







# **Effects of Acute and Chronic Exercise on Forearm Blood Flow in Patients with Chronic Heart Failure**

Submitted by

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A thesis submitted for the degree

Doctor of Philosophy

Center for Rehabilitation Exercise Sport and Science

Victoria University, Melbourne, Australia

2004

FTS THESIS

616.129062 PAT

30001007974225

Patterson, Jeremy Alan

Effects of acute and chronic  
exercise on forearm blood  
flow in patients with

## Abstract

Chronic heart failure (CHF) is a life-threatening syndrome caused by inadequate cardiac function, which may lead to reduced peripheral blood flow, deconditioning and skeletal muscle atrophy. Initially, a study of the biological and technical reliability of the techniques used in the latter chapters was conducted. Reliability of these techniques has not previously been documented in a population of CHF patients. The second study is a cross-sectional study comparing forearm blood flow (FBF) in CHF patients and age-matched healthy volunteers. The third study was the primary focus of this dissertation, with the emphases on the effects of resistance exercise training on FBF in patients with CHF using a prospective randomized design. This is the largest study of its type to be published to date. Although aerobic training can improve patients' functional status, there have been no reports of improvements in skeletal muscle strength and endurance, nor a reversal of muscle wasting, after aerobic training. Resistance training has recently been proposed as a means of partially reversing the skeletal muscle problems associated with CHF, thereby improving exercise tolerance. Since peripheral blood flow has been linked to the exercise intolerance observed in this clinical population, muscle strength and endurance and  $VO_{2peak}$  were also assessed in these patients.

The first study showed that a familiarization trial for skeletal muscle strength testing is necessary in CHF patients. Familiarization is not required for assessing FBF using strain gauge venous occlusion plethysmography, nor for aerobic power. In the second study, FBF was measured in 43 CHF patients and 8 healthy age-matched volunteers at rest, during the last minute of three submaximal exercise tasks involving repeated isometric contractions of the forearm musculature, and following brief limb occlusion. FBF was reduced in CHF patients at 15%, 30%, and 45% of maximal voluntary contraction (MVC) and during peak reactive hyperemia (PRH) compared to healthy volunteers. Peak vasodilatory capacity in healthy volunteers' was significantly higher than the CHF group. There was no significant difference between the two groups for FBF at rest. The third study investigated whether resistance exercise training is effective in restoring part of the vasodilatory impairment observed in CHF (Study 2). This was the first prospective randomized study in CHF patients on the effects of a resistance exercise training program on FBF. Thirty-seven patients with CHF initially underwent familiarization and baseline testing for

muscular strength and endurance,  $VO_{2peak}$  and a single baseline measure of FBF using the same technique and protocol as Study 2. Following baseline testing, all patients were randomized to either three months of resistance training (EX) or continuance with usual care (CON), at which time they underwent endpoint testing. FBF increased at rest, and when stimulated by submaximal exercise or limb occlusion in EX, but not in CON. In addition, EX showed significant improvements in muscular strength and endurance following training. Whilst corresponding data for CON remained almost unchanged.  $VO_{2peak}$  also improved in EX, while it decreased in CON.

In summary, patients with CHF can safely and effectively undergo moderate-intensity resistance training, with the benefits of increased peripheral blood flow,  $VO_{2peak}$ , and strength and endurance outweighing the risks of such exercise training.

## **Declaration**

This dissertation summarizes original, previously unpublished work conducted in the Centre for Rehabilitation Exercise Sport and Science at Victoria University and the Department of Cardiology at the Austin and Repatriation Medical Centre. This dissertation is the result of work performed by the author. However, considerable collaboration was also involved in the study involving resistance exercise training with chronic heart failure patients. Dr. Steve Selig and Deidre Toia helped in conducting the exercise, isokinetic, and forearm blood flow testing.

Jeremy A. Patterson

## Publications

- Selig, S., Carey, M., Menzies, D., Patterson, J., Geerling, R., Williams, A., Bamroongsuk, V., Toia, D., Krum, H., and Hare, D. (2004) "Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability and forearm blood flow." J Cardiac Failure. **10** (1), 21-30.
- Williams, A., Selig, S., Hare, D., Hayes, A., Krum H., Patterson J., Geerling R., Toia D., Carey M. (2004) "Exercise Limitation in Chronic Heart Failure is not caused by reduced Skeletal Muscle Oxidative Capacity." J Cardiac Failure. **10** (2), 145-152.
- Selig, S., Carey, M., Menzies, D., Patterson, J., Geerling, R., Williams, A., Bamroongsuk, V., Toia, D., Krum, H., and Hare, D. (2002) "Reliability of isokinetic strength and aerobic power testing for patients with chronic heart failure." J Cardiopulm Rehabil. **22** (4) Jul-Aug 282-9

## Acknowledgements

A number of people have given me most valuable assistance in the construction of this dissertation. I am greatly indebted to my supervisor, Dr. Steve Selig, for his guidance and advice. Steve consistently shared his knowledge and understanding of exercise physiology. His support, timely encouragement, commitment to perfection and most importantly patience made the task at hand much easier. Steve also supervised my Masters work, where he first introduced me to the field of rehabilitation and scientific research, and has my utmost respect and deepest gratitude.

I thank the staff in Department of Cardiology at the Austin and Repatriation Medical Centre for their understanding and embracing the research. In particular, I thank Assoc. Prof. Dr. David Hare (Senior Cardiologist) whom not only provided his analytical and physiological expertise but also a sincere friendship through some complicated years of data collection. Deidre Toia continuously offered skilful and creative advice to make the testing, analysis, and exercise training sessions an absolute pleasure. But most importantly, observing her dedication to patient care was priceless and a true privilege.

To the many patients and volunteers who made this research possible, I extend my gratitude for your participation.

A special thanks to all the staff in the Department of Human Movement Recreation and Performance at Victoria University. Especially, Professor Terry Roberts, Dr. Dennis Hemphill, Assoc. Prof. Mike McKenna, and Mr. Peter Kalmund who provided support and friendship at a time in our world when living so far away from family was difficult.

To my family, thanks for your continual support and inspiration to remain focused on such a major goal. Finally, to Emily who was there to battle through every day and page, the highs and lows, to lift my confidence, keep me organized, provide creative assistance, and share in the excitement of triumphs. Thank you so much I could not have done this without you.

## **Modifications in thesis since candidature**

The initial intention for this thesis was to recruit a sub-population of chronic heart failure volunteers to undergo a vascular reactivity study in relation to resistance exercise training. This would have involved infusing vasoactive substances in to the forearm via an arterial cannula, before and after resistance exercise training. After a fruitless two years of recruiting and other methodological problems, this intended study was reluctantly abandoned.

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# Chapter 1 INTRODUCTION

## 1.1 Chronic heart failure

Chronic heart failure (CHF) refers to the syndrome where the cardiac pump function fails to deliver sufficient blood flow (cardiac output) to satisfy the metabolic requirements of the tissues. CHF is a state of demand exceeding supply; the body requires more cardiac output than the cardiac pump can deliver. CHF is a life threatening condition that increases in prevalence with aging and is associated with high mortality (50% at 5 years from diagnosis). Currently, there are estimated to be 300,000 Australians living with heart failure in a population of 19 million, leading to 40,000 hospital admissions per year. It is the most rapidly growing diagnosis in cardiovascular medicine, and because of the advanced age of the average sufferer, one of the costliest. The cardinal symptoms of CHF are dyspnea (breathlessness) and fatigue. Reduced exercise capacity combined with fatigue and breathlessness is a major cause of morbidity in CHF patients (SOLVD 1992). CHF is of great interest to medical researchers because of its implications in quality of life, morbidity, mortality and the associated costs of these, both economic and human.

## 1.2 Exercise training for patients with chronic heart failure

CHF is characterized by inadequate cardiac function, which in turn, leads to reduced cardiac output and skeletal muscle blood flow, deconditioning and skeletal muscle atrophy. These are thought to contribute to the profound exercise intolerance in CHF, more so than central mechanisms. Peripheral abnormalities that are purported to contribute to the exercise intolerance include atrophy of type I fibers, decreased mitochondrial volume density, reduced skeletal muscle strength and endurance, reduced peripheral blood flow, impaired peak vasodilatory capacity, and early onset of muscle acidosis during exercise, compared with healthy age-matched volunteers. Exercise training programs are now thought to be safe for CHF patients and may partially reverse some of these problems. There is now good evidence that many patients with stable CHF respond well to long-term programs of progressive aerobic training. CHF patients

have displayed improvements in exercise tolerance, peripheral blood flow, quality of life, reduced rate of hospitalizations, and survival with the application of aerobic exercise. However, improvements in skeletal muscle mass and strength have not been documented with aerobic conditioning. Resistance exercise training is currently a novel form of exercise training for CHF patients and offers potential improvements of muscle strength, endurance and mass, and peripheral blood flow. Together, these may promote improvements in quality of life, enable activities of daily living to be performed at lower relative intensities, promote independence, and prevent falls. In spite of widespread recommendations for resistance training in the exercise rehabilitation of CHF patients (European 1998), there are relatively few publications investigating its effects on this clinical population. The primary focus of this thesis is to examine the peripheral effects of resistance exercise training, and should contribute valuable knowledge to the field regarding the applicability of this form of exercise training in patients with CHF, which may assist in a beneficial management in CHF.

### **1.3 Purpose**

A major cause of exercise intolerance in CHF is deconditioning of ordinary muscle that can add to patients' symptoms of fatigue and breathlessness. Resistance training is a new form of exercise training in this clinical population, and may reverse some of these abnormalities. The research may yield important data on the potential benefits of resistance training on building muscle, and improving blood flow to muscle. The primary purpose of this research is to investigate the potential benefits of resistance exercise training in CHF patients on peripheral blood flow, in this case FBF. The significance of this is that if peripheral blood flow improves with this form of exercise training, which is novel in this population of patients, then this may provide an important mechanism by which their exercise tolerance and quality of life are improved. Specifically, three studies were conducted using patients with CHF only and one study used CHF patients and age-matched healthy volunteers with the following respective purposes.

Study 1 To assess the reliability of testing forearm blood flow, skeletal muscle strength and peak aerobic power in a clinical population of patients with CHF.

- Study 2 To measure forearm blood flow at rest in CHF patients, and when activated submaximally by moderate exercise and maximally in response to limb occlusion. These were then compared to age-matched healthy volunteers.
- Study 3 To investigate the potential benefits of resistance exercise training in patients with CHF. With main objectives of examining the effects of a three-month resistance exercise training program on peripheral blood flow in a clinical population of patients with CHF.

