University of Alberta

Cardiac Rehabilitation in Heart Failure Patients

by

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DEDICATION

To my PhD mentor, Dr. H. Art Quinney,
for his empowering leadership,
inspiring guidance and
sincere kindness

ABSTRACT

The purpose of this dissertation was to gain further knowledge in the field of cardiac rehabilitation in individuals with heart failure (HF) regarding (1) the most beneficial exercise prescription, (2) local versus systemic effects of exercise training on vascular function, and (3) effects of HF etiology on mechanisms of exercise intolerance and patients' response to exercise training. To achieve this goal, a randomized controlled trial was designed to examine the effects of 12 weeks of (1) lower limb aerobic training (AT), (2) combined aerobic and resistance training (CART) of the upper and lower limbs, and (c) no-exercise training (NT) on peak oxygen consumption (VO_{2peak}), brachial and posterior tibial endothelial function, left ventricular (LV) systolic function, muscle strength and endurance, and quality of life in HF patients.

This study demonstrated, in the intention to treat analysis, that both AT and CART significantly improved total exercise time but not VO_{2peak}, while only CART improved upper extremity muscle strength and endurance compared to both AT and NT interventions. In patients attending ≥80% of sessions, both AT and CART improved VO_{2peak}, CART enhanced skeletal muscle strength and endurance, while quality of life was significantly improved in the AT group only. Exercise training, irrespective of the training modality, improved brachial but not posterior tibial endothelial function and did not have detrimental effects on resting LV systolic function.

Regarding HF etiology, reduced VO_{2peak} in ischemic versus non-ischemic HF patients was secondary to greater impairment in resting LV systolic function and peak exercise hemodynamics, while reduced vascular function and muscle endurance in the former group were secondary to age and gender differences. HF etiology did not influence patients' response to exercise training with respect to changes in VO_{2peak}, cardiovascular and skeletal muscle function, or quality of life.

Therefore, the findings of this thesis provide evidence that for compliant patients both AT and CART are effective interventions to improve VO_{2peak} and may contribute to an improved quality of life. Despite baseline differences in VO_{2peak}, both ischemic and non-ischemic HF patients respond similarly to an exercise intervention and should be encouraged to participate in cardiac rehabilitation.

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LIST OF ABBREVIATIONS

AT	Aerobic training
CART	Combined aerobic and resistance training
HF	Heart failure
HRQL	Health-related quality of life
IHF	Ischemic heart failure
LV	Left ventricular
NIHF	Non-ischemic heart failure
NT	No exercise training (standard care)
V_E/V_{CO2} slope	Slope of ventilation to carbon dioxide production
VO_{2peak}	Peak oxygen consumption

Chapter 1: GENERAL INTRODUCTION

Heart failure (HF) is a complication of heart disease characterized by defective cardiac filling and/or impaired contraction or emptying. As a result, the heart is not able to pump a sufficient amount of blood to meet the metabolic needs of body tissues or is able to do so only with an elevated filling pressure (62). With the prevalence reaching epidemic proportions in the Western World, HF has become a major challenge for health care providers (56).

A hallmark of HF is severely reduced exercise capacity (VO_{2peak}) (76,108,168) with symptoms of fatigue and shortness of breath during exercise. The reduced VO_{2peak} is a major cause of poor quality of life (116), an independent predictor of mortality in HF patients (51,113), and one of the criteria for optimal timing of cardiac transplantation (113). While accumulating evidence suggests that exercise training is a safe and effective therapeutic intervention for improving VO_{2peak} (14,73,117,151) and health-related quality of life (14,151,172) in individuals with HF, cardiac rehabilitation remains underutilized intervention in this population (120).

1.1 Study Objectives and Relevance

The overall objective of the research project presented in this thesis is to extend the current scientific knowledge in the field of cardiac rehabilitation in HF patients with respect to: 1) the most beneficial exercise prescription, 2) local versus systemic effects of exercise training on upper and lower extremity vascular function, and 3) the effect of HF etiology on mechanisms of exercise intolerance and patients' response to exercise training. Although combined

aerobic and resistance training may be the most beneficial exercise intervention in HF patients (122,144), the evidence supporting the cardiovascular and clinical benefits of this training modality in HF patients remains limited (112,133). In addition, current literature remains controversial whether the exercise-induced improvements in vascular function are greater in trained lower extremities versus untrained upper extremities in HF patients (39,98,103,112). Finally, current understanding of the effects of HF etiology on mechanisms of exercise intolerance (47,76,99,138) and patients' response to exercise training (31,94,178) remains limited.

From a clinical perspective, optimal exercise prescription and participation of HF patients in cardiac rehabilitation may delay or prevent a need for cardiac transplantation by increasing VO_{2peak} or may better prepare a patient for a surgery. From a public health policy perspective, identifying patients who would benefit most from participation in these programs may prevent imposing an unnecessary financial burden to health care resources.

1.2 Scope of the Study

This dissertation presents a randomized controlled trial designed to compare the effects of 12-week aerobic training alone (AT) or combined aerobic and resistance training (CART) versus no exercise training (NT) on VO_{2peak}, resting left ventricular (LV) systolic function, vascular endothelial function of the upper and lower limbs, skeletal muscle strength and endurance, and health-related quality of life (HRQL) in individuals with HF. A subgroup analysis examined the effect of HF etiology on mechanisms of exercise intolerance and patients'

response to an exercise intervention in ischemic (IHF) versus non-ischemic (NIHF) patients.

1.3 Study Limitations

There are several limitations to this investigation. First, one third of the patients in the current study experienced some change in medications during the 12-week intervention period. Although this reflects the clinical reality of the management of HF patients, we cannot exclude the possibility that changes in medications could have influenced our results. However, most of the findings in the current study are consistent with previously published results on exercise training in HF patients. Second, differences in occlusion location relative to the measurement site for the assessment of the brachial versus posterior tibial artery (i.e., distal versus proximal occlusion) may have influenced the observed regional differences in vascular function in our patients. However, since measurement procedures were the same for the baseline and follow-up assessment of the vascular function, I believe that differences in the occlusion placement did not have significant impact on any observed relative changes in brachial and posterior tibial endothelial function following an intervention period. Third, an assessment of the posterior tibial endothelial function was always performed after the assessment of the brachial endothelial function. Even though ≥60 minutes was allowed for the effects for the vasodilatory effects of nitroglycerin to disappear, one cannot rule out a possibility that some residual vasodilatory effects of nitroglycerin could have influenced baseline diameter and therefore measures of vascular function of the posterior tibial artery in some patients.

Fourth, a small sample size in the present study may have provided insufficient power to detect significant differences in some outcome measures between the AT and CART intervention. Fifth, although the classification of patients with regard to the etiology of HF was based on the history of coronary artery disease for IHF and absence of coronary artery disease in NIHF patients, one cannot rule out a possibility of misclassification of some patients. In addition, reduced endothelium-dependent and endothelium-independent vasodilation before adjustment for age and gender in our sample of IHF patients could be, at least in part, attributed to a greater baseline arterial diameter in IHF versus NIHF patients. Increased arterial diameter is inversely correlated with a vasodilatory response to reactive hyperemia and nitroglycerin during the assessment of endothelial function (34). Moreover, after adjusting for age and gender, IHF patients had significantly reduced LV systolic function compared to NIHF patients. Therefore, the results of the present study could be confounded by baseline differences in the severity of LV systolic dysfunction in IHF versus NIHF patients. After adjusting for area ejection fraction, the results remained the same with significant differences in VO_{2peak} and HRQL in IHF versus NIHF patients. Finally, a small sample size in a subgroup analysis examining the effects of exercise training in IHF versus NIHF patients may have provided insufficient power to detect significant differences between the groups in exercise-induced changes in VO_{2peak}, vascular and skeletal muscle function.

1.4 Definition of Terms

VO_{2peak} was defined as the highest VO_2 achieved over a one-minute period during a graded symptom-limited exercise test (78) on a cycle ergometer.

Peripheral vascular endothelial function was assessed using flow-mediated dilation on the brachial (34) and posterior tibial artery (18). Percent change in arterial diameter in response to reactive hyperemia was used as a measure of vascular endothelial function.

Area ejection fraction was used as a measure of LV systolic function. Area ejection was calculated as stroke area divided by LV end-diastolic cavity area obtained using 2-dimensional echocardiography.

Upper- and lower-extremity maximal muscle strength was assessed using the one-repetition maximum test on chest press and leg extension exercises, respectively. **Muscular endurance** was assessed by the number of repetitions performed at 80% of one-repetition maximum using the same exercises.

Health-related quality of life (HRQL) was assessed using both generic (MacNew Heart Disease Health-Related Quality of Life Questionnaire (40,81)) and disease-specific (Minnesota Living with Heart Failure (17,149)) quality of life questionnaires.

Ischemic HF was defined as one of the following: 1) history of myocardial infarction; 2) coronary artery bypass graft surgery, or 3) at least one major epicardial coronary artery with ≥50% stenosis. Individuals without a history of coronary artery disease were classified as having **non-ischemic HF**.

Intention to treat analysis compares the groups of patients who were assigned to different intervention groups, regardless of their actual adherence to the intervention (161).

Per protocol analysis compares the groups of patients who complied with the assigned intervention. In this dissertation, patients who attended ≥80% of the prescribed exercise sessions were considered compliant and were used in the per protocol analysis.

1.5 Dissertation Overview

Chapter Two reviews current literature related to this dissertation and consists of four separate but not mutually exclusive sections. The first section discusses the mechanisms of exercise intolerance in HF. The second section focuses on the effects of exercise training and different training modalities in HF patients. The third section examines regional differences in vascular function as well as local and systemic effects of exercise training on vascular function in HF patients. The final section reviews current understanding of the effects of HF etiology on mechanisms of exercise intolerance and patients' response to exercise training.

Chapter Three of this dissertation provides the details on the study design, participants' characteristics, outcome measures, and statistical procedures used in this research project.

Chapter Four provides an overview of the findings of the presented research study with a focus on: 1) effects of different exercise interventions according to the intention-to-treat analysis and per-protocol analysis; 2) effects of exercise training irrespective of training modality (intention-to-treat analysis); 3) factors

related to baseline exercise capacity and its change following the intervention period; 4) regional differences in vascular function; and 5) effects of HF etiology on baseline clinical, cardiovascular and musculoskeletal parameters, and patients' response to exercise training.

Chapter Five provides a detailed discussion of the presented findings as a comparison to and extension of the previously published studies. The first section discusses the effects of aerobic training alone versus combined aerobic and resistance training on exercise tolerance, cardiovascular and musculoskeletal function, and HRQL in individuals with HF. This section also contains a detailed discussion related to regional differences in peripheral vascular function and different effects of exercise training on vascular function of the upper versus lower extremities. The second section examines factors related to baseline exercise capacity and its change following exercise training in HF patients. The third section focuses on the effects of HF etiology on mechanisms of exercise intolerance and patients' response to exercise training. The last section provides a discussion of strengths of the study, clinical implications, design issues, future direction and conclusions.

The appendices A to D provide detailed information on study timetable, collaboration network, estimated number of eligible patients, and special considerations related to the study design. In addition, appendices E and F include the two quality of life questionnaires used in the present investigations. Finally, appendix G provides additional study results.

The overall intent of the dissertation is to provide a reader with a body of knowledge and potential clinical implications related to an optimal exercise prescription in individuals with HF, regional differences in exercise-related improvements in vascular function in HF patients, and the effect of HF etiology on mechanisms of exercise intolerance and patients' response to exercise training. It is hoped that these objectives were achieved.

Chapter 2: LITERATURE REVIEW

2.1. Global Burden of Heart Failure

The incidence of HF is reaching epidemic proportions in the Western World and has become a major challenge for health care providers (56). Moreover, with the aging of the population and improved survival after acute myocardial infarction, these trends are likely to continue (**Figure 2-01**)(105). Currently, HF affects approximately 200,000 to 300,000 individuals in Canada (57) and it is the most common cause of hospitalization in individuals over 65 years of age (85).

2.2. Syndrome of Heart Failure

HF is a complication of a heart disease characterized by defective cardiac filling and/or impaired contraction or emptying. As a result, the heart is not able to pump a sufficient amount of blood to meet the needs of body tissues or is able to do so only with an elevated filling pressure (62). In the presence of a preserved ejection fraction, HF may be a result of an impaired diastolic function caused by an impaired ventricular relaxation and/or an increase in ventricular stiffness (186). Although it begins with an inability of the cardiac pump to meet the metabolic requirements of the body, over time the syndrome of HF disturbs many systems, from the heart to the periphery. These perturbations include vascular endothelial dysfunction, tissue wasting, apoptosis, neurohomonal and inflammatory changes, and energetic imbalance in cardiac and skeletal muscle cells, causing reduced exercise capacity (121).

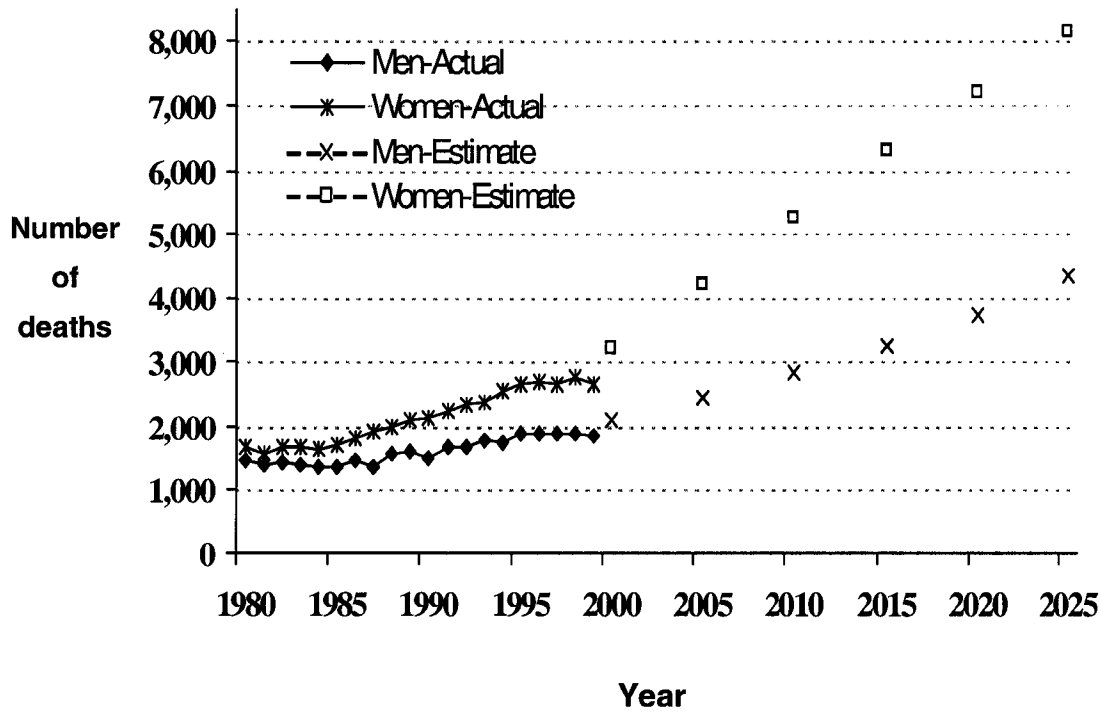


Figure 2-01. Number of actual and projected deaths due to heart failure (1980-2025) in Canada (Statistics Canada).

2.3 Exercise Intolerance is a Hallmark of HF

A cardinal feature of HF is severely reduced VO_{2peak} (76,108,168) with symptoms of fatigue and shortness of breath during exercise. The reduced VO_{2peak} is a major cause of poor quality of life (116), an independent predictor of mortality in HF patients (51,113), and one of the criteria for optimal timing of cardiac transplantion (113). In addition, reduced VO_{2peak} may limit patients' ability to perform activities of daily living resulting in activity restriction. A sedentary lifestyle that occurs with the HF syndrome also exacerbates the decline in VO_{2peak} (88,124) and quality of life (116) leading to a loss of functional independence, progression of the disease (124), and increased mortality rates in HF patients (49). Thus, interventions, such as exercise training, that can improve and/or prevent a decline in VO_{2peak} may have favourable effects on prognosis and should be an integral part of the treatment of individuals with HF.

2.3.1 Mechanisms Responsible for Exercise Intolerance in HF

The reduced VO_{2peak} in HF patients is due to alterations in cardiovascular and musculoskeletal function (**Figure 2-02**; **Table 2-01**). Although HF is characterized by a severe reduction in cardiac pump function, the underlying mechanisms responsible for the HF-mediated decline in VO_{2peak} are not exclusively related to abnormal LV systolic function. Therefore, peripheral abnormalities such as impaired blood flow to the exercising muscles (71,88,154,168) and a reduced ability of the exercising muscle to utilize oxygen (108,182) may also contribute to exercise intolerance in HF.

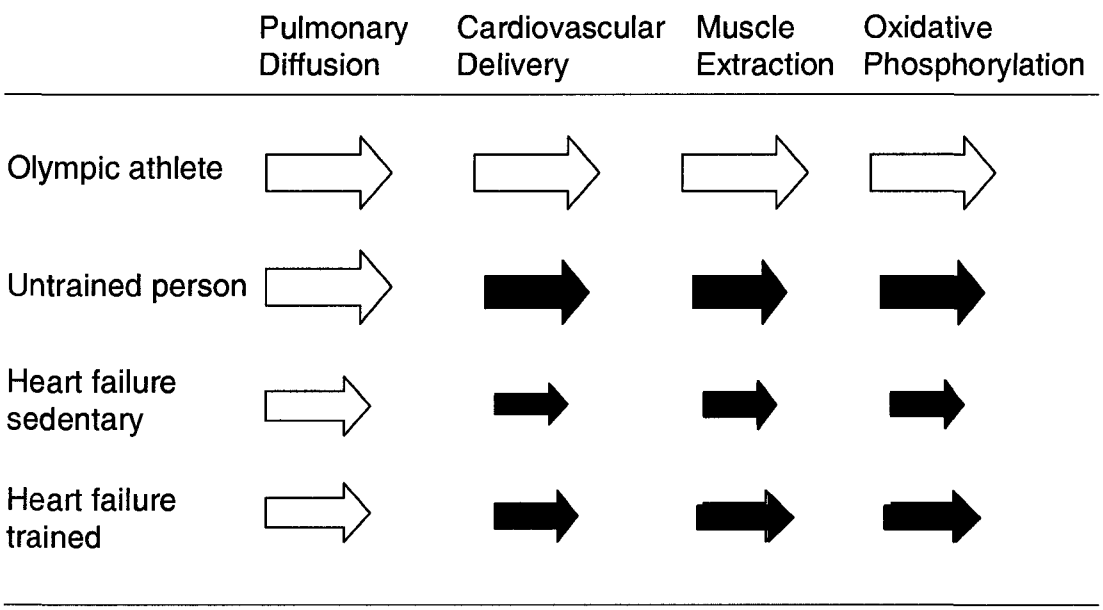


Figure 2-02. Coordinated adaptation in oxygen transport in health and disease.

Arrow size indicates capacity; and dark arrows, sites of primary limitations. Compared to untrained healthy person, the restricted cardiac output is associated with down-regulation of muscle oxygen extraction and utilization in individuals with HF. Exercise training improves vascular and skeletal muscle function in HF, but these parameters remain abnormal compared to healthy untrained individuals. (Adapted from Hsia (2001)(83).)

Table 2-01. Cardiovascular and musculoskeletal components of exercise intolerance in HF

Cardiac component

↓ Peak exercise cardiac output
↓ Left ventricular end-diastolic volume (i.e., ↓ preload) (rest and peak exercise)
↑ Left ventricular end-systolic volume (rest and peak exercise)
Chronotropic incompetence
Mitral regurgitation

Vascular component

↑ Arterial stiffness
↑ Total peripheral resistance (rest and peak exercise)
↓ Vascular endothelial function
- ↓ Nitric oxide production - due to:
  - Low shear stress conditions
  - ↓ Endothelial nitric oxide synthase (eNOS) activity
  - ↓ Availability of L-arginine
- ↑ Nitric oxide degradation – due to:
  - ↑ Oxidative stress
  - ↑ Pro-inflammatory cytokines

Skeletal muscle component

↓ Percentage of type I (oxidative) muscle fibers
↑ Percentage of type II (glycolitic) muscle fibers
↓ Capillary density
↔ Glycolytic enzymes activity
- Hexokinase
- Lactate dehydrogenase
- Phosphofructokinase
- Pyruvate kinase

↓ Oxidative enzymes activity
- Citrate synthase
- Succinate dehydrogenase

↓ 3-hydroxyacyl CoA dehydrogenase activity

Skeletal muscle atrophy
↓ Muscular strength and endurance

Other

↑ Pro-inflammatory cytokines
↑ Oxidative stress
↑ Inducible nitric oxide synthase (iNOS) activity

2.3.1.1 Cardiac Component of Exercise Intolerance in HF

Most (14,155) but not all (141) previous investigations have shown that VO_{2peak} is not related to resting or exercise LV ejection fraction, leading to the belief that abnormal exercise capacity in HF patients is not solely related to an impairment in cardiac function. However, lack of correlation between VO_{2peak} and LV ejection fraction cannot eliminate the potential contribution of impaired LV function to reduced VO_{2peak} in HF patients. Peak exercise cardiac output is closely related to VO_{2peak} (168) and maximal workload (183) in HF patients. In accordance with the Fick equation, VO_{2peak} is a product of cardiac output and arteriovenous oxygen difference (**Table 2-02**). Cardiac output (a product of heart rate and stroke volume) is determined not only by LV ejection fraction, but also by LV end-diastolic volume, and the magnitude of mitral regurgitation (**Table 2-02**). Therefore, an attenuated heart rate (i.e., chronotropic incompetence) and/or diminished preload reserve combined with increases in mitral regurgitation can lead to a blunted cardiac output and ultimately contribute to reduced VO_{2peak} despite no alteration in LV ejection fraction during exercise (**Table 2-01**).

Although the capacity of the heart to increase cardiac output contributes to VO_{2peak} in HF patients, some evidence suggests that patients with HF may not reach a true maximal cardiopulmonary capacity during a symptom-limited exercise test on a treadmill or cycle ergometer. Clinical experience suggests that individuals with HF tend to stop an exercise test abruptly, quite frequently with respiratory exchange ratio (ratio of CO_2 produced to O_2 consumed) being not much above the value of 1.0 (29). Further, Jondeau et al. (89) reported that the

Table 2-02. Fick equation (Adapted from ref (115))

$VO_2 = Q \times a\text{-}vO_{2diff}$
Since Q = SV x HR, then
$VO_2 = SV \times HR \times a\text{-}vO_{2diff}$
Since SV = EDV x EF, then
$VO_2 = EDV \times EF \times HR \times a\text{-}vO_{2diff}$
There may be some backward blood flow in individuals with heart failure and mitral regurgitation. Thus, for those individuals,
$VO_2 = EDV \times EF \times (1\text{-}MRF) \times HR \times a\text{-}vO_{2diff}$

$a\text{-}VO_{2diff}$, arterio-venous oxygen difference; EDV, end-diastolic volume; EF, ejection fraction; HR, heart rate; MRF, mitral regurgitation fraction; Q, cardiac output; SV, stroke volume; VO_2, oxygen consumption.

addition of arm exercise to maximal leg exercise increased VO_{2peak} by 22% in patients with severe HF (VO_{2peak}, <15 $ml \cdot kg^{-1} \cdot min^{-1}$) but not in patients with mild HF or healthy controls. Moreover, LeJemtel et al. (101) reported that, in contrast to normal individuals, HF patients were unable to further augment blood flow to the working limb during one-leg exercise when compared to 2-leg exercise suggesting an impaired ability of the muscular vasculature to vasodilate during exercise. Finally, restoration of normal LV function after cardiac transplantation does not acutely improve exercise performance (93). Taken together, these results indicate that cardiac output may not be the only factor limiting exercise tolerance in individuals with HF. Worsening symptoms, reduced skeletal muscle mass, impaired vasodilatory capacity, and reduced perfusion and/or oxygen utilization capacity of the skeletal muscle may play an important role in limiting exercise tolerance in HF patients. Therefore, peripheral abnormalities that occur as a consequence of the systemic effects of HF may result in impaired exercise tolerance despite abnormal cardiac function (28).

2.3.1.2 Vascular Component of Exercise Intolerance in HF

Reduced VO_{2peak} in HF patients may be in part attributed to an inadequate perfusion of skeletal muscle and resultant muscle fatigue. Peak exercise blood flow to the active muscle is closely related to peak cardiac output and VO_{2peak} in both healthy controls (168) and HF patients (168,183). In addition to the diminished cardiac output, abnormalities in peripheral vascular function including increased arterial stiffness (128) and impaired endothelial function (91,170) may contribute to reduced VO_{2peak} in HF patients (71,84,103) (**Table 2-01**). Impaired

endothelial function is present in both peripheral (82) and coronary (170) circulation of HF patients and relates closely to the severity of the disease (23). In addition, recent evidence suggests that impaired endothelial function is an independent predictor of morbidity and mortality in individuals with or without established coronary artery disease (69,129)

Impaired endothelial function is associated with a deficiency of the endothelial nitric oxide vasodilator system and exaggerated activity of the vasoconstrictor endothelin system (176). Reduced bioavailability of nitric oxide in HF (99,109) may be caused by a reduced activity of endothelial nitric oxide synthase (eNOS) secondary to a long term reduction in the luminal shear stress due to reduced cardiac output and sedentary lifestyle (127). In addition, elevated levels of circulating cytokines, nitric oxide inactivation by oxygen free radicals, and abnormal intracellular availability of nitric oxide precursor L-arginine may contribute to reduced nitric oxide bioavailability (127) (**Table 2-01**). These vascular abnormalities contribute to an attenuated decrease in vascular resistance during exercise and promote further reduction of nutritive blood flow to metabolically stressed and already abnormal skeletal muscle in HF patients (183). A combination of a reduced cardiac output and impaired vascular function (91,128,170) in HF patients may result in a reduced oxygen delivery to the active skeletal muscles (154,168) leading to an early stimulation of anaerobic metabolism and premature muscle fatigue (154) which ultimately limits exercise tolerance in HF patients. In addition, reduced muscle blood flow and subsequent accumulation of metabolites in exercising muscles may stimulate muscle

ergoreceptors. The ergoreflex system senses the metabolic state of the exercising skeletal muscle and increases ventilation through a reflex pathway. According to the "muscle hypothesis" (142), overactivation of ergoreceptors in HF patients may increase ventilation at a given sub-maximal workload, leading to reduced ventilatory efficiency (i.e., steeper slope of ventilation to carbon dioxide production, V_E/V_{CO2} slope) at submaximal exercise. Increased V_E/V_{CO2} slope was found to be a reliable predictor of poor prognosis in HF patients (25,49,51,61,145). Therefore, a greater degree of endothelial dysfunction and subsequent reduction in skeletal muscle blood flow may worsen already abnormal skeletal muscle function and lead to a further deterioration in exercise tolerance in HF patients.

2.3.1.3 Skeletal Muscle Component of Exercise Intolerance in HF

The reduced VO_{2peak} in HF patients may also be linked to impaired oxygen utilization secondary to unfavorable changes in skeletal muscle histology, biochemistry and morphology (**Table 2-01**). Compared to healthy age-matched individuals, HF patients have reduced percentage of type I (oxidative) muscle fibers (108,166), increased percentage of type II (glycolytic) muscle fibers (108,166), decreased capillary density (45,108), reduced activity of oxidative enzymes (e.i., citrate synthase (108,166) and succinate dehydrogenase (45)), reduced activity of 3-hydroxyacyl CoA dehydrogenase (45,166) (e.i., an enzyme mediating β-oxidation of fatty acids), decreased activity of mitochondrial creatine kinase (70) (e.i., an enzyme mediating rapid energy transfer from mitochondria to cytosol) and similar activity of glycolytic enzymes (i.e., hexokinase (45,108),

lactate dehydrogenase (45,108,166), phosphofructokinase (45,166), and pyruvate kinase (166)). The positive relationship between aerobic enzyme activity and VO_{2peak} (108) indicates that reduced aerobic enzyme activity is at least in part responsible for exercise intolerance in HF. Mettauer et al. (121) suggested that skeletal muscle energetic failure in HF should be viewed as a consequence of inactivity and of the systemic effects of the clinical syndrome of HF due to neurohormonal and cytokine disturbances, microvascular abnormalities and tissue oxidative stress (for more details, see section **2.3.1.4**).

In addition to histologic and metabolic abnormalities, skeletal muscle atrophy has been observed in many patients (114,169). HF patients have reduced cross sectional area of the vastus lateralis (76,108,126) compared to age-matched healthy individuals. The wasting in cardiac cachexia that affects all tissue compartments may be a result of inactivity, inflammation, catabolic/anabolic imbalance, impaired nutritional status, and the presence of apoptosis in HF patients (121). Moreover, reduced muscle strength (76,108,169) and endurance (108,126) have been consistently reported in HF patients compared to age-matched healthy controls and may contribute to reduced exercise tolerance in HF patients. It is possible that muscle fibers in an atrophied muscle experience greater work loads, and consequently greater metabolic changes and early fatigue when exposed to the same external work load as muscle fibers of the non-atrophied muscle (114). Therefore, impaired oxidative capacity, skeletal muscle atrophy and a concomitant decline in muscle strength and endurance may contribute to reduced VO_{2peak} in HF patients.

2.3.1.4 Other Factors Contributing to Exercise Intolerance in HF

In addition to abnormalities in cardiac, vascular and skeletal muscle function, other factors such as increased levels of pro-inflammatory cytokines (102), oxidative stress (102), and inducible nitric oxide synthase (iNOS) (70) may contribute to exercise intolerance in HF patients (**Table 2-01**). Proinflammatory cytokines (e.i., tumor necrosis factor-α, interleukin-1, and interleukin-6) may contribute to myocardial, skeletal muscle and endothelial cell dysfunction in patients with HF either by increasing the production of oxygen free radicals or by triggering apoptosis through oxidative stress (102). In addition, pro-inflammatory cytokines stimulate an expression of inducible nitric oxide synthase (iNOS) in the skeletal muscle of HF patients, leading to reduced mitochondrial energy transfer and, thus, impaired skeletal muscle function (70). In turn, abnormal generation of nitric oxide by over-expression of inducible nitric oxide synthase (70) leads to an increased production of reactive oxygen species and cytokines that create deleterious conditions for optimal mitochondrial functioning and thus decrease the oxidative capacity of muscle tissue (175).

In summary, a complex interplay of central hemodynamic and peripheral factors influence exercise tolerance in HF patients. Although abnormal cardiac function is the primary initiating event in the syndrome of HF, strong evidence suggests that peripheral abnormalities play an important role in exercise intolerance in HF patients. Therefore, a partial reversal of peripheral abnormalities such as impaired vascular and skeletal muscle function with

exercise training may increase exercise tolerance and ultimately improve health-related quality of life in HF patients.

2.4 Exercise Training in HF

2.4.1 Exercise Training Improves Clinical Outcomes in HF

Accumulating evidence suggests that exercise training is a safe and effective therapeutic intervention for improving VO_{2peak} in individuals with HF (14,59,60,73,117,151). In addition, the benefits of exercise training in HF patients may translate into favourable clinical outcomes including an improvement in health-related quality of life (14,59,137,148,151,172), New York Heart Association (NYHA) functional class (71,74,75,95), and reduced hospitalizations (59,143) and possibly reduced mortality rates (14,143). A cost-effective analysis of long-term exercise training in HF patients based on the study by Belardinelli et al. (14) showed that exercise training in HF is a highly cost-effective intervention (53). Exercise training prolonged survival in HF patients by an additional 1.82 years at low cost of $1,773 per year of life saved (53). Considering a categorization scheme in which cost-effective interventions range from $20,000 to $40,000 per year of life saved (100) and a cost-effectiveness of standard pharmacological therapies in HF patients such as beta blockers (carvedilol, $12,799 per year of life saved) (38) and ACE-inhibitors (enalapril, $9,700 per year of life saved) (140), exercise training represents a highly cost-effective intervention in HF patients and positively influences quality of life.

Most (14,59,133,137,148,172) but not all (78,117) randomized controlled trials found improvements in health-related quality of life (HRQL) following

exercise training in HF patients. These studies differ in training duration (range: 8 weeks to 14 months), exercise prescription including aerobic training alone (14,59,137,148) or combined aerobic and resistance training (78,117,133), and tools used to assess HRQL. Several studies used a validated and reliable (149) disease-specific measure, the Minnesota Living with Heart Failure Questionnaire (14,117,137,172). Although this questionnaire may not be sensitive to subtle changes in HRQL following an exercise intervention (152), it has been widely used in clinical trials in HF patients (14,117,137,172) and has established cut-off values for minimal clinically important differences (150). Only one study reported positive correlation between changes in VO_{2peak} and HRQL score following an exercise intervention (14).

Taken together, these findings suggest that exercise training is a safe and cost-effective intervention to improve clinical outcomes and HRQL in HF patients with impaired LV systolic function. Despite a considerable amount of evidence supporting beneficial effects of exercise training in HF patients, this therapeutic modality has been severely underutilized in the HF population (120).

2.4.2 Exercise Training Improves Exercise Tolerance in HF

The recent Cochrane review identified 29 randomized controlled trials on exercise training in HF patients published to date (151). Both aerobic training (AT) alone and combined aerobic and resistance training (CART) markedly improved VO_{2peak} by 2.16 ml/kg/min (151) (range, 12% to 30% (144)) following a 3 to 52-week exercise intervention in HF patients. A large variation in changes in VO_{2peak} could be explained by a different dose of exercise stimulus with the

greater improvements in VO_{2peak} seen for increasing "doses" of exercise training (151). The proposed mechanisms responsible for the improvement in VO_{2peak} following exercise training in HF patients have been primarily related to a partial reversal of peripheral abnormalities including an improvement in vascular endothelial function (39,71,73,82,92,98,103) and a greater utilization of oxygen by the working muscles (74,106,108,166) (**Table 2-03**).

2.4.3 Vascular Adaptations to Exercise Training in HF

During the last decade, a growing body of evidence suggests that AT improves peripheral vascular endothelial function in individuals with (39,71,73,82,92,98,103) and without HF (75,80,96,111). The improvement in endothelial function following AT in HF patients correlates positively with the improvement in VO_{2peak} (39,71,103) and is lost within 6 weeks after the cessation of exercise (82).

