.200
G x T	**0.245306**	**3.999503**	**10**	**13**	**0.011**

Marked effects at $p<0.05$

3. Expired Ventilation ($\dot{V}E$), Expired Carbon Dioxide ($\dot{V}CO2$), and $\dot{V}E$:$\dot{V}CO2$ Ratio Based Upon Three Successive Workloads of the Symptom-Limited Incremental Cycle Ergometery Test at Baseline and 3-Months

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Group (G)	0.816183	1.27622	3	17	0.314
Workload(W)	**0.028795**	**78.69981**	**6**	**14**	**0.000**
Time (T)	0.884099	0.74288	3	17	0.541

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
G x W	0.478422	2.54381	6	14	0.070
G x T	0.860657	0.91745	3	17	0.453
W x T	**0.439799**	**2.97211**	**6**	**14**	**0.044**
G x W x T	0.484230	2.48531	6	14	0.075

Marked effects at $p<0.05$

4. Heart Rate, Systolic Blood Pressure, and Double Product for Two Successive Stages of Modified Bruce Protocol During Symptom-Limited Incremental Cycle Ergometry at Baseline and 3-Months

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Group (G)	0.818479	1.47853	3	20	0.251
Stage (S)	**0.083647**	**73.03355**	**3**	**20**	**0.000**
Time (T)	0.875615	0.94703	3	20	0.437
G x S	0.876205	0.94190	3	20	0.439
G x T	0.941100	0.41724	3	20	0.743
S x T	0.805939	1.60526	3	20	0.220
G x S x T	0.803374	1.63167	3	20	0.214

Marked effects at $p<0.05$

5. Comparison of the Recovery of Power Spectral Indices in the Supine and Post-Exercise Conditions (mean heart rate (HR), low-frequency peak power (LP), low-frequency area (LA), low-frequency fractional power (PL), and low-frequency power central frequency (LC))

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Group (G)	0.512478	2.473392	5	13	0.087

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Condition(C)	**0.259898**	**7.403918**	**5**	**13**	**0.002**
Time (T)	0.928540	0.200096	5	13	0.957
G x C	0.719395	1.014146	5	13	0.448
G x T	0.568412	1.974147	5	13	0.149
C x T	0.743810	0.895516	5	13	0.512
G x C x T	0.952028	0.131011	5	13	0.982

Marked effects at $p<0.05$

6. Comparison of the Recovery of Power Spectral Indices in the Supine and Post-Exercise Conditions (high-frequency peak power (HP), high-frequency area (HA), fractional high-frequency power (PL), high-frequency central frequency (HC), LF:HF peak ratio (RP), and LF:HF area ratio (RA))

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Group (G)	0.551740	1.624893	6	12	0.223
Condition (C)	0.481860	2.150582	6	12	0.122
Time (T)	0.837978	0.386697	6	12	0.874
G x C	0.591470	1.381406	6	12	0.298
G x T	0.751757	0.660436	6	12	0.683
C x T	0.577899	1.460813	6	12	0.271
G x W x T	0.754418	0.651050	6	12	0.690

Marked effects at $p<0.05$

7. Comparison of SDNN-Index, pNN50, and r-MSSD Time Domain Parameters Derived from 24-Hour Ambulatory Holter Monitoring at Baseline, 3-Months, and 6-Months

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Group (G)	0.901604	0.582052	3	16	0.635
Time (T)	0.935050	0.370464	3	16	0.775
G x T	0.656801	2.786838	3	16	0.074

Marked effects at $p<0.05$

8. Comparison of 24-Hour Heart Rate and NN-Interval, SDNN, and SDANN Time Domain Parameters Derived from 24-Hour Ambulatory Holter Monitoring at Baseline, 3-Months, and 6-Months

Effect	Wilks' Lambda	Rao's R	df 1	df 2	p-level
Group (G)	0.730497	1.383492	4	15	0.287
Time (T)	0.815590	0.847899	4	15	0.517
G x T	0.692168	1.667760	4	15	0.210