#### **1.4 Organization of the thesis**

The current chapter (Chapter One) provides the motivation for the current research and an introduction to the problem. Chapter Two provides an account of the historical and current research, and hypotheses of exercise in CHF. The literature is reviewed in three specific areas. Firstly, the syndrome of CHF is reviewed according to pathophysiological processes, epidemiology and interventions. This is followed by a discussion of peripheral abnormalities in CHF, with an emphasis on those measured in the current thesis. Third, there is an account of exercise training and its effects and possible effects in CHF. Chapter Three details the general methods used in data collection and testing procedures common to the four studies. These studies described in Chapters Four, Five, and Six comprise the result chapters of the thesis. Chapter Four examines the reliability of testing forearm blood flow (FBF), skeletal muscle strength and endurance, and peak aerobic power ( $VO_{2peak}$ ) in a clinical population of CHF. Chapter Five was designed as a cross-sectional comparative study of CHF patients and healthy age-matched volunteers with the primary measure of FBF at rest, in response to submaximal, intermittent, isometric exercise, and following the application of limb occlusion. The final study (Chapter Six) examines the effects of resistance exercise training on blood flow localized to the forearm vascular bed and any associations with exercise tolerance in CHF patients including muscular strength and  $VO_{2peak}$ . To elucidate the process of comparing the effects of a resistance exercise training program on FBF in CHF, patients were randomized to either three months of resistance exercise training or were allocated to a non-exercise control group. Chapter Seven provides a general discussion together with conclusions from the research, based on research findings from

Chapters Four to Six inclusive. Chapter Eight outlines the contributions of this research and suggestions for further research.

## Chapter 2 REVIEW OF LITERATURE

### 2.1 Overview

Chronic heart failure (CHF) is a life-threatening condition caused by inadequate cardiac function, which leads reduced skeletal muscle blood flow and deconditioning (Poole-Wilson 1992). These are thought to contribute to the exercise intolerance found in CHF (Wilson 1984). Improvements in peripheral blood flow and peak oxygen consumption have been documented using aerobic exercise (Katz 1997). However, this form of conditioning has not resulted in reversals of skeletal muscle atrophy. Thus, several researchers have proposed that resistance training should be included in the exercise rehabilitation for CHF (Hare, Ryan et al. 1999).

This review of literature focuses on physiological and pathophysiological responses to exercise in CHF, with particular emphasis on resistance exercise training. The first section (2.2) provides an overview of CHF and a context of the problem, including epidemiology, hospital admission rates, quality of life and interventions. Section 2.3 describes the physical and chemical abnormalities associated with CHF, including evidence of increased vasoconstriction due to endothelium dysfunction and that increased blood flow stimulates vasodilatation, by producing NO. Section 2.4 focuses on exercise responses in patients with CHF such as the exercise limitations, symptoms and risks of exercise in CHF. Section 2.4.2 emphasizes literature discussing exercise training describing the beneficial outcomes of the most recent research. Namely, research into the role of resistance training in improving peripheral blood flow and muscular strength, to help alleviate symptoms of CHF. Section 2.5 is a summary and conclusion of the literature.

## 2.2 Chronic Heart Failure

### 2.2.1 Introduction

Chronic heart failure is a complicated and non-specific disease. To begin to understand the condition it is important to first understand, how a normal, healthy heart works.

The average resting heart rate is about 75 beats/min. At this rate each contraction and filling of the heart takes about 0.8 seconds (Hurst 1998). The cycle begins with systole. In this phase, the ventricles begin to contract. When the pressure rises higher in the ventricles than in the atria, the mitral and tricuspid valves close, keeping the blood from flowing back into the atrial chambers. The ventricles continue to contract, and when the pressure is greater than the aorta on the left side and the pulmonary artery on the right, the aortic and pulmonary valves open and blood flows into the aorta and the pulmonary artery (Hurst 1998). Most of the blood in the ventricles will be driven out. When contraction has ended, completing the systole phase, the pressure in the ventricles begins to fall. When it is below that in the aorta and the pulmonary artery, then the aortic and pulmonary valves close so blood will not flow back into the heart and be lost to the systemic and pulmonary circulations. The pressure will continue to fall and, when it is nearly zero, the mitral and tricuspid valves will open and the ventricles will begin to fill again (Hurst 1998). At each systole, the adult ventricle ejects about two-thirds (75 ml) of the blood it contains (stroke volume) (Fox 1993). Stroke volume multiplied by heart rate will give the cardiac output, usually about five liters per minute at rest. The heart rate is controlled by the autonomic nervous system, slowed by the vagus nerve fibers, which reach cardiac muscle, and heart rate (HR) is increased by the sympathetic nerve fibers. Stroke volume depends on diastolic filling and the venous filling pressure.

Chronic heart failure (CHF) is a life-threatening disease, which can result from any heart condition that reduces the ability of the heart to pump blood. This may be due to heart disease (resulting from myocardial infarction or congenital defects) or to hypertension, which have increased the after load of the heart. Surveys from around the developed world have repeatedly shown that acute exacerbations of (congestive) heart failure is the most common cause of hospitalization in people over 65 years (Keteyian 1997). The incidence of CHF is escalating quickly, as are the associated costs, due to the ageing of the population. On both human and

economic criteria, CHF is costly due to low functional status, poor quality of life, frequent hospitalizations and poor prognosis of patients. Hypertension and coronary disease are the predominant causes for heart failure and account for more than 80% of all clinical events (Kannel 1997).

### **2.2.2 Signs and Symptoms**

The indicative signs and symptoms of heart failure include fatigue, breathlessness, bloating, abdominal pain, ankle edema, nausea and persistent coughing (Brannon 1998). The clinical causes of CHF depend on the rate the syndrome develops and whether 'sufficient time has elapsed for compensatory mechanisms to become operative and for fluid to accumulate in the interstitial space' (Braunwald 1992).

Fatigue and weakness are often accompanied by a feeling of heaviness in the limbs. These symptoms are generally related to poor perfusion of the skeletal muscles in patients with a lowered cardiac output (Poole-Wilson 1992). The factors that contribute to the symptoms of breathlessness and fatigue, that limit exercise capacity in patients with CHF, are poorly understood. Evidence has suggested that the major mechanisms are not related to central hemodynamics (Karlsdottir 2002) but rather to a reduction of skeletal muscle mass and diminished blood flow to skeletal muscle on exercise (Poole-Wilson 1992). What is known is that the pulmonary congestion that occurs in left heart failure causes the cardinal symptom of breathlessness. Exertional dyspnea occurs in healthy subjects as well as patients with chronic heart failure. In CHF patients, the degree of physical exertion needed to cause shortness of breath is reduced. Routine tasks carried out without difficulty for many years, such as climbing stairs or walking short distances now leaves them tired and breathless. As CHF progresses, patients become less and less able to cope with physical effort.

Other developing symptoms may be confusion, impairment of memory, fever, anxiety, headache, insomnia and urinary distress. Urine formation is suppressed during the day when the patient is awake, due to a redistribution of blood flow away from the kidneys during activity (Braunwald 1992); this is similar to what occurs in healthy individuals during exercise. Urine formation increases when the patient is resting in a recumbent position and the demands of oxygen are less.

The increased urine formation during rest can interrupt periods of sleep, further increasing fatigue.

### **2.2.3 Pathophysiology of Chronic Heart Failure**

Chronic Heart Failure (CHF) is a common disabling and deadly disorder, and it has recently reached epidemic proportions. It is a major and increasing cause of cardiovascular morbidity and mortality (Love, McMurray et al. 1996), namely due to the fact that its various pathophysiological mechanisms are not completely understood. Heart failure is a syndrome with many different etiologies that reflects a fundamental abnormality in the effective mechanical performance of the heart muscle. CHF occurs when, despite normal venous pressures, the heart is unable to maintain sufficient cardiac output to meet the demands of the body over a long period of time (Fox 1993). It may result either from a damaged heart muscle that is unable to pump blood, or from excessive external demands placed on an otherwise normal heart. Heart failure may occur as an acute or chronic disorder. In patients with asymptomatic heart disease, heart failure may result from an unrelated sickness or stress. If severe damage suddenly occurs to the heart (such as following a myocardial infarction) the pumping ability of the heart is permanently depressed. As a result, two essential effects occur: (a) reduced cardiac output and (b) congestion of blood in the veins, resulting in increased systemic venous pressure (Hurst 1998).

Most heart failure is due to left ventricular systolic dysfunction, characterized by a reduced left ventricular ejection fraction and a dilated left ventricle (Keteyian 1997). A healthy ventricle ejects about two-thirds of the blood that is present in the ventricle at the end of diastole. This ratio is described as the ejection fraction. In CHF, as the myocardial dysfunction progresses, the ejection fraction slowly decreases. In very severe forms of CHF, the ejection fraction may be lower than 20% (Iseri 1983).

Adaptations occur when the heart begins to fail. If the stroke volume of either ventricle is reduced by depressed contractility or excessive afterload, end-diastolic volume and pressure in that chamber may rise (increased preload). This increases end-diastolic myocardial fiber length, resulting in a greater systolic shortening. In CHF, the ventricles become dilated, which will help

to restore cardiac output temporarily, although this eventually becomes self-defeating. The constant elevation of diastolic pressure will result in cardiac remodeling leading to permanent dilation of the ventricles and reduced performance according to the Frank-Starling law (Section 2.2.3.3). In addition, increased pressures are transmitted to atria and pulmonary and systemic venous circulations. Eventually, increased capillary pressure will cause the back-up of fluid, resulting in pulmonary and/or systemic edema. Reduced cardiac output will also trigger neural and humoral systems. Activation of the sympathetic nervous system stimulates cardiac rate, contractility of the ventricles, constriction of arterioles, increased rennin secretion and a reduction in urine output (Fox 1993). Its effect on venous tone causes a rise in the central blood volume, which causes increased preload (Hurst 1998). These adaptations are designed to increase cardiac output, but the mechanisms are soon exhausted. Ultimately, chronically low cardiac output will occur, associated with elevated blood volume as well as dilation and hypertrophy of the ventricles (Fox 1993). Elevated blood volume places a work overload on the heart, and the enlarged ventricles have a higher metabolic requirement for oxygen, according to the La Place law.

### **2.2.3.1 Left heart failure**

The left side of the heart transfers blood from the pulmonary circulation (low pressure) to the arterial side of the systemic circulation (high pressure)(Porth 1986). Left heart failure leads to an accumulation of blood in the pulmonary circulation. Left ventricular failure occurs in about 75% of patients with an acute myocardial infarction (Hurst 1998). Left-sided failure can also be caused by an aneurysm of the left ventricle following myocardial infarction, or sometimes due to mitral regurgitation if the papillary muscles have been damaged by ischaemic heart disease (Braunwald 1992). Untreated high blood pressure will be tolerated by the left ventricle for many years, but eventually failure will occur, either gradually or suddenly. When the left ventricular muscle fails, it is unable to expel all the blood that it contains. Thus, the pressure at the end of diastole fails to fall to zero, and is instead raised, so the pressure needed to fill the ventricle must be increased, and the pressure in the left atrium rises. Because there are no valves between the left atrium and the pulmonary veins, the pressure in the pulmonary veins also increases. When the pressure becomes sufficiently high, fluid is forced out of the circulation into the alveoli, resulting in oedema of the lungs (Porth 1986). The excess fluid in the alveoli restricts the blood

from being properly oxygenated, which may lead to an increase in the respiratory distress. The hemoglobin leaves the pulmonary circulation without being fully oxygenated. The fluid also stiffens the lungs and increases the work of breathing.