The cellular mechanisms underlying an exercise-induced improvement in endothelial function in HF are related to an increased bioavailability of nitric oxide (**Table 2-03**). It is well established that shear stress and pulsatile flow provide a physiological stimulus to nitric oxide production (131). Exercise training increases nitric oxide production through shear stress-mediated upregulation of endothelial nitric oxide synthase (eNOS) (174). In addition, exercise training reduces nitric oxide degradation by enhancing expression (46) and activity (102) of antioxidant enzymes and reducing local production of reactive oxygen species (60,130). Increased nitric oxide bioavailability and therefore improved peripheral endothelial function in HF patients facilitates delivery of oxygen and nutrients to

Table 2-03. Effects of exercise training on cardiovascular and skeletal muscle function in HF patients

Effects of Exercise Training in HF	Consequences
Cardiac function	
↔↑ Peak exercise cardiac output ↔↑ Stroke volume ↔↑ Left ventricular diastolic filling (↑ preload reserve) ↔↑ Left ventricular ejection fraction	↑ Oxygen delivery to active muscles
Vascular function	
↑ Vascular endothelial function ↑ Nitric oxide production - due to: - ↑ Shear stress - ↑ Endothelial nitric oxide synthase (eNOS) activity ↓ Nitric oxide degradation – due to: - ↑ Anti-oxidative enzymes activity - ↓ Oxidative stress - ↓ Pro-inflammatory cytokines	↑ Vasodilation ↓ Total peripheral resistance (i.e., reduced afterload) ↑ Nutritive flow to skeletal muscle (hypothesized)
Skeletal muscle function	
↑ Oxidative enzymes activity - Citrate synthase - Succinate dehydrogenase ↑ 3-hydroxyacyl CoA dehydrogenase activity ↓ Blood lactate levels at submax exercise ↓ PCr depletion and intracellular acidosis ↑ Capillary density ↓ % of type II (glycolytic) muscle fibers ↑ % of type I (oxidative) muscle fibers ↑ Muscle cross sectional area ↑ Muscular strength and endurance	↑ Skeletal muscle oxidative capacity ↓ Skeletal muscle atrophy ↓ Workload imposed on individual muscle fibers
Other	
↓ Pro-inflammatory cytokines ↓ Oxidative stress ↓ Neuroendocrine activation - ↓ Angiotensin - ↓ Aldosterone - ↓ Vasopressin - ↓ Atrial natriuretic peptide	Anti-inflammatory effects Anti-oxidative effects ↓ Adverse long-term effects of neuroendocrine activation

PCr, phosphocreatine.

the exercising muscle by improving vasodilation of both conduit (71,112) and resistance (92) vessels, reducing total peripheral resistance during exercise (73), and possibly improving skeletal muscle nutritive blood flow (33,175). Taken together, these findings indicate that exercise training results in favourable vascular adaptations that improve oxygen delivery to the exercising muscle and contribute to the improvement in VO_{2peak} in HF patients.

2.4.4 Musculoskeletal Adaptations to Exercise Training in HF

An exercise-induced improvement in skeletal muscle function in HF is largely explained by the correction of impaired muscle oxidative capacity (64,106,147) and partially by reversal of HF-mediated decline in skeletal muscle mass (147) (**Table 2-03**). A number of investigations have shown that exercise training increases the activity of oxidative enzymes (i.e., citrate synthase (64,106), lactate dehydrogenase (173) and 3-hydroxyacyl CoA dehydrogenase (106)), reduces blood lactate levels at submaximal exercise (74,173), attenuates phosphocreatine depletion and development of intracellular acidosis during exercise (1,132,165), shortens phosphocreatine recovery (1), and increases mitochondrial density (16,74), indicating improvement in the oxidative capacity of the trained muscle. The exercise-related improvement in skeletal muscle oxidative capacity has been linked to the increase in exercise capacity in HF patients (16,74). Although improvement in muscle energetics is independent of muscle blood flow in HF patients (125), a favourable redistribution of nutritive blood flow and oxygen within the skeletal muscle may occur after exercise training in HF patients (33,175). In addition, exercise training may increase

capillary to fiber ratio (108) and result in a favourable "reshift" from type II to type I muscle fibers in HF patients (72). Moreover, exercise training increases the cross-sectional area of the quadriceps muscle (108), calf muscle (132), and type I and type II muscle fibers of the vastus lateralis muscle (16) in HF patients. Exercise programs involving resistance exercises also improve skeletal muscle strength (106,110,117,147,160) and endurance (106,160) in HF patients. It has been speculated that an increased muscle mass following exercise training in HF patients may reduce the workload imposed on muscle fibers and consequently reduce metabolic stress (33). In addition, increased muscle mass also increases muscular oxygen consumption and therefore oxygen extraction from the blood during exercise leading to an increase in total body oxygen consumption. Taken together, these findings suggest that training-related improvements in skeletal muscle biochemistry, histology, morphology, and function may ultimately contribute to improved exercise tolerance in HF patients.

2.4.5 Cardiac Adaptations to Exercise Training in HF

A number of previous studies reported no change in LV systolic function at rest following AT (14,43,167), resistance training (147) or CART (37,117) in HF patients. However, several studies found that AT may improve stroke volume (73) and maximal cardiac output (42,73,74), enhance LV diastolic filling (12,13), improve LV ejection fraction at rest (58,73,164), and attenuate unfavourable LV remodelling in HF patients (58) (**Table 2-03**).

Several mechanisms may contribute to an observed improvement in LV function following exercise training in HF. Improvement in LV systolic function

could be, in part, related to the exercise-mediated reduction in systemic vascular resistance (73,74) and reduced afterload, secondary to the improvement in peripheral vascular endothelial function (73). Alternatively, exercise training may improve oxygen and substrate supply to the failing heart by improving in coronary endothelial function. Hambrecht et al. (75) found improved coronary blood flow and endothelium-dependent vasodilation after 4 weeks of high intensity aerobic training in patients with coronary artery disease. Finally, reduced neuroendocrine activation (20) and decreased levels of proinflammatory cytokines (2,60,102) following exercise training in HF patients may reduce the oxidative stress within the cardiac tissue and therefore improve intracellular energetics (175). However, although exercise training may have beneficial effects on cardiac function in HF patients, strong evidence suggests that an improvement in exercise tolerance following exercise training in HF patients is primarily attributed to a partial reversal of peripheral abnormalities.

2.4.6 Anti-Inflammatory and Anti-Oxidative Effects of Exercise Training in HF

In addition to its effects on vascular, skeletal muscle and cardiac function, exercise training has also anti-inflammatory and anti-oxidative effects in HF patients (**Table 2-03**). Regular exercise partially reduces inflammation by decreasing local expression (60,102) and plasma levels (2) of pro-inflammatory cytokines (e.i., tumor necrosis factor-α (2,60,102), interleukin-1 (60,102), and interleukin-6 (60)) and inducible nitric oxide synthase (60) in HF patients. In addition, exercise training in HF reduces local oxidative stress (102) and

increases an expression (46) and activity (102) of antioxidative enzymes (i.e., superoxide dismutase (46), catalase (102) and glutathionine peroxidise (46,102)). Decreased levels of cytokines and reduced local oxidative stress following exercise training reduce muscle damage and skeletal muscle apoptosis (102) and may create a better environment for mitochondrial energy production.

Therefore, the mechanisms responsible for the improvement in VO_{2peak} following exercise training in HF have been attributed to favorable changes in cardiac, vascular, and skeletal muscle function that result in improved O_2 delivery and/or utilization by the active muscle.

2.4.7 Combined Aerobic and Resistance Training is an Optimal Exercise Intervention in HF

From a clinical perspective, a combination of resistance exercises and whole body AT is important to provide patients with optimal training stimulus (171). Currently, the effects of resistance training performed alone or combined with AT on improving cardiovascular and skeletal muscle function in HF patients have not been well studied. Current understanding of the benefits of exercise training in HF comes primarily from a number of investigations that prescribed AT (39,71-74,82,92,98,103,132). Although both AT (39,71-74,82,92,98,103,132) and resistance training (112,147,160) may partially reverse vascular and skeletal muscle abnormalities in HF patients, recent studies revealed that resistance training alone may also attenuate the HF-mediated decline in muscle mass (147) and improve muscle strength (147,160) and endurance (160) without altering LV systolic function in HF patients (147). Increases in muscle strength and

endurance following resistance training may translate into improved quality of life in HF patients (133). Therefore, the beneficial effects of aerobic and resistance training modalities in HF patients may be additive.

The few investigations examining the effects of CART mainly focused on muscular component of exercise intolerance in HF and reported improved VO_{2peak} (26,37,110,117,123,164,172) and skeletal muscle strength (106,110,117,172) and endurance (106,110). In addition, this training modality improved quadriceps femoris cross-sectional area (106), capillary to fiber ratio (106), and citrate synthase activity (106) in individuals with HF. Only 2 studies reported improved peripheral vascular endothelial function (112) and quality of life (133) following CART in individuals with HF. Preliminary evidence from a recent non-randomized trial suggests improved LV ejection fraction, reduced right and left ventricular oxidative metabolism, and improved LV forward efficiency in HF patients with idiopathic dilated cardiomyopathy (164). Therefore, CART may be the optimal exercise intervention to reverse or attenuate the loss of muscle mass and improve VO_{2peak}, muscle strength, and quality of life in individuals with HF. However, evidence supporting the cardiovascular and clinical benefits of this training modality in HF patients remains limited.

To date, only 2 studies without a non-exercising control group compared the effects of AT versus CART and reported inconsistent results in HF patients (36,78). Delagardelle et al. (36) randomized 20 HF patients to a 4-month AT or CART intervention. The AT group performed interval training on a cycle ergometer for 40 minutes. The CART group performed the same aerobic interval

training for 20 minutes as well as 6 resistance exercises for major muscle groups (3 sets of 10 repetitions at 60% of 1-repetition maximum). The CART group increased VO_{2peak} and LV ejection fraction at rest, and improved leg muscle strength and endurance. In contrast, the AT group decreased LV ejection fraction, improved leg muscle endurance, and did not improve VO_{2peak}. The authors concluded that CART was superior to AT alone to improve VO_{2peak}, LV function, and muscle strength in HF patients. In a more recent study, Haykowsky et al. (78) randomized 20 older women with HF to a 3-month supervised AT or CART intervention. The authors reported increased upper extremity muscle strength in the CART group while no change was observed in the AT group. Changes in VO_{2peak}, leg muscle strength, and HRQL following AT or CART were not different between the groups and were not reported for each group separately. The results of these 2 studies need to be interpreted with caution due to important methodological limitations such as the lack of a non-exercising control group, statistical adjustment for baseline differences in age and VO_{2peak} in the study by Delagardelle et al. (36), or assessment of vascular function. Accordingly, the cardiovascular and skeletal muscle benefits of CART versus AT compared to standard care (i.e., no training, NT) remain largely unknown. Therefore, the primary purpose of the research project presented in this thesis was to examine the effects of 12 weeks of AT and CART versus standard care (i.e., no exercise training (NT)) on VO_{2peak}, LV systolic function, peripheral vascular endothelial function, skeletal muscle strength and endurance, and HRQL in HF patients.

2.5 Regional Differences May Influence Changes in Vascular Function Following Exercise Training in HF Patients

Regional Differences in Vascular Function. Despite the extensive literature on the beneficial effects of exercise training on peripheral vascular endothelial function in HF patients (73,82,98,103), the regional specificity of endothelial function and its potential impact on the magnitude of exercise-induced changes have been largely overlooked. Current evidence suggests that the severity of peripheral vascular endothelial dysfunction may not be uniform across vascular beds. Previous studies reported preserved upper extremity but impaired lower extremity endothelial function in patients with HF (88), peripheral artery disease (158), and healthy elderly women (136), but not in healthy elderly men (185). A regional specificity in endothelial function in HF patients may be attributed to differences in vascular beds' susceptibility to atherosclerosis. Lower extremity arteries are particularly susceptible to atherosclerosis (52), while the brachial artery rarely develops structural atherosclerotic changes (6). An alternative explanation may be related to disuse and deconditioning. Jondeau et al. (88) speculated that HF patients may purposely avoid activities involving large muscle mass of lower limbs to prevent an exacerbation of the symptoms of fatigue and shortness of breath, while still performing less demanding activities of daily living involving a small muscle mass of the upper limbs. Irrespective of the mechanisms, the presence of regional specificity in endothelial function may influence HF patients' response to an exercise intervention leading to a greater improvement in more severe endothelial dysfunction in the lower limbs compared

to the uppers limbs. Moreover, if this regional specificity is secondary to physical deconditioning, an improvement in VO_{2peak} following lower-limb exercise training used in most studies may be attributed, in part, to the improvement in lower-limb endothelial function.

Systemic Effects of Exercise Training on Vascular Function in HF. Two recent studies found that lower limb exercise training improved endothelial function in untrained upper limbs in HF patients (103,112). Therefore, exercise training may have beneficial systemic effects on peripheral vascular function if exercise of moderate intensity is performed with the large muscle mass of the lower limbs (103,112). Mechanisms underlying an exercise-induced improvement in vascular function of non-exercising limbs may be related to a local increase in nitric oxide bioactivity, possibly via a hemodynamic-mediated shear stress phenomenon. It is well established that shear stress and pulsatile flow provide a physiological stimulus to nitric oxide production (131). Increased blood flow (66), the presence of antegrade/retrograde flow pattern (67) and change in central hemodynamics (65) during lower limb exercise may provide a potent stimulus for shear-stress mediated increase in nitric oxide production and consequently improved endothelial function in the upper limb vasculature. However, these investigations may have underestimated the magnitude of an exercise-induced improvement in endothelial function by assessing the changes in untrained limbs.

Local Effects of Exercise Training on Vascular Function in HF. Three studies that measured endothelial function in both upper and lower limbs reported contrasting findings with improved lower limb but not upper limb

vascular function following AT on a cycle ergometer in individuals with HF (39,98) or coronary artery disease (63). These investigations support the hypothesis that exercise-induced increase in blood flow may upregulate nitric oxide synthase activity predominately in the trained extremities. In addition, other mechanisms such as reduced local expression of circulating pro-inflammatory cytokines (60) and upregulated activity of antioxidative enzymes (102) may contribute to improvement of endothelial function in the vascular beds of the exercising musculature in HF patients. Finally, the mechanisms responsible for exercise training adaptations in the vasculature may differ according to the vascular beds involved. Green et al. (68) reported that short-term exercise training improved endothelial function in both conduit and resistance vessels in the forearm in individuals with cardiovascular disease and risk factors, but the magnitude of these improvements were not related. However, the studies that examined the effects of exercise training on endothelial function in both upper and lower limbs in individuals with HF or coronary artery disease had important methodological limitations such as a lack of a non-exercising control group (39), non-randomized group assignment (63), or a lack of statistical adjustment for younger age and greater VO_{2peak} at the baseline in the exercise versus control group (98). Thus, additional studies need to examine whether local effects of lower limb exercise on peripheral vascular endothelial function are significantly underestimated by an assessment of endothelial function in untrained upper limbs. Therefore, the secondary objective of the research project presented in this thesis was to

examine the effects of exercise training on vascular function in trained versus untrained limbs.

2.6 Effects of HF Etiology on Exercise Intolerance and Patients' Response to Exercise Training

In the past decades the most common causes of HF were hypertension and valvular heart disease (non-ischemic heart failure (NIHF)) (56). However, the most common cause of HF in the Western world at present is ischemic heart failure (IHF), secondary to the complications of coronary artery disease (68%) (56). Recent clinical trials suggest that IHF and NIHF patients routinely present with different clinical characteristics (3,4,10,55) and prognosis (10), and may respond differently to pharmacological (50) or surgical interventions (139). From a clinical perspective, it is important to determine whether HF etiology identifies patients with different exercise tolerance and potentially different responses to an exercise intervention. Understanding the influence of HF etiology on the mechanisms of exercise intolerance in HF patients is essential for optimizing future therapeutic interventions such as exercise training to meet the needs of individual patients.

2.6.1 Ischemic Etiology Influences Exercise Tolerance in HF Patients: Mechanisms Remain Unknown

Previous studies suggest that a decrease in VO_{2peak} may be more exaggerated in IHF compared to NIHF patients (7,8,27,35,178). However, the mechanisms responsible for this difference remain largely unknown. Although reduced LV function is the primary initiating event in the syndrome of HF, strong

evidence suggests that peripheral abnormalities such as impaired blood flow to the exercising muscles (71,88,154,168) and a reduced ability of the exercising muscle to utilize oxygen (108,182) play an important role in limiting exercise tolerance in HF patients (see section **2.3.1** for details). In addition, reduced muscle mass (76,114,169) and a concomitant decline in muscle strength (21,76) and endurance (107) may contribute to reduced VO_{2peak} in HF patients. Therefore, a difference in the severity of peripheral abnormalities such as impaired vascular and/or skeletal muscle function could partially explain the difference in VO_{2peak} between IHF and NIHF patients.

Clark et al. (27) speculated that exercise capacity in IHF patients may be limited by peripheral vascular factors due to widespread vascular disease while NIHF patients may have more pronounced skeletal muscle abnormalities. To date, only 4 studies examined the effects of HF etiology on skeletal muscle and peripheral vascular function. Harrington et al. (76) reported no difference in skeletal muscle size, muscle strength and fatigue in men with IHF versus NIHF. Similarly, 3 studies that examined the effects of HF etiology on vascular function reported no difference in peripheral vascular endothelial function between IHF and NIHF patients (47,99,138). Despite no difference in endothelial function between IHF and NIHF patients, Erbs et al. (47) suggested that the mechanisms of endothelial dysfunction may be different in patients with IHF and NIHF secondary to differences in local levels of oxidative stress associated with inflammatory factors and neurohumoral activation in HF. These findings imply that HF etiology could potentially influence therapeutic effects of exercise training

on peripheral endothelial function in HF patients.

Other factors such as advanced age (7,8,10,27,35) and a greater degree of chronotropic incompetence (90,178) may contribute to reduced VO_{2peak} in IHF compared to NIHF patients. However, VO_{2peak} remained significantly reduced in IHF versus NIHF patients even after adjustment for age in a study by Clark et al. (27). Thus, although strong evidence suggests reduced VO_{2peak} in IHF compared to NIHF patients, the mechanisms underlying this difference remain largely unknown.

2.6.2 HF Etiology May Influence Patients' Response to Exercise Training

Despite the finding that most patients with HF respond favourably to regular exercise training, a considerable degree of uncertainty remains whether the training response is similar in patients with different HF etiology. To date, most of the exercise intervention studies have combined IHF and NIHF patients and have failed to report exercise-induced changes in VO_{2peak} for individual subgroups (14,59,60,73,117). However, previous studies suggest that HF etiology may influence patients' response to different therapeutic interventions such as pharmacological interventions (50) or cardiac transplantation (139).

Although contradictory (31), preliminary data from observational studies suggest that patients with IHF may achieve less improvement in VO_{2peak} following exercise training compared to their NIHF counterparts (94,178). In a subgroup analysis of a randomized trial with a 6-month AT intervention, Keteyian et al. (94) reported improved absolute VO_{2peak}, peak heart rate and power output in NIHF but not IHF patients. Similarly, Webb-Peploe et al. (178) reported improved VO_2

at peak exercise and ventilatory threshold, increased exercise time, and reduced LV end-diastolic and end-systolic dimensions in NIHF but not IHF patients following an 8-week AT intervention. However, the results of this study need to be interpreted with caution due to has several important limitations including: (1) unknown exercise training intensity; (2) discrepancy between exercise testing and training modalities (i.e., treadmill test versus cycle ergometer training); and (3) increased peak exercise respiratory exchange ratio at the follow-up in NIHF but not in IHF patients which may suggest a greater effort during follow-up testing in the former group. In contrast to the first two studies, in a subgroup analysis of a non-randomized trial with a 4-month CART intervention, Conraads et al. (31) reported a significant improvement in VO_2 at peak exercise and ventilatory threshold only in individuals with IHF while no change was observed in NIHF patients. Exercise training reduced NYHA functional class and increased power output at peak exercise and ventilatory threshold in both IHF and NIHF patients. The limitation of all these studies was a lack of a comparison of exercise-induced changes in IHF and NIHF patients to those observed in a corresponding non-exercising control group. Taken together, limited number of studies, poor methodology, and controversial results imply that the effects of HF etiology on patients's response to exercise training remain unknown and need to be addressed in future studies. Determining whether cardiac rehabilitation is an effective intervention to improve VO_{2peak} in both IHF and NIHF patients will have important implications on the distribution of limited health care resources and future referrals of HF patients to cardiac rehabilitation. Therefore, the third

objective of the a research project presented in this thesis was to determine the effects of HF etiology on mechanisms of exercise intolerance and patients' response to exercise training.

2.7 Summary

HF patients have poor exercise tolerance that can be improved with AT. However, CART may be the optimal exercise intervention to reverse or attenuate the loss of muscle mass and improve VO_{2peak} in HF patients. The evidence supporting the cardiovascular and clinical benefits of this training modality in HF patients remains limited. Moreover, although exercise training improves vascular function in HF patients, it remains controversial whether the improvements are greater in trained versus untrained limbs. Finally, current understanding of the mechanisms of exercise intolerance and the effects of exercise training in patients with IHF versus NIHF remains limited. Therefore, we designed a randomized controlled trial to compare the effects of 12-week AT or CART versus NT on VO_{2peak}, LV systolic function, vascular endothelial function of the upper and lower limbs, skeletal muscle strength and endurance, and HRQL in individuals with HF. In a subgroup analysis, we examined the effects of HF etiology on mechanisms of exercise intolerance and patients' response to an exercise intervention.

Chapter 3: METHODOLOGY

3.1. Objectives and Hypotheses

Primary objective: To examine the effects of 12 weeks of (a) the lower limb AT, (b) the upper and lower limb CART, and (c) standard care (NT) on VO_{2peak}, peripheral vascular endothelial function, LV systolic function, muscle strength and endurance, and HRQL in HF patients.

Hypothesis 1. CART will improve VO_{2peak}, muscle strength and endurance, brachial and posterior tibial endothelial function, and HRQL to a greater extent compared to AT or NT, without altering LV systolic function.

Secondary objective: To examine the effects of lower limb AT versus whole body CART on upper and lower limb vascular endothelial function.

Hypothesis 2. Both lower limb AT and whole body CART would improve posterior tibial endothelial function compared to NT while whole body CART would be more effective in improving brachial endothelial function compared to lower limb AT or NT.

Hypothesis 3. The improvement in vascular function will correlate positively with the increase in VO_{2peak}.

Tertiary objective: To determine the effects of HF etiology on exercise capacity and patients' response to exercise training.

Hypothesis 4. Individuals with ischemic HF will have significantly reduced VO_{2peak}, peripheral vascular and skeletal muscle function but not LV systolic function compared to non-ischemic HF patients.

Hypothesis 5. Exercise training will improve VO_{2peak} and brachial endothelial function in non-ischemic HF but not in ischemic HF patients.

An additional objective of the study was to examine the effects of 12 weeks of AT, CART or NT on blood lipid profile, insulin sensitivity, and C-reactive protein. The hypothesis was that 12 weeks of CART would result in a more favourable improvement in blood lipid profile, insulin sensitivity and C-reactive protein compared to AT or NT intervention.

3.2. Overview of the Study Design

This randomized controlled trial compared the effects of 12-week exercise programs on VO_{2peak}, vascular endothelial function of the upper and lower limbs, LV systolic function, muscle strength and endurance, and HRQL in individuals with HF. The participants were randomized to the lower limb AT (n=14), the upper and lower limb CART (n=15) and NT (n=13). Outcome measures (see Section **3.5.**) were assessed before and after the intervention period.

3.3. Study Population

Forty-two individuals with clinically stable HF participated in this study (NYHA functional class I to III, age: 62 ± 12 years; 32 males, 10 females). All participants were on standard medical therapy at the time of the investigation (**Table 4-01**). Patients were recruited from 2 outpatient clinics located at the University of Alberta Hospital and the Royal Alexandra Hospital (Edmonton, Canada) between October 1, 2003 and September 30, 2005 (please see **Appendix A** for the **Study Timetable** and **Appendix B** for an established **Collaboration Network** to ensure support for all aspects of this project). In 2004, each outpatient clinic

registered approximately 300 HF patients, with ~50 new patients entering these clinics each year. Results of our **Pilot Survey** showed that only 19% of the patients attending these clinics were eligible for this study (see **Appendix C**).

3.3.1. Inclusion Criteria

Inclusion criteria were: 1) ≥35 years of age, 2) absence of orthopedic or pulmonary limitations to performing a graded exercise test, and 3) ability to give informed consent.

3.3.2. Exclusion Criteria

Exclusion criteria included: 1) presence of absolute contraindication for exercise training in HF (i.e., NYHA functional class IV, active myocarditis, unstable angina pectoris, ischemia at low workloads, myocardial infarction within previous 6 months, ventricular tachycardia, or aortic stenosis), 2) diagnosed chronic obstructive pulmonary disease, 3) insulin therapy, 4) hypotension (systolic blood pressure <80 mm Hg), 5) residence outside of the Capital Health Region, and 6) unwillingness to participate, accept random assignment, and/or attend follow-up visits.

Insulin therapy and hypotension were exclusion criteria for the assessment of vascular function. Insulin has vasoactive effects but, unlike other vasoactive medications, it cannot be discontinued for at least 24 hours before the testing. Hypotensive patients were excluded because a use of nitroglycerin as a part of the assessment of vascular function could significantly lower blood pressure and cause headache and dizziness. Ethics approval for this investigation was obtained from the University of Alberta biomedical ethical review panel in June

2003 and informed consent was obtained from the subjects prior to study participation.

3.3.3. Patient Recruitment

A nurse and the primary investigator screened patients' charts to identify eligible patients and approached patients during their clinical visits. Basic verbal information was provided about the study, emphasized importance of becoming more active, and referred to an opportunity of receiving a free supervised exercise program for 12 weeks. Patients who hesitated to take part in the study at that time were approached again during their next clinical visit. Upon patients' approval, names and contact information of interested patients were forwarded to the investigator. The investigator contacted patients by phone and sent them written information about the study. The patients were given at least 1 week after their clinical visit to reflect on the proposal and discuss it with family, friends, and/or a family physician. During the second phone call, the investigator provided additional verbal explanations, answered any potential questions regarding the study, and, if the individual volunteered for the study, they were scheduled for the first clinical visit for signing consent. To enhance patient recruitment, the investigator attended the outpatient clinics on a regular basis and kept a log of patients that were approached, noting those interested in participating and the reasons some refused.

3.4. Study Design

Study design is presented in **Figure 3-01.** After the baseline testing, subjects were randomly assigned using sealed envelopes prepared by the EPICORE

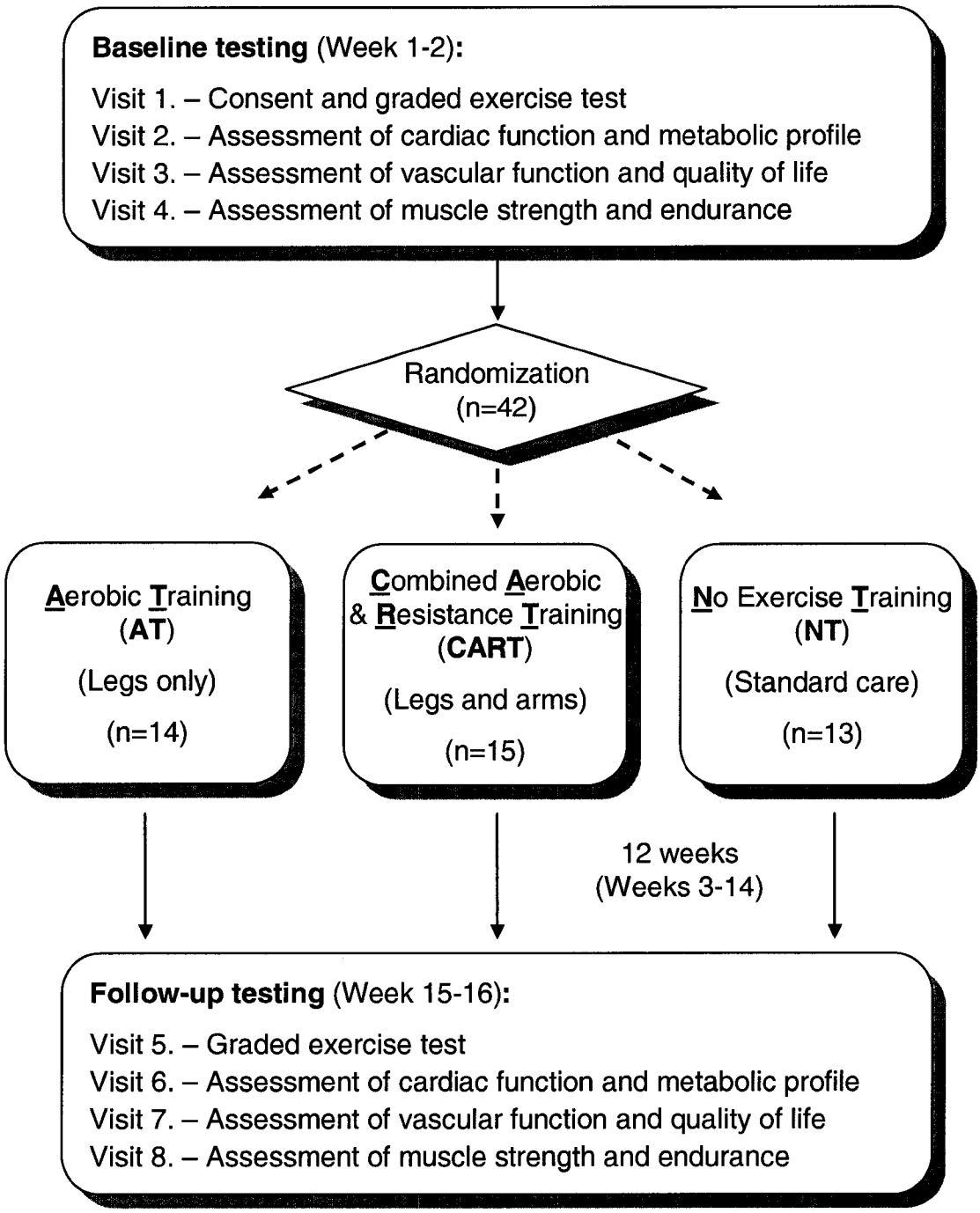


Figure 3-01. Study design

Centre (www.epicore.ualberta.ca). Randomization was blocked with variable block sizes between 3 and 9, unknown to the investigators. Consistent with prior exercise intervention trials, patients and investigators were not blinded to patients' group assignments. However, outcome assessors were blinded to the baseline data and, whenever possible, to the group assignment. Please see Section **5.10** for further discussion related to the study design and **Appendix D Special Considerations** for a list of strategies used to maximize treatment effects and exercise adherence, and to minimize loss to follow-up and measurement variability.

3.5. Outcome Measures

Primary outcome: Exercise capacity measured as peak oxygen consumption (VO_{2peak}) during an incremental cycle ergometer test.

Secondary outcomes:

1) Vascular endothelial function of the upper (brachial artery) and lower limbs (posterior tibial artery) measured as a percent change in the arterial diameter in response to reactive hyperemia

2) LV systolic function assessed as LV area ejection fraction from 2-dimensional echocardiography

3) Maximal muscle strength and muscle endurance of upper and lower body measured on chest press and leg extension exercises, respectively

4) HRQL assessed by Minnesota Living with Heart Failure Questionnaire and MacNew Questionnaire.

Additional outcomes:

1) Lipoprotein profile including total cholesterol, triglycerides, HDL- and LDL-cholesterol measured using standard laboratory procedures

2) Fasting glucose measured using standard laboratory procedures

3) C-Reactive protein measured from a blood sample using ELISA procedure

4) Insulin sensitivity measured by the ^{13}C-glucose breath test

3.5.1. Exercise Capacity (VO_{2peak})

Symptom-limited incremental exercise testing was performed on an electrically braked cycle ergometer (Quinton) with expired gas analysis (Parvomedics TrueMax, Sandy, UT). The metabolic cart was calibrated before and after each test. The initial power output was set at 15-20 watts and increased by 15 watts every 2 minutes. Heart rate, blood pressure and rate of perceived exertion were obtained at the end of each stage. A continuous 12-lead ECG was monitored throughout the test. The exercise test was performed in the exercise stress laboratory at the University of Alberta Hospital, and was supervised by a cardiologist and an exercise physiologist.

Peak aerobic power was calculated as the highest VO_2 achieved over a one-minute period (78). Age-predicted VO_{2peak} was calculated from the regression equations of Wilson and Tanaka (184) and Fitzgerald et al. (48) for healthy sedentary men and women, respectively. Ventilatory threshold was defined as the time during the exercise test at which expired carbon dioxide increased non-linearly relative to oxygen consumption. Ventilatory threshold was determined visually by 2 independent observers using V-slope method (11). Any

disagreement was resolved with a consensus. Ventilatory efficiency (V_E/V_{CO2} slope) was calculated by linear regression analysis using the linear part of the data below the onset of ventilatory threshold (32). The rate pressure product was calculated as heart rate multiplied by systolic blood pressure.

3.5.2. Peripheral Vascular Endothelial Function

Brachial artery. Peripheral vascular endothelial function was assessed using flow-mediated dilation on the brachial artery in accordance with the International Brachial Artery Reactivity Task Force guidelines (34). Specifically, each patient was positioned supine with the right arm in a comfortable position for imaging the brachial artery ~5 cm above the antecubital fossa. The longitudinal image of the artery was obtained with a commercially available ultrasound instrument (Sonos 5500, Hewlett Packard) at rest and in response to reactive hyperemia (endothelium-dependent stimuli) and nitroglycerin (endothelium-independent stimuli). Reactive hyperemia was induced by an inflation of a blood pressure cuff placed on the forearm to at least 50 mm Hg above the systolic blood pressure for 5 minutes. A single dose of sublingual nitroglycerin spray was given 5 min after reactive hyperemia. (**Figure 3-02, A-C**).

Posterior tibial artery. Endothelial function of the posterior tibial artery was assessed using flow-mediated dilation as described by Black et al. (18). The assessment was performed ≥60 minutes after the testing of the brachial artery to allow sufficient time for the vasodilatory effects of nitroglycerin to disappear. The participant was positioned supine with a blood pressure cuff around the middle-calf region, proximal to the measurement site. The testing was performed

following the same protocol used for the assessment of endothelial function on the brachial artery (**Figure 3-02, D-F**).

Endothelial function testing was performed in the morning after the participant had fasted for ≥12 hours. All vasoactive medications were withheld for ≥24 hours prior to the testing. An experienced vascular sonographer performed the brachial ultrasound studies. Arterial diameter was quantified manually, at end-diastole, using semi-automatic edge detection software (DEA 2000) and averaged over three cardiac cycles. A software algorithm automatically calculated the average diameter (15 to 20 points) over the selected segment. The absolute and percent change in arterial diameter in response to reactive hyperemia and nitroglycerin were calculated. All images were analyzed by the same investigator who was blinded to the baseline data.