Marked effects at $p<0.05$

CHI-SQUARE ANALYSIS Summary Tables

1. Baseline Patient Demographics: Analysis of Gender

	AERWT	UC	TOTAL
MALE	11	10	21
FEMALE	5	2	7
TOTAL	16	12	28

Chi-Square=0.78, df=1; p=0.3778
Yates Corrected Chi-Square=0.19, df=1; p=0.6592

2. Baseline Patient Demographics: Analysis of NYHA Functional Class

	NYHA CLASS I	II	III	TOTAL
AERWT	1	9	6	16
UC	0	7	5	12
TOTAL	1	16	11	28

Observed-Expected Contingency Table

Cell Row Column (Group)(Class)		Observed Frequency (O)	Expected Frequency (E)	O - E	$(O - E)^2$	$(O - E)^2/E$
1	1	1	0.57	0.43	0.1849	0.324386
1	2	9	9.14	-0.14	0.0196	0.002144
1	3	6	6.29	-0.29	0.0841	0.013370
2	1	0	0.43	-0.43	0.1849	0.420000
2	2	7	6.86	0.14	0.0196	0.002857
2	3	5	4.71	0.29	0.0841	0.017856

Cell Row Column (Group)(Class)	Observed Frequency (O)	Expected Frequency (E)	O - E	$(O - E)^2$	$(O - E)^2/E$
$\sum$	28	28	0		χ^2_{obs}=0.78061

χ^2_{obs}=0.78061 (df=2, p=0.978252), χ^2_{crit} (0.05, 2)=5.99

3. Baseline Patient Demographics: Analysis of Etiology of CHF (Ichemic, Idiopathic, Hypertensive, Viral)

	ETIOLOGY				
	ISCH	**IDIO**	**HYPER**	**VIRAL**	**TOTAL**
AERWT	12	1	3	0	16
UC	9	1	0	2	12
TOTAL	21	2	3	2	28

Observed-Expected Contingency Table

Cell Row Column (Group)(Etiology)		Observed Frequency (O)	Expected Frequency (E)	O - E	$(O - E)^2$	$(O - E)^2/E$
1	1	12	12	0	0	0
1	2	1	1.14	-0.14	0.020	0.018
1	3	3	1.71	1.29	1.66	0.97
1	4	0	1.14	-1.14	1.30	1.14
2	1	9	9	0	0	0
2	2	1	0.86	0.14	0.020	0.023
2	3	0	1.29	-1.29	1.66	1.29
2	4	2	0.86	1.14	1.30	1.51
$\sum$		28	28	0		χ^2_{obs}=4.95

χ^2_{obs}=4.95 (df=3, p=0.665539), χ^2_{crit} (0.05, 3)=7.81

4. Independent Analyses of Improvements in Power Spectral Response to Orthostatic Stress

a) **Evaluator 1 (T.C.B.): 2 X 2 TABLE**

	IMPROVEMENT YES	NO	TOTAL
AERWT	6	5	11
UC	2	8	10
TOTAL	8	13	21

Chi-Square=2.65, df=1; p=0.1035
Yates Corrected Chi-Square=1.39, df=1; p=0.2387

b) **Evaluator 2 (E.L.F.): 2 X 2 TABLE**

	IMPROVEMENT YES	NO	TOTAL
AERWT	7	4	11
UC	2	8	10
TOTAL	9	12	21

Chi-Square=4.07, df=1; p=0.0436
Yates Corrected Chi-Square=2.49, df=1; p=0.1149

5. Phi Coefficient for Relationship of Independent Evaluations of Improvement in Power Spectral Response to Orthostatic Stress

		T.C.B. IMPROVEMENT YES	NO	TOTAL
E.L.F. IMPROVEMENT	**YES**	7	2	9
	NO	1	11	12
	TOTAL	8	13	**21**

Phi coefficient=0.71