The pulmonary circuit (the blood vessels in the lungs) usually becomes congested in heart failure, because heart disease most frequently affects the left ventricle. If heart disease impedes the ability of the left ventricle to pump blood into the systemic circulation, the left side of the heart is unable to receive the normal flow of oxygenated blood from the lungs. Consequently, back pressure develops, and blood accumulates in the blood vessels in the lungs. Congestion of the pulmonary vessels occurs and lessens the amount of space available in the lungs for air and tends to stiffen the lungs. Ultimately, pulmonary capillary pressure may reach the point at which fluid flows into the tissues outside the vessels, causing a condition called pulmonary oedema. These phenomena account for the frequency of difficulty in breathing, inability to breathe except in an upright position, attacks of respiratory distress without apparent cause during sleep at night (paroxysmal nocturnal dyspnea), and other respiratory symptoms associated with congestive heart failure.

#### **2.2.3.2 Right heart failure**

Left-sided heart failure is the term often used in reference to signs and symptoms of elevated pressure and congestion in the pulmonary veins and capillaries, whereas right-sided heart failure is a term that describes elevated pressures and congestion in the systemic veins and capillaries (Hurst 1998). The right side of the heart pumps deoxygenated blood from the systemic circulation into the pulmonary circulation (Porth 1986). The anatomical structure of the right ventricle is not as solid or durable as the left ventricle and is therefore more susceptible to failure. Right-sided failure may also be secondary to left ventricular failure. Right-sided heart failure is characterized by an accumulation or damming of blood in the systemic venous system. If the right ventricle cannot pump enough blood forward to match the venous blood flowing into it, the venous pressure in the systemic circulation rises. This leads to distension of the veins, distension of the liver, and ultimately to oedema. The oedema arises because the osmotic pressure keeping the fluid in the peripheral venous capillaries is overcome by the hydrostatic pressure within the capillaries (Braunwald 1992). The cardiac output is inadequate and the blood

supply to the organs is redistributed. The kidneys are affected, resulting in increased retention of sodium and therefore an increase in the amount of fluid in the body.

### **2.2.3.3 Frank-Starling law of the heart**

When the cardiac muscle fibers are subjected to increased amounts of stretching, they contract more strongly. Stroke volume increases by an increase in ventricular end-diastolic volume. The increased volume leads to an increased filling and stretching of the myocardial fibers during diastole and a resultant increase in the force of the next contraction (Porth 1986). The more the heart is filled during diastole, the greater the force of contraction during systole. This proportional increase is the Frank-Starling law of the heart.

The output of the right and left ventricles are controlled by the Frank-Starling law, assuring that the volume of blood flowing to both the systemic and the pulmonary circulations are equal. In CHF, an increase in ventricular end-diastolic volume results from an increase in vascular volume, leading to an increase in venous return to the heart. When the ventricle fails to eject a normal quantity of blood, the end-systolic volume increases. Patients suffering from CHF have an increase in effective blood volume (Hurst 1998) due to the kidneys retaining salt and water, leading to an increased ventricular filling volume to return toward normal stroke output (Hurst 1998). Although the stroke volume may be normalizing, an increased venous pressure in the pulmonary venous or the systemic venous systems still remains. The Frank-Starling law of the heart becomes futile when the heart is overfilled and the cardiac fibers over stretched. This occurs with increased physical activity (Porth 1986); a rise in left ventricular end-diastolic volume and pressure, with an elevation of pulmonary capillary pressure, leads to dyspnea, a primary symptom of CHF (Braunwald 1992). Eventually clinical heart failure ensues.

### **2.2.3.4 Manifestations of chronic heart failure**

Normal heart function is determined by the contractile state of the myocardium, the preload of the ventricle, the afterload applied to the ventricles, and the heart rate (Hurst 1998). If change occurs to any of these factors, heart function will become inadequate for the body's needs. In the majority of patients with heart failure, the underlying cause of their heart condition is either by loss of functional muscle through myocardial infarction (Keteyian 1997) or by processes

affecting the myocardium. Pump function may also be inadequate when the heart rate is too slow or too rapid. The diseased or failing heart cannot tolerate variations in preload, afterload, and heart rate like that of a healthy heart.

The causes of CHF can be separated into three categories: (1) Failure primarily related to work overloads or mechanical abnormalities, (2) Failure primarily related to primary myocardial abnormalities, and (3) Failure related to abnormal cardiac rhythm or conduction disturbances (Hurst 1994).

Coronary artery disease, hypertension, valvular disease and cardiomyopathies are common causes of CHF, accounting for the majority of all heart failure cases. Table 2.1 lists the primary causes of CHF. Heart failure can also arise through diastolic dysfunction of the heart. In these cases, filling of the left or right ventricle is impaired because the chamber is stiff (scarred) from excessive hypertrophy or changes in composition of the myocardium.

**Table 2.1.** Causes of CHF

<b>Impaired Cardiac Function</b>	<b>Excess Work Demands</b>
Myocardial Disease	Increased Pressure Work
Cardiomyopathies	Systemic hypertension
Myocarditis	Pulmonary hypertension
Coronary insufficiency	Coarctation of the aorta
Myocardial infarction	
Valvular Heart disease	Increased Volume Work
Stenotic Valvular disease	Arteriovenous shunt
Regurgitant valvular disease	Excessive administration of intravenous fluids
Congenital Heart Defects	Increased Perfusion Work
	Thyrotoxicosis
	Anemia
Constrictive Pericarditis	

### 2.2.3.5 Diagnosis of Heart Failure

When a patient with heart disease begins to show symptoms of fatigue, dyspnoea, or oedema, their doctors will diagnosis heart failure. In most cases, patients have a past history of heart disease or other systemic pathologies (Porth 1986), commonly myocardial infarction or some form of coronary heart disease (See Table 2.1). The clinical diagnosis can be straight forward in a patient that has all the cardinal symptoms of fluid retention, fatigue, and dyspnoea and sometimes signs such as tachycardia, a third heart sound (with or without a gallop rhythm), and cardiomegaly (Dargie 1994). The most helpful test used in diagnosis is echocardiography. This test can quickly indicate the presence of a dilated poorly contracting left ventricle and calculate left ventricular ejection fraction (Dargie 1994).

With the use of electrocardiography (ECG), a doctor can recognize whether the patient has previous myocardial infarction (Dargie 1994). It is extremely rare to find a normal ECG tracing in heart failure. Other investigative means are the valsalva maneuver (patient blows against an aneroid manometer and maintains a pressure of 40 mmHg for 30 seconds, while an arterial

pressure tracing is recording; a “square-wave” appearance to the recording indicates heart failure) (Braunwald 1992), the chest roentgenogram (shows the size and shape of the cardiac silhouette) (Braunwald 1992), and exercise testing.

### **2.2.3.6 Factors of impaired function**

Several measurable factors can show deteriorating cardiac muscle function including an enlarged heart, ECG abnormalities, a poor vital capacity, and a rapid resting heart rate (Dargie 1994). Each of these factors alone increase the risk of developing CHF. Combined, the incidence is high (Kannel and Belanger 1991). When the heart rate exceeds 85 beats per minute, the chance of CHF doubles compared to those with heart rates below this rate (Kannel and Belanger 1991).

An ECG is a simple and inexpensive test that can give vital information. Abnormalities in tracings can indicate left ventricular hypertrophy, intraventricular conduction disturbance, and nonspecific repolarization abnormalities (Kannel and Belanger 1991). It is well established that a key feature to the development of CHF is cardiac hypertrophy. Evaluation of ECG tests displaying cardiac hypertrophy (left ventricular hypertrophy – LVH) is an important consideration in devising means for prevention and effective treatment of CHF.

### **2.2.3.7 Exercise testing**

Until recently, CHF was considered an absolute contraindication to exercise testing. A number of researchers have used this approach to try to understand functional changes, to establish mechanisms, and to measure response to therapy (Franciosa, Park et al. 1981). The methods of testing patients with CHF are similar to the standard protocol used with other types of heart disease. Exercise tests done on these patients use a steady state (3min/stage) protocol, such as a modified Bruce, Naughton, or modified Naughton (Keteyian 1997). Recently more studies (Keteyian 1997; Maiorana, O'Driscoll et al. 2000; Tanabe 2000) are using a steady state cycle ergometer protocol and increasing work rates by a set amount of watts (eg. 25W) every 3 minutes or a increased work rate (eg. 10W) every minute (Hare, Ryan et al. 1999). Continuous measurement of  $\text{VO}_2$  and  $\text{VCO}_2$  allows determination of peak oxygen consumption ( $\text{VO}_{2\text{peak}}$ ) and anaerobic threshold (Braunwald 1992). This testing can be useful in determining short-term prognosis. Peak values of less than  $14 \text{ mL}^{-1} \cdot \text{kg} \cdot \text{min}^{-1}$  are associated with a 60% to 70% 1-year

survival rate (Keteyian 1997). A peak  $\text{VO}_2$  greater than  $18 \text{ mL}^{-1} \cdot \text{kg} \cdot \text{min}^{-1}$  is associated with a 94% to 100% 1-year survival rate (Keteyian 1997). If the reduction of  $\text{VO}_2$  is caused by a cardiac abnormality it can be used to classify the severity of heart failure, to follow the progress of the patient, and to assess the efficacy of treatment (Braunwald 1992).

## **2.2.4 Epidemiology of chronic heart failure**

In the past three decades there has been a major reduction in the number of deaths caused by heart disease. Despite this improvement, heart disease continues to be a leading cause of morbidity and mortality. Hypertension, coronary disease, and damage to the cardiac valves continue to result in CHF. As more and more people are prevented from having, or survive myocardial infarctions, it can be expected that the incidence of CHF will rise.

### **2.2.4.1 Incidence and prevalence**

The National Heart, Lung and Blood Institute estimates that more than 2 million Americans are afflicted with heart failure (with 500,000 new events occur yearly), requiring 900,000 hospitalizations each year (Yancy CW 1988). CHF is the most common cause of hospital admissions in people over 65 years and represents a leading cause of death and disability in the United States (Keteyian 1997). Prevalence of CHF have been estimated to increase progressively with age from about 1% prevalence in those aged 50 years, 4% at age 65, to a prevalence of about 10% in persons 75 years old (Eriksson 1995). Almost doubling with each decade within that age group. The annual incidence also increased with age, from about 0.2% in persons 45 to 54 years, to 4.0% in men 85 to 94 years, approximately doubling with each decade of age (Kannel and Belanger 1991). Approximately 50% of patients with CHF die within 2 years of diagnosis, either from the progression of heart failure or sudden death (Kumar 1994). If a patient has New York Heart Association (NYHA) Class III or IV heart failure, he or she has a 40% chance of surviving for one year (Keteyian 1997). The six year mortality rate is 82% for men and 67% for women, corresponding to a death rate fourfold to eightfold greater than that of the general population of the same age (Kannel and Belanger 1991). In an eight year survey of 7286 people aged at least 70 years at entry, 7% were hospitalized with a primary discharge diagnosis of CHF and a further 8% had secondary diagnoses (Wolinsky, Overhage et al. 1997).