3.5.3. Left Ventricular Function

Systolic function was assessed using 2-dimensional echocardiography in accordance with the American Society of Echocardiography guidelines (157) using a commercially available ultrasound system (Sonos 5500, Hewlett Packard). LV end-systolic and end-diastolic cavity areas were obtained from the parasternal short-axis view. Area ejection fraction was calculated as stroke area divided by LV end-diastolic cavity area. All echocardiographic images were averaged over 3 cardiac cycles. Images were obtained, recorded to a tape and analyzed offline by a echocardiographer blinded to the baseline data and group assignment.

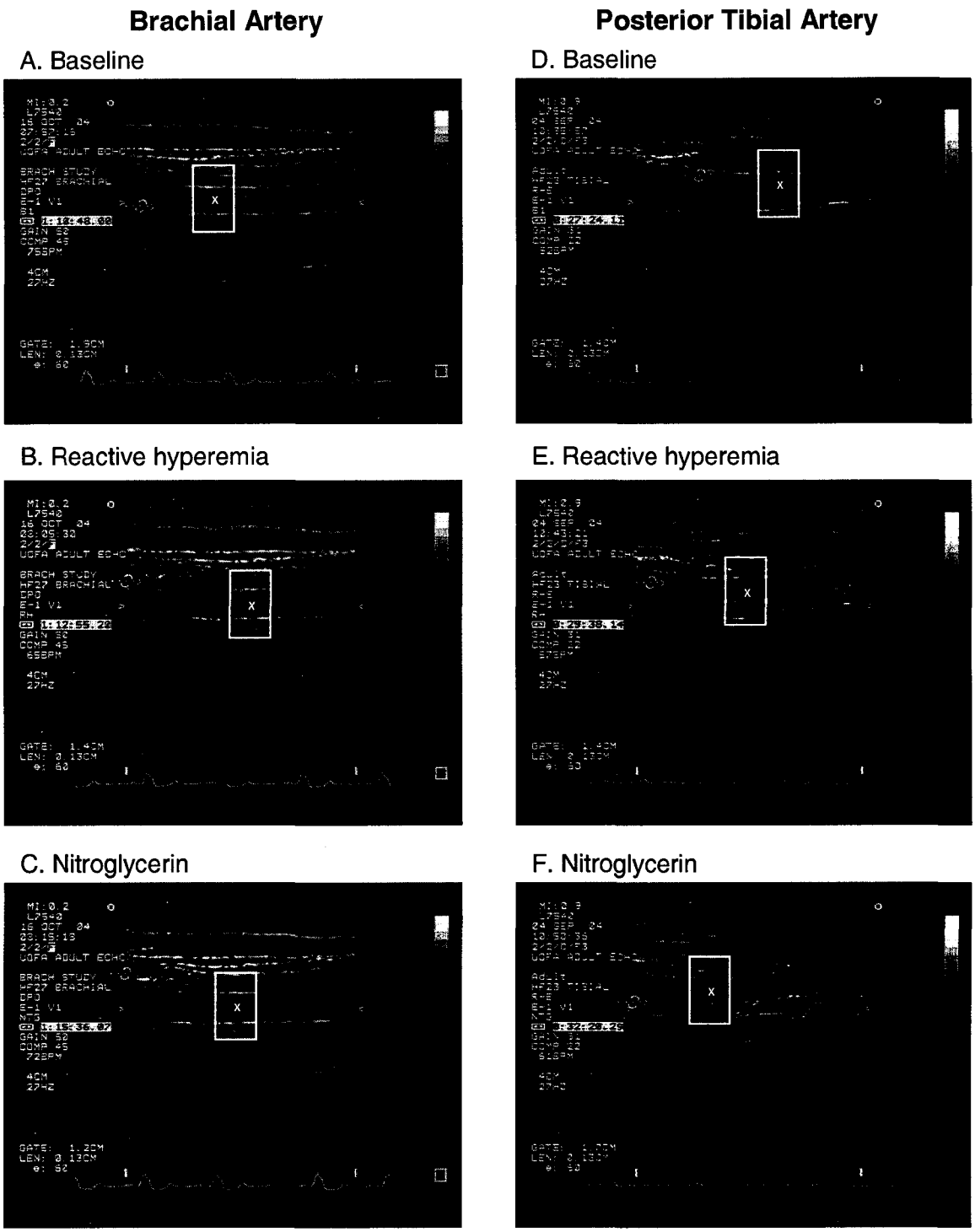


Figure 3-02. Vascular ultrasound images of the brachial (A to C) and posterior tibial (D to F) artery at baseline and in response to reactive hyperemia (endothelium-dependent dilation) and nitroglycerin (endothelium-independent dilation).

3.5.4. Muscle Strength and Endurance

Upper- and lower-extremity maximal muscle strength was assessed using the one-repetition maximum test on commercially available weight machines for 6 predetermined resistance exercises (see Section **3.6 Interventions**). The first set of 10 repetitions was performed at moderate intensity. The weight was progressively increased with each subsequent set until only one repetition could be performed while adhering to strict technique. Chest press and leg extension muscular endurance was assessed by the number of repetitions performed at 80% of one-repetition maximum. Patients were instructed to avoid a Valsalva manuever. The results were used to design moderate intensity resistance training for patients assigned to the CART group. Maximum weights and number of repetitions at 80% of one-repetition maximum achieved on chest press and leg extension exercises were used in the analysis as measures of the upper and lower body muscle strength and endurance, respectively.

3.5.5. Health-Related Quality of Life

HRQL was assessed using both generic (MacNew Heart Disease Health-Related Quality of Life Questionnaire (40,81)) and disease-specific (Minnesota Living with Heart Failure (17,149)) quality of life questionnaires. Both questionnaires were administered by the investigator and completed during a clinical visit.

The MacNew Heart Disease Health-Related Quality of Life Questionnaire (see **Appendix E**) is a valid and reliable tool to measure the perceptions of HRQL in patients with heart disease (40,81). This questionnaire is currently used

to evaluate the effects of cardiac rehabilitation on HRQL in patients attending the program at the Glenrose Rehabilitation Hospital.

The Minnesota Living with Heart Failure Questionnaire (see **Appendix F**) is a valid and reliable disease-specific tool that measures patients' perceptions of the effects of HF on their lives (149). This questionnaire measures the impact of symptoms related to HF and the side effects of HF medications. A total score integrates the physical, psychological, and socioeconomic burdens of HF with subscales for physical and emotional components of HRQL. The score achieved on this questionnaire is inversely related to HRQL. Although this questionnaire may not be sensitive to subtle changes in HRQL (153), it has been widely used in clinical trials in HF patients (14,117,137,172) and has established cut-off values for minimal clinically important differences (i.e., 5 points for the total score, and 3 points for the physical component) (150).

3.5.6. Additional Measures

As a part of a standard care for individuals with HF, lipoprotein profile and fasting blood glucose were measured. Blood samples were collected and analyzed by the University of Alberta Hospital clinical laboratory. Lipoprotein profile including total cholesterol, triglycerides, HDL- and LDL-cholesterol was measured spectrophotometrically while fasting blood glucose was assessed by a potentiometric essay using a commercially available device (Beckman LX 20 Pro, Terrytown, New York). In addition, w C-reactive protein was measured using the ELISA procedure. Blood samples were obtained after ≥12 hours of fasting.

Finally, insulin sensitivity was measured by the ^{13}C-glucose breath test (Diatest®, IsoDiagnostica Inc.). The technique involves non-radioactive isotopes and is judged to be clinically safe. The test kit (Diatest®) has been approved by Health Canada (Dr. Richard Lewanchuk, personal communication). Initially, patients in a fasted state blew into a gas-impermeable tube. Next, patients ingested 100 ml of an orange flavored drink consisting of 25 g of ^{12}C-glucose and 75 g of ^{13}C-glucose. Ninety minutes later, patients blew into another tube, completing the test. The breath test utilizes only 25 g of glucose compared to the 75 g oral glucose tolerance test and to date has not been associated with any side effects.

3.6. Interventions

Exercise sessions were performed at the Northern Alberta Cardiac Rehabilitation Program (Glenrose Rehabilitation Hospital, Capital Health) and were supervised by a registered nurse and exercise physiologist/specialist. Patients exercised 3 times per week, 40 to 60 minutes per session, for 12 weeks. The exercise sessions commenced and concluded with 5 min of warm-up and cool-down. Interventions are summarized in **Table 3-01**.

Aerobic training. AT consisted of 30 min of lower-extremity exercise on a treadmill (15 min) and cycle ergometer (15 min) at moderate intensity (50% to 70% of heart rate reserve). Heart rate (HR) reserve was calculated using Karvonen method: Target HR = ([HR_{max} – HR_{rest}] × intensity) + HR_{max}; where intensity is expressed as a desired percentage of heart rate reserve (for example, .50 for 50% and .70 for 70% of heart rate reserve).

Combined aerobic and resistance training. The aerobic component for the CART group consisted of 30 min of whole-body aerobic exercise at 50% to 70% of heart rate reserve using a treadmill (15 min) and a Schwinn (arm/leg) ergometer (15 min). This group also performed the following supplemental resistance training exercises: 1) chest press, 2) shoulder press, 3) vertical row, 4) bicep curl, 5) tricep extension and 6) leg extension using commercially available weight machines (APEX, Victoria, BC). Resistance training was initiated with 1 set of 10 repetitions at 50% of 1-repetition maximum. Once the patients were able to perform 15 repetitions with this weight, the weight was increased by 5% and a number of repetitions reduced to 10. Using the same progression, the weight was progressively increased from 50% to 70% of 1-repetition maximum. After 6 weeks, the second set was added. The patients were instructed to perform exercises while adhering to strict technique and avoided a Valsava maneuver.

Standard care (NT). Participants randomly assigned to the NT group were not provided with a formal exercise prescription. These individuals were allowed to continue their usual activities of daily living. The investigator contacted these patients by telephone every 2 to 3 weeks to assess any cardiac-related symptoms and compliance with the study protocol.

Table 3-01. Study interventions

	AT (Legs only)	CART (Legs and arms)	NT (Standard care)
Aerobic component			
Mode (Duration)	Treadmill (15 min) Cycle ergometer (15 min)	Treadmill (15 min) Schwinn (arm/leg) ergometer (15 min)	Maintain usual daily activities (i.e., no formal exercise prescription provided)
Intensity	50%-70% HR reserve RPE 11-14/20	50%-70% HR reserve RPE 11-14/20	
Resistance component			
Exercises*	-	6 exercises	
Reps (n)		10-15 reps	
Sets (n)	-	Weeks 1-6: 1 set Weeks: 7-12: 2 sets	
Intensity	-	50%-70% 1-RM	

*Resistance exercises included 1) chest press, 2) shoulder press, 3) vertical row, 4) bicep curl, 5) tricep extension and 6) leg extension using commercially available weight machines (APEX, Victoria, BC).

HR, heart rate; RPE, Borg's rating of perceived exertion; 1-RM, one-repetition maximum.

3.7. Statistical Considerations

3.7.1. Sample Size Justification

The primary parameter used to determine a sample size was the percent improvement in VO_{2peak} following 12 weeks of exercise training. Our preliminary data using the chosen exercise protocol in 21 individuals with HF showed a mean (SD) increase in VO_{2peak} of 11.9% (12.8) and 2.4% (8.7) in an exercise training and control group, respectively, with the effect size of 0.09. Based on those data, we needed a minimum sample of 14 patients in each group to detect a 12% improvement in VO_{2peak} following either AT or CART relative to no exercise training with a power of 75% at a 5% significance level (two-sided). Estimating a drop out rate of 10%, a total of 45 patients was needed for randomization (15 patients per group). This sample size was also powered to detect the differences in increase in VO_{2peak} in individuals with ischemic versus non-ischemic HF.

3.7.2. Statistical Analysis

The data were tested for a normal distribution using the Kolmogorov-Smirnov test, and for homogeneity of variances using Levene's test. Baseline characteristics were compared using one-way ANOVA or t-test for independent samples. The effects of different training modalities on all outcome measures were analysed using separate 2-way repeated measures ANOVA (RM ANOVA) followed by Tukey's post-hoc multiple comparisons. To adjust for age and gender differences in analyses that compared baseline differences in patients with IHF and NIHF, secondary analysis was performed by 1-way ANCOVA using age and

gender as covariates. Three-way RM ANOVA using etiology, intervention and time as independent factors was performed to compare the effects of exercise training versus standard care in IHF and NIHF patients. In a subsequent analysis, a t-test for independent samples was used to examine separately the effects of exercise training versus standard care in each subgroup of HF patients. Non-parametric data were analyzed by a Chi-square test. Correlations were determined using Pearsons' linear regression analysis. Multivariate stepwise regression analysis was used to determine predictors of VO_{2peak}. The alpha level was set a priory at $p<0.05$ and data are reported as mean ± SD. Data were analyzed using SPSS 12.0 statistical package for Windows.

The primary analysis compared the effects of AT, CART and NT on all outcome measures according to the intention-to-treat principle. In the following analyses we examined whether the results were influenced by patients' compliance with the prescribed exercise program or small sample size in each training group. Therefore, the secondary analysis compared the effects of AT, CART and NT on all outcome measures with the AT and CART groups consisting of patients who attended ≥80% of the sessions (per protocol analysis). In a subsequent analysis, AT and CART groups were combined to increase power and were compared to NT using the intention to treat principle. The effects of exercise training in patients with IHF and NIHF was examined by RM ANOVA using per protocol analysis (i.e., with the exercise groups including only the patients who attended ≥80% of the scheduled sessions). Patients with incomplete data sets were excluded from the analysis for a particular variable.

Chapter 4: RESULTS

4.1. Patient Characteristics

Patient characteristics, cardiovascular risk factors, and pharmacologic therapy for a total sample of 42 recruited HF patients are presented in **Table 4-01**. The sample consisted of 32 men and 12 women. Nineteen patients had ischemic HF while 23 patients were non-ischemic. On average, the patients presented with a total of 2.0±1.1 risk factors for cardiovascular disease. One half of the patients were obese and had a history of hypertension while two thirds of patients were hyperlipidemic. Diabetes was diagnosed in approximately 20% of the patients. The majority of patients were on a standard medical therapy for HF including beta blockers (100%), angiotensin converting enzyme (ACE) inhibitors (93%), and diuretics (90%). Two thirds of patients were also treated with lipid lowering agents.

4.2. Complications

Atrial fibrillation occurred in one subject during an exercise session during the 5^{th} week of training in a CART participant. This individual did not continue with the exercise program due to prolonged waiting time for a Holter monitor. However, he returned for follow up testing. No other exercise-related complications were observed during the study. One CART patient had a minor stroke 4 days after the last exercise session. As a result, this individual did not perform the follow-up graded exercise test and skeletal muscle testing. Another CART patient was diagnosed with a severe carotid artery stenosis and did not

Table 4-01. Patient population

	Males (n=32)	**Females** (n=10)	**Total** (n=42)
Age (yrs)	63 ± 11	57 ± 12	62 ± 12
Weight (kg)	89.6 ± 13.4	85.3 ± 22.0	88.6 ± 15.7
Body mass index (kg/m^2)	29.8 ± 4.9	33.1 ± 8.6	30.6 ± 6.0
VO_{2peak} (ml/kg/min)	16.8 ± 6.1	15.4 ± 5.1	16.4 ± 5.8
LV Area ejection fraction (%)	31.2 ± 12.4	31.6 ± 11.2	31.3 ± 12.0
HF Etiology (ischemic/non-ischemic)	18/14	1/9	19/23
Risk Factors (n (%))			
Hypertension	19 (59)	5 (50)	24 (57)
Diabetes	9 (28)	0 (0)	9 (21)
Obesity	13 (41)	6 (60)	19 (45)
Hyperlipidemia	28 (88)	2 (20)	30 (71)
Smoking	3 (9)	1 (10)	4 (10)
Total n of risk factors (n)	2.2 ± 1.2	1.4 ± 0.8	2.0 ± 1.1
Medications (n (%))			
Beta blockers	32 (100)	10 (100)	42 (100)
ACE Inhibitors	30 (94)	9 (90)	39 (93)
Diuretics	27 (84)	9 (90)	38 (90)
Lipid lowering	23 (72)	5 (50)	28 (67)

Descriptive data. No statistical analysis performed.
LV, left ventricular; VO_{2peak}, peak oxygen consumption.

and did not start the exercise program. Other clinical events unrelated to exercise training included hospitalizations for decompensated HF (1 NT), undiagnosed chest pain (1 CART), and hyperglycemia (1 AT); gout (1 AT); pacemaker resetting (1 CART; 2 NT); and prolonged severe fatigue due to an increased dose of beta blocker medications (1 AT).

4.3. Change in Medications

In total, 16 individuals (38% of participants) had a change in their medications during the investigation (8 AT; 5 CART; 3 NT). These changes included: 1) modification in a dose or type of beta blocker (n=6), ACE inhibitor (n=4), diuretic (n=6), statins (n=1), and amiodarone (n=1); 2) initiation of therapy with aspirin (n=2), and glycemic control agents (n=1) and 3) discontinuation of warfarin (n=1) and digoxin (n=1). Overall, participants with a change in medications had a reduced number of cardiovascular risk factors (1.4±1.1 vs. 2.3±1.1, p=0.015) and lower body mass index (28.0±4.9 vs. 31.9±6.2, p=0.039) compared to those without a change in medications. The groups were similar with respect to age, etiology, VO_{2peak}, area ejection fraction, and a total score for generic and disease-specific HRQL (for details see **Appendix G, Table 7-01**).

4.4. Exercise Training Compliance

Three patients (7%) dropped out from the exercise intervention groups because of time constraints and work responsibilities (2 AT; 1 CART). Two of these patients returned for follow-up testing. In addition, one CART participant did not start the exercise program and did not complete follow-up testing due to medical problems described above (see section **4.2. Complications**). The

number of patients with incomplete data sets for each outcome measure are presented in **Table 4-02**.

Twenty-nine patients were randomly assigned to the AT (n=14) or CART (n=15) group. The patients assigned to the exercise intervention groups attended 78±25% of scheduled exercise sessions (range: 0% to 100%). Twenty patients (69%) attended ≥80% of scheduled exercise sessions (AT, n=9 (64%); CART, n=11 (73%)) and were included in the per protocol analysis as compliant patients. Nine patients (AT, n=5; CART, n=4) attended <80% of scheduled exercise sessions and were considered non-compliant.

4.5. Exercise Training Data

All participants performed 30 minutes of aerobic exercise per session including 15 minutes of walking on a treadmill and 15 minutes of cycling on a cycle (AT) or Schwinn ergometer (CART). Two patients (1 AT; 1 CART) were unable to exercise continuously for 15 minutes. These patients performed a training program consisting of 2 min of exercise followed by 2 min of recovery to achieve the required exercise duration. On average, patients in the AT and CART groups exercised at the same intensity of 50% of heart rate reserve both on the treadmill (average HR: 91±14 bpm) and cycle/Schwinn ergometer (average HR: 90±16 bpm). The average Borg rating of perceived exertion was 12.0 and 12.6 for treadmill and cycle/Schwinn ergometer, respectively.

Patients assigned to the CART group performed, on average, 1.4 sets of 10 to 15 repetitions at 50% of 1-repetition maximum for both chest press (weight used: 21.1±5.4 kg) and leg extension exercises (weight used: 22.5±9.4 kg). Two

patients assigned to the CART group were not able to perform resistance training due to morbid obesity (n=1) and detached retina not related to the study (n=1).

4.6. Effects of Different Exercise Interventions – Intention to Treat Analysis

The primary analysis was performed according to the intention to treat principle (161). Baseline characteristics of the AT, CART and NT groups are presented in **Table 4-02**. The groups were not statistically different with respect to all measurement outcomes at the baseline.

Resting and Acute Cardiovascular Responses during Exercise. Following the 12-week intervention period, the total exercise time was significantly increased in both AT and CART groups while peak power output was increased in the AT group only (**Table 4-03**). Heart rate at rest was significantly reduced in the AT group only (**Table 4-03**). Neither AT nor CART had significant effects on heart rate, blood pressure and rate pressure product at the ventilatory threshold or peak exercise. Similarly, no exercise intervention had significant effects on V_E/V_{CO2} slope, percent of predicted VO_{2peak}, or absolute and relative VO_2 at the ventilatory threshold or peak exercise (**Table 4-03**). No changes in resting or acute cardiovascular responses were observed in the NT group.

Table 4-02. Descriptive characteristics of patients (**Intention to treat analysis**)

	AT (n=14)	CART (n=15)	NT (n=13)
Age (yrs)	63 ± 11	59 ± 11	62 ± 13
Gender (M/F)	11/3	11/4	10/3
Weight (kg)	87.4 ± 17.2	92.9 ± 15.8	84.8 ± 13.7
Body mass index (kg/m^2)	29.8 ± 5.6	32.1 ± 7.3	29.8 ± 5.0
VO_{2peak} (ml/kg/min)	16.5 ± 6.4	16.3 ± 5.6	16.6 ± 6.0
Area ejection fration (%)	30.7 ± 10.9	33.4 ± 13.3	29.4 ± 12.1
HF Etiology (ischemic/non-ischemic)	7/7	8/7	4/9
Risk Factors (n (%))			
Hypertension	7 (50)	9 (60)	8 (62)
Diabetes	5 (36)	2 (13)	2 (15)
Obesity	6 (43)	8 (53)	5 (38)
Hyperlipidemia	11 (76)	9 (60)	10 (77)
Smoking	0 (0)	3 (20)	1 (8)
Total n of risk factors (n)	2.0 ± 1.4	2.1 ± 1.1	1.9 ± 1.1
Medications (n (%))			
Beta blockers	14 (100)	15 (100)	13 (100)
ACE Inhibitors	14 (100)	13 (87)	12 (92)
Diuretics	10 (71)	14 (93)	12 (92)
Lipid lowering	12 (86)	8 (53)	8 (62)
Incomplete Data Sets			
Exercise testing	2	2	0
Ventilatory threshold	5	5	3
Echocardiography	4	2	2
Brachial endothelial function	4	1	2
Posterior tibial endothelial function	6	5	3
Skeletal muscle function	2	3	0
Metabolic profile	1	1	0
Quality of life	0	1	1

LV, left ventricular; VO_{2peak}, peak oxygen consumption.

All comparisons p>0.05

Table 4-03. Effects of different exercise programs on cardiorespiratory function at rest and during acute exercise. (**Intention to treat analysis**)

	AT		CART		NT	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Rest	(n=12)		(n=13)		(n=13)	
HR (bpm)	68 ± 13	61 ± 9*	69 ± 15	67 ± 12	67 ± 8	73 ± 15
SBP (mm Hg)	112 ± 18	108 ± 19	115 ± 18	115 ± 15	112 ± 19	114 ± 19
DBP (mm Hg)	67 ± 8	68 ± 13	72 ± 9	71 ± 8	70 ± 11	69 ± 10
RPP (bpm·mmHg·10^3)	7.6 ± 1.5	6.6 ± 1.3*	7.9 ± 1.7	7.7 ± 1.2	7.4 ± 1.4	8.3 ± 2.4
Ventilatory Threshold	(n=9)		(n=10)		(n=10)	
HR (bpm)	92 ± 21	89 ± 18	99 ± 24	93 ± 20	102 ± 30	102 ± 27
SBP (mm Hg)	127 ± 13	115 ± 19	145 ± 22	137 ± 14	138 ± 22	133 ± 22
DBP (mm Hg)	72 ± 5	72 ± 5	77 ± 10	74 ± 5	71 ± 8	74 ± 8
RPP (bpm·mmHg·10^3)	11.7 ± 3.1	10.4 ± 3.1	14.4 ± 4.5	12.8 ± 3.4	14.4 ± 5.7	13.9 ± 4.7
VO_2 (ml·kg^{-1}·min^{-1})	10.4 ± 1.8	11.5 ± 2.9	13.5 ± 5.0	14.2 ± 4.8	12.8 ± 3.7	12.5 ± 3.2
VO_2 (L·min^{-1})	0.90 ± 0.21	1.00 ± 0.31	1.22 ± 0.45	1.24 ± 0.42	1.07 ± 0.39	1.05 ± 0.36
% of VO_2 peak (%)	66 ± 11	68 ± 11	75 ± 10	75 ± 10	69 ± 12	69 ± 10
Power output (watts)	48 ± 16	58 ± 21	73 ± 27	78 ± 23	66 ± 23	58 ± 22
Exercise time (min)	5.4 ± 2.3	7.0 ± 3.2	8.6 ± 3.4	9.3 ± 3.3	7.9 ± 2.9	6.8 ± 3.3
V_E/V_{CO2} Slope	32.5 ± 5.5	33.5 ± 10.1	27.9 ± 3.9	27.6 ± 5.4	31.2 ± 8.1	31.5 ± 6.5
Peak Exercise	(n=12)		(n=13)		(n=13)	
HR (bpm)	112 ± 28	114 ± 31	109 ± 28	112 ± 27	117 ± 38	121 ± 36
SBP (mm Hg)	144 ± 28	138 ± 25	149 ± 30	151 ± 25	146 ± 31	141 ± 28
DBP (mm Hg)	73 ± 7	67 ± 11	77 ± 8	76 ± 9	71 ± 10	71 ± 8
RPP (bpm·mmHg·10^3)	16.3 ± 5.8	16.2 ± 6.5	16.4 ± 5.8	17.3 ± 6.4	17.8 ± 8.3	17.5 ± 6.9
VO_2 (ml·kg^{-1}·min^{-1})	16.0 ± 5.1	17.3 ± 6.4	16.1 ± 6.0	17.2 ± 6.9	16.6 ± 6.0	16.7 ± 6.1
VO_2 (L·min^{-1})	1.42 ± 0.38	1.40 ± 0.45	1.48 ± 0.55	1.54 ± 0.60	1.39 ± 0.53	1.42 ± 0.61
VO_2 % predicted (%)	64 ± 23	60 ± 29	56 ± 16	58 ± 18	65 ± 37	67 ± 29
Power output (watts)	76 ± 31	94 ± 41*	85 ± 30	93 ± 39	84 ± 38	82 ± 41
Exercise time (min)	11.1 ± 4.0	13.1 ± 5.2*	11.9 ± 4.3	13.4 ± 5.3*	12.1 ± 5.1	11.7 ± 5.1
RER	1.06 ± 0.06	1.07 ± 0.07	1.08 ± 0.10	1.05 ± 0.09	1.06 ± 0.08	1.04 ± 0.07

DBP, diastolic blood pressure; HR, heart rate; RER, respiratory exchange ratio; RPP, rate pressure product; SBP, systolic blood pressure; VO_2, oxygen consumption.

*$p<0.05$ versus change from baseline in NT

Left Ventricular Systolic Function. Neither AT nor CART had significant effects on LV end-diastolic and end-systolic cavity area, or area ejection fraction compared to the NT intervention (**Table 4-04**).

Brachial and Posterior Tibial Endothelial Function. Brachial artery responses to reactive hyperemia (endothelium-dependent dilation) or nitroglycerin (endothelium-independent dilation) were not changed following the AT or CART compared to the NT intervention (**Table 4-04**). Similarly, neither AT nor CART intervention had effects on the posterior tibial response to reactive hyperemia or nitroglycerin (**Table 4-04**).

Muscle Strength and Endurance. The CART group significantly increased upper and lower extremity muscle strength and improved upper extremity muscle endurance compared to the NT group (**Figure 4-01, Table 4-04**). The increase in upper extremity muscle strength and endurance in the CART group was significantly greater from changes in the AT group (**Figure 4-01, A and C; Table 4-04**). Although lower extremity muscle endurance was increased after training in both AT and CART, these changes were not statistically significant.

Metabolic Profile. No exercise intervention had a significant effect on total cholesterol, triglycerides, HDL- and LDL-cholesterol, total cholesterol to HDL-cholesterol ratio, C-reactive protein, or fasting glucose compared to the NT group (**Table 4-05**).

Health-Related Quality of Life. Neither AT nor CART had any significant effects on disease-specific or generic HRQL (**Table 4-05**).

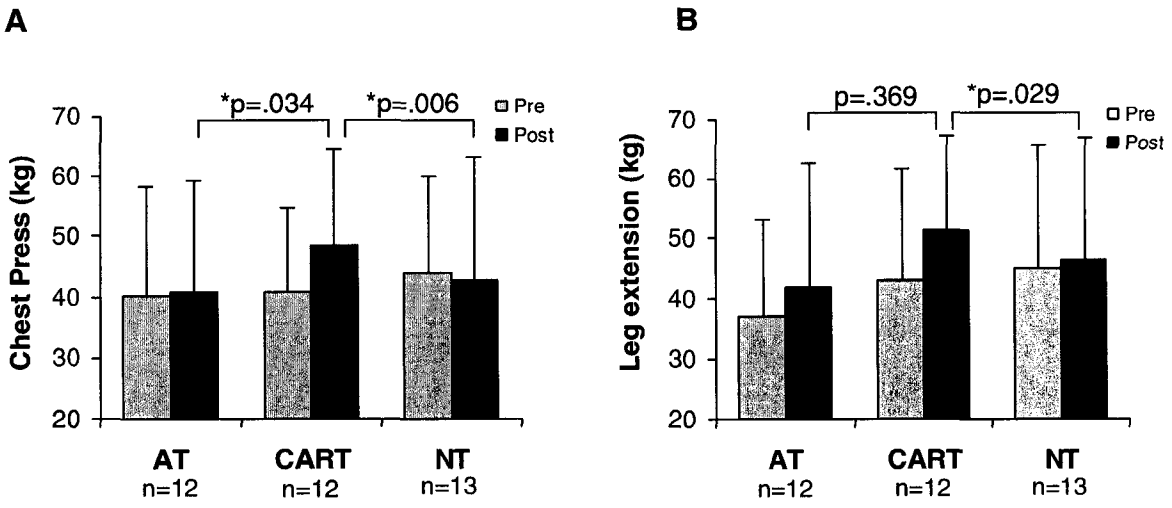
Table 4-04. Effects of different exercise programs on left ventricular, vascular and skeletal muscle function. (**Intention to treat analysis**)

	AT		CART		NT	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Left Ventricular Function	(n=10)		(n=13)		(n=11)	
LV EDCA (cm^2)	29.8 ± 11.0	29.5 ± 15.0	27.3 ± 7.9	28.2 ± 10.9	27.9 ± 7.7	28.3 ± 9.6
LV ESCA (cm^2)	21.7 ± 11.0	20.8 ± 13.1	18.8 ± 7.9	18.6 ± 9.7	20.6 ± 7.5	20.8 ± 8.1
Area ejection fraction (%)	30.0 ± 11.4	32.8 ± 10.4	33.2 ± 13.8	36.0 ± 10.7	27.4 ± 10.3	27.4 ± 8.4
Vascular Function						
Brachial Artery	(n=10)		(n=14)		(n=11)	
Baseline AD (mm)	5.03 ± 0.83	4.82 ± 1.09	4.75 ± 0.80	4.74 ± 0.68	4.98 ± 0.77	5.01 ± 0.88
RH AD (mm)	5.21 ± 0.85	5.05 ± 1.13	4.97 ± 0.74	5.07 ± 0.67	5.14 ± 0.70	5.09 ± 0.86
RH AD (% Δ)	3.6 ± 4.9	5.2 ± 6.6	5.1 ± 5.4	7.3 ± 5.1	3.4 ± 3.9	1.8 ± 2.8
NTG AD (mm)	5.89 ± 0.86	5.63 ± 0.97	5.42 ± 0.73	5.35 ± 0.63	5.48 ± 0.64	5.55 ± 0.84
NTG AD (% Δ)	14.7 ± 8.1	15.2 ± 12.5	16.1 ± 8.4	14.7 ± 8.3	8.3 ± 7.5	9.2 ± 4.1
Posterior Tibial Artery	(n=8)		(n=10)		(n=10)	
Baseline AD (mm)	3.24 ± 0.64	3.33 ± 0.67	2.97 ± 0.47	2.91 ± 0.37	2.94 ± 0.89	3.04 ± 1.00
RH AD (mm)	3.55 ± 0.57	3.70 ± 0.47	3.31 ± 0.57	3.25 ± 0.44	3.13 ± 0.91	3.27 ± 1.07
RH AD (% Δ)	10.5 ± 8.4	13.0 ± 12.2	11.3 ± 6.8	11.4 ± 5.5	6.8 ± 6.5	7.4 ± 9.6
NTG AD (mm)	3.60 ± 0.70	3.71 ± 0.62	3.21 ± 0.26	3.39 ± 0.57	3.51 ± 0.92	3.67 ± 1.03
NTG AD (% Δ)	11.4 ± 7.1	12.6 ± 10.3	12.0 ± 8.5	14.2 ± 8.1	11.9 ± 12.3	9.2 ± 11.1
Skeletal Muscle Function						
Maximal Muscle Strength	(n=12)		(n=12)		(n=13)	
Chest press (kg)	40.1 ± 17.5	40.8 ± 17.3	40.7 ± 14.0	48.5 ± 16.0*†	43.8 ± 16.6	42.8 ± 19.3
Leg extension (kg)	37.1 ± 15.9	41.8 ± 18.9	42.9 ± 18.4	51.5 ± 16.8*	45.1 ± 19.8	46.3 ± 18.8
Muscle Endurance						
Chest press (reps)	6.3 ± 2.5	7.2 ± 4.0	5.7 ± 2.7	11.6 ± 7.6*†	6.1 ± 2.6	5.3 ± 3.0
Leg extension (reps)	8.7 ± 3.0	10.2 ± 5.0	7.3 ± 2.6	12.0 ± 4.9	8.0 ± 2.2	7.0 ± 2.9

AD, arterial diameter; DBP, diastolic blood pressure; HR, heart rate; LV, left ventricular; EDCA, end-diastolic cavity area; ESCA, end-systolic cavity area; NTG, nitroglycerin; RH, reactive hyperemia.

*$p<0.05$ versus change from baseline in NT
†$p<0.05$ versus change from baseline in AT.

Muscle Strength



Muscle Endurance

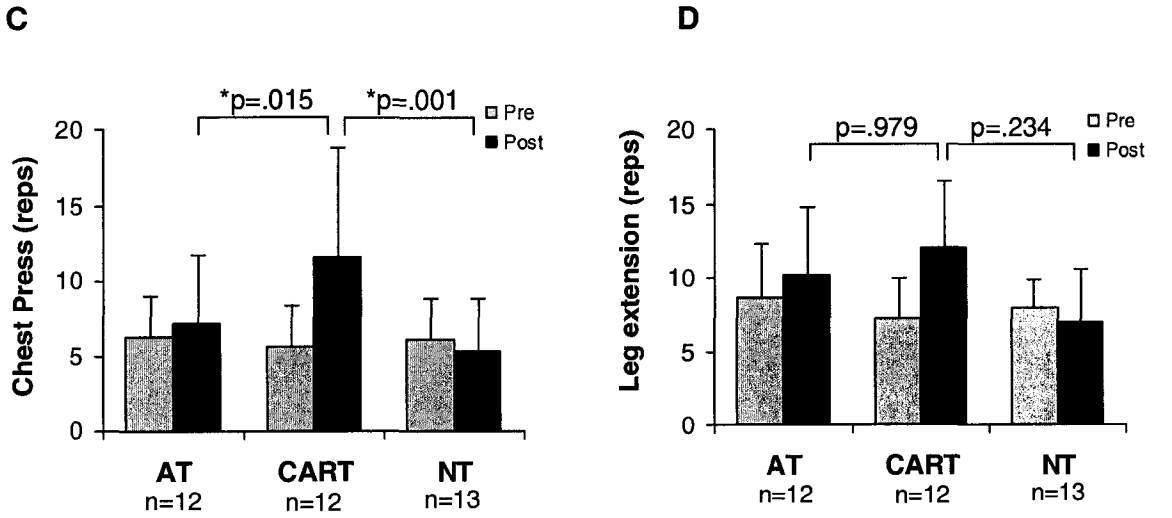


Figure 4-01. Effects of AT, CART and NT interventions on muscle strength (A-B) and endurance (C-D). (**Intention to treat analysis**)

*p<.05 versus change from baseline in the AT or NT group.