The risks of hospitalization and mortality are high. The SOLVD treatment study reported that 37% of the CHF patients treated with placebo were hospitalized within one year (SOLVD 1991). Forty four percent of patients admitted for CHF were readmitted within six months (Konstam and Remme 1998). Even the SOLVD prevention study of patients with asymptomatic LV dysfunction documented high rates of hospitalization (21%) within 12 months, and of these, 22% were readmitted (SOLVD 1992). Similar high risks of admission have been reported, whilst survival at 4 years post-discharge averaged only 64% (McDermott, Feinglass et al. 1997). CHF is the most common discharge diagnosis for hospitalized Medicare patients with a half million new cases diagnosed each year in the U.S. and 120,000 cases each year in the U.K. representing 5% of all adult medical and geriatric admissions (Dargie 1994). It is estimated that the total number of heart failure patients who may be candidates for cardiac rehabilitation is 5 million (AACPR 1999).

Vasodilator drugs have clearly been shown to improve symptoms and prolong survival (Nakamura 1994), but CHF still impairs quality of life more than any other common chronic medical illness and carries a poorer prognosis than many life threatening diseases. The above mentioned survival rates are worse than for many of the common forms of cancer, emphasizing that CHF is a severe condition.

#### **2.2.4.2 Prognosis**

Survival following diagnosis of CHF is worse in men than women, but even in women, only about 20 percent survive much longer than 8 to 12 years (Kannel and Belanger 1991). The fatality rate for CHF is high, with one in five persons dying within 1 year (Kannel and Belanger 1991). Sudden death is common in these patients, occurring at a rate of 6-9 times that of the general population. Thus, CHF remains a highly lethal condition. With the use of angiotensin-converting enzyme (ACE) inhibitors as a possible exception, advances in the treatment of hypertension, myocardial ischemia, and valvular heart disease have not resulted in substantial improvements in survival once CHF ensues. Once the heart failure symptoms appear, the average patient will live 5 years and if they have NYHA class III or IV heart failure, they have a 40% chance of living 1 year (Keteyian 1997). If the heart condition cannot be repaired, such as a valvular deformity, then heart failure is often a lethal condition. In a recent study (Kannel and

Belanger 1991), it was found that within 6 years of onset, 25% of men and 13% of women experienced sudden death. This is five times the rate for the general population. To make it worse, the same study examined trends over three decades with no indication of improvement in any age group in spite of an increased antihypertensive therapy over that time period.

#### **2.2.4.3 Mortality**

The death rate for CHF increased most years between 1968 and 1993 in the U.S. These increases are in contrast to mortality declines for most cardiovascular diseases. In 1993, there were 42,000 deaths where CHF was identified as the primary cause of death and another 219,000 deaths where it was listed as a secondary cause on the death certificate (Kannel 1997).

#### **2.2.4.4 Associated costs**

Heart failure is a serious public health problem. Incidences of CHF are estimated at 10 per 1000 over 65 years of age (Kumar 1994) and escalating quickly, leading to a great expense. There has been a rise in associated costs, due to the aging of the population. CHF not surprisingly represents a major economic problem, with recent analyses indicating that it accounts for 1 to 2% of total health care expenditure in Europe and the U.S. (Love, McMurray et al. 1996). In 1990, the United States reported 770,000 hospital separations due to CHF, resulting in five million hospital days and expending a minimum of US\$8 billion in direct costs. Management of CHF in most Western countries was estimated at 1.5% of the total health budget (Sharpe 1998). CHF is costing England's health care management (NHS) £360 million per year in diagnosis and management, 60% of which is spent on hospital treatment (Dargie 1994).

#### **2.2.5 Quality of life**

Symptoms of heart failure and consequences from treatment can have a great impact on the lives of patients with heart failure, and therefore improving quality of life is generally recognized as one of the major goals of treatment (Cohn 1997). Patients with CHF experience dramatic changes in their health status and other aspects of their lives. How they view these changes can determine their quality of life. Functional capabilities, symptoms, and psychosocial perceptions are aspects of quality of life CHF patients consider most important (Jaarsma 2000).

Vasodilator drugs have clearly been shown to improve symptoms and prolong survival, but established CHF still impairs quality of life more than any other common chronic medical illness, carrying a poorer prognosis than many serious conditions (Love, McMurray et al. 1996), including arthritis or chronic, obstructive airways disease (Cleland 1998). Patients with severe limitation are often more concerned with symptomatic relief, even if it means that their lifespan is shortened. Asymptomatic patients are typically more concerned with improving their long-term survival prospects (Cleland 1998).

Depression is a predictor of mortality after myocardial infarction (Frasure-Smith, Lesperance et al. 1995) and anxiety may predict impending hospital admissions in CHF patients (Bennett, Pressler et al. 1997). Using the Cardiac Depression Scale (CDS), a sensitive measure of depressed mood in cardiac patients (Hare and Davis 1996), it has been shown that CHF patients have higher levels of depressed mood than has been seen in patients after acute myocardial infarction or coronary artery surgery. This depressed mood is related to both the levels of symptoms and functional capacity, even though these two factors are unrelated (Hare, Phillips et al. 1997).

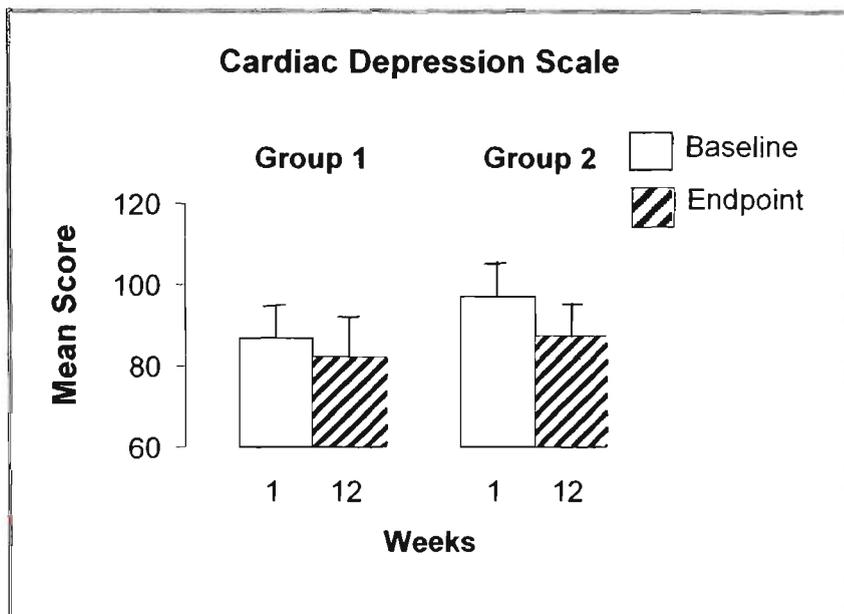
#### **2.2.5.1 Quality of life and exercise**

Research has also shown that exercise can produce significant and lasting changes in heart failure patients' quality of life (Squires 1987; Sullivan 1996). Squires and coworkers (1987) found that 50% of patients returned to work after exercise training. Three years after the study, 92% were still physically active, 31% were asymptomatic during activity, and 46% reported minimal impairment in daily life.

Worcester (1993) found, in a study of three months of exercise training, that intensive aerobic training did not produce any additional benefit over a program of lower intensity exercise on quality of life parameters such as anxiety, depression and occupational adjustment (Worcester 1993). Data for the CDS (Figure 2.1) indicates an improving trend in both exercising groups. However a limitation of all the investigated exercise training interventions was that they were supervised, group programs. The effects of additional social contact and reassurance may have

contributed to these improvements and according to (Willenheimer, Erhardt et al. 1998), such supervised exercise training can improve quality of life in CHF patients.

**Figure 2.1** Cardiac Depression Scale before and after three months of resistance exercise training in CHF patients. **Group 1** performed high intensity aerobic exercise training. **Group 2** performed low intensity intensity aerobic exercise



### 2.2.6 Interventions for Managing CHF

It is in the interests of patients and the community as a whole that medical programs are designed and validated toward the management of CHF. These systems should aim to relieve symptoms, optimize cardiac function, increase functional capacity, and improve quality of life while in turn reducing morbidity, mortality and costs. Recently, various models have been proposed for the management of CHF. These include models adapted from generic models of chronic disease management as well as models designed specifically for the management of CHF, based on consensus guidelines emanating from the body of basic clinical research and empirical evidence. For example, early intervention with angiotensin converting-enzyme (ACE) inhibitors can retard cardiac remodeling following acute myocardial infarction (Cohn 1998). ACE inhibitor interventions reduce morbidity and mortality, in both symptomatic and asymptomatic patients with left ventricular dysfunction (SOLVD 1991; SOLVD 1992). Beta blockers also reduce morbidity and mortality in patients with CHF (Krum 1997). Nevertheless, morbidity and mortality remain high. Several non-pharmacological interventions have yielded encouraging

improvements in rates of hospitalization, morbidity and mortality in high-risk patients (Stewart, Pearson et al. 1998;(Rich, Beckham et al. 1995; Fonarow, Stevenson et al. 1997). A recent study of patients with higher functional status and lower risk than examined in other studies reported a fall in medical consultations and emergency room attendances (West, Miller et al. 1997); both of these are surrogates for morbidity and mortality. The cost savings estimated for these interventions ranged from A\$460 per patient for a three month intervention, after accounting for the cost of the intervention (Rich, Beckham et al. 1995), to as high as US\$9,800 per patient for six months for a cohort awaiting cardiac transplant (Fonarow, Stevenson et al. 1997).

Most of the non-pharmacological intervention studies to date have had two major limitations. First, due to the multi-disciplinary nature of the studies, usually including ongoing nurse counseling to patients to monitor symptoms, sodium and fluid balance and medication compliance, it was impossible to identify which individual components of the interventions were beneficial, neutral, or perhaps even harmful. Although several of these models permitted, encouraged, or even prescribed exercise as part of the overall management plan, it was not possible to evaluate exercise training as an independent intervention. Exercise of up to 200 min/week was prescribed as part of a multi-disciplinary intervention for high risk patients (New York Heart Association (NYHA) class III or IV)(Fonarow, Stevenson et al. 1997), but specific details of the exercise program were somewhat vague. Second, it was difficult to assess whether the intervention was optimal in terms of cost-effectiveness, because the nature of a multi-disciplinary intervention uses more than a minimalist approach. Another problem with some interventions was the lack of randomization in the study designs. Some derived their cohorts from the retrospective review of patients' medical records or hospital databases. They then prospectively intervened with a management program and compared their intervention data with that of the previous period, typically six months prior to the intervention (Fonarow, Stevenson et al. 1997; West, Miller et al. 1997). Any effects that were purportedly due to an intervention using this design could have been contaminated seriously by an order effect, a Hawthorne effect, or both.

### **2.2.6.1 Treatment**

Treatment of CHF should focus on three aims. First, to prevent any further progression of the heart condition, it is necessary to reduce the work of the heart. The second aim is to maintain or improve the patient's quality of life, relieve symptoms. Thirdly, treatment should aim to improve mortality and morbidity.

#### **2.2.6.1.1 Correction of reversible causes**

The most desirable approach for the treatment of CHF is to physically correct the dysfunctional component of the heart with surgery. Congenital malformations, acquired valvular lesions, or left ventricular aneurysm can be corrected this way. The major causes of CHF that can surgically repaired, include ischemic left ventricular dysfunction, thyrotoxicosis, myxedema, valvular lesions, intracardiac shunts, high-output states, arrhythmias, and alcohol- or drug-induced myocardial depression (Hurst 1998). Reversible causes of diastolic dysfunction include pericardial disease and left ventricular hypertrophy due to hypertension.