Table 4-05. Effects of different exercise programs on metabolic profile and health-related quality of life. (**Intention to treat analysis**)

	AT		CART		NT	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Metabolic Profile	(n=13)		(n=14)		(n=13)	
Cholesterol ($mmol \cdot L^{-1}$)	4.22 ± 0.82	3.84 ± 0.74	4.44 ± 1.14	4.35 ± 0.97	4.64 ± 1.16	4.51 ± 1.19
Triglycerides ($mmol \cdot L^{-1}$)	2.17 ± 1.51	2.36 ± 2.57	1.71 ± 0.75	1.58 ± 0.37	2.23 ± 1.34	2.33 ± 1.79
HDL Cholesterol ($mmol \cdot L^{-1}$)	1.14 ± 0.16	1.22 ± 0.28	1.13 ± 0.31	1.17 ± 0.30	1.14 ± 0.29	1.20 ± 0.26
LDL Cholesterol ($mmol \cdot L^{-1}$)	2.12 ± 0.66	1.67 ± 0.40	2.54 ± 0.87	2.46 ± 0.73	2.56 ± 0.95	2.33 ± 0.96
Total cholesterol/ HDL cholesterol	3.6 ± 0.7	3.0 ± 0.5	4.0 ± 0.7	3.8 ± 0.8	4.1 ± 1.0	3.9 ± 1.2
C-reactive protein ($mg \cdot L^{-1}$)	2.7 ± 3.0	2.2 ± 1.9	4.3 ± 4.4	5.1 ± 3.5	3.7 ± 2.7	4.8 ± 5.6
Fasting glucose ($mmol \cdot L^{-1}$)	6.2 ± 3.1	5.6 ± 1.1	5.4 ± 0.5	5.7 ± 0.5	6.0 ± 0.4	6.1 ± 0.8
Insulin sensitivity[§]	11.4 ± 7.0	9.5 ± 2.1	9.0 ± 2.9	8.8 ± 2.0	9.5 ± 4.4	9.5 ± 3.7
Health-Related Quality of Life						
Disease-Specific HRQL	(n=14)		(n=14)		(n=12)	
Physical	21.9 ± 8.9	18.0 ± 9.7	18.2 ± 10.2	14.9 ± 11.7	16.7 ± 9.6	16.9 ± 9.9
Emotional	9.0 ± 5.4	8.2 ± 6.5	9.4 ± 7.8	7.0 ± 5.9	9.6 ± 7.8	8.2 ± 8.0
Total	45.9 ± 16.8	41.4 ± 23.2	40.0 ± 19.8	32.6 ± 20.2	40.2 ± 22.5	37.8 ± 24.7
Generic HRQL (MacNew)	132 ± 24	139 ± 32	141 ± 24	146 ± 24	144 ± 33	142 ± 37

HRQL, health-related quality of life.
[§]Insulin sensitivity was measured using ^{13}C-glucose breath test.

All comparisons $p>0.05$ versus change from baseline in NT

4.7. Effects of Different Exercise Interventions in Compliant Patients – Per Protocol Analysis

To examine whether the effects of AT or CART versus NT were influenced by patients' compliance with the prescribed exercise program, a secondary analysis was performed using exercise compliance data with the AT and CART groups consisting of patients who attended ≥80% of the sessions (per protocol analysis). Twenty patients (9 AT, 11 CART) were included in this analysis as compliant patients while 9 patients (5 AT, 4 CART) were considered non-compliant.

Baseline characteristics, cardiovascular risk factors, pharmacologic therapy, and HRQL data for compliant and non-compliant patients are presented in **Table 4-06**. Non-compliant patients had higher body weight and body mass index and reduced total score for both generic and disease-specific HRQL compared to the compliant individuals. The groups were similar with respect to age, gender, VO_{2peak}, area ejection fraction, and HF etiology. Baseline characteristics of the patients included in the per protocol analysis were not statistically different for all 3 intervention groups (for details see **Appendix G**, **Table 7-02**).

The results of the per protocol analysis showed similar results as the intention to treat analysis for most measurement outcomes (for details see **Appendix G**, **Table 7-03** to **Table 07-05**). Neither AT nor CART had significant effects on hemodynamic parameters, V_E/V_{CO2} slope (**Figure 4-02, B**), LV systolic function (**Figure 4-02, E**), posterior tibial endothelial function (**Figure 4-02, D**), or metabolic profile. Increased upper and lower extremity muscle strength and

Table 4-06. Baseline characteristics of compliant and non-compliant patients assigned to exercise training.

	Compliant (n=20)	**Non-compliant** (n=9)	p-value
Group: AT/CART [n(%)]	9(64%)/11(73%)	5(36%)/4(27%)	
Age (yrs)	62 ± 11	60 ± 11	.602
Gender (M/F)	15/5	7/2	
Weight (kg)	86.3 ± 13.0	99.0 ± 20.4‡	.051
Body mass index (kg/m^2)	29.3 ± 4.5	34.7 ± 8.7*	.035
VO_{2peak} (ml/kg/min)	16.1 ± 5.3	16.9 ± 7.2	.759
Area ejection fraction (%)	31.9 ± 13.8	32.0 ± 10.4	.987
HF Etiology (ischemic/non-ischemic)	10/10	5/4	.785
Risk Factors (n (%))			
Hypertension	11 (55)	5 (56)	.978
Diabetes	3 (15)	4 (44)	.092
Obesity	9 (45)	5 (56)	.605
Hyperlipidemia	14 (70)	6 (67)	.860
Smoking	2 (10)	1 (11)	.929
Total n of risk factors (n)	2.0 ± 1.3	2.2 ± 1.1	.593
Medications (n (%))			
Beta blockers	20 (100)	9 (100)	1.000
ACE Inhibitors	18 (90)	9 (100)	1.000
Diuretics	16 (80)	8 (89)	.180
Lipid lowering	14 (70)	6 (67)	.944
Disease-Specific HRQL (Minnesota)			
Physical	18.2 ± 8.7	25.2 ± 10.1	.064
Emotional	8.3 ± 6.6	12.6 ± 7.2	.128
Total	38.6 ± 16.9	55.2 ± 17.0*	.021
Generic HRQL (MacNew)			
Total	142 ± 23	121 ± 21*	.027

HRQL, health-related quality of life; LV, left ventricular; VO_{2peak}, peak oxygen consumption.

*$p<0.05$ and ‡$p<0.10$ vs. compliant patients

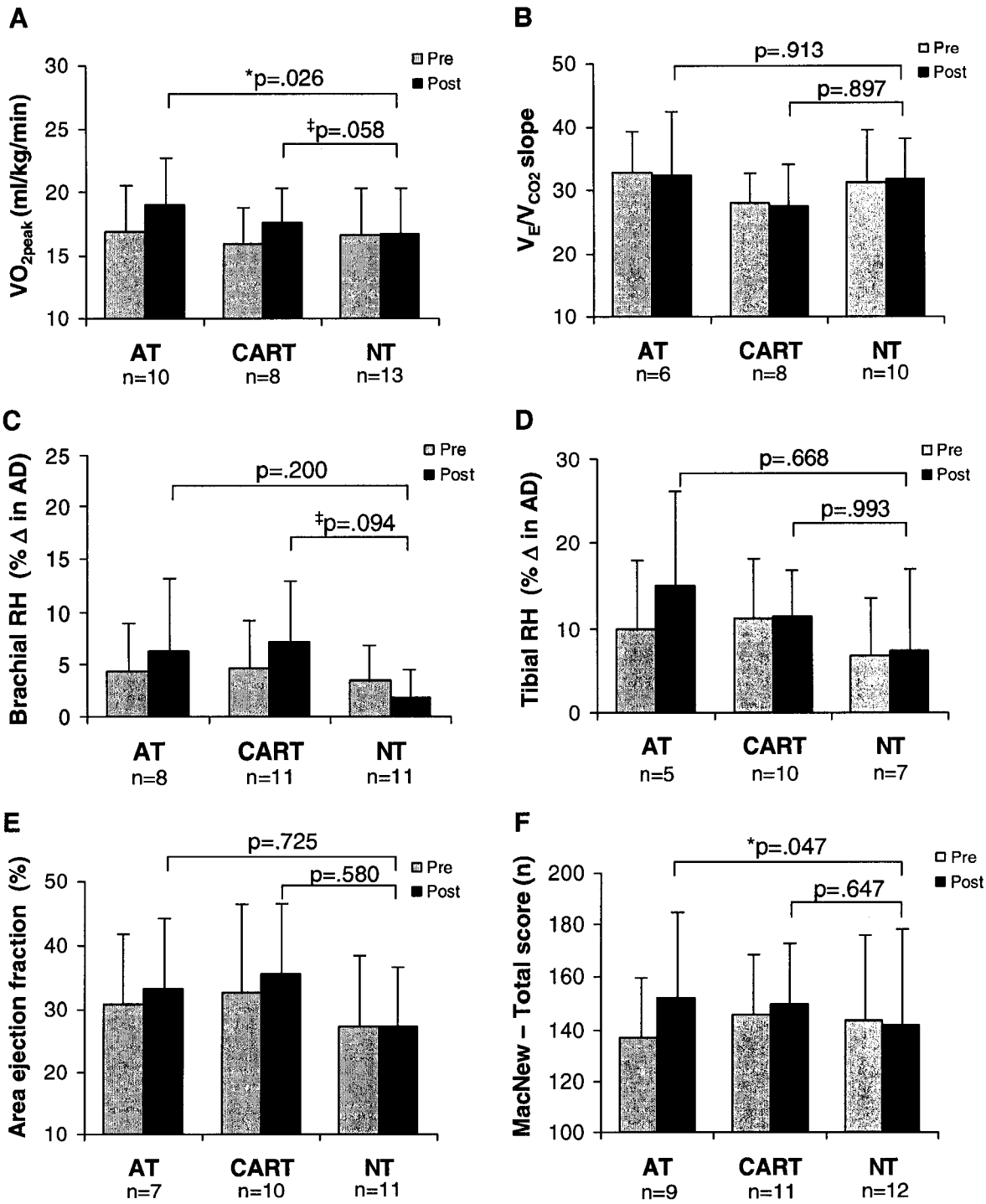


Figure 4-02. Effect of AT or CART versus NT on (A) VO_{2peak}, (B) V_E/V_{CO2} slope, (C) brachial and (D) posterior tibial endothelial function, (E) left ventricular systolic function, and (F) generic quality of life in compliant patients. **(Per protocol analysis).**

AD, arterial diameter; RH, reactive hyperemia.
*p<.05 and ‡p<.10 versus change from baseline in the NT group

improved upper extremity muscle endurance were observed only in the CART compared to the NT group (for details see **Appendix G, Table 7-04**). In contrast to the intention to treat analysis, per protocol analysis showed that both AT and CART improved VO_{2peak} by 12% and 11%, respectively (**Figure 4-02, A**). In addition, brachial artery response to reactive hyperemia was increased, although not significantly, following CART while no changes were observed in the AT and NT groups (**Figure 4-02, C**). Moreover, upper body skeletal muscle endurance but not strength was significantly increased in CART versus AT group (for details see **Appendix G, Table 7-04**). Finally, the AT group significantly improved generic HRQL while no changes were observed in the CART or NT group (**Figure 4-02, F**).

4.8. Effects of Exercise Training Irrespective of Training Modality

To increase the statistical power to differentiate the effects of exercise training versus NT, in the final analysis the AT and CART groups were combined to examine the effects of exercise training, irrespective of training modality, versus NT on all measurement outcomes according to the intention to treat principle.

The groups were similar with respect to age, gender, VO_{2peak}, LV systolic function, and HF etiology at the baseline (**Table 4-07**). Compared to the NT intervention, exercise training did not have significant effects on relative VO_{2peak} (**Figure 4-03, A; Table 4-08**) and area ejection fraction (**Figure 4-03, B; Table 4-09**). Although VO_{2peak} was improved by 7.5% following training, this improvement was not statistically significant in the intention to treat analysis (p=.135). Exercise training increased exercise time and power output at the ventilatory threshold.

Table 4-07. Baseline characteristics of patients assigned to exercise training (pooled AT and CART groups) versus standard care (NT). (**Intention to treat analysis**)

	Exercise (AT+CART) (n=29)	**Standard Care (NT)** (n=13)
Age (yrs)	61 ± 11	62 ± 13
Gender (M/F)	22/7	10/3
Weight (kg)	90.2 ± 16.4	84.8 ± 13.7
Body mass index (kg/m^2)	31.0 ± 6.5	29.8 ± 5.0
VO_{2peak} (ml/kg/min)	16.4 ± 5.9	16.6 ± 6.0
LV Area ejection fraction (%)	32.1 ± 12.1	29.4 ± 12.1
HF Etiology (ischemic/non-ischemic)	15/14	4/9
Risk Factors (n (%))		
Hypertension	16 (55)	8 (62)
Diabetes	7 (24)	2 (15)
Obesity	14 (48)	5 (38)
Hyperlipidemia	20 (69)	10 (77)
Smoking	3 (10)	1 (8)
Total n of risk factors (n)	2.0 ± 1.2	1.9 ± 1.0
Medications (n (%))		
Beta blockers	29 (100)	13 (100)
ACE Inhibitors	27 (93)	12 (92)
Diuretics	24 (83)	12 (92)
Lipid lowering	20 (69)	8 (62)

LV, left ventricular; VO_{2peak}, peak oxygen consumption.

All comparisons p>0.05.

Table 4-08. Effects exercise versus standard care on cardiorespiratory function at rest and during acute exercise. (**Intention to treat analysis**)

	Exercise (AT+CART)		Standard Care (NT)	
	Pre	**Post**	**Pre**	**Post**
Rest	(n=25)		(n=13)	
HR (bpm)	69 ± 14	64 ± 11*	67 ± 8	73 ± 15
SBP (mm Hg)	114 ± 18	112 ± 17	112 ± 19	114 ± 19
DBP (mm Hg)	70 ± 9	69 ± 10	70 ± 11	69 ± 10
RPP (bpm·mmHg·10^3)	7.8 ± 1.6	7.1 ± 1.4*	7.4 ± 1.4	8.3 ± 2.4
Ventilatory Threshold	(n=19)		(n=10)	
HR (bpm)	95 ± 22	91 ± 19	102 ± 30	102 ± 27
SBP (mm Hg)	137 ± 20	127 ± 19	138 ± 22	133 ± 22
DBP (mm Hg)	75 ± 8	71 ± 11	71 ± 8	74 ± 8
RPP (bpm·mmHg·10^3)	13.1 ± 4.0	11.6 ± 3.4	14.4 ± 5.7	13.9 ± 4.7
VO_2 (ml·kg^{-1}·min^{-1})	12.1 ± 4.1	12.9 ± 4.1	12.8 ± 3.7	12.5 ± 3.2
VO_2 (L·min^{-1})	1.07 ± 0.39	1.13 ± 0.38	1.08 ± 0.39	1.06 ± 0.36
% of VO_2 peak (%)	71 ± 11	71 ± 11	69 ± 12	69 ± 10
Power output (watts)	61 ± 25	69 ± 24*	66 ± 23	58 ± 22
Exercise time (min)	7.1 ± 3.3	8.2 ± 3.4*	7.9 ± 2.9	6.8 ± 3.3
V_E/V_{CO2} Slope	30.1 ± 5.2	30.4 ± 8.3	31.2 ± 8.1	31.4 ± 6.5
Peak Exercise	(n=25)		(n=13)	
HR (bpm)	110 ± 28	113 ± 28	117 ± 38	121 ± 36
SBP (mm Hg)	146 ± 28	145 ± 26	146 ± 31	141 ± 28
DBP (mm Hg)	75 ± 8	72 ± 10	71 ± 10	71 ± 8
RPP (bpm·mmHg·10^3)	16.3 ± 5.7	16.8 ±6.3	17.8 ± 8.3	17.5 ± 6.9
VO_2 (ml·kg^{-1}·min^{-1})	16.0 ± 5.4	17.2 ± 6.5	16.6 ± 6.0	16.7 ± 6.1
VO_2 (L·min^{-1})	1.45 ± 0.47	1.47 ± 0.52	1.39 ± 0.53	1.42 ± 0.61
VO_2 % predicted (%)	60 ± 20	59 ± 24	65 ± 37	67 ± 29
Power output (watts)	81 ± 30	94 ± 39*	84 ± 38	82 ± 41
Exercise time (min)	11.5 ± 4.1	13.3 ± 5.1*	12.01 ± 5.1	11.7 ± 5.1
RER	1.07 ± 0.08	1.06 ± 0.08	1.06 ± 0.08	1.04 ± 0.07

DBP, diastolic blood pressure; HR, heart rate; RPP, rate pressure product; RER, respiratory equivalent ratio; SBP, systolic blood pressure; VO_2, oxygen consumption.

*$p<0.05$ versus change from baseline in NT

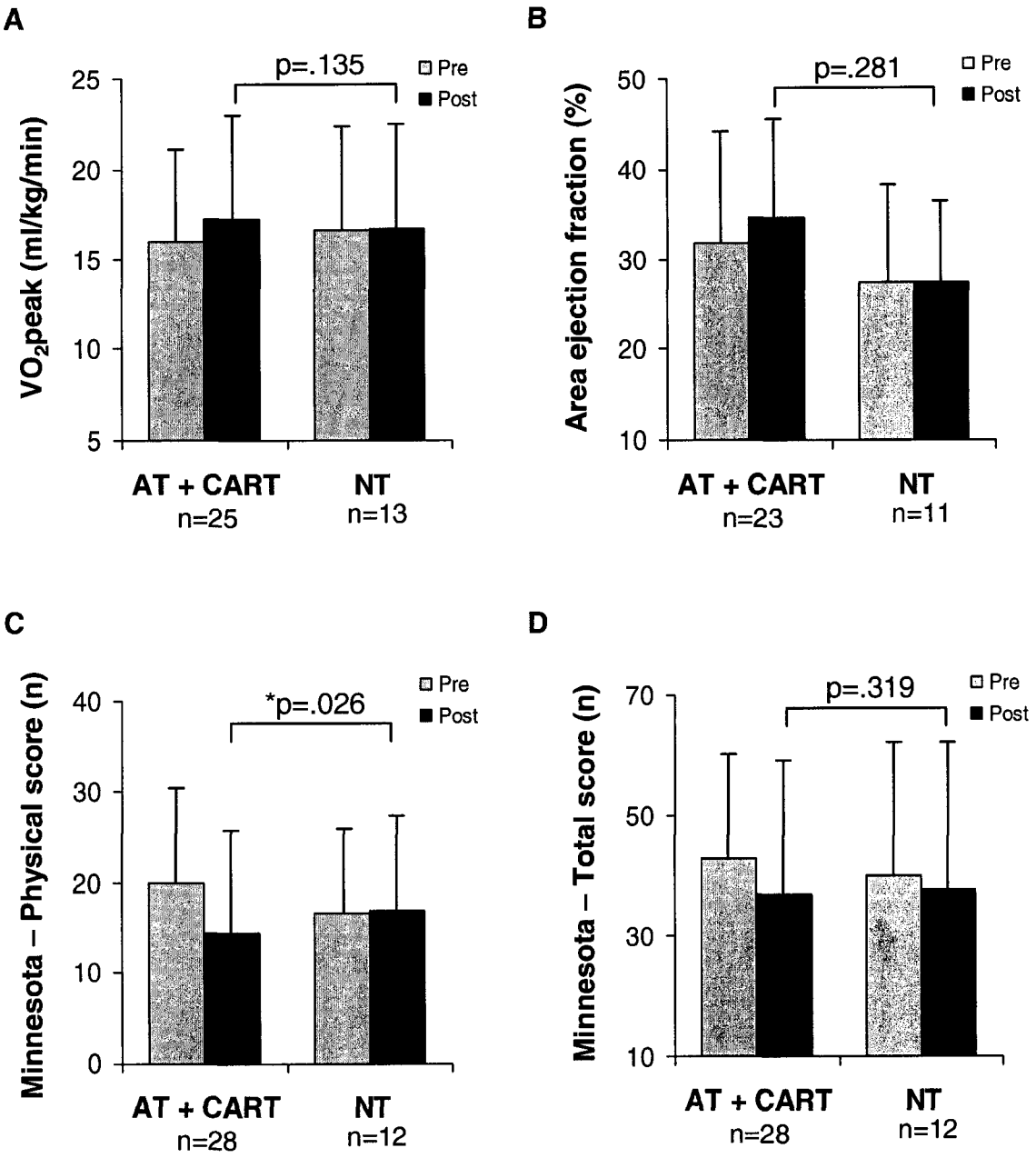


Figure 4-03. Effects of exercise training (pooled AT and CART data) versus standard care on (A) VO_{2peak}, (B) LV systolic function, and (C) total score and (D) physical component of the disease-specific quality of life. (**Intention to treat analysis**).

*p<.05 versus change from baseline in the NT group

Exercise training significantly improved endothelium-dependent but not endothelium-independent dilation of the brachial artery (**Table 4-09**). In contrast, neither endothelium-dependent nor endothelium-independent dilation of the posterior tibial artery were altered following exercise training compared to the NT intervention (**Table 4-09**).

Upper- and lower-extremity muscle strength and endurance were improved in the exercise training group while no change was observed in the NT group (**Table 4-09**). However, these results should be interpreted with caution as the results of the primary analysis have shown that improvements in skeletal muscle strength and endurance are primarily attributed to the resistance component of exercise prescription in the CART group (**Figure 4-01**).

Exercise training did not affect total cholesterol, triglycerides, HDL- and LDL-cholesterol, total cholesterol to HDL-cholesterol ratio, fasting glucose, or C-reactive protein compared to standard care (**Table 4-10**).

Finally, exercise training significantly improved the physical component of the disease-specific HRQL (**Figure 4-03, D**) but did not significantly alter the total score of the disease-specific (**Figure 4-03, C**) or generic HRQL compared to the NT group (**Table 4-10**).

Table 4-09. Effects of exercise versus standard care on left ventricular, vascular and skeletal muscle function. (**Intention to treat analysis**)

	Exercise (AT+CART)		Standard Care (NT)	
	Pre	**Post**	**Pre**	**Post**
Left Ventricular Systolic Function	(n=23)		(n=11)	
LV ED cavity area (cm^2)	28.4 ± 9.2	28.8 ± 12.5	27.9 ± 7.7	28.3 ± 9.6
LV ES cavity area (cm^2)	20.0 ± 9.3	19.6 ± 11.1	20.6 ± 7.5	20.8 ± 8.1
Area ejection fraction (%)	31.8 ± 12.6	34.6 ± 10.4	27.4 ± 10.3	27.4 ± 8.4
Peripheral Vascular Endothelial Function				
Brachial Artery	(n=24)		(n=11)	
Baseline AD (mm)	4.87 ± 0.80	4.77 ± 0.85	4.98 ± 0.77	5.01 ± 0.88
Reactive hyperemia AD (mm)	5.07 ± 0.78	5.05 ± 0.87	5.14 ± 0.70	5.09 ± 0.86
Reactive hyperemia AD (% Δ)	4.5 ± 5.1	6.4 ± 5.7*	3.4 ± 3.9	1.8 ± 2.8
Nitroglycerin AD (mm)	5.62 ± 0.81	5.47 ± 0.78	5.48 ± 0.63	5.55 ± 0.84
Nitroglycerin AD (% Δ)	15.5 ± 8.1	14.9 ± 10.0	8.3 ± 7.5	9.2 ± 4.1
Posterior Tibial Artery	(n=18)		(n=10)	
Baseline AD (mm)	3.09 ± 0.55	3.10 ± 0.55	2.94 ± 0.89	3.04 ± 1.00
Reactive hyperemia AD (mm)	3.42 ± 0.56	3.45 ± 0.50	3.13 ± 0.91	3.27 ± 1.07
Reactive hyperemia AD (% Δ)	10.9 ± 7.3	12.1 ± 8.8	6.8 ± 6.5	7.4 ± 9.6
Nitroglycerin AD (mm)	3.40 ± 0.55	3.55 ± 0.60	3.51 ± 0.92	3.67 ± 1.03
Nitroglycerin AD (% Δ)	11.7 ± 7.6	13.4 ± 9.0	11.9 ± 12.3	9.2 ± 11.1
Skeletal Muscle Function				
Maximal Dynamic Muscle Strength	(n=24)		(n=13)	
Chest press (kg)	40.4 ± 15.5	44.7 ± 16.8*	43.8 ± 16.6	42.8 ± 19.3
Leg extension (kg)	40.1 ± 17.1	46.9 ± 18.1*	45.1 ± 19.8	46.3 ± 18.8
Muscle Endurance	(n=24)		(n=13)	
Chest press (reps)	6.0 ± 2.6	6.4 ± 6.3*	6.1 ± 2.6	5.3 ± 3.0
Leg extension (reps)	8.0 ± 2.8	11.1 ± 5.0*	8.0 ± 2.2	7.0 ± 2.9

AD, arterial diameter; LV, left ventricular; LV ED, left ventricular end-diastolic; LV ES, left ventricular end-systolic, NT, standard care (no exercise training).

*p>0.05 versus change from baseline in the NT group.

Table 4-10. Effects of different exercise programs on metabolic profile and health-related quality of life. (**Intention to treat analysis**)

	Exercise (AT+CART)		Standard Care (NT)	
	Pre	**Post**	**Pre**	**Post**
Metabolic Profile	(n=27)		(n=13)	
Cholesterol ($mmol \cdot L^{-1}$)	4.34 ± 0.99	4.11 ± 0.89	4.64 ± 1.16	4.51 ± 1.19
Triglycerides ($mmol \cdot L^{-1}$)	1.93 ± 1.18	1.95 ± 1.81	2.23 ± 1.34	2.33 ± 1.79
HDL Cholesterol ($mmol \cdot L^{-1}$)	1.13 ± 0.25	1.20 ± 0.29	1.14 ± 0.29	1.20 ± 0.26
LDL Cholesterol ($mmol \cdot L^{-1}$)	2.34 ± 0.79	2.10 ± 0.71	2.56 ± 0.95	2.33 ± 0.96
Total cholesterol/ HDL cholesterol	3.8 ± 0.7	3.4 ± 0.8	4.1 ± 1.0	3.9 ± 1.2
C-reactive protein ($mg \cdot L^{-1}$)	3.5 ± 3.8	3.7 ± 3.1	3.7 ± 2.7	4.8 ± 5.6
Fasting glucose ($mmol \cdot L^{-1}$)	5.8 ± 2.2	5.6 ± 0.84	6.0 ± 0.4	6.1 ± 0.8
Insulin sensitivity[§]	10.0 ± 4.9	9.1 ± 2.0	9.5 ± 4.4	9.5 ± 3.7
Health-Related Quality of Life (HRQL)				
Disease-specific HRQL (Minnesota)	(n=28)		(n=12)	
Physical	20.1 ± 9.6	14.5 ± 10.7*	16.7 ± 9.2	16.9 ± 9.9
Emotional	9.2 ± 6.6	7.6 ± 6.1	9.6 ± 7.8	8.2 ± 8.0
Total	43.0 ± 18.3	37.0 ± 21.8	40.2 ± 22.5	37.8 ± 24.7
Generic HRQL (MacNew)	136 ± 24	142 ± 28	144 ± 33	142 ± 37

HRQL, health-related quality of life.
[§]Insulin sensitivity was measured using ^{13}C-glucose breath test.

*$p<0.05$ versus change from baseline in the NT group

4.9. Factors Related to Baseline Exercise Capacity and its Change Following the Intervention Period

Factors Related to Baseline VO_{2peak}. Univariate predictors of relative VO_{2peak} are presented in **Table 4-11**. Relative VO_{2peak} was correlated to area ejection fraction (**Figure 4-04, A**), lower extremity muscular strength (**Figure 4-04, B**), total number of cardiovascular risk factors (**Figure 4-04, C**), C-reactive protein (**Figure 4-04, D**), HDL-cholesterol, peak heart rate, peak systolic blood pressure, and peak rate pressure product. Multivariate stepwise regression analysis revealed that the best predictors of VO_{2peak} were lower extremity muscle strength, total number of cardiovascular disease risk factors and area ejection fraction (**Table 4-12, A**). These 3 variables explained 51% of the variance in VO_{2peak}. When peak exercise hemodynamics variables were introduced in the analysis, the best predictors of VO_{2peak} were peak exercise rate pressure product, total number of cardiovascular disease risk factors, and lower extremity muscle strength and explained 61% of variance in VO_{2peak} (**Table 4-12, B**).

VO_{2peak} and Health-Related Quality of Life. VO_{2peak} were significantly related to the total score on both disease-specific (**Figure 4-04, E**) and generic HRQL ($r=.33$, $p=0.037$) as well as a physical component of disease-specific HRQL (**Figure 4-04, F**). Disease-specific HRQL was not significantly related to LV area ejection fraction ($r=.04$, $p=0.808$), lower extremity muscle strength ($r=.17$, $p=.276$), or total number of cardiovascular risk factors ($r=.16$, $p=0.331$).

Factors Related to the Change in VO_{2peak} after the Intervention Period. A change in VO_{2peak} following the intervention period significantly was correlated

Table 4-11. Univariate predictors of VO_{2peak}. (Linear regression analysis)

	Pearson r	P-value
Age	-.244	.119
Total number of CVD risk factors	-.348*	.024
Peak exercise HR	.645*	.000
Peak exercise SBP	.520*	.000
Peak exercise RPP	.697*	.000
Area ejection fraction	.338*	.038
Brachial endothelial function	.163	.314
Posterior tibial endothelial function	.052	.776
Leg extension maximal strength	.408*	.010
Leg extension muscle endurance	.090	.586
HDL-Cholesterol	.398*	.009
C-Reactive protein	-.404*	.129

CVD, cardiovascular disease; HR, heart rate; LV, left ventricular; RPP, rate pressure product; SBP, systolic blood pressure.

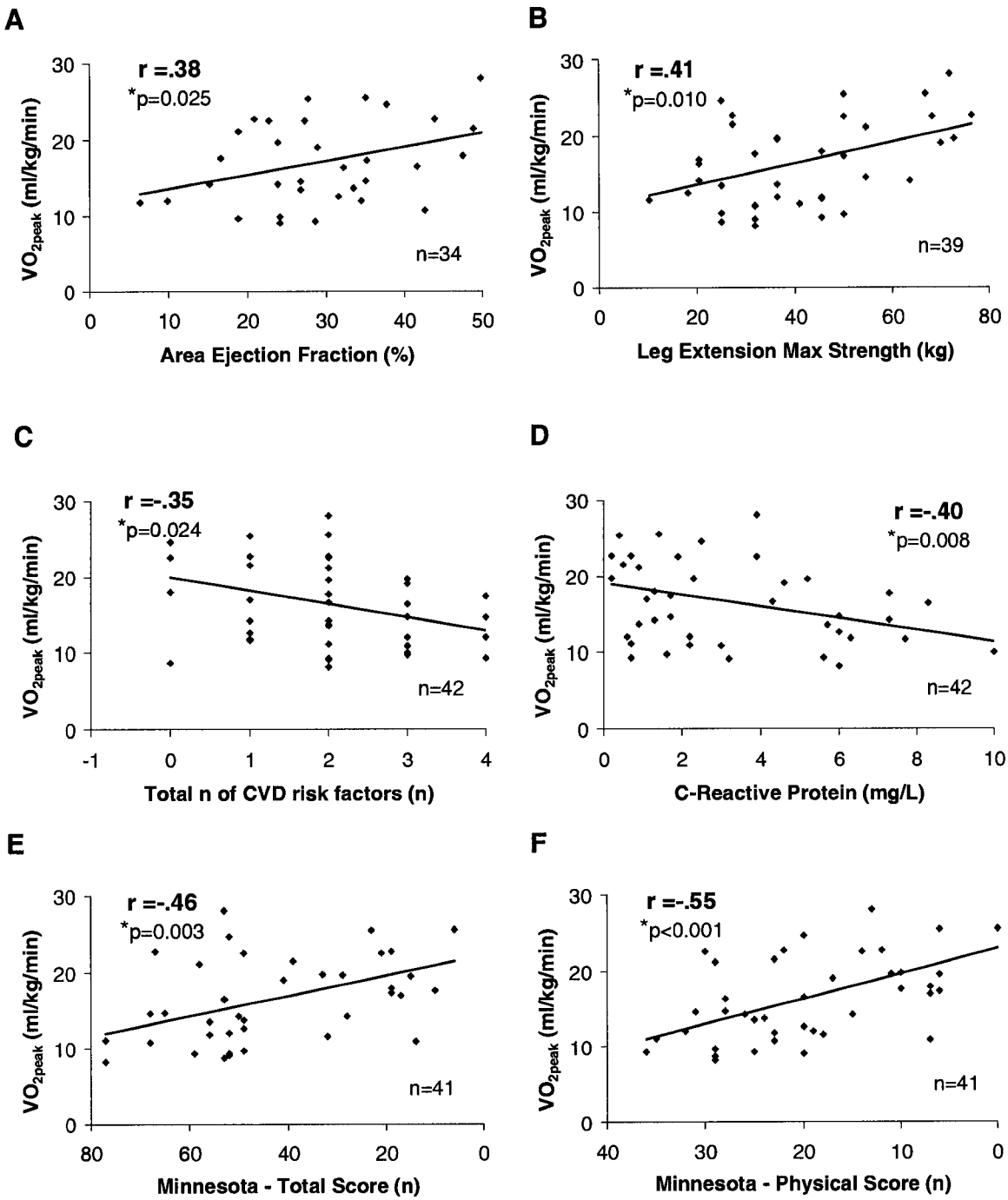


Figure 4-04. Relationship between VO_{2peak} and (A) left ventricular systolic function; (B) leg extension maximal strength; (C) total number of cardiovascular risk factors; (D) C-reactive protein; (E) a total score and (F) physical components of the disease-specific quality of life.

AD, arterial diameter; CVD, cardiovascular disease; RH, reactive hyperemia.