#### **2.2.6.1.2 Diet**

The average daily sodium intake of the unrestricted American diet is between 3.0 to 6.0 gm. This should be reduced for those with CHF to 1.2 to 1.5gm/day (Braunwald 1992) or no more than 3 gm/day (Hurst 1998). Eating too much sodium may cause patients to drink more and to retain fluids, causing the heart to work harder to pump the added fluid. It is important that patients with CHF control their weight and cholesterol levels, therefore, dietary fat intake should also be monitored. Due to the damaging affects that alcohol contributes to heart muscle, most patients are advised to abstain from it completely.

#### **2.2.6.1.3 Physical activity (Exercise)**

CHF patients were traditionally prescribed to rest and withdraw from activity in order to delay disease progression and to promote diuresis induced by bed rest (Sullivan 1996). However, understanding of the CHF syndrome and clinical practice have improved dramatically, especially in the last decade, as research has demonstrated that exercise offers much gain at little risk. CHF patients entering an exercise training program appear to markedly improve their functional status and quality of life (Squires 1987). The main challenge for most patients is to find exercise programs that they enjoy and can maintain on a long-term basis. Apart from quality of life,

exercise training may reduce the risk of death for CHF patients, just as it does for patients living with coronary artery disease (McKelvie 1995).

Exercise training programs in patients with CHF have been shown to significantly enhance exercise capacity, reduce lactate production, improve use of ventilatory reserve, increase skeletal muscle blood flow, endothelial function, skeletal muscle biochemical and histological characteristics, and are associated with an improved quality of life with less symptoms (Coats 1999). This topic will be addressed in full in Section 2.4.

#### 2.2.6.1.4 Medication

**Table 2.2** Categories of medications commonly prescribed to patients with CHF.

Medication class	Action(s)
ACE inhibitors & Angiotensin II Receptor Blockers	ACE inhibitors cause vasodilation and inhibition of increased neurohormonal activity, lowering BP and reducing the work load of the heart and increasing the blood flow to the kidneys, making them the standard therapy for CHF (Bergin and Holst 2000). These agents block the rennin-angiotensin-aldosterone system, producing vasodilation by blocking angiotensin II-induced vasoconstriction and decreasing sodium retention (Braunwald 1992). They also inhibit the degradation of bradykinin and increase the production of vasodilating prostaglandins. ACE inhibitors have been proven to prolong survival and alleviate symptoms.
Diuretics	Diuretics are among the most commonly prescribed pharmaceutical intervention for CHF (Braunwald 1992). Diuretics remove extra fluid from the body; decreasing oedema and breathlessness.
Beta-Blockers	Block the over stimulation of the heart by adrenaline and allows the heart to work more efficiently (Bergin and Holst 2000). A number of trials have suggested that beta-blockers are capable of decreasing morbidity and mortality in patients with CHF, whilst improving left-ventricular ejection fraction and exercise tolerance.
Potassium or magnesium	Replace potassium or magnesium, which can be lost with increased urination when taking certain diuretics (Bergin and Holst 2000).
Vasodilators	Similar to ACE inhibitors; lower BP by inducing relaxation of arterial and venous vascular smooth muscle (Bergin and Holst 2000). When arterial smooth tone is reduced, left-ventricular afterload is decreased and cardiac output increases. Some vasodilators ( <i>eg</i> , nitroprusside) have a balanced action on venous and arterial smooth muscle, but other agents ( <i>eg</i> , nitrates) act predominantly on venous smooth muscle
Inotropic agents	Improve the heart's pumping ability and regulate the heart's rate and rhythm (Bergin and Holst 2000).
Antiarrhythmics	Control abnormal heart rhythm.

Vasodilators, such as ACE inhibitors and hydralazine, and digoxin have been shown to improve exercise capacity, but to a lesser extent than exercise training. The combination of these medications and exercise appears to be more effective than either medication alone in this regard (Coats 1993).

## **2.3 Peripheral Blood Flow**

### **2.3.1 Introduction**

The blood vessels are a semi-closed system of conduits transporting blood from the heart through the body circulation and back to the heart. The function of circulation is to service the needs of the tissues transport nutrients, electrolytes, gases, metabolites and hormones to maintain homeostasis (Hurst 1998). The pumping action of the heart is the primary cause of forward blood flow, but systemically diastolic recoil of the walls of the arteries, compression of the veins by skeletal muscles during exercise, and the negative pressure in the thorax during inspiration also move the blood forward. The flow of the blood is controlled by local chemical and general neural and humoral mechanisms that dilate or constrict the vessels of the tissue. Viscosity of the blood and the diameter and length of the vessels are the determinants of resistance to flow.

#### **2.3.1.1 Anatomy**

Conduit or elastic arteries are large vessels, with muscular and relatively elastic walls, whose function is to "conduct" the bulk of the blood to regions of the body where it is to be distributed. Examples include the aorta, subclavian, and pulmonary arteries. The walls of arteries are made up of an outer layer of connective tissue (the adventitia); a middle layer of smooth muscle (the media); and an inner layer (the intima), made up of the endothelium and underlying connective tissue (Braunwald 1992). The aorta and other large arteries have elastic tissue which allows them to stretch during systole and recoil during diastole. The latter serves to assist forward flow during diastole. As arteries become smaller towards the periphery, their tunica media contains more smooth muscle and less elastic fibers, allowing greater vasoconstriction and vasodilation to adjust the rate of blood flow (Hurst 1994). Resistance vessels such as the arterioles have less elastic tissue but contain a higher amount of smooth muscle. This muscle is innervated by noradrenergic nerve fibers that constrict and cholinergic fibers that dilate. The arterioles are the

major source of changes to the resistance to the flow of blood, and small changes in their caliber cause large changes in the total peripheral resistance.

### 2.3.1.2 Methods of measuring blood flow

The volume of blood that flows through any tissue in a given period of time is the blood flow. For a given rate of blood flow, the velocity of blood flow is inversely related to the cross-sectional area of the blood vessels. As a result the flow of blood is at its slowest where the cross-sectional area is at its largest (eg the great veins). In addition to the caliber of vessels, the friction between blood and the walls of blood vessels contributes to resistance. The overall resistance is therefore dependent upon three factors:

- 1) *Blood viscosity*: The “thickness” of blood depends largely, but not solely, on the ratio of red blood cells to plasma volume.
- 2) *Total blood vessel length*: The longer a blood vessel, the greater the resistance as blood flows through it.
- 3) *Blood vessel radius*: The smaller the radius of the blood vessel, the greater the resistance it offers to blood flow; arterioles need to vasodilate or vasoconstrict only slightly to have a large effect on peripheral resistance.

#### 2.3.1.2.1 Venous occlusion plethysmography

The noninvasive technique of venous occlusion plethysmography (VOP) has been established for nearly a century and the method of strain gauge VOP has been used for more than 50 years (Whitney 1953). The principle of measurement is to determine the rate of increase in limb volume during brief cessation of venous return while arterial inflow is unimpeded (Benjamin 1995). This is achieved by inflating a cuff device to a pressure between venous and diastolic pressures. The forearm engorges at a rate proportional to the rate of arterial inflow (Benjamin 1995). Changes in volume are usually determined by calculating the changes in limb circumference and applying an algorithm to convert to volume (Wilkinson 2001).

#### 2.3.1.2.2 Doppler Ultrasound

A Doppler probe is placed over an artery and estimates blood flow *velocity*. To deduce values for blood flow *rate*, the vessel diameter is measured simultaneously. This technique allows the study

of large conduit vessels (arterial function) by measurement of artery diameter. The measurement of the vessel cross sectional area is determined by imaging the anterior and posterior vessel walls (Wilkinson 2001). Area is calculated by squaring the diameter (Wilkinson 2001). Thus, any error in diameter results in doubling of the error for area and therefore flow.

#### **2.3.1.2.3 Thermodilution**

The thermodilution technique requires catheterization of the femoral vein or artery and is advanced until the tip is just below the inferior vena cava (Barlow 1998). For periodic determination of flow rates, the thermodilution method uses a small temperature probe to monitor the temperature drop when a bolus (a known volume of known temperature) of cool fluid is injected into the circulation just upstream from the thermistor. The area under the curve formed, as the temperature is plotted versus time, can be used to calculate the blood flow and is particularly useful for cardiac output measurements. Positioning of the temperature probe is crucial for reproducible results.

#### **2.3.2 Peripheral blood flow in chronic heart failure**

Chronic heart failure patients have an increase in peripheral vascular resistance due to several factors, including increased sympathetic adrenergic vasoconstrictor activity and increased plasma concentrations of NE, angiotensin II, endothelin-1, and AVP (Love, McMurray et al. 1996). Severity of CHF can depend upon the degree of circulatory inadequacy (Leithe 1984; Ganong 1999).

In patients with CHF, exercise tolerance is usually limited by symptoms of dyspnea or fatigue. The causes of fatigue are not fully understood, but decreases in peripheral blood flow have been implicated (Wilson 1984). During exercise, patients with CHF have an impaired arterial vascular dilatation (Maiorana, O'Driscoll et al. 2000). Blood flow to exercising muscle increases in CHF patients as the intensity of exercise rises, however, the rate of increase is blunted compared to healthy volunteers (Zelis 1974; Mancini 1987; Sullivan 1989). Vascular resistance has been suggested to be five times greater in CHF patients compared to healthy volunteers (Mancini 1987). In contrast, other researchers have reported no significant differences between CHF patients and healthy volunteers with respect to the rates of increases of peripheral blood flow

during exercise (Arnold 1990; Bank 1998). Cardiac output is reduced in CHF patients at rest and during submaximal and maximal exercise compared to healthy volunteers (Sullivan 1989) and this has been linked to the impaired aerobic power in this disorder (Wilson 1984). As a result of impaired cardiac output, exercise performance becomes limited due to impaired skeletal muscle perfusion. However, there is some indirect evidence that impaired peripheral blood flow at rest is not directly related to reduced cardiac output or other central hemodynamic factors: forearm resistance is increased following cardiac transplantation and does not return to levels of health age-matched volunteers for four weeks (Sinoway 1988), even though cardiac output is restored by the surgery. There is other evidence that exercise intolerance is not directly related to reduced cardiac output or other central hemodynamic factors: ACE inhibitors cause rapid improvements in central hemodynamics (Enseleit F 2001), but improvements in exercise tolerance are delayed (Wilson 1984; ACC 1999), sometimes for months. In a trial on ACE inhibitors an increase in lower limb blood flow was observed with a delayed increase in exercise capacity (Drexler 1989).

CHF causes a significant redistribution of cardiac output at rest. This redistribution is qualitatively similar to that occurring in healthy volunteers during exercise. In CHF patients at rest, blood is shunted away from the kidneys and skin, whereas this only occurs in healthy volunteers during exercise (Hurst 1998). Blood flow to the splanchnic circulation is reduced in proportion to the impairment of cardiac output (Bartorelli 1970). These compensations enable blood flow to be relatively preserved to heart and skeletal muscle, which have high metabolic demands relative to blood flow.

Basal blood flow to vascular beds comprising mainly skeletal muscle (eg the forearm) is similar in healthy volunteers and CHF patients (Hayoz 1993; Welsch 2002). However in earlier studies that were conducted prior to the widespread prescription of vasodilators (such as ACE inhibitors, angiotensin receptor-blockers, and beta-blockers) in CHF patients, resting peripheral blood flow was reported to be abnormally low in CHF patients compared to healthy volunteers (Zelis 1968; Zelis 1974; Leithe 1984). These differences may be explained by improved medical management since these studies and/or selection of lower risk patients in the more recent studies. In addition limb blood flow is reduced in CHF during exercise compared to healthy volunteers (Zelis 1974; Longhurst 1976; Wilson 1984) and is associated with decreased exercise tolerance (Wilson 1984;

Sullivan, Higginbotham et al. 1988), but a cause and effect relationship has not been established. The more severe the degree of CHF, the more severe is the exercise intolerance, associated with a greater impairment of blood flow (Wilson 1984). Low exercise capacity has been independently correlated with morbidity and mortality in CHF patients (Bittner, Weiner et al. 1993), and this limitation is linked to the impairment of peripheral blood flow (Wilson 1984).

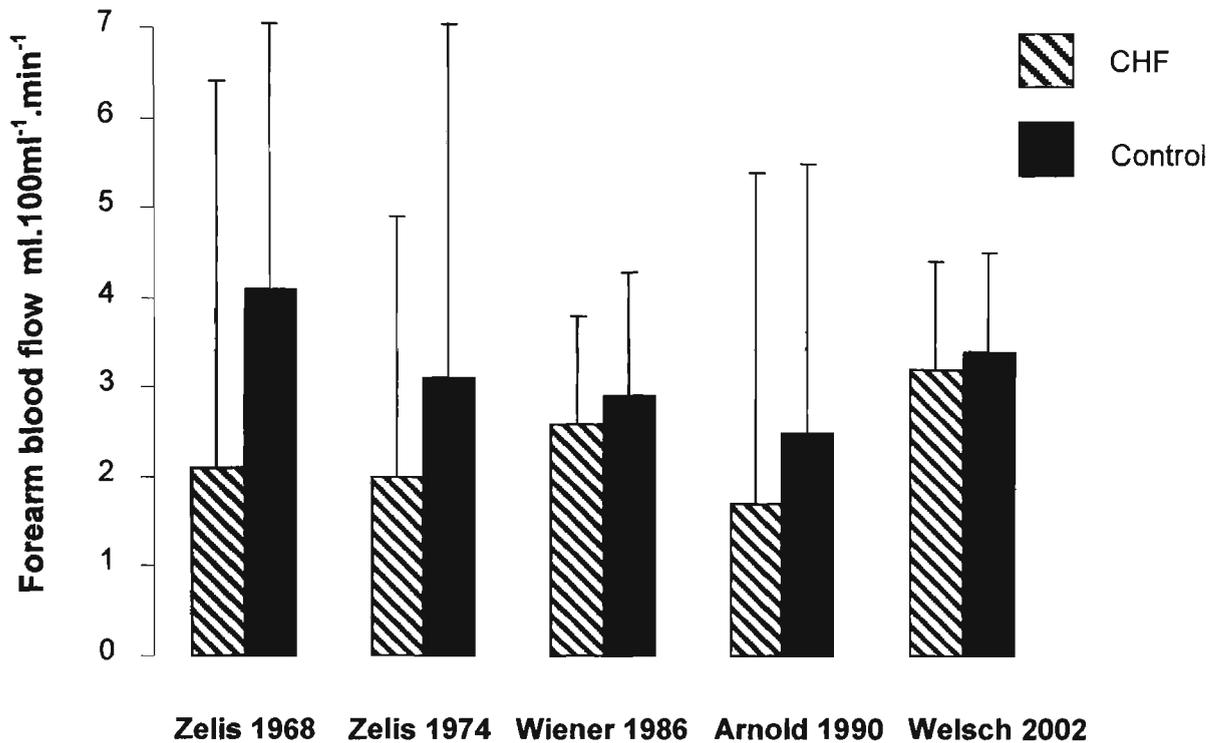
There are only six previous cross-sectional studies that have compared the function of forearm resistance vessels in CHF patients with healthy age-matched volunteers (Table 2.3) (Zelis 1968; Zelis 1974; Leithe 1984; Arnold 1990; Hayoz 1993; Welsch 2002). Studies in which the patient groups were observed to have a reduced  $FBF_{rest}$  compared to healthy age-matched volunteers were not taking ACE inhibitors (Zelis 1968; Zelis 1974; Leithe 1984; Arnold 1990). Recently two studies showed no significant difference in resting FBF ( $FBF_{rest}$ ) between CHF patients and healthy volunteers (Hayoz 1993; Welsch 2002). One other study found no significant difference in  $FBF_{rest}$  between CHF patients and healthy volunteers (Wiener DH 1986). Interestingly, they included CHF patients receiving vasodilator medication, however measurements were recorded in an upright position (Wiener DH 1986). Welsch et al. (2002) and Hayoz et al. (1993) used a patient populations that were receiving ACE inhibitors (60% and 100%, respectively). In a much earlier study, Leithe and colleagues (1984) who examined FBF in three groups of CHF patients that were classified as NYHA class II, III, or IV and reported that blood flow became attenuated as the severity of CHF progressed (Leithe 1984). Leithe et al. (1984) used CHF patients that were studied before the widespread prescription of ACE inhibitors. These findings on  $FBF_{rest}$  can also be seen in resting leg blood flow ( $LBF_{rest}$ ). Sullivan et al. (1989) studied 30 CHF patients which were not receiving ACE inhibitors and found  $LBF_{rest}$  was significantly reduced in CHF patients compared with healthy volunteers (Sullivan 1989). More recently, Barlow et al. (1998) and Piepoli et al. (1996), using mostly patients on ACE inhibitors (83% and 90% respectively), showed no difference in  $LBF_{rest}$  between patients with CHF and healthy volunteers (Piepoli 1996; Barlow 1998).

**Table 2.3** FBF data from previous cross-sectional studies comparing CHF patients (upper panel) to healthy volunteers (lower panel) in the same investigations.

Author	Journal	NYHA	FBF rest	15% MVC	30% MVC	45% MVC	PRH
<b>Chronic Heart Failure Patients</b>							
Welsh et al. 2002	JCR	I & III, not II	3.2 ± 1.2				14.8 ± 6.31
Hayoz et al. 1993	Circulation	III	31.3 ± 8.4*				121.7 ± 24.4*
Arnold et al. 1990	Circulation	III & IV	1.7 ± 3.7	5.04 ± 4.2	7.64 ± 4.6	12.56 ± 4.8	
Wiener et al. 1986	Circulation	II & III	2.6 ± 1.2				
Leithe et al. 1984	Circulation	II, III, & IV	4.5 ± 1.7				
Zelis et al. 1974	Circulation	III & IV	2.0 ± 2.9	4.0 ± 3.3	5.5 ± 3.3	6.6 ± 5.7	
Zelis et al. 1968	J Clin Inv	III & IV	2.1 ± 4.3				20 ± 6.1
<b>Healthy Volunteers</b>							
Welsh et al. 2002		age-matched	3.4 ± 1.1				22.2 ± 6.30
Hayoz et al. 1993		age-matched	37.2 ± 9.8*				164.4 ± 24.5*
Arnold et al. 1990		age-matched	2.5 ± 3.0	7.25 ± 3.7	9.2 ± 3.9	14.62 ± 4.4	
Wiener et al. 1986		age-matched	2.9 ± 1.4				
Leithe et al. 1984		age-matched	8.2 ± 3.1				
Zelis et al. 1974		young adults	3.1 ± 4.9	7.1 ± 5.4	11.1 ± 5.9	20.3 ± 6.6	
Zelis et al. 1968		young adults	4.1 ± 4.2				45.7 ± 5.7

JCR: Journal of Cardiopulmonary Rehabilitation, J Clin Inv: Journal of Clinical Investigation, Units measured as mL/100mL tissue/min; except \* mL/min. Values are means ± SD

**Figure 2.2** Forearm blood flow at REST: CHF patients compared to healthy volunteers (Control), historical data.



Reactive hyperemic blood flow has been shown to be lower in patients with CHF compared with healthy volunteers (Zelis 1968; Hayoz 1993). Several previous studies which included  $FBF_{rest}$ , during exercise, and/or following brief limb occlusion measured blood flow in the leg (Sullivan 1989; Reading 1993; Hambrecht 1997; Barlow 1998; Dziekan 1998; Taylor 1999). Reactive hyperemic blood flow to the legs has been shown to be reduced in CHF patients by up to 25% to 50% compared to healthy volunteers (Zelis 1968; Arnold 1990; Reading 1993). It has been suggested that the reduced blood flow shown in this patient population affect large muscle mass, as opposed to small muscle mass such as the forearm (Squires 1998). The results from Welsh et al. suggest that the impaired vasodilatory capacity observed in the leg is also found in the smaller muscle mass of the forearm.

During upright exercise, blood flow to an exercising limb remains reduced, but this can be attributed to either a reduction in cardiac output and arterial pressure or increased vascular tone (Arnold 1990). Body posture has been shown to have a direct influence on peripheral blood flow. In an upright position FBF is reduced in healthy volunteers but not in CHF patients (Goldsmith

1983). Although it is not fully understood it has been suggested that the differences may be associated with abnormalities in reflex control of the circulation in CHF patients (Goldsmith 1983). Thus any difference between the two groups in supine would be reduced in the upright position. Also during exercise it has been found that blood pressure is slightly reduced compared with normal subjects (Poole-Wilson 1992). In CHF, neuroendocrine changes occur in an attempt to maintain central arterial pressure by increasing total peripheral resistance and hence reducing limb blood flow (Maguire 1998).

A reduced  $VO_{2peak}$  in the CHF patients compared to healthy volunteers has been well documented and it has been suggested that this may attribute to the explanation of the reduced FBF during exercise and following limb occlusion compared to healthy volunteers (Wilson 1984). Lactate concentration during exercise in CHF patients is increased compared to healthy volunteers (Wilson 1984). The increased lactate production to exercising muscle may be attributed to a reduction of blood flow (Bylund-Fellenius 1981). Wilson et al. (1984) studied aerobic capacity, cardiac output, femoral blood flow, and leg metabolism in 23 CHF patients with a range of severity's and 23 healthy volunteers (Wilson 1984). Their results suggest that the exercise intolerance observed with CHF is directly linked to reduced peripheral blood flow and primary cause of fatigue.