Table 4-12. Multivariate predictors of VO_{2peak} including cardiovascular risk factors and measures of cardiac, vascular, skeletal muscle and metabolic function. (Stepwise multiple regression analysis)

A

	Standardized coefficient Beta	P-value
Leg extension maximal strength	.516*	.000
Total n of CVD risk factors	-.417*	.002
Area ejection fraction	.354*	.011
C-reactive protein	-.236	.080
HDL-Cholesterol	.197	.120

Adjusted R^2=.514

CVD, cardiovascular disease; LV, left ventricular.

B

	Standardized coefficient Beta	P-value
Peak exercise rate pressure product	.575*	.000
Total number of CVD risk factors	-.327*	.007
Leg extension maximal strength	.299*	.015
C-Reactive protein	-.189	.108
Area ejection fraction	.176	.192
HDL-Cholesterol	.161	.139
Peak exercise SBP	.064	.719
Peak exercise HR	.004	.988

Adjusted R^2=.607

CVD, cardiovascular disease; HR, heart rate: LV, left ventricular; SBP, systolic blood pressure.

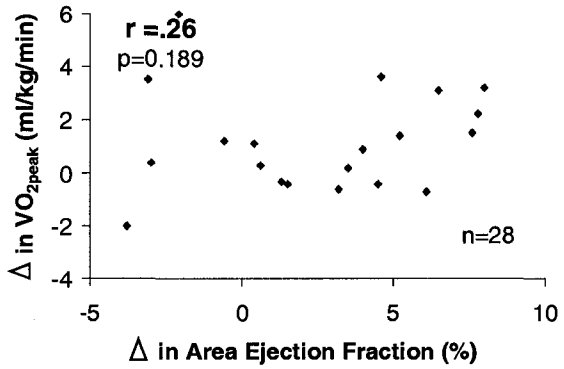
with a change in peak exercise heart rate (r=.43, p=0.007) and brachial endothelial function (r=.40, p=0.020) (**Figure 4-05, C**). The improvement in VO_{2peak} was not related to the change in area ejection fraction (r=.15, p=0.406) (**Figure 4-05, A**), posterior tibial endothelial function (r=.17, p=0.404) (**Figure 4-05, C**), lower extremity endurance (r=.05, p=0.775), or disease-specific HRQL (r=-.06, p=0.178). A correlation between a change in lower extremity muscle strength and VO_{2peak} was not significant in neither the CART (r=.55, p=0.066) nor in the AT group (r=.-16, p=0.634).

4.10. Regional Differences in Vascular Function

Baseline Differences. VO_{2peak} was not correlated to either brachial (r=.16, p=0.314) or posterior tibial endothelial function (r=-.05, p=0.776) at the baseline (**Figure 4-06**). In addition, brachial and posterior tibial response to reactive hyperemia (r=.12, p=0.537) and nitroglycerin (r=.21, p=0.306) were not correlated at the baseline. Brachial endothelial function was significantly related to the total number of cardiovascular disease risk factors (r=-.45; p=0.004). Posterior tibial endothelial function did not correlate with any of the measurement outcomes.

Chest press muscular endurance correlated with the brachial artery response to reactive hyperemia (endothelium-dependent dilation; r=.37; p=0.023), but not nitroglycerin (endothelium-independent dilation; r=.25; p=0.137) (**Figure 4-07**). No similar correlation was observed between leg extension muscle endurance and posterior tibial endothelial function (r=-.12, p=.562).

A



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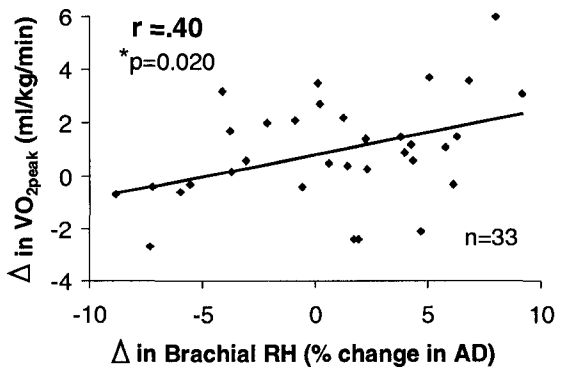

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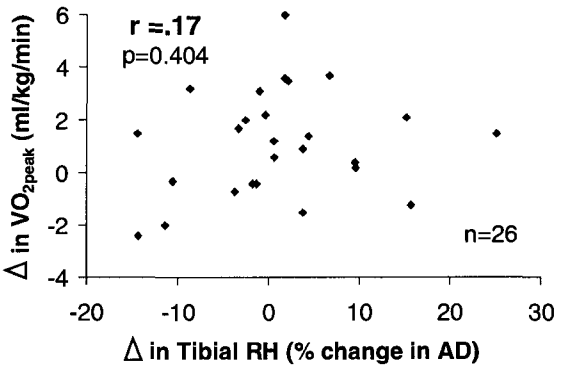
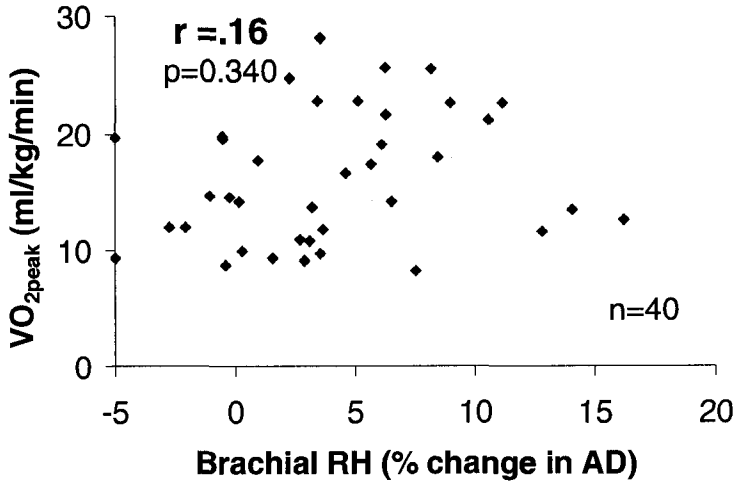


Figure 4-05. Relationship between changes in VO_{2peak} and (A) left ventricular systolic function; B) brachial endothelial function; and (C) posterior tibial endothelial function.

AD, arterial diameter; LV, left ventricular; RH, reactive hyperemia.

A



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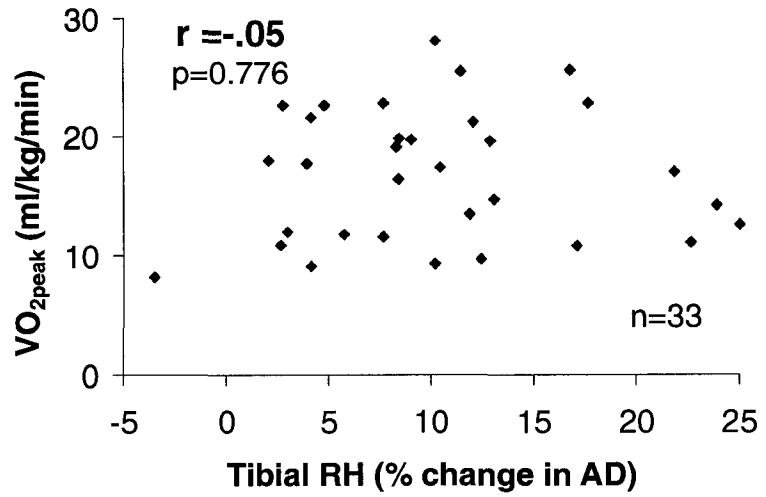
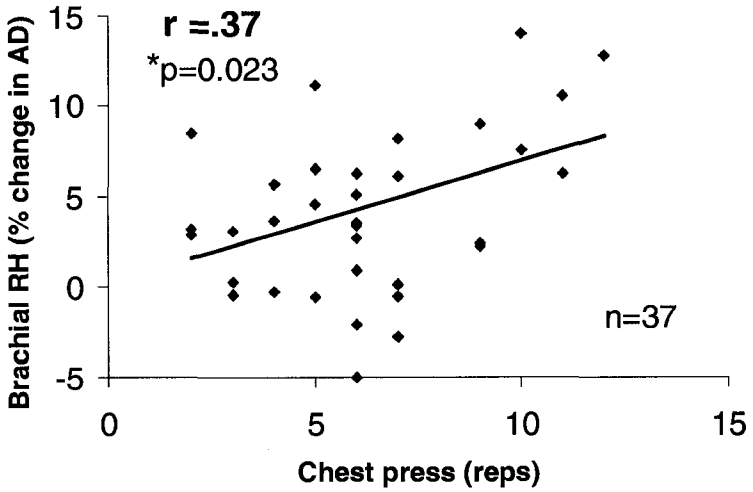


Figure 4-06. Relationship of VO_{2peak} to (A) brachial and (B) posterior tibial endothelial function at the baseline.

AD, arterial diameter; RH, reactive hyperemia.

A



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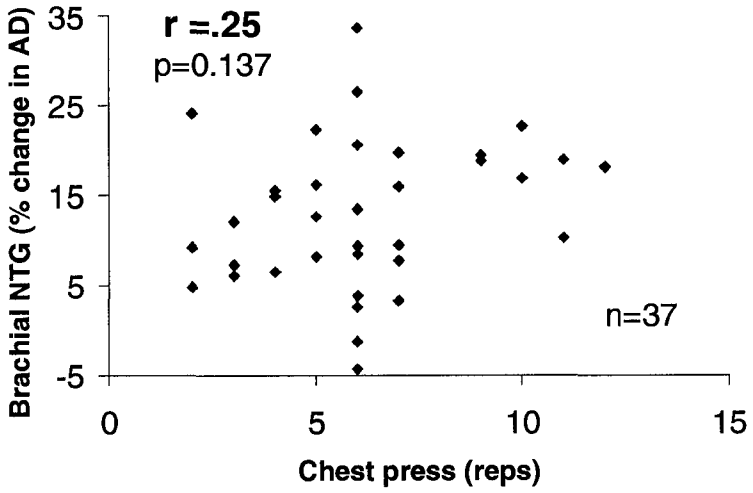

Figure 4-07. Relationship between muscular endurance of the upper extremities and the brachial artery response to (A) reactive hyperemia and (B) nitroglycerin at the baseline.

AD, arterial diameter; NTG, nitroglycerin; RH, reactive hyperemia.

Effects of Exercise Training on Upper and Lower Limb Endothelial Function. In compliant patients, the CART group showed a trend toward an improvement in the brachial artery response to reactive hyperemia compared to the NT group (**Figure 4-02, C**). Neither CART nor AT had effects on the brachial artery response to nitroglycerin (**Table 4-09**) or posterior tibial artery response to reactive hyperemia (**Figure 4-02, D**) or nitroglycerin (**Table 4-09**).

In the intention to treat analysis with combined AT and CART groups, exercise training significantly improved brachial artery response to reactive hyperemia but not nitroglycerin when compared to the NT group (**Figure 4-08, A-B**). Exercise training did not have effects on posterior tibial endothelial function (**Figure 4-08, C-D**). A change in VO_{2peak} following the intervention period significantly correlated with a change in brachial (r=.40, p=0.020) (**Figure 4-05, C**) but not posterior tibial endothelial function (r=.17, p=0.404) (**Figure 4-05, D**). No correlation was found between changes in endothelium-dependent dilation of the brachial and posterior tibial artery following an intervention period (r=.14, p=0.493).

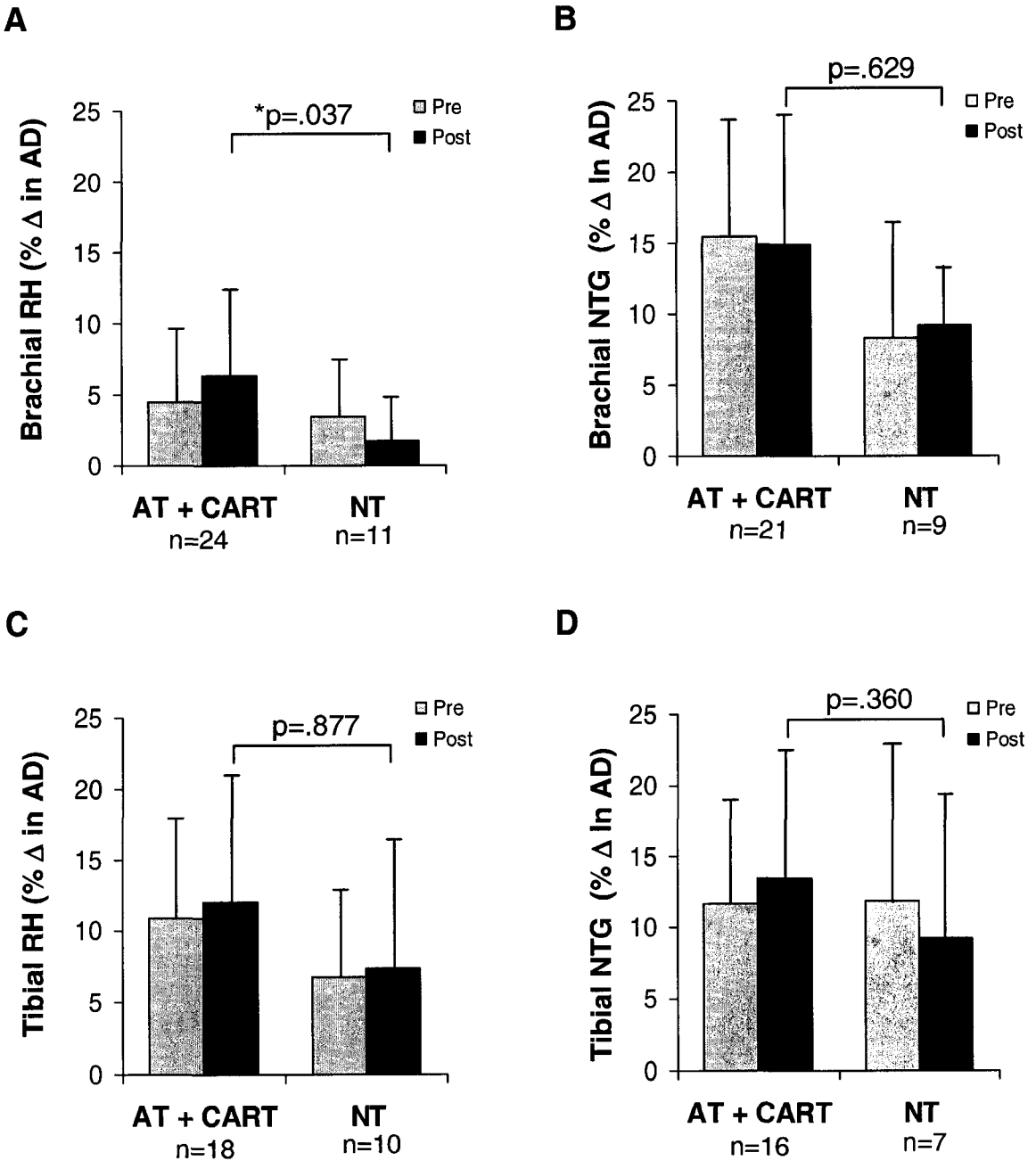

Figure 4-08. Effects of exercise training (pooled exercise training groups, AT+CART) versus standard care (NT) on endothelium-dependent and endothelium-independent vasodilation of (A-B) the brachial artery and (C-D) posterior tibial artery. (**Intention to treat analysis**).

AD, arterial diameter; RH, reactive hyperemia.
*p<.05 versus change from baseline in the NT group

4.11. Heart Failure Etiology: Baseline Differences

Baseline Characteristics. Patient characteristics, cardiovascular risk factors, and pharmacologic therapy are presented in **Table 4-13**. Individuals with IHF were older, predominantly male with a higher number of cardiovascular disease risk factors compared to the NIHF group. In addition, pacemakers were more present in IHF versus NIHF patients (IHF, n=11 vs. NIHF, n=2, p<0.001). A percentage of a maximal dose of beta blocker medication was not significantly different between the groups (IHF, 54±28 % vs. NIHF, 67±27 %, p=0.123).

Health-Related Quality of Life. Compared to individuals with NIHF, the IHF group had a reduced total score and physical component of the disease-specific HRQL (**Figure 4-09; Table 4-13**). The differences between the groups remained significant after controlling for age and gender (total score: p=0.008; physical component: p=0.030). No difference was found between the groups for the generic HRQL or emotional component disease-specific HRQL (**Table 4-13**). The results remained the same after adjustment for age and gender.

Resting and Acute Cardiovascular Responses During Exercise. At rest and at the ventilatory threshold, individuals with IHF had a significantly lower heart rate and rate pressure product while systolic and diastolic blood pressures were not different between the groups (**Table 4-14**). Both groups reached their ventilatory threshold at ~70% of VO_{2peak}. However, the IHF group had reduced VO_2 (**Figure 4-10, C**) and power output at ventilatory threshold compared to NIHF patients while difference in V_E/V_{CO2} slope did not reach statistical significance

Table 4-13. Baseline characteristics of IHF and NIHF patients.

	Ischemic HF (n=19)	**Non-Ischemic HF** (n=23)	p-value
Age (yrs)	67.4 ± 7.7*	56.7 ± 12.2	.002
Gender (M/F)	18/1*	14/9	.007
Weight (kg)	90.4 ± 15.0	87.1 ± 16.4	.506
Body mass index (kg/m^2)	30.5 ± 6.3	30.6 ± 5.9	.958
Risk Factors n (%)			
Hypertension	16 (80)*	9 (39)	.013
Diabetes	6 (32)	3 (13)	.150
Obesity	8 (42)	11 (48)	.714
Dyslipidemia	16 (84)*	12 (52)	.010
Smoking	4 (20)	1 (4)	.116
Total (n)	2.5 ± 1.6*	1.6 ± 1.1	.006
Medications n (%)			
Beta blockers	19 (100)	23(100)	.999
ACE-inhibitors	17 (89)	22 (96)	.397
Diuretics	16 (84)	20 (87)	.856
Lipid lowering	14 (74)	14 (61)	.195
Health-Related Quality of Life (HRQL)			
Disease-specific HRQL	(n=18)	(n=23)	
Physical	23 ± 10*	16 ± 8	.024
Emotional	11 ± 7	9 ± 7	.457
Total	51 ± 19*	36 ± 18	.014
Generic HRQL (MacNew)	130 ± 28	144 ± 26	.120
Incomplete Data Sets			
Exercise testing	0	0	
Ventilatory threshold	3	3	
Echocardiography	3	1	
Brachial endothelial function	2	1	
Skeletal muscle function	2	0	
Metabolic profile	0	0	
Quality of life	1	0	

HRQL, health-related quality of life. P-values for a total score and physical component of disease-specific HRQL adjusted for age and gender difference were p=0.008 and p=0.030, respectively.

*p<0.05 versus NIHF patients

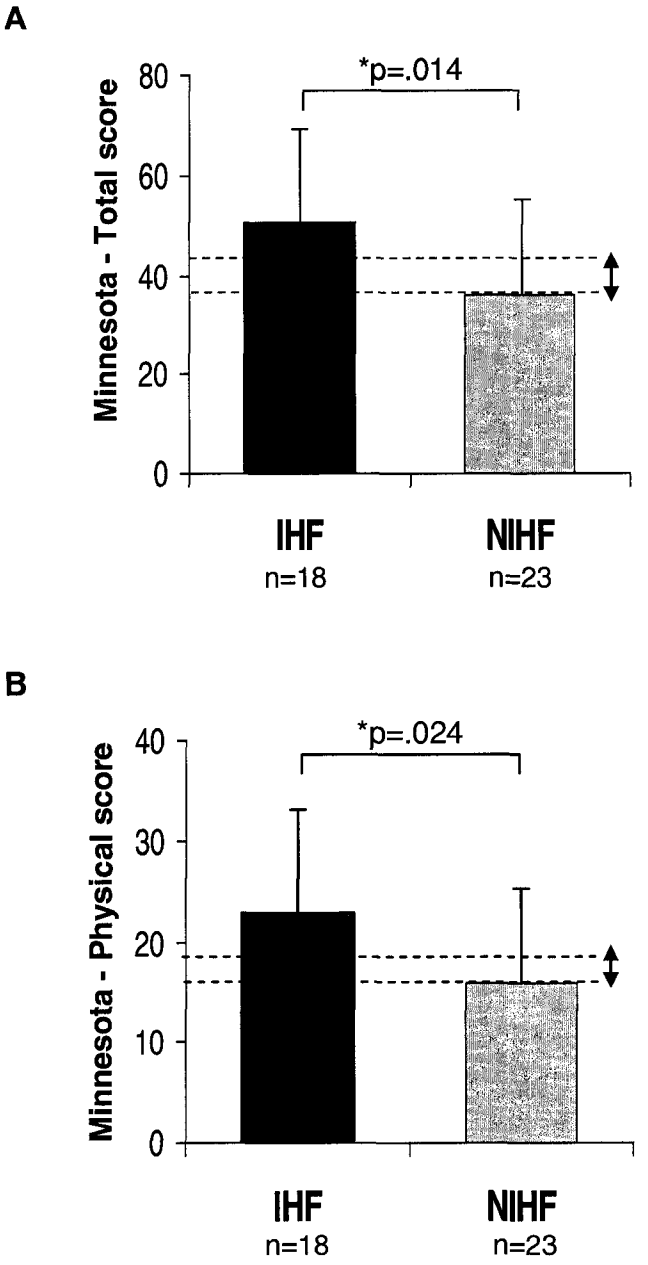

Figure 4-09. Health-related quality of life (HRQL) in IHF and NIHF patients. (A) Total score and (B) physical component of disease-specific HRQL assessed by Minnesota Living with Heart Failure questionnaire in IHF and NIHF patients.

The score obtained with this questionnaire is inversely related to HRQL. Space between dotted lines indicates minimal clinically important difference in HRQL in HF patients.

*p<0.05 versus NIHF patients

Table 4-14. Cardiorespiratory variables at rest and during exercise in IHF and NIHF patients.

	IHF	NIHF	P-value	P-value (Adjusted)[§]
Rest	(n=19)	(n=23)		
HR (bpm)	64 ± 8*	72 ± 13	.027	.325
SBP (mm Hg)	112 ± 18	114 ± 19	.728	.225
DBP (mm Hg)	69 ± 9	70 ± 10	.605	.876
RPP (bpm·mmHg·10^3)	7.1 ± 1.4*	8.1 ± 1.5	.042	.101
Ventilatory Threshold	(n=16)	(n=20)		
HR (bpm)	82 ± 15*	106 ± 23	.001	.012
SBP (mm Hg)	132 ± 29	139 ± 21	.421	.232
DBP (mm Hg)	72 ± 8	74 ± 9	.447	.441
RPP (bpm·mmHg·10^3)	10.9 ± 3.6*	15.0 ± 4.6	.006	.022
VO_2 (ml·kg^{-1}·min^{-1})	9.8 ± 2.4*	13.5 ± 4.2	.004	.001
VO_2 (L·min^{-1})	0.90 ± 0.25*	1.16 ± 0.40	.028	.013
VO_2 % peak (%)	70.2 ± 10.4	70.6 ± 10.7	.911	.851
Power output (watts)	48 ± 20*	74 ± 24	.001	<.001
Exercise time (min)	5.3 ± 2.7*	8.2 ± 3.0	.005	.004
V_E/V_{CO2} Slope	33.2 ± 7.9	28.1 ± 2.8	.067	.245
Peak Exercise	(n=19)	(n=23)		
HR (bpm)	95 ± 23*	127 ± 26	.001	.002
SBP (mm Hg)	143 ± 35	156 ± 24	.172	.051
DBP (mm Hg)	74 ± 8	74 ± 10	.997	.809
RPP (bpm·mmHg·10^3)	13.8 ± 5.7*	20.2 ± 5.7	.001	.002
VO_2 (ml·kg^{-1}·min^{-1})	13.7 ± 5.0*	18.7 ± 5.6	.005	.003
VO_2 (L·min^{-1})	1.25 ± 0.47*	1.61 ± 0.44	.013	.017
VO_2 % predicted (%)	50.1 ± 17.1*	71.5 ± 29.4	.008	.006
Power output (watts)	72 ± 32*	93 ± 30	.034	.032
Exercise time (min)	10.0 ± 4.2*	13.3 ± 4.0	.012	.011
RER	1.07 ± 0.08	1.05 ± 0.08	.469	.276

DBP, diastolic blood pressure; HR, heart rate; RER, respiratory exchange ratio; RPP, rate pressure product; SBP, systolic blood pressure; VO_2, oxygen consumption.

*$p<0.05$ versus NIHF patients
[§]P-value adjusted for age and gender difference.

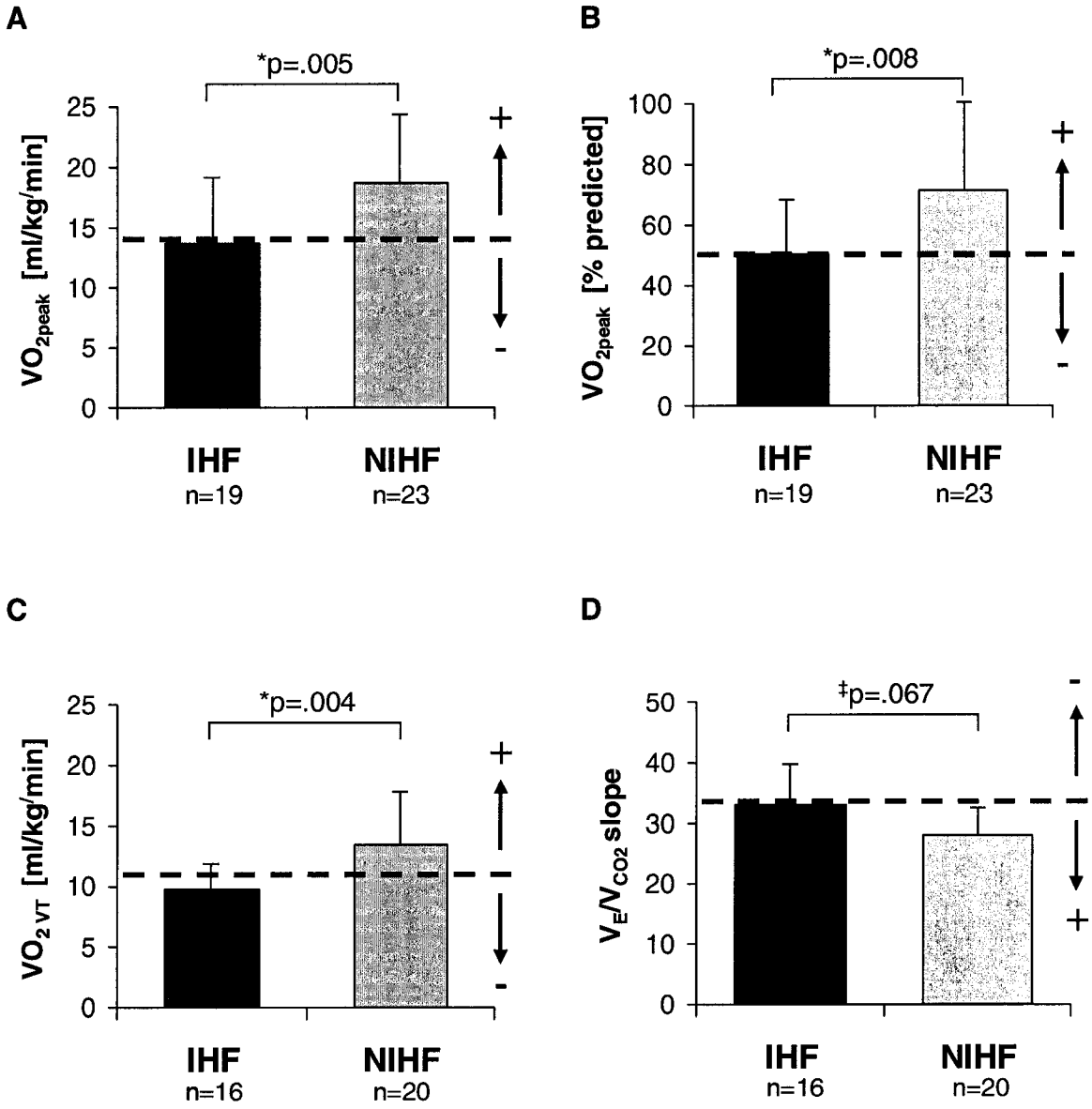

Figure 4-10. Comparison of (A) VO_{2peak}, (B) percent of predicted VO_{2peak}, (C) VO_2 at ventilatory threshold ($VO_{2\,VT}$), and (D) V_E/V_{CO2} slope in IHF and NIHF patients.

Dotted lines represent threshold values suggested by previous studies to identify HF patients with poor prognosis (VO_{2peak} of ≤14 ml/kg/min(7,113); VO_{2peak} ≤ 50%(163), $VO_{2\,VT}$ <11 ml/kg/min(61), and V_E/V_{CO2} slope ≥34(7,61)). Arrows indicate directions of good (+) and poor (-) prognosis.

*p<0.05 and ‡p<0.10 versus NIHF patients.

(**Figure 4-10, D**). At peak exercise, IHF patients achieved significantly lower maximal heart rate, rate pressure product, power output, exercise duration and VO_{2peak} (**Figure 4-10, A**) compared to NIHF participants (**Table 4-14**).

After adjusting for age and gender differences, both absolute and relative VO_{2peak}, percent of age-predicted VO_{2peak} and VO_2 at the ventilatory threshold remained significantly reduced in IHF compared to NIHF patients (**Table 4-14**). Similarly, peak exercise heart rate, systolic blood pressure, rate pressure product, power output, and exercise duration but not V_E/V_{CO2} slope remained significantly reduced in the IHF compared to NIHF group (**Table 4-14**).

Left Ventricular Systolic Function. No significant difference was found for LV end-diastolic and end-systolic cavity area, and area ejection fraction in IHF versus NIHF patients in the primary analysis (**Table 4-15**). After adjusting for age and gender, IHF patients had significantly reduced LV area ejection fraction and borderline significant increase in LV end-systolic cavity area compared to NIHF patients (**Table 4-15**).

Brachial Endothelial Function. IHF patients had a greater brachial artery diameter at baseline (**Table 4-15**), and reduced percent change in arterial diameter in response to both reactive hyperemia and nitroglycerin (**Figure 4-11**). After adjusting for age and gender, the difference between the groups in baseline arterial diameter and percent change in arterial diameter in response to reactive hyperemia and nitroglycerin became non-significant (**Table 4-15**).

Table 4-15. Left ventricular, peripheral vascular and skeletal muscle function in IHF and NIHF patients.

	IHF	NIHF	P-value	P-value (Adjusted)[§]
Left Ventricular Systolic Function	(n=16)	(n=22)		
LV EDCA (cm^2)	30.3 ± 8.6	26.4 ± 8.0	.156	.103
LV ESCA (cm^2)	22.0 ± 7.6	18.3 ± 8.8	.185	.063
Area ejection fraction (%)	28.2 ± 8.2	33.5 ± 13.9	.181	.049
Brachial Endothelial Function	(n=17)	(n=23)		
Baseline AD (mm)	5.25 ± 0.56*	4.69 ± 0.78	.018	.986
Reactive hyperemia AD (mm)	5.33 ± 0.52	4.93 ± 0.78	.187	.467
Reactive hyperemia (% Δ in AD)	1.9 ± 4.4*	5.3 ± 4.8	.024	.149
Nitroglycerin AD (mm)	5.75 ± 0.47	5.39 ± 0.85	.126	.239
Nitroglycerin (% Δ in AD)	8.9 ± 6.3*	15.3 ± 8.1	.012	.178
Skeletal Muscle Function				
Maximal Muscle Strength	(n=17)	(n=23)		
Chest press (kg)	44.6 ± 11.1	40.0 ± 18.0	.349	.989
Leg extension (kg)	41.2 ± 13.4	41.0 ± 20.2	.969	.217
Muscle Endurance				
Chest press (reps)	5.3 ± 2.6	6.7 ± 2.3	.089	.362
Leg extension (reps)	7.3 ± 2.3	8.7 ± 2.6	.093	.394

AD, arterial diameter; EDCA, end-diastolic cavity area; ESCA, end-systolic cavity area; LV, left ventricular; Δ, change.

*p<0.05 versus NIHF.
[§]P-value adjusted for age and gender difference.

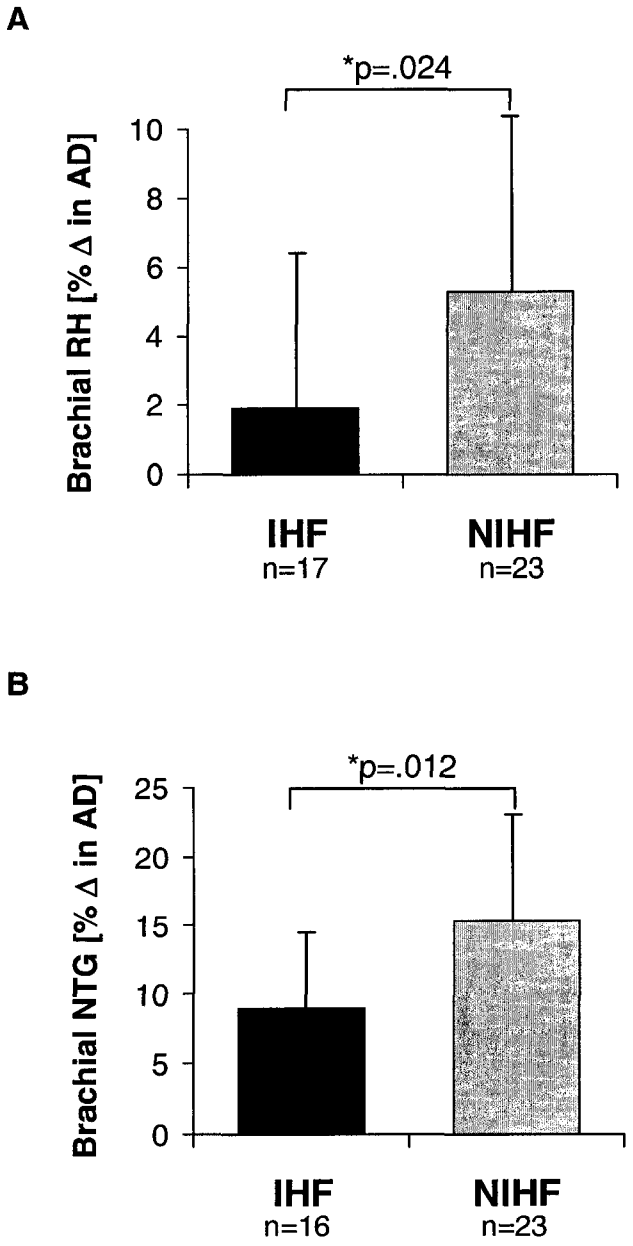

Figure 4-11. Brachial endothelial function in IHF and NIHF patients: Brachial artery response to (A) reactive hyperemia and (B) nitroglycerin.

AD, arterial diameter; NTG, nitroglycerin; RH, reactive hyperemia.

*p<0.05 versus NIHF group

Maximal Muscle Strength and Endurance. No significant difference was found between the groups for chest press or leg extension maximal muscle strength (**Table 4-15**). Reduced upper and lower extremity muscular endurance in IHF versus NIHF patients did not reach statistical significance (**Table 4-15**). After adjusting for age and gender, no significant difference in skeletal muscle strength or endurance was observed between the groups (**Table 4-15**).

Metabolic Profile. High-density lipoprotein was significantly lower in the IHF compared to NIHF group (IHF, 1.03±0.19 vs. NIHF, 1.24±0.30 $mmol \cdot L^{-1}$, p=0.014), but this difference became non-significant after adjusting for age and gender (p=.081). No significant difference was found for total cholesterol, triglycerides, LDL-cholesterol, fasting glucose and C-reactive protein between the groups (for details see **Appendix G, Table 7-10**).

4.12. Heart Failure Etiology and Exercise Training

The effects of exercise training versus standard care in IHF and NIHF patients were compared with the exercise groups including only compliant patients who attended ≥80% of the scheduled sessions (IHF, n=10 (67%); NIHF, n=10 (71%)).

Baseline Characteristics. The exercise groups were similar to the corresponding standard care groups with respect to age, gender, weight, body mass index, VO_{2peak}, LV systolic function, prevalence of cardiovascular risk factors, and pharmacological therapy for HF (**Table 4-16**).

Effects of Exercise Training in IHF versus NIHF Patients. Compared to the standard care intervention in each subgroup of HF patients, exercise training

Table 4-16. Baseline characteristics of IHF and NIHF patients included in the exercise training vs. standard care groups.

	Ischemic HF		Non-ischemic HF	
	Exercise (n=10)	**Standard Care** (n=4)	**Exercise** (n=10)	**Standard Care** (n=9)
Age (yrs)	67 ± 9	70 ± 2	57 ± 11	58 ± 15
Gender (M/F)	10/0	4/0	5/5	3/6
Weight (kg)	85.8 ± 12.5	86.0 ± 3.7	86.8 ± 14.1	84.3 ± 16.6
Body mass index (kg/m^2)	27.7 ± 3.9	30.4 ± 4.3	30.9 ± 4.8	29.5 ± 2.4
VO_{2peak} (ml/kg/min)	14.8 ± 5.8	11.7 ± 5.4	17.5 ± 4.7	18.8 ± 5.1
LV Fractional area change (%)	27.4 ± 10.9	24.0 ± 0.2	35.9 ± 14.7	31.2 ± 13.7
Risk factors (n (%))				
Hypertension	8 (80)	3 (75)	3 (30)	5 (56)
Diabetes	2 (20)	1 (25)	1 (10)	1 (11)
Obesity	3 (30)	2 (50)	6 (60)	3 (33)
Hyperlipidemia	9 (90)	4 (100)	5 (50)	6 (67)
Smoking	2 (20)	1 (25)	0 (0)	0 (0)
Total n of risk factors (n)	2.4 ± 1.3	2.5 ± 0.6	1.5 ± 1.3	1.7 ± 1.0
Medications (n (%))				
Beta blockers	10 (100)	4 (100)	10 (100)	9 (100)
ACE Inhibitors	8 (80)	4 (100)	10 (100)	8 (89)
Diuretics	8 (80)	4 (100)	8 (80)	8 (89)
Lipid lowering	8 (80)	1 (25)	6 (60)	7 (78)

LV, left ventricular; VO_{2peak}, peak oxygen consumption.

$p>0.05$ for all comparisons versus corresponding standard care group.

significantly increased peak power output in both IHF and NIHF patients (**Table 4-17**). Although exercise training increased relative VO_{2peak} by 11% in both IHF and NIHF, the improvement in VO_{2peak} following exercise training versus standard care was significant only in NIHF patients (**Figure 4-12, A-B**). Similarly, exercise training improved brachial endothelial function (**Figure 4-12, C-D; Table 4-18**) and total exercise time (**Table 4-17**) versus standard care only in NIHF patients. Upper extremity muscle endurance was increased following exercise training only in IHF patients while changes in muscle strength and endurance in NIHF patients did not reach statistical significance (**Table 3-19**). However, the etiology by intervention interactions for these measurement outcomes were not statistically significant (VO_{2peak}, p=0.618; brachial endothelial function, p=0.251; total exercise time, p=0.205; upper extremity muscle strength, p=0.268)

Significant etiology by intervention interactions were found only for heart rate and rate pressure product at rest (p=0.018 and p=0.006, respectively). Resting heart rate and rate pressure product were reduced following exercise training and increased following standard care intervention in NIHF patients while no change was observed in IHF patients (**Figure 4-13**). Exercise training did not have effects on peak exercise hemodynamics (**Table 4-17**), LV systolic function (**Table 4-18**), HRQL (**Table 4-19**), or metabolic profile (for details, see **Appendix G, Table 7-10**) in IHF versus NIHF patients. All the results remained the same when data were re-analyzed using age and gender as covariates.

Table 4-17. Effects of exercise training vs. standard care on cardiorespiratory function at rest and at ventilatory threshold in individuals with IHF and NIHF patients.

	Ischemic HF				Non-Ischemic HF			
	Exercise		Standard Care		Exercise		Standard Care	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Rest	(n=8)		(n=4)		(n=10)		(n=9)	
HR (bpm)	59 ± 9	61 ± 12	64 ± 3	63 ± 15	73 ± 14	64 ± 11†*	68 ± 10	77 ± 13
SBP (mm Hg)	112 ± 19	117 ± 13	113 ± 21	109 ± 19	119 ± 20	114 ± 19	112 ± 20	116 ± 19
RPP (bpm·mmHg·10^3)	6.6 ± 1.5	7.1 ± 1.5	7.2 ± 1.4	6.9 ± 2.2	8.5 ± 1.0	7.3 ± 1.3†*	7.5 ± 1.5	8.9 ± 2.3
Peak Exercise	(n=8)		(n=4)		(n=10)		(n=9)	
HR (bpm)	90 ± 25	99 ± 30	96 ± 35	97 ± 37	127 ± 22	127 ± 22	126 ± 37	131 ± 33
SBP (mm Hg)	146 ± 26	144 ± 35	120 ± 25	128 ± 29	152 ± 25	144 ± 23	157 ± 27	147 ± 27
RPP (bpm·mmHg·10^3)	13.3 ± 5.2	14.8 ± 7.5	12.0 ± 7.2	13.1 ± 8.1	19.3 ± 4.9	18.7 ± 5.3	20.3 ± 7.7	19.4 ± 5.7
VO_2 (L/min)	1.27 ± 0.57	1.40 ± 0.68	1.05 ± 0.50	1.05 ± 0.51	1.57 ± 0.41	1.63 ± 0.35	1.55 ± 0.50	1.59 ± 0.60
VO_2 (ml/kg/min)	14.9 ± 6.0	16.6 ± 7.6	11.7 ± 5.4	12.1 ± 5.7	17.5 ± 4.5	19.5 ± 4.4*	18.8 ± 5.1	18.8 ± 5.3
VO_2 % predicted (%)	52 ± 19	51 ± 30	44 ± 17	44 ± 26	70 ± 19	74 ± 14	75 ± 40	77 ± 24
Exercise time (min)	11.0 ± 5.1	13.0 ± 6.1	8.9 ± 5.3	9.2 ± 5.4	12.5 ± 3.9	14.6 ± 3.5*	13.5 ± 4.6	12.8 ± 4.8
Power output (watts)	81 ± 38	92 ± 46*	63 ± 38	56 ± 43	86 ± 27	104 ± 27*	93 ± 36	93 ± 37
RER	1.09 ± 0.8	1.05 ± 0.10	1.09 ± 0.10	1.09 ± 0.10	1.07 ± 0.09	1.09 ± 0.08	1.05 ± 0.07	1.02 ± 0.04

HR, heart rate; RER, respiratory exchange ratio; RPP, rate pressure product; SBP, systolic blood pressure; VO_2, oxygen consumption.
†$p<0.05$ for interaction: time (pre/post) by intervention (exercise/standard care) x etiology(IHF/NIHF)
*$p<0.05$ vs. change from baseline in a corresponding standard care group

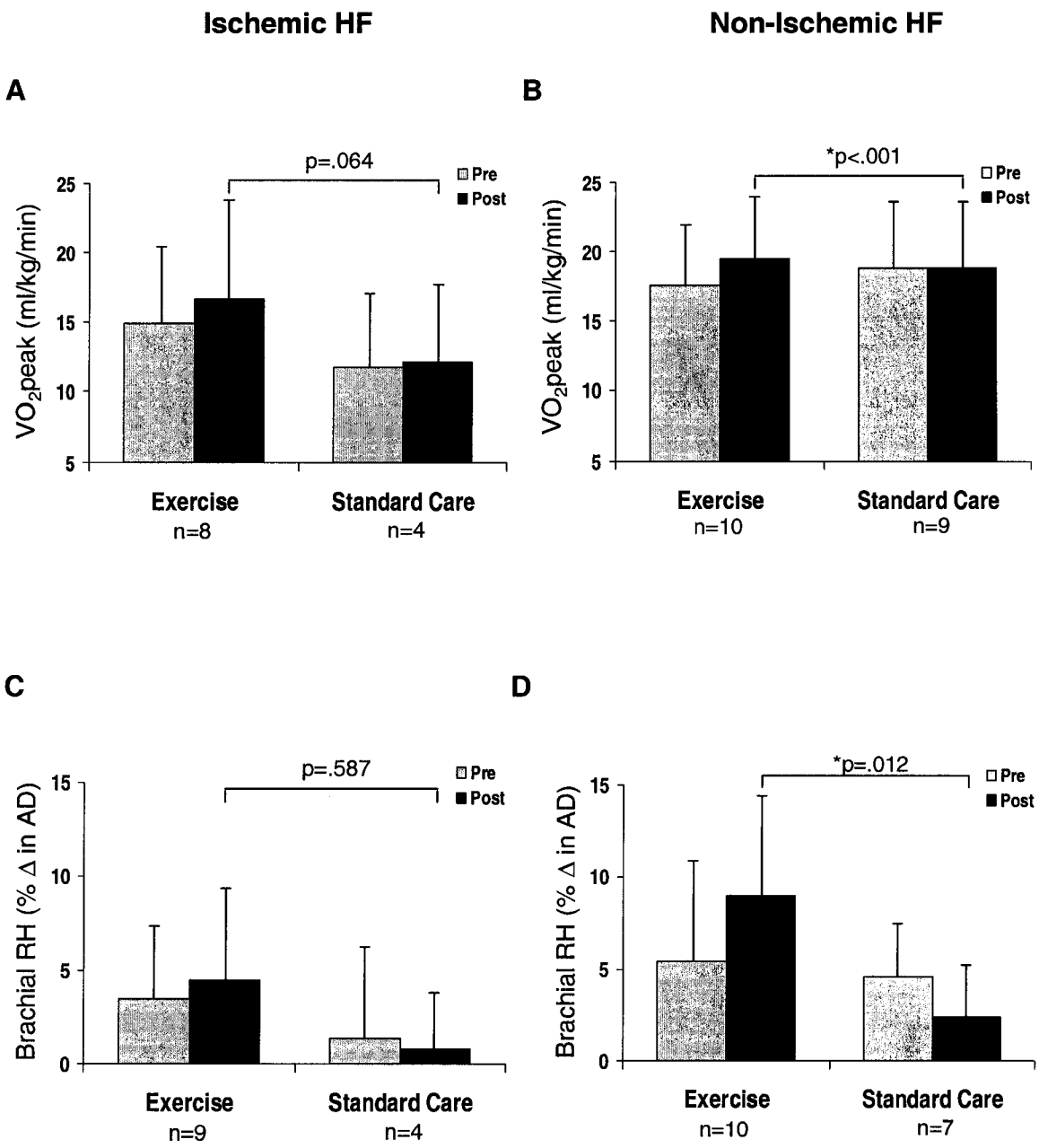

Figure 4-12. Effects of exercise training versus standard care intervention on VO_{2peak} (A-B) and brachial endothelial function (B-C) in patients with IHF (A and C) and NIHF (B and D).

RH, reactive hyperemia.

*p<0.05 versus change from baseline in the standard care group

Table 4-18. Effects of exercise training vs. standard care on left ventricular systolic function and brachial endothelial function in individuals with IHF and NIHF.

	Ischemic HF				Non-Ischemic IHF			
	Exercise		Standard Care		Exercise		Standard Care	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Left Ventricular Systolic Function	(n=8)		(n=3)		(n=9)		(n=8)	
LV EDCA (cm^2)	30.2 ± 9.1	32.9 ± 14.1	26.7 ± 5.4	29.1 ± 16.3	24.1 ± 6.2	24.0 ± 9.6	28.3 ± 8.7	28.0 ± 7.3
LV ESCA (cm^2)	22.4 ± 9.1	23.1 ± 13.0	20.3 ± 4.1	21.7 ± 12.4	16.1 ± 7.4	15.9 ± 8.6	20.7 ± 8.7	20.5 ± 7.1
Area ejection fraction (%)	27.5 ± 10.9	32.6 ± 8.5	24.0 ± 0.2	25.9 ± 1.7	35.9 ± 14.7	36.2 ± 12.9	28.6 ± 12.0	28.0 ± 9.9
Brachial Endothelial Function	(n=9)		(n=4)		(n=10)		(n=7)	
Baseline AD (mm)	5.29 ± 0.54	5.15 ± 0.47	5.51 ± 0.69	5.86 ± 0.18	4.53 ± 0.84	4.33 ± 0.95	4.68 ± 0.67	4.52 ± 0.72
RH AD (mm)	5.47 ± 0.51	5.38 ± 0.59	5.56 ± 0.43	5.91 ± 0.35	4.77 ± 0.88	4.70 ± 0.99	4.90 ± 0.74	4.62 ± 0.67
RH AD (% Δ)	3.5 ± 4.2	4.5 ± 5.3	1.4 ± 5.3	0.8 ± 3.3	5.5 ± 5.9	9.0 ± 6.3*	4.6 ± 2.7	2.4 ± 2.6
Nitroglycerin AD (mm)	5.79 ± 0.57	5.70 ± 0.60	5.85 ± 0.35	6.21 ± 0.28	5.43 ± 0.90	5.23 ± 0.82	5.19 ± 0.69	5.03 ± 0.76
Nitroglycerin AD (% Δ)	10.7 ± 5.8	9.2 ± 8.4	7.0 ± 8.8	5.9 ± 3.0	18.8 ± 9.4	19.9 ± 11.1	9.3 ± 7.1	11.9 ± 2.8

AD, arterial diameter; LV, left ventricular; LV EDCA, left ventricular end-diastolic cavity area; LV ESCA, left ventricular end-systolic cavity area; RH, reactive hyperemia.

p=ns for all interactions (time (pre/post) by intervention (exercise/standard care) x etiology(IHF/NIHF))
*p<0.05 versus change from baseline in the corresponding standard care group (t-test).

Table 4-19. Effects of exercise training vs. standard care on skeletal muscle strength and endurance and health-related quality of life in individuals with IHF and NIHF.

	Ischemic HF				Non-Ischemic IHF			
	Exercise		Standard Care		Exercise		Standard Care	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Skeletal muscle function								
Maximal dynamic muscle strength	(n=8)		(n=4)		(n=10)		(n=8)	
Chest press (kg)	42.0 ± 10.3	49.9 ± 12.5	42.5 ± 15.8	40.5 ± 16.8	33.6 ± 18.1	35.7 ± 17.9	44.3 ± 17.9	43.9 ± 21.2
Leg extension (kg)	42.8 ±10.5	52.9 ± 13.7	40.5 ± 21.9	42.0 ± 19.3	32.5 ± 18.4	38.9 ± 19.5	47.4 ± 19.8	48.4 ± 19.6
Muscle endurance								
Chest press (reps)	5.3 ± 2.9	11.6 ± 8.3*	5.3 ± 3.6	4.0 ± 3.4	6.4 ± 2.6	9.6 ± 5.4	6.4 ± 2.2	5.9 ± 2.8
Leg extension (reps)	7.3 ± 2.5	11.8 ± 2.3	7.5 ± 3.0	5.0 ± 1.8	9.2 ± 3.2	12.7 ± 6.3	8.3 ± 1.8	8.0 ± 2.9
Health-related quality of life (HRQL)								
Disease-specific HRQL	(n=10)		(n=3)		(n=10)		(n=9)	
Physical	19.6 ± 9.9	16.6 ± 10.7	20.0 ± 9.0	22.7 ± 12.7	16.7 ± 7.5	12.8 ± 8.5	15.6 ± 9.5	15.0 ± 8.9
Emotional	8.4 ± 6.8	6.5 ± 6.2	13.3 ± 7.8	11.7 ± 9.8	8.2 ± 6.7	6.9 ± 6.8	8.3 ± 7.8	7.0 ± 7.5
Total	43.8 ± 18.1	36.2 ± 20.8	52.7 ± 24.0	52.3 ± 31.4	33.3 ± 14.8	28.4 ± 20.5	36.0 ± 21.8	32.9 ± 21.9
Generic HRQL	139 ± 25	146 ± 24	130 ± 45	120 ± 53	144 ± 21	156 ± 22	149 ± 30	150 ± 30

HRQL, health-related quality of life.
p=ns for all interactions (time (pre/post) by intervention (exercise/standard care) x etiology(IHF/NIHF))

*p<0.05 versus change from baseline in the corresponding standard care group (t-test).

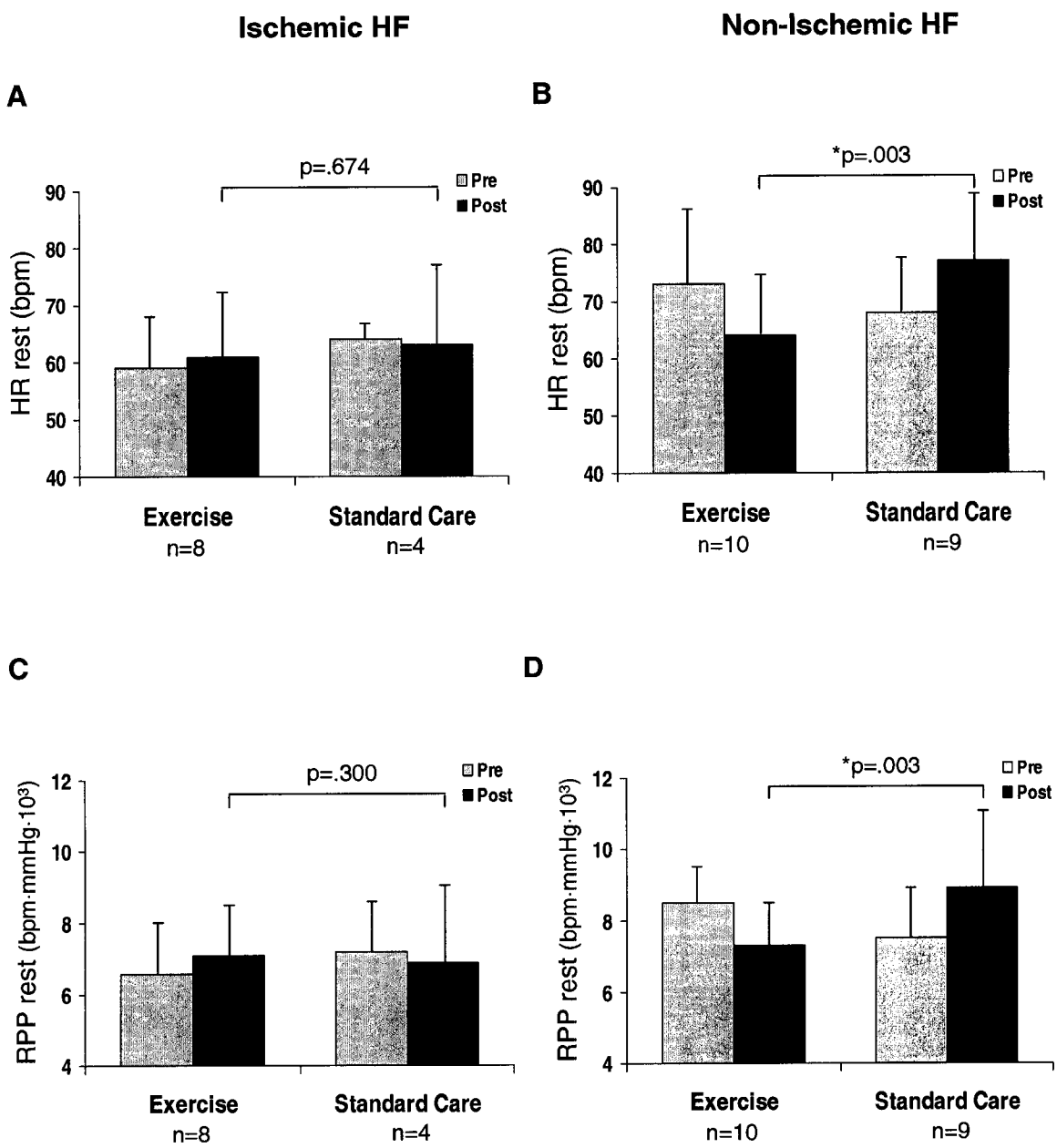

Figure 4-13. Effects of exercise training versus standard care intervention on resting heart rate (A-B) and rate pressure product (B-C) in patients with IHF (A and C) and NIHF (B and D).

HR, heart rate; RPP, rate pressure product.

*p<0.05 versus change from baseline in the standard care group

Chapter 5: DISCUSSION

There are several important findings in the present study:

(1) Both AT and CART, using intention-to-treat analysis, significantly improved total exercise time but not VO_{2peak}, while only CART improved skeletal muscle strength and endurance compared to NT. The improvement in upper extremity muscle strength and endurance was greater in CART compared to the AT alone.

(2) In compliant participants, AT and CART improved VO_{2peak} compared to NT. Skeletal muscle strength and endurance were improved in the CART group, while generic HRQL was significantly improved in the AT group only.

(3) Exercise training, irrespective of the training modality, improved brachial but not posterior tibial endothelial function and did not have effects on LV systolic function.

(4) Lower extremity muscle strength, peak exercise rate pressure product, and a total number of cardiovascular risk factors were the best multivariate predictors of VO_{2peak}. An improvement in VO_{2peak} following exercise training in HF patients was related to an improvement in brachial endothelial function and peak exercise heart rate.

(5) Brachial endothelial function was significantly related to upper extremity skeletal muscle endurance at the baseline and to improvement in VO_{2peak} following the intervention period.

(6) IHF patients had reduced HRQL and lower VO_{2peak} secondary to more

severe LV systolic dysfunction and impaired peak exercise hemodynamics compared to NIHF patients. Reduced vascular and skeletal muscle endurance in IHF versus NIHF patients were secondary to age and gender differences between the groups.

(7) HF etiology did not influence patients' response to exercise training with respect to changes in exercise tolerance, LV systolic function, vascular and skeletal muscle function, or HRQL in the present study.

Taken together, the results of the present study suggest that both AT and CART are effective interventions to improve exercise tolerance in compliant HF patients even though they may have different effects on skeletal muscle function and HRQL. In addition, a reversal of peripheral vascular abnormalities with exercise training in HF patients may be specific to the vascular bed with an exercise-mediated improvement in endothelial function of the brachial but not posterior tibial artery. Moreover, the present results support an extensive body of evidence that exercise training improves exercise tolerance, HRQL, peripheral vascular and skeletal muscle function without negatively altering LV systolic function. Further, reduced vascular and skeletal muscle function but not impaired exercise tolerance in IHF versus NIHF patients may be secondary to age and gender effects on these outcomes. Finally, HF etiology may not have effects on patients' response to an exercise intervention.

5.1. Aerobic Training Versus Combined Aerobic and Resistance Training

To date, only 2 investigations compared the effects of AT or CART in HF patients; however, neither investigation had a non-exercise control group (36,78). Delagardelle et al. (36) randomized 20 HF patients to a 4-month AT or CART intervention. The CART group increased VO_{2peak} and LV ejection fraction at rest, and improved leg muscle strength and endurance. In contrast, the AT group decreased LV ejection fraction, improved leg muscle endurance, and did not improve VO_{2peak}. Based on these findings, it was suggested that CART was superior to AT for improving VO_{2peak}, LV systolic function, and muscle strength in HF. Our group (78) recently reported on the effects of supervised and unsupervised AT or CART in 20 older women with HF. The primary finding was that supervised CART improved upper extremity muscle strength with no change in the AT group. Changes in VO_{2peak}, leg muscle strength, and HRQL following AT or CART were not different between the groups. The results of these 2 studies need to be interpreted with caution due to important methodological limitations such as a lack of a non-exercising control group, and lack of statistical adjustment for baseline differences in age and VO_{2peak} in the study by Delagardelle et al. (36). The present study extends previous findings by demonstrating, contrary to our "a priori hypothesis", that both AT and CART are effective interventions compared to the standard care to improve exercise tolerance in compliant HF patients. In addition, CART intervention is more effective in improving muscle strength and endurance while AT intervention may

be more effective in improving generic HRQL in HF patients. Therefore, both exercise regimes can be used effectively in the treatment of HF patients to tailor exercise programs to the needs of individual patients.

5.1.1. Exercise Training and Exercise Tolerance

In the intention to treat analysis, both AT and CART significantly improved exercise time but not VO_{2peak} compared to the NT intervention in the present study. However, both AT and CART increased VO_{2peak} in patients who attended ≥80% of prescribed exercise sessions by 12% and 11%, respectively, even though the improvement in VO_{2peak} in the CART group was borderline significant (p=0.058). The results of the present study are in agreement with previous studies that consistently reported improved VO_{2peak} (range, 8% to 26%) following AT (14,43,59,71,73), resistance training (160), or CART (26,110,117,172) in compliant HF patients. Our results are in contrast with Delagardelle et al. (36) that found improved VO_{2peak} following CART but no change with the AT intervention. It is possible that older age and higher VO_{2peak} in the AT versus CART group at the baseline could have influenced their results. Therefore, this is the first study to report that both AT and CART are similarly effective to improve exercise tolerance compared to NT in HF patients.

5.1.2. Exercise Training and Left Ventricular Systolic Function

In the present study, neither AT nor CART altered resting LV systolic function. Our findings are consistent with a number of previous studies that reported no change in LV systolic function at rest following AT (14,43,167), resistance training (147) or CART (37,117) in HF patients. Several prior investigations have

found that AT is associated with an improvement in preload (12,13), myocardial contractile reserve (42,73,74), and LV ejection fraction (58,73,164) in HF patients. Improved LV function in these studies could be, in part, related to the exercise-mediated reduction in systemic vascular resistance(73,74), secondary to the improvement in vascular endothelial function (73). In contrast, Delagardelle et al. (36) reported that 12 to 16 weeks of CART improved while AT reduced LV ejection fraction at rest in HF patients. A discrepancy between the present study and findings by Delagardelle et al. (36) may be due to a lack of comparison to changes in a control group and a presence of more severe HF in the CART versus AT group in the latter investigation. Therefore, the present study adds further evidence that moderate intensity exercise training, irrespective of training modality, does not further impair resting LV function in HF patients.

5.1.3. Exercise Training and Skeletal Muscle Strength and Endurance

Recent guidelines emphasize the importance of incorporating resistance training for optimal exercise prescription in HF patients (122,144). These recommendations are based on the finding that resistance training may be more effective than AT alone in attenuating and/or reversing skeletal muscle atrophy in HF patients (19). In addition, improved muscle strength and endurance following resistance training may increase patients' capacity to perform activities of daily living and promote independent living (5). Previous studies have shown that resistance training alone (106,147,160) or in combination with AT (106,110,117) may attenuate the HF-mediated decline in muscle mass (147), improve muscle strength (106,110,117,147,160) and endurance (106,160), and ultimately

contribute to improved quality of life in HF patients (133). In the present study, CART significantly improved skeletal muscle strength and endurance compared to the NT intervention. In addition, CART was superior to AT alone in improving upper but not lower extremity muscle strength and endurance. The results of the present study are consistent with Haykowsky et al. (78) who found a greater improvement in the upper but not lower extremity muscle strength with CART versus AT intervention in elderly women with HF. It is possible that the strength component of lower limb cycling may improve muscle strength in severely deconditioned lower extremities of HF patients. In contrast to the present study, Delagardelle et al. (36) found that CART significantly improved lower extremity muscle strength compared to the AT alone. The divergent findings between studies may be due to differences in techniques used for assessment of muscular strength (isokinetic dynamometer versus 1-repetition maximum testing), volume (3 versus 1.5 sets), or intensity of prescribed resistance program (60% versus 50% 1-repetion maximum). Our findings suggest that CART is an effective intervention to improve skeletal muscle strength and endurance in HF patients and may be more effective then AT alone in improving skeletal muscle function of the upper extremities.

Notably, the improvement in skeletal muscle strength and endurance with CART versus AT did not lead to a greater improvement in VO_{2peak} in the CART group. Similarly, a correlation between a change in lower extremity muscle strength and VO_{2peak} was not significant in either AT or CART group. Therefore, future studies need to examine further whether an increased lower extremity

muscle strength following exercise training with a resistance component may contribute to improvement in VO_{2peak} in HF patients.

5.1.4. Exercise Training and Peripheral Vascular Function: Regional Differences

An important and interesting finding in the present study, and contrary to our hypothesis, was that exercise training including predominately lower limbs with or without upper extremity exercise improved brachial but not posterior tibial endothelial function in HF patients. A number of investigations have demonstrated that exercise training improves peripheral vascular function in trained extremities of HF patients (71,73,82,92). However, 2 recent studies suggest that lower limb exercise training may improve endothelial function in untrained upper limbs in HF patients (103,112). Therefore, the enhancement of endothelial function with exercise training may not be restricted to the trained limbs if exercise of moderate intensity is performed with large muscle mass of lower limbs (103). In contrast, 3 studies that measured endothelial function in both upper and lower limbs reported improved lower limb but not upper limb vascular function following AT on a cycle ergometer in individuals with HF (39,98) or coronary artery disease (63). On the contrary, the results of the present study suggest improved brachial but not posterior tibial endothelial function with exercise training involving predominately lower limbs in HF patients.

An observed improvement in upper limb endothelial function with lower limb exercise training in previous (103,112) and current study supports the hypothesis that exercise training may increase nitric oxide bioactivity in vascular beds distant

from the exercising musculature, possibly via a hemodynamic-mediated shear stress phenomenon. It is well established that shear stress and pulsatile flow provide a physiological stimulus to nitric oxide production (131). Increased blood flow, the presence of antegrade/retrograde flow pattern (67), and change in central hemodynamics (65) during lower limb exercise may provide a potent stimulus for shear-stress mediated increase in nitric oxide production and consequently improved endothelial function in the upper limb vasculature. However, we cannot exclude a potential contribution of other mechanisms such as reduced local expression of circulating pro-inflammatory cytokines (60) and upregulated activity of antioxidative enzymes (46,102).

Several explanations exist for the observed improvement in brachial but not posterior tibial endothelial function following predominately lower limb exercise training in HF patients in the present study.

The results of the present study support an evolving hypothesis that the mechanisms responsible for exercise training adaptations in the vasculature differ according to the vascular beds involved. Green et al. (68) reported that short-term exercise training improved endothelial function in both conduit and resistance vessels in the forearm in individuals with cardiovascular disease and risk factors, but the magnitude of these improvements were not related. In the present study, no correlation was found between endothelium-dependent dilation of the brachial and posterior tibial artery at the baseline or in response to exercise training.

An alternative explanation may be related to the evidence that lower extremity arteries are particularly susceptible to atherosclerosis (52), while the brachial artery rarely develops structural atherosclerotic changes (6). Therefore, a degree of endothelial dysfunction and accompanying structural changes may be more severe in the posterior tibial versus brachial artery of HF patients. Consistent with this hypothesis, previous studies reported preserved upper extremity but impaired lower extremity endothelial function in patients with peripheral artery disease (158) and HF (88). Therefore, 12-week exercise training may improve reduced endothelial function in the brachial artery, but may represent an insufficient stimulus to attenuate or reverse structural and functional changes in the endothelium of the posterior tibial artery in HF patients.

Another explanation may be related to regional differences in vascular function in HF patients secondary to disuse and deconditioning. Jondeau et al. (88) speculated that HF patients may purposely avoid activities involving large muscle mass of lower limbs to prevent an exacerbation of the symptoms of fatigue and shortness of breath, while still performing less demanding activities of daily living involving a small muscle mass of the upper limbs. Proctor and Newcomer (146) concluded that physical activity can indeed contribute to limb-specific differences in vascular function. Therefore, it is possible that longer exercise training may be required to attenuate endothelial dysfunction of the deconditioned lower limbs in HF patients.

Another possibility relates to differences in measurement techniques used for the assessment of the upper and lower extremity vascular function in the present

study. Blood flow occlusion was placed distal to the measurement site for the brachial artery and proximal to the measurement site for the assessment of the posterior tibial artery. Distal versus proximal occlusion may influence percent change in arterial diameter in response to reactive hyperemia and may alter mechanisms underlying hyperemic response (mainly flow-dependent and nitric oxide-mediated versus additional direct effects of ischemia) (34). Moreover, proximal occlusion may lead to arterial spasm and make assessment of vascular function impossible as seen in several patients in the present study.

Finally, smaller arterial diameter and the tortuous shape of posterior tibial artery was technically more challenging for accurate data acquisition compared to the larger brachial artery. Therefore, we cannot rule out the possibility that measurement procedures used in the present study were not sensitive enough to detect subtle changes in vascular function of the posterior tibial artery following the exercise intervention.

Regardless of the mechanisms, our results extend previous findings by showing that even though exercise training may improve endothelial function in the vasculature distant from the exercising limbs in HF patients, the effects of exercise training on peripheral vascular function may depend on regional differences in vascular function and the characteristics of vascular bed(s) where endothelial function is assessed.

5.1.5. Exercise Training and Health-Related Quality of Life

In the present study, the AT intervention significantly improved generic HRQL in compliant patients, while no intervention had statistically significant effects on

disease-specific HRQL. When exercise groups were combined, exercise training improved the physical component of the disease-specific HRQL compared to the NT intervention. Previous studies reported both improvement (14,59,133,137,148,151,172,179) and no change (78,94,117) in HRQL following AT (14,59,94,137,148,151,172,179) or CART (78,117,133,172) intervention in HF patients. Although Minnesota Living with Heart Failure questionnaire may not be sensitive to detect subtle changes in disease-specific HRQL (153), it has been widely used in exercise training studies in HF patients (14,78,94,117,172) and has established cut-off values for minimal clinically important differences (i.e., 5 points for the total score, and 3 points for the physical component) (149). Even though statistically non-significant, the changes in a total score following CART and changes in a physical component of disease-specific HRQL following both AT and CART were greater than established cut-off values for minimal clinically important differences. Therefore, the results of the present study indicate that both AT and CART may lead to a clinically significant improvement in HRQL in HF patients.