### **2.3.3 Endothelial function and dysfunction in CHF**

#### **2.3.3.1 Normal endothelial function**

In recent years, the importance of endothelial cell function on the control of circulation has been recognized (Drexler 1997). The role of the endothelium in maintaining a healthy vasculature has also been increasingly recognized, particularly with respect to endothelial release of nitric oxide (NO) and its mediated functions (Katz 2002). The endothelium is a key factor in the coagulation regulation, lipid transport, immunological reactivity and vascular tone (Haynes and Webb 1998). Endothelial cells produce substances that play an important role in the normal regulation of peripheral vasomotor tone to assist in vasorelaxation and vasoconstriction. The vascular endothelium is a simple squamous membrane, a single cellular layer that lines all blood vessels and plays a very active role in interactions between the circulating blood and vascular smooth muscle. The cells are arranged with the direction of blood flow, parallel to the main axis of the

vessel (Vanhoutte 1996). The endothelium has three functions: as a metabolically active, endocrine organ tissue; as an anticoagulant, antithrombotic surface; and as a barrier to indiscriminant passage of blood constituents into the arterial wall (Hurst 1998). It is now known that this interface between blood and the vessel wall helps to actively regulate blood flow and fluidity by releasing a number of important regulatory factors (Charo 1998), including vasodilators such as NO, prostacyclin, and endothelial-derived hyperpolarizing factor (EDHF), and the vasoconstrictor endothelin.

#### **2.3.3.1.1 Nitric oxide (EDRF)**

Furchgott and Zawadzki (Furchgott and Vanhoutte 1989), first described the effect of endothelial derived relaxing factor (EDRF), when they discovered that an intact endothelial layer was necessary for acetylcholine (ACh)-induced vasodilation. The study used isolated strips of rabbit aorta that were first precontracted with norepinephrine (NE) then introduced to increasing doses of ACh. Strips that had the presence of endothelium produced dose-dependent relaxation, while those without induced only constriction by ACh. Therefore, it was suggested that ACh has two opposite and opposing actions; direct constriction of vascular smooth muscle and an indirect vasodilator action that is mediated by endothelium (Furchgott and Vanhoutte 1989; Braunwald 1992). The study also showed that endothelium dependent dilatation was initiated by a humoral substance (EDRF) and was separate from prostacyclin. EDRF, Furchgott and Zawadzki concluded, was the mode of action of a variety of vasodilators including adenosine diphosphate, adenosine triphosphate, histamine, bradykinin, substance P, thrombin, and calcitonin gene-related peptide.

Many different stimuli act on the endothelial cells to produce NO. NO is synthesized in endothelial cells from the amino acid L-arginine through the action of endothelial nitric oxide synthase (eNOS) (Charo 1998). Three isoforms of NOS have been identified: NOS 1, found in the nervous system; NOS 2, found in macrophages and other immune cells; and NOS 3, found in endothelial cells (Gross 1995). NOS 1 and 3 are activated by agents that increase intracellular calcium concentration, which include ACh and bradykinin. The NOS in immune cells is not induced by calcium but is activated by cytokines. The NO that is formed in the endothelium diffuses, easily crosses the smooth muscle cell membrane and binds to the heme part of the

soluble guanylate cyclase, to produce cyclic guanosine monophosphate (cGMP). This in turn causes the relaxation of vascular smooth muscle (Gross 1995) by decreasing the amount of intracellular calcium (Hurst 1998). A rise in the concentration of calcium in the cytoplasm of endothelial cells triggers the release of NO. The calcium ionophores create channels in the endothelial membrane where the extracellular calcium can enter and stimulate the release of NO (Umans and Levi 1995). The vascular relaxation that occurs is caused by its interaction with the heme group of soluble guanylate cyclase leading to stimulation of this enzyme and to an increased formation of (cGMP) in vascular smooth muscle cells (Dusting 1995).

In addition to regulating blood flow to skeletal and cardiac muscle at rest and during exercise, NO also possesses a number of antiatherogenic properties, including inhibition of platelet and monocyte adhesion to the endothelium of vessel walls and inhibition of cellular transmigration, vascular smooth muscle production, and LDL oxidation (Moncada 1991). Endothelial NO-dilator function is abnormal in subjects with atherosclerosis (Drexler, 1999), NIDDM (Desouza 2002), hyperchoesterolaemia (Shimokawa 1988; Cooper 2002) and CHF (Drexler, Hayoz et al. 1992).

#### **2.3.3.1.2 Endothelin**

The characteristic vasoconstriction of CHF may be secondary to enhanced synthesis or activity of some endogenous contracting factor (Love, McMurray et al. 1996). Endothelin is a peptide hormone with very strong and uniquely sustained vasoconstrictor properties, which are synthesized by the endothelium and has been implicated in the pathophysiological vasoconstriction of CHF (Love, McMurray et al. 1996).

Endothelial cells produce endothelin-1, the strongest vasoconstrictor agent in the vasculature (Haynes and Webb 1998). This potent vasoconstrictor substance influences homeostasis of salt and water and stimulates the rennin-angiotensin-aldosterone and sympathetic nervous systems (Haynes and Webb 1998). Endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin-3 (ET-3) are the members of a family of three similar 21-amino-acid polypeptides.

Endothelin acts on an endothelin receptor that stimulates calcium entry through channels, triggering the formation of substances which increase calcium in vascular smooth muscle (Hurst

1998). The result is a powerful vasoconstriction. The release of endothelin can be caused by a number of substances, including vasopressor hormones, such as angiotensin II, epinephrine, and arginine vasopressin; coagulation products, such as thrombin; cytokines, such as interleukin 1; oxygen free radicals; and substances derived from aggregating platelets, such as transforming growth factor  $\beta$  (Haynes and Webb 1998)

Plasma levels of ET-1 are markedly increased in patients with CHF in comparison to healthy volunteers (Stewart, Cernacek et al. 1992; Haynes and Webb 1998). Studies have found that endothelin concentrations are increased by up to three fold (Love, McMurray et al. 1996) and appear to be a sensitive prognostic indicator in this condition (Tsutamoto 1988). It should also be noted that plasma levels of endothelin-1 are highest in the CHF patients with the greatest severity of the syndrome and levels correlate with the New York Heart Association clinical classifications (Love, McMurray et al. 1996). The exercise intolerance experienced by CHF patients may be caused by increased concentrations of ET-1 by impairing peripheral vasodilation in response to exercise. It has been shown that a significant inverse relationship between levels of plasma ET-1 during maximal exercise and  $VO_{2peak}$  achieved by patients with CHF (Krum, Goldsmith et al. 1995). Similar findings have been observed (Love, McMurray et al. 1996), giving further evidence that ET-1 plays a key role in the impairment of skeletal muscle perfusion and resultant exercise intolerance. Thus, impaired endothelial function in CHF leads to decreased vasodilatation of the vasculature in exercising skeletal muscles and to decreased capacity for exercise (Hornig 1996; Love, McMurray et al. 1996; Katz 1997). The same deadaptation occurs with inactivity of muscle and is restored over time with muscle use (exercise) (Hurst 1998).

### **2.3.3.2 Endothelial dysfunction in CHF**

The impaired vasodilatory responses to exercise in CHF have been linked to several factors such as, sodium and water retention in the blood vessel wall, neurohormonal activation, and intrinsic abnormalities of vascular smooth muscle structure and function (Zelis 1982). In addition, endothelial dysfunction appears to contribute to the impaired peripheral vasodilatory capacity in CHF patients (Katz 2002). Endothelial dysfunction is characterized by reduced release of the endothelium-derived relaxing factor nitric oxide and increased release of endothelium-derived constricting factors including ET-1, prostaglandins, and superoxide anion (Katz 2002). NO is

released continuously from the endothelium, and this provides a constant counteracting force to vasoconstrictor substances such as noradrenaline or angiotensin II (Drexler 1994). NO can be released from the endothelium upon stimulation such as increased blood flow from exercise. There are several pathophysiological conditions where either the basal or stimulated release of NO is altered. Recent data has shown that endothelial dysfunction in the peripheral circulation is involved in the impairment of both reactive hyperemia and increase in blood flow in CHF (Drexler 1994; Maguire 1998). The stimulated release of NO from the endothelium has repeatedly been documented to be reduced in the peripheral vasculature of patients with CHF (Love, McMurray et al. 1996). Studies suggest that it is not associated with age, plasma levels of norepinephrine or renin activity in this patient group, atherosclerosis, or hypercholesterolemia (Chin-Dusting 1996). The cardiovascular system is effected by the endothelial dysfunction in two ways: 'first, endothelial dysfunction of resistance vessels may impair peripheral perfusion, and second, endothelial dysfunction of large conduit vessels may limit the increase in blood flow provided by the supplying large vessels and may increase impedance of the failing left ventricle and consequently impair left ventricular ejection' (Hornig 1996). Thus, the endothelium can lose its vasodilator response, become less thrombolytic, begin to support leukocyte adherence, or stimulate smooth muscle migration and proliferation. Endothelial dysfunction also damages the elastic properties of large conduit vessels, which can cause a negative feedback on the pumping ability of the left ventricle (Drexler 1997).

The endothelial dysfunction in CHF shown in both the coronary and peripheral circulation may be caused by several different factors. As mentioned above, basal NO production is altered in patients with CHF. The standard research method used to assess NO production is the infusion of N-monomethyl-L-arginine (L-NMMA), a competitive inhibitor of NO synthase in the vascular wall (Dusting 1996; Kingwell, Sherrard et al. 1997; Maguire 1998). NO is synthesized from L-arginine by NO synthase; L-NMMA competes with L-arginine for the active site on the enzyme. In vitro, L-NMMA causes endothelium-dependent contractions of isolated conduit arteries, an effect mediated by inhibition of basal NO release (Palmer 1987). Infusion of L-NMMA into the brachial artery or dorsal hand veins inhibit endothelium-dependent relaxation to bradykinin and acetylcholine (Vallance 1989). In healthy subjects, L-NMMA caused a 50 percent fall in basal blood flow (Vallance 1989). Drexler (1994) reported that as L-NMMA

inhibits the basal release of NO, an exaggerated vasoconstrictor response in patients with CHF compared with healthy volunteers is consistent with the notion that the basal release of NO is increased in the peripheral circulation of patients with CHF (Drexler 1994). This implies that there is an increased spontaneous release of NO in CHF. In the same cohort of patients, endothelium-dependent relaxation to ACh attenuated compared to healthy volunteers. Thus, endothelium dependent dilatation of forearm resistance vessels is impaired in patients with CHF, suggesting a reduced stimulated release of NO in response to ACh (Drexler 1994). It has been suggested that NO is released in proportion to the severity of heart failure (Dusting 1996). This was based on data indicating that the magnitude of the vasoconstrictor response to L-NMMA (and hence the level of endogenous NO release) was directly proportional to the systemic vascular resistance measured prior to L-NMMA infusion (Dusting 1996).

It is unknown why patients with CHF have this enhanced vascular release of NO. Endogenous factors that stimulate the endothelium to release NO may be involved. Plasma levels of endothelin are elevated in CHF and have been shown to stimulate release of NO from the endothelium in different vessels. 'It is likely that endothelial dysfunction accounts ultimately for a large portion of all cardiovascular disease (Hurst 1998).'