5.2. Intention-to-Treat versus Per-Protocol Analysis

In the present study, data were analyzed according to the intention to treat principle and compared the results to the more commonly used per protocol analysis. The results of the 2 analyses were consistent for exercise-induced changes in LV systolic function, peripheral vascular function, skeletal muscle strength and endurance as well as measures of exercise tolerance such as peak exercise power output and total exercise time. In contrast to the results of the

intention to treat analysis, exercise training significantly improved VO_{2peak} and generic HRQL only in compliant patients (per protocol analysis). Therefore, even though exercise training is an efficacious intervention to improve VO_{2peak} and HRQL in compliant patients, the effectiveness of the cardiac rehabilitation programs to improve these variables in a general population of HF patients in everyday clinical practice may be reduced due to high non-compliance rates. The results of the present study indicate that overweight HF patients with poor HRQL are particularly predisposed to non-compliance with a cardiac rehabilitation program. Considering multiple physiological and clinical benefits of exercise training in HF patients (144), high drop-out rates from the long-term exercise interventions, and a quick loss of benefits of exercise training with inactive lifestyle (123,180), it is essential to design enjoyable and safe cardiac rehabilitation programs to increase adherence and promote regular physical activity in HF patients.

5.3. Factors Related to VO_{2peak} in HF

Multivariate Predictors. Multiple factors contribute to reduced exercise tolerance in HF patients. In the present study, the best multivariate predictors of VO_{2peak} were lower extremity muscle strength, area ejection fraction at rest, and a total number of cardiovascular disease risk factors. These 3 variables explained 51% of variance in VO_{2peak}. When peak exercise hemodynamic variables were introduced in the regression model, the best predictors of VO_{2peak} were peak exercise rate pressure product, lower extremity muscle strength, and total number of cardiovascular disease risk factors and explained 61% of variance in

VO_{2peak}.

Muscle Strength. A significant positive correlation between VO_{2peak} and dynamic muscle strength in HF patients has been previously reported (21,76,104). It is possible that the strength component related to lower limb cycling may, in part, determine a workload and consequently a metabolic demand imposed on the skeletal muscles of lower extremities in HF patients. Therefore, reduced lower extremity muscle strength may force patients to terminate an exercise test at a lower peak power output with a correspondingly reduced muscle oxygen utilization which ultimately contributes to reduced VO_{2peak}.

LV Systolic Function. In contrast to the present findings, most previous studies reported a lack of correlation between VO_{2peak} and LV ejection fraction (14,155). The discrepancy between the present study and previously published findings could in part be explained by inclusion of HF patients with both reduced and normal LV systolic function in the present study. However, due to a small sample size, the results of the present study should be interpreted with caution.

Central Hemodynamics. In accordance with the Fick equation, VO_{2peak} is directly related to central hemodynamic factors such as peak exercise stroke volume and heart rate. Therefore, severely reduced VO_{2peak} in HF patients compared to the healthy age-matched individuals is, in part, related to reduced peak exercise stroke volume and heart rate in the former group (97,154,168). In the present study, peak exercise heart rate, systolic blood pressure and rate pressure product were the strongest univariate predictors of VO_{2peak}. When these

variables were included in the multivariate regression model, peak exercise rate pressure product became the strongest multivariate predictor of VO_{2peak} while the contribution of resting LV systolic function became non-significant, suggesting that peak exercise hemodynamics have a strong impact on exercise tolerance in HF patients.

Vascular Function. Despite a robust evidence of the contribution of vascular dysfunction to exercise intolerance in HF (71,103), VO_{2peak} was not significantly correlated to brachial or posterior tibial endothelial function in the present study. A positive correlation between VO_{2peak} and upper extremity endothelial function has been previously reported in healthy individuals (156) but not in HF patients (88). However, lack of a correlation between VO_{2peak} and peripheral vascular function cannot eliminate a contribution of vascular dysfunction to exercise intolerance in HF patients. Impaired endothelial function may contribute to reduced exercise tolerance in HF secondary to increased muscle fatigue and reduced skeletal muscle endurance. The present study supports that hypothesis with a novel finding of a positive correlation between upper extremity muscle endurance and endothelium-dependent but not endothelium-independent dilation of the brachial artery. Therefore, reduced skeletal muscle endurance and premature fatigue in HF patients may be, at least in part, attributed to a reduced skeletal muscle blood flow secondary to impaired peripheral vascular function. In addition, reduced muscle blood flow and subsequent accumulation of metabolites in exercising muscles may stimulate muscle ergoreceptors. According to the "muscle hypothesis", overactivation of ergoreceptors may increase ventilation at

a given sub-maximal workload, leading to reduced ventilatory efficiency (i.e., elevated V_E/V_{co2} slope) at submaximal exercise (142). Therefore, impaired endothelial function in HF patients and subsequent reduction in skeletal muscle blood flow may worsen already abnormal skeletal muscle function and lead to further reduction in VO_{2peak} and ventilatory efficiency (ie., elevated V_E/V_{co2} slope) in HF patients.

Cardiovascular Disease Risk Factors. In the present study, the total number of cardiovascular disease risk factors was one of the strongest multivariate predictors of VO_{2peak} in HF patients. We speculate that the presence of multiple cardiovascular disease risk factors may contribute to exercise intolerance in HF patients secondary to their negative effects on vascular function. This hypothesis is supported by a number of previous studies that demonstrated impaired vascular endothelial function in individuals with diabetes (118,181), hypertension (135), hyperlipidemia (44), obesity (77,162), and smoking (79,119), and more marked endothelial dysfunction in individuals with multiple risk factors (177). In the present study, the total number of cardiovascular disease risk factors correlated negatively with brachial endothelial function.

Taken together, the results of the present study suggest that exercise tolerance in HF patients is determined by lower extremity muscle strength, LV systolic function, central hemodynamics at peak exercise, and presence of multiple cardiovascular disease risk factors possibly due to their effects on vascular function.

5.4. Factors Related to Improvement in VO_{2peak} Following Exercise Training

In the present study, a change in VO_{2peak} following the intervention period significantly correlated with a change in peak exercise heart rate and brachial endothelial function but not LV systolic function at rest, or posterior tibial endothelial function. An improvement in lower extremity muscle strength was related to improvement in VO_{2peak} in the CART but not in the AT group.

Peak Exercise Heart Rate. Previous studies reported an increase (15,73) or no change (43,87,167) in peak exercise heart rate following exercise training in HF patients but did not comment on the relationship between changes in peak exercise heart rate and VO_{2peak}. In the present study, exercise training did not significantly increase peak exercise heart rate compared to the standard care intervention. However, a change in VO_{2peak} correlated with a change in peak exercise heart rate. This finding further emphasizes the strong impact of central hemodynamic variables on VO_{2peak} in HF patients.

Brachial Endothelial Function. The results of the present study are consistent with previous studies that reported a positive correlation between changes in forearm endothelial function and VO_{2peak} following AT in HF patients (71,103), supporting the hypothesis that partial reversal of peripheral vascular abnormalities may improve exercise tolerance in HF patients.

Lower Extremity Muscle Strength. Although lower extremity strength was improved following exercise training in the CART group in the present study, a correlation between a change in lower extremity strength and VO_{2peak} was not

significant in either the CART or the AT group. Similarly, Pu et al. (147) reported a positive correlation between improvements in lower extremity strength and the distance walked in 6 minutes but not VO_{2peak} following high intensity resistance training in HF patients. Therefore, an increased lower extremity muscle strength following exercise training with a resistance component may promote functional independence but may not translate into an improvement in VO_{2peak} in HF patients.

In summary, increased peak exercise heart rate and improved peripheral vascular function following exercise training may contribute to an improvement in VO_{2peak} in HF patients.

5.5. Mechanisms Responsible for Reduced Exercise Capacity in Ischemic versus Non-Ischemic HF Patients

Previous studies consistently reported reduced VO_{2peak} in IHF compared to NIHF patients (7,27,31,35,178). However, the mechanisms responsible for this difference remain largely unknown.

Effects of Age and Gender. Differences in clinical characteristics of IHF and NIHF patients found in the present study are consistent with previous findings of an advanced age (7,8,10,27,35), higher prevalence of males (4,10,55), and a higher incidence of cardiovascular disease risk factors (10) in IHF versus NIHF patients. Since both age and gender have independent effects on VO_{2peak} (48,184), vascular (24,54,159) and skeletal muscle function (41) in healthy individuals, these factors need to be taken into account when examining the effects of HF etiology on mechanisms of exercise intolerance in a heterogenous

sample of HF patients. In the present study, absolute and relative VO_{2peak}, percent of age-predicted VO_{2peak} and VO_2 at the ventilatory threshold remained significantly reduced in IHF compared to NIHF patients after adjusting for age and gender differences. Therefore, factors other then aging and gender differences contribute to reduced exercise tolerance in IHF versus NIHF patients.

Peripheral Vascular Function. Three studies published to date reported no difference in peripheral vascular endothelial function in IHF and NIHF patients (47,99,138). These studies included only male patients with an exception of 1 woman in a study by Kubo et al. (99) and reported no difference in age between the groups. In the present study, IHF patients had both reduced endothelium-dependent and endothelium-independent dilation of the brachial artery compared to NIHF patients. Reduced brachial endothelial function in IHF versus NIHF patients could be secondary to a higher prevalence of cardiovascular disease risk factors and an increased baseline arterial diameter in the former group. However, after adjusting for age and gender, differences in vascular function between IHF and NIHF patients became non-significant. Therefore, age and gender but not HF etiology itself may explain more severe vascular dysfunction observed in IHF versus NIHF patients in the present study.

Skeletal Muscle Function. Harrington et al. (76) reported no difference in skeletal muscle mass, muscle strength and fatigue in men with IHF versus NIHF. In the present study, IHF patients showed a trend toward reduced muscle endurance but not muscle strength compared to NIHF patients. However, after adjusting for age and gender, no difference in muscle strength or endurance was

found in IHF versus NIHF patients. Therefore, factors other then skeletal muscle strength or endurance contribute to more severe exercise intolerance in IHF versus NIHF patients.

LV Systolic Function and Peak Exercise Hemodynamics. After adjusting for age and gender, IHF patients had significantly reduced area ejection fraction, peak exercise heart rate, systolic blood pressure, and rate pressure product compared to NIHF patients. Both area ejection fraction and peak exercise hemodynamic variables were among the strongest predictors of VO_{2peak} in univariate and multivariate regression analyses (see Section **4.3.**). Therefore, reduced VO_{2peak} in IHF versus NIHF patients in the present study may be attributed to more severe LV systolic dysfunction and impaired peak exercise hemodynamics in the former group.

Reduced area ejection fraction in IHF versus NIHF patients in the present study was secondary to an increased LV end-systolic cavity area. It is possible that an increased afterload due to greater severity of peripheral vascular dysfunction and consequently increased total peripheral resistance could contribute to an increased LV end-systolic cavity area and ultimately reduced area ejection fraction in IHF versus NIHF patients.

Previous studies reported reduced peak exercise heart rate in IHF versus NIHF patients (90,178). A greater degree of chronotropic incompetence in IHF versus NIHF patients in the present study could not be explained by differences in medications, presence of pacemakers, or patients' effort on the graded exercise test. All patients were treated with beta blockers with no significant

difference in the percentage of a maximum dose used in IHF versus NIHF patients. Although heart rate reserve was significantly reduced in patients with, versus without, pacemakers (data not presented), peak exercise heart rate remained significantly attenuated in IHF compared to NIHF patients after adjusting for the number of pacemakers. Finally, respiratory exchange ratio at peak exercise was not different between the groups. Irrespective of the mechanisms, reduced peak exercise heart rate coupled with abnormal vascular function may reduce O_2 delivery to exercising muscle and may ultimately contribute to early fatigue and reduced VO_{2peak} in IHF versus NIHF patients.

Taken together, the present study extends previous findings by examining the physiological mechanisms that may explain reduced VO_{2peak} in IHF compared to NIHF patients. The results of the present study showed that reduced exercise tolerance in IHF versus NIHF patients could be in part related to impaired O_2 delivery to exercising muscle secondary to impaired vascular function. A greater degree of endothelial dysfunction in IHF patients and subsequent reduction in skeletal muscle blood flow may worsen already abnormal skeletal muscle function, leading to reduced skeletal muscle endurance, and ultimately limited exercise tolerance. In addition, abnormal vascular function coupled with reduced peak exercise heart rate may further impair O_2 delivery to exercising muscle resulting in an early stimulation of anaerobic metabolism and premature fatigue in IHF versus NIHF patients. Moreover, increased total peripheral resistance as a result of impaired vascular function may increase afterload leading to increased LV end-systolic volume and reduced LV ejection fraction. However, although

reduced exercise tolerance in IHF versus NIHF patients is independent of age and gender differences, the results of the present study suggest that differences in vascular and skeletal muscle function in a heterogenous sample of IHF and NIHF patients may be secondary to group differences in age and gender but not HF etiology itself. Therefore, age and gender need to be taken into account when examining the impact of HF etiology on peripheral mechanisms of exercise intolerance in HF patients.

5.6. HF Etiology and Health-Related Quality of Life

No previous study has examined the effects of HF etiology on HRQL. In the present study, individuals with IHF had both reduced generic and disease-specific HRQL, secondary to greater physical limitations compared to NIHF patients. The differences between the groups remained significant after adjusting for age and gender. In addition, the observed differences in disease-specific HRQL score in IHF versus NIHF patients were clinically important because these differences were greater than minimal clinically important differences established by previous investigations (i.e., 5 and 3 points for the total and physical score, respectively, measured by Minnesota Living with Heart Failure Questionnaire) (17). The current results are consistent with a previous study that reported positive correlation between HRQL and VO_{2peak} in HF patients (86). Therefore, intense counselling and encouragement to incorporate regular physical activity in everyday life may be especially warranted in individuals with IHF.

5.7. HF Etiology and Patients' Response to Exercise Training

To date, most of the intervention studies have combined IHF and NIHF patients and have failed to report exercise-induced changes in VO_{2peak} for individual subgroups (14,59,60,73,117). Preliminary data from 3 recent studies reported contradictory results. In a subgroup analysis of a randomized trial with a 6-month AT intervention, Keteyian et al. (94) reported improved absolute VO_{2peak}, peak heart rate and power output in NIHF but not IHF patients. Although both NIHF and IHF patients improved VO_{2peak} by 15% and 11%, respectively, only improvement in VO_{2peak} in NIHF patients reached statistical significance. In a subsequent study, Webb-Peploe et al. (178) reported improved VO_2 at peak exercise and ventilatory threshold, increased exercise time, and reduced LV end-diastolic and end-systolic dimensions following an 8-week AT intervention in NIHF patients while no change was observed in IHF patients. However, the results of this study should be interpreted with caution due to important methodological limitations including: (1) unknown exercise training intensity; (2) discrepancy between exercise testing and training modalities (i.e., treadmill test versus cycle ergometer training); and (3) increased peak exercise respiratory exchange ratio at the follow-up in NIHF but not in IHF patients which may suggest a greater effort during follow-up testing in the former group. In contrast to the first two studies, in a subgroup analysis of a non-randomized trial with a 4-month CART intervention, Conraads et al. (31) reported a significant improvement in VO_2 at peak exercise and ventilatory threshold only in individuals with IHF while no changes were observed in NIHF patients. Exercise training

reduced NYHA functional class and increased power output at peak exercise and ventilatory threshold in both IHF and NIHF patients. The limitation of all these studies was a lack of a comparison of exercise-induced changes in IHF and NIHF patients to those observed in a corresponding non-exercising control group.

Exercise Tolerance. Exercise training increased relative VO_{2peak} by 11% in both IHF and NIHF in the present study. However, the improvement in VO_{2peak} following exercise training versus NT was significant only in NIHF patients, consistent with the results by Keteyian et al. (94) and Webb-Peploe et al. (178). In addition, total exercise time was significantly increased only in NIHF patients. These findings may be explained by a small sample size, especially in the control group of IHF patients (n=4), and consequently reduced power to detect significant changes. However, the etiology by intervention interactions for VO_{2peak} and total exercise time were not statistically significant. Exercise training increased peak exercise power output compared to the NT intervention in both IHF and NIHF patients, consistent with the results by Conraads et al. (31). Therefore, the present study suggests that HF etiology may not influence an improvement in exercise tolerance following exercise training in HF patients.

Resting Hemodynamics. Significant etiology by intervention interactions were found only for heart rate and rate pressure product at rest while peak exercise hemodynamics remained unchanged in both IHF and NIHF patients. Resting heart rate and rate pressure product were reduced following exercise training and increased following the NT intervention in NIHF patients while no

change was observed in IHF patients. In contrast, Keteyian et al. (94) reported reduced resting heart rate in both IHF and NIHF patients. Reduced resting heart rate following exercise training in HF patients has been reported in previous studies (73,94,155) and could be related to reduced sympathetic activation (155) and reduced plasma norepinephrine concentration (94).

Left Ventricular Systolic Function. Exercise training did not have effects on LV function in IHF or NIHF patients in the present study. In contrast, Webb-Peploe et al. (178) reported reduced LV end-diastolic and end-systolic dimensions following 8-week AT in NIHF but not IHF patients. These findings should be interpreted with caution due to a small sample size, short training duration, and other methodological study limitations discussed above.

Peripheral Vascular Function. No previous studies examined the effects of exercise training on peripheral vascular function in IHF versus NIHF patients. In the present study, exercise training significantly improved brachial endothelial function in NIHF but not IHF patients compared to the NT intervention. However, the etiology by intervention interactions for this outcome was not statistically significant. Lack of significant interaction could be due to a small sample size in the present study. Alternatively, the exercise program used in the present study may not represent a sufficient stimulus to attenuate or reverse more severe endothelial dysfunction and accompanying structural changes in the peripheral vasculature of IHF compared to NIHF patients.

Skeletal Muscle Function. In the present study, exercise training increased upper extremity muscle endurance in IHF but not NIHF patients, while no

changes were observed in skeletal muscle strength. However, etiology by intervention interaction was not significant for this outcome. Due to a small sample size and different exercise programs used in the current study, these results should be interpreted with caution.

Health-Related Quality of Life. Exercise training did not have significant effects on HRLQ in IHF or NIHF patients.

5.8. Strengths of the Study

There are several methodological strengths of the present study. First, the present study was a randomized controlled trial with a non-exercising control group. Second, the study was performed in a clinical cardiac rehabilitation setting with the exercise prescription based on current recommendations for exercise training in HF patients (122,144). Therefore, the results of the present study are transferable to current clinical practice. Finally, data were analyzed using both the intention-to-treat and per-protocol analyses to examine both effectiveness (i.e., treatment effect in a real-world setting) and efficacy (i.e., treatment effect in a controlled environment) of the cardiac rehabilitation programs in HF patients.

5.9. Clinical Implications

Cardiac rehabilitation is an effective but underutilized therapeutic intervention to improve exercise capacity and HRQL in individuals with HF. The results of this investigation extend current scientific knowledge in the field of cardiac rehabilitation in HF patients and have several important clinical implications. First, the results of the present investigation suggest that both AT and CART are similarly effective in improving exercise tolerance and lead to a clinically

significant improvement in HRQL in compliant HF patients. However, CART is superior to AT in improving skeletal muscle strength and endurance. Therefore, both AT and CART may be used interchangeably to improve exercise tolerance and HRQL in HF patients, depending on a patient's preference. However, CART may be a preferable intervention to AT in frail and cachexic HF patients. From a clinical perspective, it is important to emphasize that regular exercise may be beneficial in HF patients even if it does not significantly improve VO_{2peak} but it reduces/prevents the decline in VO_{2peak} that is exacerbated by sedentary lifestyle in HF patients. The decline in VO_{2peak} (88,124) and quality of life (116) as a result of a sedentary lifestyle in HF patients leads to a loss of functional independence, progression of the disease (124), and is associated with increased mortality rates (49). Thus, interventions, such as exercise training, that can improve and/or prevent a decline in VO_{2peak} may have favourable effects on clinical outcomes and should be an integral part of the treatment of individuals with HF. Second, although both IHF and NIHF patients seem to benefit from participation in a cardiac rehabilitation program, IHF patients enter cardiac rehabilitation programs with a reduced exercise tolerance and HRQL compared to NIHF patients. Therefore, IHF patients may require reduced exercise workloads and a more gradual progression of exercise training compared to NIHF patients. Third, the results of the present investigation suggest that overweight HF patients and patients with poor HRQL are less likely to comply with the cardiac rehabilitation program. Therefore, these patients may need extra counselling and encouragement to complete a cardiac rehabilitation program and incorporate

physical activity in their everyday life. Finally, the achieved benefits of cardiac rehabilitation programs in HF patients are highly dependent on patients' compliance with the prescribed exercise programs. Considering the multiple benefits of exercise training in HF patients (144), high drop out rates and poor adherence with cardiac rehabilitation programs (9,30,134), and a quick loss of benefits with deconditioning (123,180), it is essential to design enjoyable and safe cardiac rehabilitation programs with additional personal support to increase patients' compliance and motivate patients to incorporate regular physical activity in their everyday life (22,134). Taken together, the results of the present study have direct clinical implications on: 1) optimizing an exercise prescription with the addition of resistance training to meet the needs of individual patients; 2) identifying HF patients that may require different exercise prescription; 3) identifying patients that are prone to non-compliance with an exercise program; and 4) encouraging referrals of HF patients to cardiac rehabilitation. From a clinical perspective, the participation of HF patients in cardiac rehabilitation improves VO_{2peak} and may ultimately delay or prevent a need for cardiac transplantation. From a public health policy perspective, encouraged referrals and increased compliance of HF patients with cardiac rehabilitation programs may prevent imposing an unnecessary financial burden on health care resources by decreasing hospitalization rates and reducing a need for a cardiac transplant. Thus, it is essential to design enjoyable cardiac rehabilitation programs to increase adherence, promote regular physical activity and facilitate independent

living in HF patients. We hope that the results of this investigation will facilitate knowledge transfer from research findings into clinical practice.

5.10. Design Issues

Generalizability. A recruited sample of selected compliant and motivated patients in the present study may reduce generalizability of the results to a general population of HF patients. However, the intent was to document the effects of the exercise intervention when patients comply with the prescribed exercise program. Poor compliance with lifestyle interventions, including exercise training, is one of the major problems in current clinical practice but it does not diminish the benefits of these interventions.

Selection Bias. A selection bias may be a potential limitation of the present study because patients recruited from the outpatient clinics may have a more advanced disease compared to HF patients followed by family physicians. Nevertheless, a recruitment of a clinical sample of HF patients was chosen for practical reasons such as easy accessibility and low cost as well as an opportunity to review patients' charts and recent clinical status. We believe that our eligibility criteria do not reduce generalizability of the study results to the patients with similar clinical characteristics followed by family physicians.

Lack of Blinding. A lack of blinding of the patients and the investigators to the group allocation could bias the results of the present study due to possible placebo effect and co-intervention. Blinding of patients is extremely challenging in the exercise intervention studies. In addition, the principal investigator coordinated this project and could not be blinded to the patients' group allocation.

For practical and logistic reasons we were not able to eliminate these issues. However, outcome assessors were blinded to the baseline data and, whenever possible, to the patients' group assignment.

Clinical Diagnosis of HF Etiology. Using a clinical diagnosis of the HF etiology may be a controversial issue due to a potential misclassification of patients with undiagnosed coronary artery disease. This misclassification may further complicate the interpretation of the results related to the mechanisms underlying exercise intolerance and a different response to exercise training in IHF versus NIHF patients. However, clinically documented HF etiology was chosen for practical reasons and we believe that this was an acceptable and feasible approach for the current investigation.

Additional Training Volume in CART versus AT Group. An addition of the resistance exercises to AT in the CART group increased exercise volume performed by the CART versus AT group. Therefore, it could be argued that the physiological benefits observed in the CART group could be, at least in part, influenced by additional training volume performed by patients randomized to this intervention. However, beneficial effects of AT on cardiovascular, musculoskeletal and clinical outcomes in HF patients have been documented in a number of previous studies. Thus, the intent of the present study was to examine potential further benefits of adding resistance component to an already beneficial AT prescription. Therefore, we believe that an addition of resistance exercises to the already established AT prescription was an acceptable approach for designing the CART intervention in the present study.

5.11. Future Directions

Although recent research has improved our basic understanding of the importance and benefits of exercise training in HF patients, a large number of unanswered questions remain in this area with respect to optimal training prescription, physiological adaptations to different training modalities such as AT or CART training, the effects of HF etiology on patients' response to exercise training, and identifying patients that would benefit most from participation in a cardiac rehabilitation program. Future research should compare different training modalities in large, prospective, randomized controlled studies of longer duration. In addition, future studies with a larger number of patients are necessary to examine the mechanisms of exercise intolerance in IHF versus NIHF patients and explore physiological adaptations to exercise training and the optimal exercise prescription for patients with different HF etiology.

5.12. Conclusions

In the intention to treat analysis, both AT and CART significantly improved total exercise time but not VO_{2peak}, while only CART improved skeletal muscle strength and endurance compared to the NT intervention. In addition, an improvement in upper extremity muscle strength and endurance was greater in CART compared to the AT alone. In compliant patients, both AT and CART improved VO_{2peak}. Skeletal muscle strength and endurance were enhanced in the CART group, while generic HRQL was significantly improved in the AT group only. Exercise training, irrespective of the training modality, improved brachial but not posterior tibial endothelial function and did not have detrimental effects on

resting LV systolic function. Therefore, despite their different effects on skeletal muscle function and HRQL, both AT and CART are effective interventions to improve exercise tolerance and may contribute to an improved HRQL in compliant HF patients. Thus, it is essential to design enjoyable and safe cardiac rehabilitation programs to promote adherence and regular physical activity in HF patients.

Lower extremity muscle strength, peak rate pressure product, and a total number of cardiovascular risk factors were the best multivariate predictors of VO_{2peak}. An improvement in VO_{2peak} following exercise training in HF patients was related to an improvement in brachial endothelial function and peak exercise heart rate.

IHF patients had reduced HRLQ and lower VO_{2peak} secondary to more severe LV systolic dysfunction and impaired peak exercise hemodynamics compared to NIHF patients. Reduced vascular and skeletal muscle endurance in IHF versus NIHF patients were secondary to age and gender differences between the groups. HF etiology did not influence patients' response to exercise training with respect to changes in exercise tolerance, LV systolic function, vascular and skeletal muscle function, or HRQL in the present study. Taken together, our findings emphasize importance of considering the etiology of the disease when designing comprehensive exercise programs to improve VO_{2peak} and HRQL in individuals with HF.

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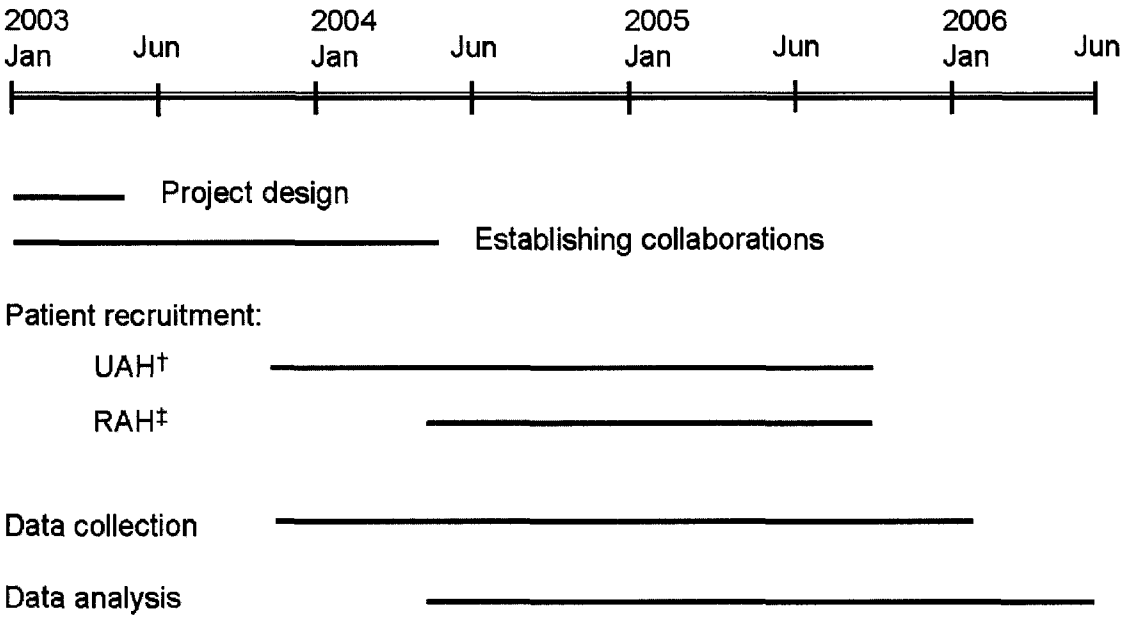
APPENDICES

APPENDIX A

Study Timetable

TIMETABLE



†UAH – University of Alberta Hospital; Heart Function Clinic

‡RAH – Royal Alexandra Hospital; Heart Function Stabilization Program

APPENDIX B

Collaboration Network

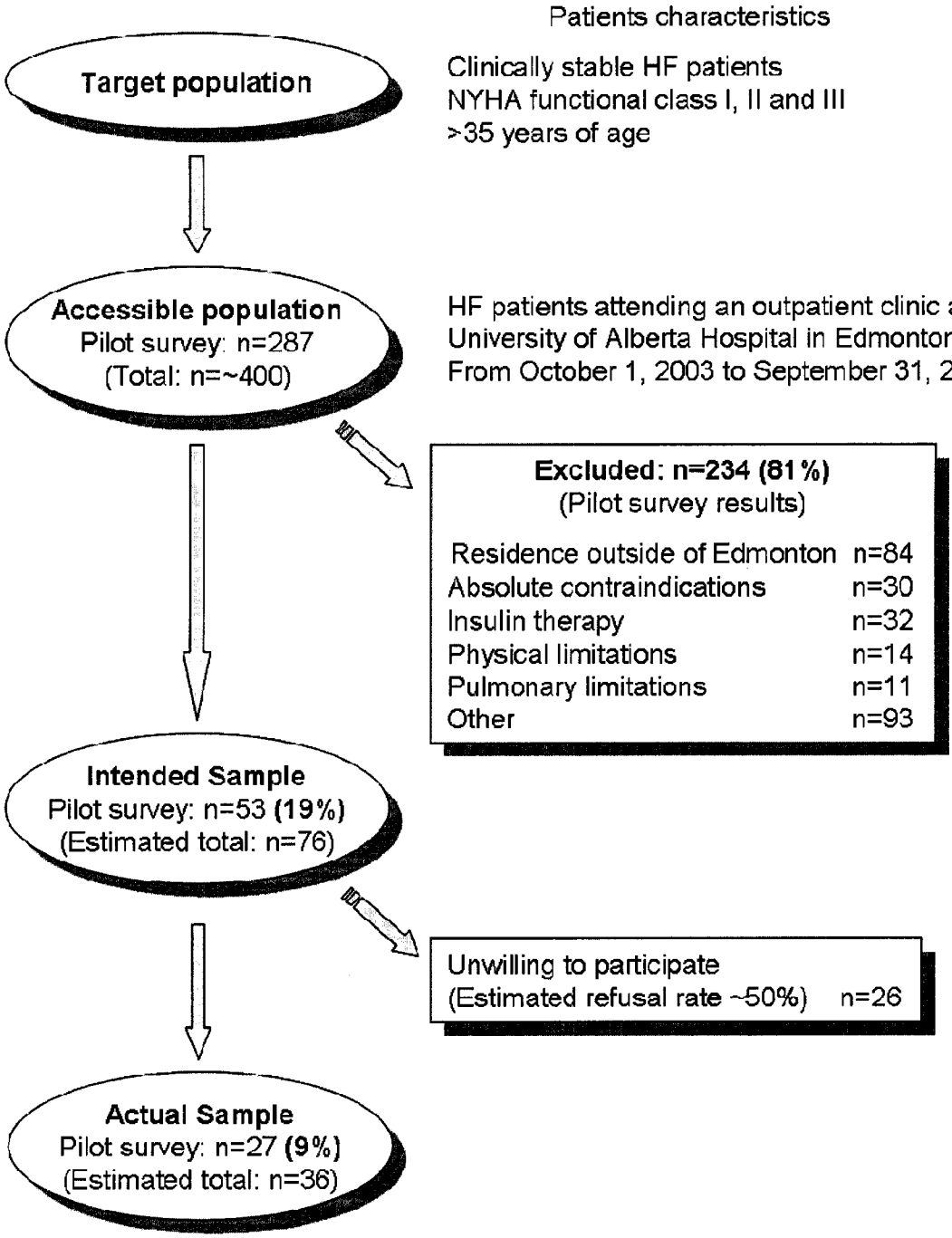
A wide network of collaborations has been established to ensure a successful completion of this project:

- Faculty of Physical Education and Recreation, Faculty of Rehabilitation Medicine, and Faculty of Medicine; University of Alberta
  - Academic support
- Division of Cardiology, University of Alberta Hospital:
  - Technical support and equipment for exercise stress testing, cardiac and vascular assessment and data analysis
  - Clinical support
- Heart Function Clinic, University of Alberta Hospital
  - Clinical support for patient recruitment
- Heart Function Stabilization Program, Royal Alexandra Hospital
  - Clinical support for patient recruitment
- Cardiac Rehabilitation Program, Glenrose Rehabilitation Hospital
  - Facility, equipment and clinical support for supervised exercise training program
- Endothelial Function Laboratory, Foothills Hospital (Calgary)
  - Technical support and equipment for the analysis of vascular function data.

APPENDIX C

Estimated Number of Eligible Heart Failure Patients: Results of a Pilot Survey

Pilot Survey was conducted at the Outpatient Clinic at the University of Alberta Hospital in March 2004



APPENDIX D

Special Considerations

A. Strategies Used for Maximizing Treatment Effects:

1) Recruited a sample of compliant HF patients predominantly with an intermediate risk (NYHA functional class II and III) that are most likely to gain the greatest benefits from an exercise intervention;
2) Prescribed an exercise program that would provide a sufficient stimulus for improving exercise capacity in this population; and
3) Used several strategies to ensure high compliance rates with the exercise intervention:
    a. Provided supervised exercise sessions with a variety of exercise modalities;
    b. Prescribed individualized exercise programs of moderate intensity;
    c. Offered flexible exercise times (Monday to Friday, 8 am to 2 pm);
    d. Arranged weekly contact with one of the investigators.

B. Strategies Used for Maximizing Adherence to Follow-Up.

From our experience with similar trials in HF patients, we estimated less then a 10% loss to follow up. To further minimize this problem, we employed the following strategies:

1) Clearly explained study commitments during the initial contact;
2) Recruited highly compliant patients;
3) Ensured weekly meeting in person or phone contact by one of the investigators;
4) Provided reimbursement of parking expenses at the University of Alberta Hospital; and
5) Addressed specific concerns and reinforced the importance of completing the intervention period.

When these strategies were unsuccessful, the investigators contacted the participants for the follow-up testing. We reported the number of patients that were randomized and dropped out during the intervention phase as well as their reasons for dropping out.

C. Strategies Used for Minimizing Sources of Variation:

1) Random allocation of patients to intervention groups;
2) Ensured high compliance rates in all intervention groups as described above; and
3) Maximized precision and consistency in the outcome assessment by choosing more objective outcome measures and by reporting an average of multiple (3 to 4) values of the outcome measures.

APPENDIX E

MacNew Heart Disease Health-Related Quality of Life Questionnaire

We would now like to ask you some questions about how you have been feeling DURING THE LAST 2 WEEKS. Please check the box € that matches your answer.

1. In general, how much of the time during the last 2 weeks have you felt frustrated, impatient or angry?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

2. How often during the last 2 weeks have you felt worthless or inadequate?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

3. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your heart problem?

1 € NONE OF THE TIME
2 € A LITTLE OF THE TIME
3 € SOME OF THE TIME
4 € A GOOD BIT OF THE TIME
5 € MOST OF THE TIME
6 € ALMOST ALL OF THE TIME
7 € ALL OF THE TIME

4. In general how much of the time did you feel discouraged or down in the dumps during the last 2 weeks?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

5. How much of the time during the past 2 weeks did you feel relaxed and free of tension?

1 € NONE OF THE TIME
2 € A LITTLE OF THE TIME
3 € SOME OF THE TIME
4 € A GOOD BIT OF THE TIME
5 € MOST OF THE TIME
6 € ALMOST ALL OF THE TIME
7 € ALL OF THE TIME

6. How often during the last 2 weeks have you felt worn out or low in energy?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

7. How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks?

1 € VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 € GENERALLY DISSATISFIED, UNHAPPY
3 € SOMEWHAT DISSATISFIED, UNHAPPY
4 € GENERALLY SATISFIED, PLEASED
5 € HAPPY MOST OF THE TIME
6 € VERY HAPPY MOST OF THE TIME
7 € EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED

8. In general, how often during the last 2 weeks have you felt restless, or as if you were having difficulty trying to calm down?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

9. How much shortness of breath have you experienced during the last 2 weeks while doing your day-to-day physical activities?

1 € EXTREME SHORTNESS OF BREATH
2 € VERY SHORT OF BREATH
3 € QUITE A BIT OF SHORTNESS OF BREATH
4 € MODERATE SHORTNESS OF BREATH
5 € SOME SHORTNESS OF BREATH
6 € A LITTLE SHORTNESS OF BREATH
7 € NO SHORTNESS OF BREATH

10. How often during the last 2 weeks have you felt tearful, or like crying?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

11. How often during the last 2 weeks have you felt as if you are more dependent than you were before your heart problem?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

12. How often during the last 2 weeks have you felt you were unable to do your usual social activities or social activities with your family?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

13. How often during the last 2 weeks have you felt as if others no longer have the same confidence in you as they did before your heart problem?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

14. How often during the last 2 weeks have you experienced chest pain while doing your day-to-day activities?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

15. How often during the last 2 weeks have you felt unsure of yourself for lacking in self-confidence?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

16. How often during the last 2 weeks have you been bothered by aching or tired legs?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

17. During the last 2 weeks, how much have you been limited in doing sports or exercise as a result of your heart problem?

1 € EXTREMELY LIMITED
2 € VERY LIMITED
3 € LIMITED QUITE A BIT
4 € MODERATELY LIMITED
5 € SOMEWHAT LIMITED
6 € LIMITED A LITTLE
7 € NOT LIMITED AT ALL

18. How often during the last 2 weeks have you felt apprehensive or frightened?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

19. How often during the last 2 weeks have you felt dizzy or lightheaded?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

20. In general during the last 2 weeks, how much have you been restricted or limited as a result of your heart problem?

1 € EXTREMELY LIMITED
2 € VERY LIMITED
3 € LIMITED QUITE A BIT
4 € MODERATELY LIMITED
5 € SOMEWHAT LIMITED
6 € LIMITED A LITTLE
7 € NOT LIMITED AT ALL

21. How often during the last 2 weeks have you felt unsure as to how much exercise or physical activity you should be doing?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

22. How often during the last 2 weeks have you felt as if your family is being over-protective toward you?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

23. How often during the past 2 weeks have you felt as if you were a burden on others?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

24. How often during the past 2 weeks have you felt excluded from doing things with other people because of your heart problem?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

25. How often during the past 2 weeks have you felt unable to socialize because of your heart problem?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

26. In general, during the last 2 weeks how much have you been physically restricted or limited as a result of your heart problem?

1 € EXTREMELY LIMITED
2 € VERY LIMITED
3 € LIMITED QUITE A BIT
4 € MODERATELY LIMITED
5 € SOMEWHAT LIMITED
6 € LIMITED A LITTLE
7 € NOT LIMITED AT ALL

27. How often during the last 2 weeks have you felt your heart problem limited or interfered with sexual intercourse?

1 € ALL OF THE TIME
2 € MOST OF THE TIME
3 € A GOOD BIT OF THE TIME
4 € SOME OF THE TIME
5 € A LITTLE OF THE TIME
6 € HARDLY ANY OF THE TIME
7 € NONE OF THE TIME

That is the end. Thank you very much for answering the questions.

APPENDIX F

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

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

APPENDIX G

Additional Tables

Table of Content:

Table 7-01. Baseline characteristics of patients with versus without change in medication during the intervention period.

	No Change in Meds (n=25)	Change in Meds (n=16)	p-value
Age (yrs)	63.3 ± 10.7	59.1 ± 13.0	.262
Gender (M/F)	19/6	12/4	
Weight (kg)	90.6 ± 14.9	84.0 ± 16.0	.189
Body mass index (kg/m^2)	31.9 ± 6.2	28.0 ± 4.9*	.039
HF Etiology (ischemic/non-ischemic)	12/13	6/10	
Total n of risk factors (n)	2.3 ± 1.1	1.4 ± 1.1*	.015
Outcome Measures			
VO_{2peak} (ml/kg/min)	16.1 ± 5.7	17.7 ± 6.3	.593
Area ejection fraction (%)	29.9 ± 10.2	30.0 ± 14.7	.452
Brachial RH AD (% Δ)	4.3 ± 4.9	3.6 ± 5.0	.682
Posterior tibial RH AD (% Δ)	8.9 ± 6.2	11.9 ± 8.2	.249
Leg ext. strength (kg)	40.9 ± 17.5	41.3 ± 17.8	.939
Chest press strength (kg)	41.2 ± 14.2	43.1 ± 17.5	.715
Leg ext. endurance (reps)	8.1 ± 2.3	8.0 ± 2.9	.877
Chest press endurance (reps)	6.6 ± 2.8	5.4 ± 1.9	.157
Disease-Specific HRQL (Minnesota)			
Physical	18.8 ± 10.4	19.4 ± 8.4	.836
Emotional	7.6 ± 6.9	11.8 ± 6.3	.059
Total	39.9 ± 20.6	45.4 ± 17.5	.385
Generic HRQL (MacNew)	143 ± 28	131 ± 24	.165

AD, arterial diameter; HRQL, health-related quality of life; Leg ext., leg extension; LV, left ventricular; RH, reactive hyperemia; VO_{2peak}, peak oxygen consumption.

*$p<0.05$ vs. patients with no change in medications

Table 7-02. Baseline characteristics (**Per protocol analysis**)

	AT (n=9)	**CART** (n= 11)	**NT** (n=13)
Age (yrs)	65 ± 11	60 ± 11	62 ± 13
Gender (M/F)	6/3	9/2	10/3
Weight (kg)	84.1 ± 15.8	89.9 ± 11.9	84.8 ± 13.7
Body mass index (kg/m^2)	28.8 ± 5.1	30.5 ± 4.8	29.8 ± 5.0
VO_{2peak} (ml/kg/min)	16.1 ± 6.1	16.1 ± 4.7	16.6 ± 6.0
LV Area ejection fraction (%)	30.9 ± 12.2	32.7 ± 14.7	29.4 ± 12.1
HF Etiology (ischemic/non-ischemic)	4/5	6/5	4/9
Risk Factors (n (%))			
Hypertension	4 (44)	7 (64)	8 (62)
Diabetes	2 (22)	1 (9)	2 (15)
Obesity	4 (44)	5 (45)	5 (38)
Hyperlipidemia	7 (78)	7 (64)	10 (77)
Smoking	0 (0)	2 (18)	1 (8)
Total n of risk factors (n)	1.9 ± 1.5	2.1 ± 1.2	1.9 ± 1.0
Medications (n (%))			
Beta blockers	9 (100)	11 (100)	13 (100)
ACE Inhibitors	9 (100)	9 (82)	12 (92)
Diuretics	6 (67)	10 (91)	12 (92)
Lipid lowering	8 (89)	6 (55)	8 (62)

LV, left ventricular; VO_{2peak}, peak oxygen consumption.

All comparisons $p>0.05$.

Table 7-03. Effects of different exercise programs on cardiorespiratory function at rest and during acute exercise. (**Per protocol analysis**)

	AT		CART		NT	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Rest	(n=8)		(n=10)		(n=13)	
HR (bpm)	67 ± 13	61 ± 11	67 ± 15	64 ± 12	67 ± 8	73 ± 15
SBP (mm Hg)	115 ± 21	114 ± 17	116 ± 20	116 ± 17	112 ± 19	114 ± 19
DBP (mm Hg)	65 ± 8	68 ± 11	73 ± 10	70 ± 9	70 ± 11	69 ± 10
RPP ($bpm \cdot mmHg \cdot 10^3$)	7.7 ± 1.7	6.9 ± 1.4	7.6 ± 1.6	7.4 ± 1.3	7.4 ± 1.4	8.3 ± 2.4
Ventilatory Threshold	(n=6)		(n=8)		(n=10)	
HR (bpm)	93 ± 22	90 ± 17	94 ± 24	89 ± 12	102 ± 30	102 ± 27
SBP (mm Hg)	127 ± 11	112 ± 18	141 ± 22	136 ± 12	138 ± 22	133 ± 22
DBP (mm Hg)	73 ± 6	68 ± 18	75 ± 10	73 ± 4	71 ± 8	74 ± 8
RPP ($bpm \cdot mmHg \cdot 10^3$)	11.9 ± 3.4	10.3 ± 3.4	13.2 ± 4.2	12.1 ± 3.0	14.4 ± 5.7	13.9 ± 4.7
VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	10.4 ± 2.2	12.1 ± 3.1	12.7 ± 3.7	13.9 ± 4.0	12.8 ± 3.7	12.5 ± 3.1
VO_2 ($L \cdot min^{-1}$)	0.80 ± 0.16	0.95 ± 0.26	1.16 ± 0.44	1.20 ± 0.38	1.08 ± 0.39	1.06 ± 0.36
% of VO_2 peak (%)	65 ± 13	67 ± 14	74 ± 11	75 ± 11	69 ± 12	69 ± 10
Power output (watts)	48 ± 20	58 ± 22	70 ± 28	77 ± 22	66 ± 23	58 ± 22
Exercise time (min)	5.5 ± 2.8	7.0 ± 3.1	8.2 ± 3.5	9.1 ± 3.2	7.9 ± 2.9	6.8 ± 3.3
V_E/V_{CO2} Slope	32.8 ± 6.6	33.7 ± 12.7	28.1 ± 4.4	27.9 ± 6.0	31.2 ± 8.1	31.5 ± 6.5
Peak Exercise	(n=8)		(n=10)		(n=13)	
HR (bpm)	118 ± 30	119 ± 33	105 ± 30	110 ± 26	117 ± 38	121 ± 36
SBP (mm Hg)	149 ± 23	136 ± 29	150 ± 28	151 ± 27	146 ± 31	141 ± 28
DBP (mm Hg)	72 ± 6	66 ± 12	76 ± 8	77 ± 9	71 ± 10	71 ± 8
RPP ($bpm \cdot mmHg \cdot 10^3$)	17.7 ± 6.0	17.1 ± 7.5	15.8 ± 5.7	16.9 ± 5.9	17.8 ± 8.3	17.5 ± 6.9
VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	16.9 ± 6.0	19.0 ± 6.8*	15.9 ± 5.0	17.6 ± 5.6‡	16.6 ± 6.0	16.7 ± 6.1
VO_2 ($L \cdot min^{-1}$)	1.43 ± 0.41	1.51 ± 0.49	1.44 ± 0.58	1.54 ± 0.57	1.39 ± 0.53	1.42 ± 0.61
VO_2 % predicted (%)	73 ± 23	71 ± 29	53 ± 15	58 ± 19	65 ± 37	67 ± 29
Power output (watts)	81 ± 36	101 ± 41*	86 ± 29	96 ± 34	84 ± 38	82 ± 41
Exercise time (min)	11.6 ± 4.6	13.9 ± 5.2*	12.0 ± 4.4	13.9 ± 4.7*	12.01 ± 5.1	11.7 ± 5.1
RER	1.05 ± 0.05	1.08 ± 0.09	1.10 ± 0.11	1.06 ± 0.09	1.06 ± 0.08	1.04 ± 0.07

DBP, diastolic blood pressure; HR, heart rate; RER, respiratory exchange ratio; RPP, rate pressure product; SBP, systolic blood pressure; VO_2, oxygen consumption.

*$p<0.05$ versus change from baseline in NT
‡$p<0.10$ versus change from baseline in NT

Table 7-04. Effects of different exercise programs on left ventricular, vascular and skeletal muscle function. (**Per protocol analysis**)

	AT		CART		NT	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Left Ventricular Function	(n=7)		(n=10)		(n=11)	
LV EDCA (cm^2)	28.7 ± 10.9	31.0 ± 16.8	25.8 ± 5.6	26.2 ± 8.7	27.9 ± 7.7	28.3 ± 9.6
LV ESCA (cm^2)	20.7 ± 11.0	22.2 ± 15.2	17.9 ± 6.9	17.3 ± 7.6	20.6 ± 7.5	20.8 ± 8.1
LV Area ejection fraction (%)	30.9 ± 12.2	33.2 ± 12.6	32.7 ± 14.7	35.4 ± 10.1	27.4 ± 10.3	27.4 ± 8.4
Vascular Function						
Brachial Artery	(n=8)		(n=11)		(n=11)	
Baseline AD (mm)	4.98 ± 0.77	5.01 ± 0.88	4.83 ± 0.75	4.75 ± 0.63	4.98 ± 0.77	5.01 ± 0.88
RH AD (mm)	5.17 ± 0.95	4.95 ± 1.22	5.05 ± 0.71	5.08 ± 0.58	5.14 ± 0.70	5.09 ± 0.86
RH AD (% Δ)	4.3 ± 5.2	6.3 ± 7.0	4.7 ± 5.3	7.2 ± 5.8‡	3.4 ± 3.9	1.8 ± 2.8
NTG AD (mm)	5.81 ± 0.95	5.49 ± 1.03	5.45 ± 0.62	5.42 ± 0.53	5.48 ± 0.63	5.55 ± 0.84
NTG AD (% Δ)	14.0 ± 9.1	15.6 ± 14.2	15.7 ± 8.9	14.4 ± 9.1	8.3 ± 7.5	9.2 ± 4.1
Posterior Tibial Artery	(n=5)		(n=10)		(n=7)	
Baseline AD (mm)	3.22 ± 0.82	3.18 ± 0.76	2.97 ± 0.47	2.91 ± 0.37	2.94 ± 0.89	3.04 ± 1.00
RH AD (mm)	3.50 ± 0.71	3.59 ± 0.53	3.31 ± 0.57	3.25 ± 0.44	3.13 ± 0.91	3.27 ± 1.07
RH AD (% Δ)	10.0 ± 8.4	15.0 ± 11.5	11.3 ± 6.8	11.4 ± 5.5	6.8 ± 6.5	7.4 ± 9.6
NTG AD (mm)	3.57 ± 0.92	3.52 ± 0.61	3.21 ± 0.26	3.39 ± 0.57	3.51 ± 0.92	3.67 ± 1.03
NTG AD (% Δ)	11.0 ± 7.5	12.1 ± 11.8	12.0 ± 8.5	14.2 ± 8.1	11.9 ± 12.3	9.2 ± 11.1
Skeletal Muscle Function						
Maximal Muscle Strength	(n=8)		(n=10)		(n=12)	
Chest press (kg)	33.0 ± 16.0	33.9 ± 16.0	40.8 ± 14.7	48.5 ± 15.4*	43.8 ± 16.6	42.8 ± 19.3
Leg extension (kg)	31.1 ± 13.2	35.6 ± 16.8	41.8 ± 16.8	52.7 ± 16.2*	45.1 ± 19.8	46.3 ± 18.8
Muscle Endurance						
Chest press (reps)	6.8 ± 2.9	8.5 ± 3.7	5.2 ± 2.5	12.1 ± 8.2*†	6.1 ± 2.6	5.3 ± 3.0
Leg extension (reps)	9.6 ± 3.8	12.1 ± 4.5	7.3 ± 2.7	12.4 ± 5.4	8.0 ± 2.2	7.0 ± 2.9

AD, arterial diameter; DBP, diastolic blood pressure; HR, heart rate; LV, left ventricular; EDCA, end-diastolic cavity area; ESCA, end-systolic cavity area; NTG, nitroglycerin; RH, reactive hyperemia.

*$p<0.05$ and ‡$p<0.10$ versus change from baseline in NT
†$p<0.05$ versus change from baseline in AT

Table 7-05. Effects of different exercise programs on metabolic profile and health-related quality of life. (**Per protocol analysis**)

	AT		CART		NT	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Metabolic Profile	(n=9)		(n=11)		(n=13)	
Cholesterol ($mmol \cdot L^{-1}$)	4.23 ± 0.86	3.85 ± 0.90	4.38 ± 1.26	4.24 ± 1.05	4.64 ± 1.16	4.51 ± 1.19
Triglycerides ($mmol \cdot L^{-1}$)	2.00 ± 1.61	2.40 ± 3.10	1.85 ± 0.78	1.66 ± 0.37	2.23 ± 1.34	2.33 ± 1.79
HDL Cholesterol ($mmol \cdot L^{-1}$)	1.12 ± 0.14	1.21 ± 0.29	1.11 ± 0.35	1.18 ± 0.29	1.14 ± 0.29	1.20 ± 0.26
LDL Cholesterol ($mmol \cdot L^{-1}$)	2.24 ± 0.76	1.74 ± 0.47	2.43 ± 0.93	2.31 ± 0.75	2.56 ± 0.95	2.33 ± 0.96
Total cholesterol/ HDL cholesterol	3.6 ± 0.6	2.9 ± 0.4	4.0 ± 0.7	3.6 ± 0.7	4.1 ± 1.0	3.9 ± 1.2
C-reactive protein ($mg \cdot L^{-1}$)	1.9 ± 2.3	2.2 ± 2.2	4.1 ± 5.0	5.2 ± 3.8	3.7 ± 2.7	4.8 ± 5.6
Fasting glucose ($mmol \cdot L^{-1}$)	5.4 ± 0.4	5.4 ± 0.5	5.5 ± 0.5	5.7 ± 0.5	6.0 ± 0.4	6.1 ± 0.8
Insulin sensitivity[§]	12.4 ± 7.1	9.4 ± 2.3	9.0 ± 2.9	8.8 ± 2.0	9.5 ± 4.4	9.5 ± 3.7
Health-Related Quality of Life						
Disease-Specific HRQL	(n=9)		(n=11)		(n=12)	
Physical	20.2 ± 7.2	16.7 ± 7.9	16.5 ± 9.7	13.9 ± 11.1	16.7 ± 9.2	16.9 ± 9.9
Emotional	8.9 ± 5.2	6.8 ± 6.5	7.8 ± 7.7	6.6 ± 6.6	9.6 ± 7.8	8.2 ± 8.0
Total	42.1 ± 11.1	34.4 ± 20.1	35.6 ± 20.3	30.5 ± 21.6	40.2 ± 22.5	37.8 ± 24.7
Generic HRQL (MacNew)	137 ± 23	152 ± 21*	146 ± 23	150 ± 25	144 ± 33	142 ± 37

HRQL, health-related quality of life. [§]Insulin sensitivity was measured using ^{13}C-glucose breath test.

*$p<0.05$ versus change from baseline in NT

Table 7-06. Baseline characteristics of patients in the pooled exercise group and standard care group. (**Per protocol analysis**)

	Exercise (AT+CART) (n=20)	**Standard Care (NT)** (n=13)
Age (yrs)	62 ± 11	62 ± 13
Gender (M/F)	15/5	10/3
Weight (kg)	86.3 ± 13.0	84.8 ± 13.7
Body mass index (kg/m^2)	29.3 ± 4.5	29.8 ± 5.0
VO_{2peak} (ml/kg/min)	16.1 ± 5.3	16.6 ± 6.0
LV Fractional area change (%)	31.9 ± 13.3	29.4 ± 12.1
HF Etiology (ischemic/non-ischemic)	10/10	4/9
Risk Factors (n (%))		
Hypertension	11 (55)	8 (62)
Diabetes	3 (15)	2 (15)
Obesity	9 (45)	5 (38)
Hyperlipidemia	14 (70)	10 (77)
Smoking	2 (10)	1 (8)
Total n of risk factors (n)	2.0 ± 1.3	1.9 ± 1.0
Medications (n (%))		
Beta blockers	20 (100)	13 (100)
ACE Inhibitors	18 (90)	12 (92)
Diuretics	16 (80)	12 (92)
Lipid lowering	14 (70)	8 (62)

LV, left ventricular; VO_{2peak}, peak oxygen consumption.

All comparisons $p>0.05$.

Table 7-07. Effects exercise versus standard care on cardiorespiratory function at rest and during acute exercise. (**Per protocol analysis**)

	Exercise (AT+CART)		Standard Care (NT)	
	Pre	**Post**	**Pre**	**Post**
Rest	(n=21)		(n=13)	
HR (bpm)	67 ± 14	63 ± 11*	67 ± 8	73 ± 15
SBP (mm Hg)	116 ± 20	115 ± 16	112 ± 19	114 ± 19
DBP (mm Hg)	69 ± 10	69 ± 10	70 ± 11	69 ± 10
RPP (bpm·mmHg·10^3)	7.6 ± 1.6	7.2 ± 1.3*	7.4 ± 1.4	8.3 ± 2.4
Ventilatory Threshold	(n=14)		(n=10)	
HR (bpm)	93 ± 22	90 ± 19	102 ± 30	102 ± 27
SBP (mm Hg)	135 ± 19	125 ± 19	138 ± 22	133 ± 22
DBP (mm Hg)	74 ± 8	71 ± 12	71 ± 8	74 ± 8
RPP (bpm·mmHg·10^3)	12.6 ± 3.8	11.3 ± 3.2	14.4 ± 5.7	13.9 ± 4.7
VO_2 (ml·kg^{-1}·min^{-1})	11.7 ± 3.2	13.1 ± 3.6	12.8 ± 3.7	12.5 ± 3.2
VO_2 (L·min^{-1})	1.01 ± 0.39	1.09 ± 0.35	1.08 ± 0.39	1.06 ± 0.36
% of VO_2 peak (%)	70 ± 12	71 ± 12	69 ± 12	69 ± 10
Power output (watts)	65 ± 31	69 ± 24*	71 ± 19	58 ± 22
Exercise time (min)	7.0 ± 3.4	8.2 ± 3.2*	7.9 ± 2.9	6.8 ± 3.3
V_E/V_{CO2} Slope	30.1 ± 5.8	30.4 ± 9.5	31.2 ± 8.1	31.4 ± 6.5
Peak Exercise	(n=18)		(n=13)	
HR (bpm)	110 ± 30	114 ± 29	117 ± 38	121 ± 36
SBP (mm Hg)	149 ± 25	144 ± 28	146 ± 31	141 ± 28
DBP (mm Hg)	74 ± 7	72 ± 12	71 ± 10	71 ± 8
RPP (bpm·mmHg·10^3)	16.7 ± 5.8	16.9 ± 6.5	17.8 ± 8.3	17.5 ± 6.9
VO_2 (ml·kg^{-1}·min^{-1})	16.3 ± 5.3	18.2 ± 6.0*	16.6 ± 6.0	16.7 ± 6.1
VO_2 (L·min^{-1})	1.43 ± 0.50	1.52 ± 0.52	1.39 ± 0.53	1.42 ± 0.61
VO_2 % predicted (%)	62 ± 21	64 ± 24	65 ± 37	67 ± 29
Power output (watts)	83 ± 31	98 ± 36*	84 ± 38	82 ± 41
Exercise time (min)	11.8 ± 4.4	13.9 ± 4.8*	12.01 ± 5.1	11.7 ± 5.1
RER	1.08 ± 0.9	1.07 ± 0.9	1.06 ± 0.08	1.04 ± 0.07

DBP, diastolic blood pressure; HR, heart rate; RPP, rate pressure product; RER, respiratory equivalent ratio; SBP, systolic blood pressure; VO_2, oxygen consumption.

*$p<0.05$ versus change from baseline in the NT group

Table 7-08. Effects of exercise versus standard care on left ventricular, vascular and skeletal muscle function. (**Per protocol analysis**)

	Exercise (AT+CART)		Standard Care (NT)	
	Pre	**Post**	**Pre**	**Post**
Left Ventricular Systolic Function	(n=17)		(n=11)	
LV ED cavity area (cm^2)	27.0 ± 8.1	28.2 ± 12.4	27.9 ± 7.7	28.3 ± 9.6
LV ES cavity area (cm^2)	19.1 ± 8.6	19.3 ± 11.2	20.6 ± 7.5	20.8 ± 8.1
LV Area ejection fraction (%)	31.9 ± 13.3	34.5 ± 10.9	27.4 ± 10.3	27.4 ± 8.4
Peripheral Vascular Endothelial Function				
Brachial Artery	(n=19)		(n=11)	
Baseline AD (mm)	4.89 ± 0.80	4.72 ± 0.85	4.98 ± 0.77	5.01 ± 0.88
Reactive hyperemia AD (mm)	5.10 ± 0.80	5.02 ± 0.88	5.14 ± 0.70	5.09 ± 0.86
Reactive hyperemia AD (% Δ)	4.5 ± 5.1	6.9 ± 6.2*	3.4 ± 3.9	1.8 ± 2.8
Nitroglycerin AD (mm)	5.60 ± 0.77	5.45 ± 0.74	5.48 ± 0.63	5.55 ± 0.84
Nitroglycerin AD (% Δ)	15.0 ± 8.8	14.9 ± 11.1	8.3 ± 7.5	9.2 ± 4.1
Posterior Tibial Artery	(n=15)		(n=7)	
Baseline AD (mm)	3.05 ± 0.59	3.00 ± 0.52	2.94 ± 0.89	3.04 ± 1.00
Reactive hyperemia AD (mm)	3.37 ± 0.60	3.36 ± 0.48	3.13 ± 0.91	3.27 ± 1.07
Reactive hyperemia AD (% Δ)	10.9 ± 7.1	12.6 ± 7.8	6.8 ± 6.5	7.4 ± 9.6
Nitroglycerin AD (mm)	3.34 ± 0.59	3.44 ± 0.56	3.51 ± 0.92	3.67 ± 1.03
Nitroglycerin AD (% Δ)	11.6 ± 7.8	13.4 ± 9.3	11.9 ± 12.3	9.2 ± 11.1
Skeletal Muscle Function				
Maximal Dynamic Muscle Strength	(n=18)		(n=12)	
Chest press (kg)	37.3 ± 15.4	42.0 ± 16.9*	43.8 ± 16.6	42.8 ± 19.3
Leg extension (kg)	37.1 ± 15.8	45.1 ± 18.2*	45.1 ± 19.8	46.3 ± 18.8
Muscle Endurance	(n=18)		(n=12)	
Chest press (reps)	5.9 ± 2.7	10.5 ± 6.7*	6.1 ± 2.6	5.3 ± 3.0
Leg extension (reps)	8.3 ± 3.0	12.3 ± 4.9*	8.0 ± 2.2	7.0 ± 2.9

AD, arterial diameter; LV, left ventricular; LV ED, left ventricular end-diastolic; LV ES, left ventricular end-systolic, NT, standard care (no exercise training).

*p>0.05 versus change from baseline in the NT group.

Table 7-09. Effects of exercise versus standard care on metabolic profile and health-related quality of life. (**Per protocol analysis**)

	Exercise (AT+CART)		Standard Care (NT)	
	Pre	**Post**	**Pre**	**Post**
Metabolic Profile	(n=20)		(n=13)	
Cholesterol ($mmol \cdot L^{-1}$)	4.31 ± 1.07	4.07 ± 0.98	4.64 ± 1.16	4.51 ± 1.19
Triglycerides ($mmol \cdot L^{-1}$)	1.92 ± 1.19	1.99 ± 2.07	2.23 ± 1.34	2.33 ± 1.79
HDL Cholesterol ($mmol \cdot L^{-1}$)	1.11 ± 0.27	1.20 ± 0.28	1.14 ± 0.29	1.20 ± 0.26
LDL Cholesterol ($mmol \cdot L^{-1}$)	2.35 ± 0.85	2.07 ± 0.70	2.56 ± 0.95	2.33 ± 0.96
Total cholesterol/ HDL cholesterol	3.8 ± 0.7	3.3 ± 0.7	4.1 ± 1.0	3.9 ± 1.2
C-reactive protein ($mg \cdot L^{-1}$)	3.1 ± 4.1	3.9 ± 3.4	3.7 ± 2.7	4.8 ± 5.6
Fasting glucose ($mmol \cdot L^{-1}$)	5.4 ± 0.5	5.6 ± 0.5	6.0 ± 0.4	6.1 ± 0.8
Insulin sensitivity[§]	10.3 ± 5.0	9.0 ± 2.1	9.5 ± 4.4	9.5 ± 3.7
Health-Related Quality of Life (HRQL)				
Disease-specific HRQL (Minnesota)	(n=20)		(n=12)	
Physical	18.2 ± 8.7	14.7 ± 9.6[‡]	16.7 ± 9.2	16.9 ± 9.9
Emotional	8.3 ± 6.6	6.7 ± 6.4	9.6 ± 7.8	8.2 ± 8.0
Total	38.6 ± 16.9	32.3 ± 20.5	40.2 ± 22.5	37.8 ± 24.7
Generic HRQL (MacNew)	142 ± 23	151 ± 23[‡]	144 ± 33	142 ± 37

HRQL, health-related quality of life.
[§]Insulin sensitivity was measured using ^{13}C-glucose breath test.

[‡]$p<0.10$ versus change from baseline in the NT group

Table 7-10. Metabolic profile in IHF and NIHF patients.

	IHF	NIHF	P-value	P-value (Adjusted)[§]
Metabolic Profile	(n=19)	(n=23)		
Cholesterol ($mmol \cdot L^{-1}$)	4.12 ± 0.85[‡]	4.66 ± 1.10	.090	.464
Triglycerides ($mmol \cdot L^{-1}$)	2.19 ± 1.58	1.87 ± 0.81	.402	.331
HDL Cholesterol ($mmol \cdot L^{-1}$)	1.03 ± 0.19*	1.24 ± 0.30	.014	.081
LDL Cholesterol ($mmol \cdot L^{-1}$)	2.12 ± 0.54	2.58 ± 0.93	.080	.352
Total cholesterol/ HDL cholesterol	4.1 ± 1.1	3.9 ± 0.8	.395	.316
C-reactive protein ($mg \cdot L^{-1}$)	4.0 ± 4.3	3.2 ± 2.5	.427	.475
Fasting glucose ($mmol \cdot L^{-1}$)	5.5 ± 0.7	6.2 ± 2.3	.306	.453
Insulin sensitivity[†]	8.0 ± 2.9	10.5 ± 5.1	.102	.178

[†]Insulin sensitivity was measured using ^{13}C-glucose breath test.

*$p<0.05$ versus NIHF patients
[§]P-value adjusted for age and gender difference.

Table 7-11. Effects of exercise training vs. standard care on metabolic profile and C-reactive protein in individuals with IHF and NIHF.

	Ischemic HF				Non-Ischemic HF			
	Exercise (n=10)		Standard Care (n=4)		Exercise (n=10)		Standard Care (n=9)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Cholesterol ($mmol \cdot L^{-1}$)	3.92 ± 0.94	3.99 ± 1.00	4.81 ± 0.55	4.71 ± 0.61	4.71 ± 1.10	4.15 ± 1.01	4.57 ± 1.37	4.42 ± 1.40
Triglycerides ($mmol \cdot L^{-1}$)	1.85 ± 1.54	2.37 ± 2.91	3.06 ± 2.10	3.30 ± 2.70	1.98 ± 0.78	1.60 ± 0.49	1.86 ± 0.75	1.90 ± 1.19
HDL Cholesterol ($mmol \cdot L^{-1}$)	1.00 ± 0.15	1.06 ± 0.19	1.04 ± 0.23	1.15 ± 0.26	1.23 ± 0.31	1.33 ± 0.31	1.19 ± 0.31	1.22 ± 0.27
LDL Cholesterol ($mmol \cdot L^{-1}$)	2.09 ± 0.63	2.05 ± 0.67	2.67 ± 0.06	2.34 ± 0.27	2.58 ± 0.98	2.10 ± 0.75	2.53 ± 1.06	2.33 ± 1.07
Total cholesterol/ HDL cholesterol	3.7 ± 0.7	3.5 ± 0.8	4.8 ± 1.1	4.3 ± 1.5	3.9 ± 0.7	3.2 ± 0.6	3.9 ± 0.9	3.7 ± 1.1
C-reactive protein ($mg \cdot L^{-1}$)	3.3 ± 5.2	3.2 ± 3.0	5.4 ± 3.6	4.1 ± 2.2	3.0 ± 2.9	4.6 ± 3.6	2.9 ± 2.0	5.1 ± 6.8
Fasting glucose ($mmol \cdot L^{-1}$)	5.5 ± 0.2	5.8 ± 0.3*	6.0 ± 0.4	7.2 ± 0.2	5.4 ± 0.6	5.3 ± 0.6	6.0 ± 0.4	5.8 ± 0.6
Insulin sensitivity†	8.8 ± 3.2	8.4 ± 2.1	5.6 ± 2.4	6.2 ± 3.8	11.5 ± 6.0	9.5 ± 2.1	11.0 ± 4.1	10.8 ± 3.0

†Insulin sensitivity was measured using ^{13}C-glucose breath test.
*$p<0.05$ vs. change from baseline in the corresponding standard care group (t-test).