### **2.3.3.3 Influence of flow on endothelium function: shear stress**

It is well established that endothelial cells are the sensor of fluid dynamic shear forces that reduce arterial diameter when blood flow rate decreases and enlarge the diameter when the flow rate increases (Noris 1995). Rapid flow of blood through the arteries and arterioles causes shear stress on the endothelial cells because of viscous drag of the blood against the vascular walls. This stress contorts the endothelial cells in the direction of flow and causes greatly increased release of NO (Miller 1988; Noris 1995; Umans and Levi 1995). The NO then relaxes the local arterial wall, causing it to dilate. NO release initiated by shear stress stimulation of the endothelium has been studied extensively both *in vitro* (Koller 1995; Noris 1995) and *in vivo* (Panza 1990; Calver 1993). When blood flows over the surface of the endothelial cells a tangential frictional force is created (Kanai 1995). The nature of the shear stress (laminar or turbulent) influences the amount of NO released (Busse 1993; Noris 1995). Turbulent flow, which occurs in vessel bifurcations, has shown a diminished NO release while pulsatile or

laminar flow produces a greater NO release (Noris 1995). It has been suggested that chronic increases in blood flow through an intact artery increase tonic and receptor-mediated synthesis of NO (Miller 1992). When the flow through large arteries is increased, they dilate. This flow-induced vasodilatation, which probably optimizes the supply of blood to tissues where the arteriolar resistance has suddenly decreased, can be attributed to the release of NO (Furchgott and Vanhoutte 1989). In a recent study, it was shown in canine femoral arteries that the release of NO increases proportionally with rate of flow (either continuous or pulsatile) (Furchgott and Vanhoutte 1989). It would appear that there is a flow-dependent release of NO that is related to shear stress on the luminal surface of the endothelial cells. Thus, release of NO is enhanced by shear stress, which may be one mechanism whereby long-term elevation in blood flow and exercise training increase the endothelial production of NO (Vanhoutte 1996). Exercise has been postulated as a mechanism for increasing shear stress and thus increasing NO release (Koller 1995; Hornig 1996). Exercise-induced improvements in NO release have been indicated in aerobic training (Kingwell, Sherrard et al. 1997) and specific forearm resistance training (Hornig 1996; Katz 1997). Katz et al. indicated that physical training improvements in endothelial function in CHF patients were specific to the forearm trained (Katz 1997).

### **2.3.4 Substances affecting endothelial function**

There have been several recent studies that have looked at the various interventions to restore endothelial dysfunction. Summaries of the main interventions are as follows:

#### **2.3.4.1 L-arginine**

L-arginine the precursor of NO was one of the initial interventions considered. Responses to vasodilators, such as acetylcholine, are reduced in patients with CHF, giving evidence of endothelial dysfunction. These vasodilator responses are improved by intraarterial infusion with L-arginine. Thus, L-arginine may assist in the synthesis of NO, which improves endothelial dysfunction (Drexler 1997). Although it is clear that L-arginine improves endothelial dysfunction in some cardiovascular diseases, it is currently not well understood. Hirooka and coworkers (1994) showed an improvement of reactive hyperemic forearm blood flow and improved the vasodilator action of acetylcholine with intraarterial infusions of L-arginine in CHF patients (Hirooka 1994). More recently L-arginine as a dietary supplement has been shown to have an

ineffective response (Chin-Dusting 1996). L-arginine is a semiessential amino acid and can be taken orally as a dietary supplement. The results, of the study investigating L-arginine effects on endothelium-dependent vasodilation in CHF showed that endothelium-dependent vasodilation is impaired despite vasoactive medication and that oral administration of L-arginine 20g/day for 28 days, has no effect on the endothelium dysfunction in CHF. Even though L-arginine as a dietary supplement was found to be ineffective, there are researchers (Drexler 1997) that think L-arginine may still have other beneficial effects for patients with CHF.

#### **2.3.4.2 Cholesterol-lowering therapy**

Given that individuals with high cholesterol levels run an increased risk of developing endothelial dysfunction, it is reasonable to hypothesize that decreasing cholesterol levels may improve endothelial dysfunction. This hypothesis has been justified in to recent studies (Drexler 1997; Charo 1998). However, most studies using this therapeutic approach exclude patients with CHF. O'Driscoll and researchers (1997) have shown cholesterol-lowering improves endothelial function in patients with hypercholesterolaemia in response to the endothelium-dependent NO-agonist, acetylcholine (ACh) (O'Driscoll 1997). In an earlier study, a placebo controlled trial showed that cholesterol-lowering therapy reduces the risk for cardiovascular events and reduces mortality in subjects with coronary artery disease (Group 1994). A fast and dramatic decrease in cholesterol can improve endothelial vasomotor function almost immediately (Charo 1998). The results are encouraging, but there is little published regarding its effects on patients with CHF.

#### **2.3.4.3 Omega-3 fatty acids**

Treatment for atherosclerosis is widely studied, and a therapeutic approach that is gaining interest is the use of omega-3 fatty acids. It has been demonstrated that oral ingestion of dietary fish oil (rich in omega-3 fatty acids) improves endothelium-dependent relaxation of normal pig coronary arteries (Shimokawa 1988). The same researchers have shown in pigs that oral administration of omega-3 fatty acids is effective in reversing the impaired endothelium-dependent relaxation in experimental coronary atherosclerosis (Shimokawa 1988). As research continues omega-3 fatty acid may potentially be a useful intervention for atherosclerosis and other coronary artery disease, but its effects on CHF is uncertain.

#### **2.3.4.4 Endothelin-1 blockade**

As mentioned above CHF patients have increased plasma concentrations of endothelin-1 (ET-1) a potent vasoconstrictor and associated with both increased symptoms and increased mortality. Therefore, a pharmacological blockade of this system may be of potential therapeutic benefit in CHF. Two endothelin receptors have been identified in humans: ET<sub>A</sub> and ET<sub>B</sub> (Love, McMurray et al. 1996; Haynes and Webb 1998; Cowburn 1999). Both receptor subtypes have been identified on vascular smooth muscle cells and found to mediate vasoconstriction, but ET<sub>B</sub> is also found on endothelial cells (Love, McMurray et al. 1996; Cowburn 1999). Activating both receptors on vascular smooth muscle cells mediates vasoconstriction (Love, McMurray et al. 1996; Cowburn 1999). Activating the ET<sub>B</sub> receptors on vascular endothelial cells mediates vasodilation via nitric oxide (Love, McMurray et al. 1996; Cowburn 1999). Antagonists for ET<sub>A</sub>/ET<sub>B</sub> and selective ET<sub>A</sub> receptors have been created to assess the contribution of ET-1 to various cardiovascular diseases. Bosentan is a combination ET<sub>A</sub>/ET<sub>B</sub> receptor antagonist, which has shown favourable hemodynamic (Haynes and Webb 1998) and neurohormonal (Suetsch, Christen et al. 1997) responses in CHF. There has been debate if selective ET<sub>A</sub> blockade or non-selective ET<sub>A</sub>/ET<sub>B</sub> blockade would be most beneficial (Haynes and Webb 1998). Love and coworkers (1996) suggest that a non-selective receptor antagonist is needed for optimal inhibition of the ET-1 constrictor effects (Love, McMurray et al. 1996). The exact actions of endothelin receptors are not fully understood and the potential for this therapeutic approach is still unclear.

#### **2.3.4.5 Vasodilator therapy (ACE inhibitors)**

Morbidity and mortality in CHF has been impacted by the development of vasodilator therapies such as angiotensin converting enzyme (ACE) inhibitors. Vasodilating agents induce relaxation of arterial and venous vascular smooth muscle. ACE inhibitors reduce the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor (Love, McMurray et al. 1996), to improve the prognosis and help prevent progression of heart failure in patients with CHF (Nakamura 1994). ACE inhibitors act directly on systemic and pulmonary resistance vessels to interrupt neuroendocrine vasoconstrictor reflexes and cause vasodilatation (Love, McMurray et al. 1996). Experimental evidence with ACE inhibitors suggest that they help to reverse ultrastructure abnormalities of skeletal muscle in patients with CHF and that long-term treatment

restores endothelial function (Drexler 1994; Nakamura 1994). Nakamura and coworkers (1994) showed low dose intra-arterial infusion of the ACE inhibitor alone did not affect basal forearm blood flow, but it did augment an increase in blood flow induced by acetylcholine; suggesting an endothelium-dependent mechanism in the peripheral vascular bed plays an important role in endothelial dysfunction (Nakamura 1994).

## **2.4 Exercise in Chronic Heart Failure**

### **2.4.1. Exercise limitations in CHF**

Patients with CHF, when compared to healthy persons, have impaired cardiorespiratory, peripheral, and autonomic nervous system responses during exercise. Ventricular dysfunction is the main event that triggers CHF, therefore, researchers assumed that the intolerance to exercise was linked to the severity of the left ventricular dysfunction (Cohn 1998). Left ventricular ejection fraction (LVEF) is a predictor of survival in CHF, but aerobic capacity of CHF patients has been shown to be poorly correlated with either LVEF (Cohn 1998) or central haemodynamic factors (Wilson, Fink et al. 1985). It is highly problematic to predict a patient's exercise capacity from LVEF or end-diastolic dimensions (Lipkin 1986). The severity of CHF can be categorized by measuring  $VO_{2peak}$  (Keteyian 1997) using a system designed by Weber et al. (Weber 1987), who documented that  $VO_{2peak}$  is related to exercise cardiac reserve. In this system, patients can be classified in categories A-D according to their  $VO_{2peak}$ . Category A is classified by a  $VO_{2peak}$  of greater than  $20 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  and at the lower end of the scale D is less than  $10 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ . In CHF patients during exercise, the cardiac output does not increase adequately relative to the increased oxygen requirements of the body. At peak exercise power output was reduced by 45%, cardiac output by 40%,  $VO_2$  by 44%, stroke volume by 50%, and heart rate by 20%, when compared to healthy volunteers (Keteyian 1997). During rapid exercise a metabolic acidosis occurs, which may stimulate peripheral chemoreceptors and contribute to the hyperventilatory response and the feeling of breathlessness (Lipkin 1986).

#### **2.4.1.1 Symptoms which limit exercise in CHF**

In patients with CHF, exercise capacity is usually limited by symptoms of dyspnea or fatigue (Arnold 1990). CHF patients limit their activities to avoid these symptoms. This self-induced limitation of activities leads to a deconditioning effect in their skeletal muscle (Drexler 1994).

This in turn leads to a feed forward loop of progressively worsening exercise tolerance. Many of these deconditioning effects can be reversed by exercise training in most patients with CHF (Minotti and Massie 1992; Magnusson, Gordon et al. 1996; Maiorana, O'Driscoll et al. 2000). It is difficult to consistently evaluate the broad symptoms that limit exercise in CHF. The cardinal symptoms of shortness of breath and fatigue vary from patient to patient and are difficult to quantify. Shortness of breath can often be confused with angina or exhaustion, and fatigue is difficult to differentiate from tiredness, exhaustion or lethargy (Poole-Wilson 1992). The symptoms, which restrict exercise in these patients, depend on the type of exercise being performed. Fast paced exercises cause breathlessness and slow paced exercises often end due to fatigue (Lipkin 1986). Wilson et al. demonstrated that fatigue arose when the under perfusion of muscle came to a critical level (Wilson 1984). It was concluded that maximal exercise capacity of CHF patients was caused by an impaired nutritive flow to the skeletal muscle. More recent studies have found similar results, showing that CHF patients rely on their anaerobic metabolic pathways to produce energy at an earlier stage of exercise than the healthy person, leading to a faster increase in blood lactate, increased ventilation and carbon dioxide production and fatigue (Keteyian 1997). Therefore, fatigue limited patients may have an inadequate supply of oxygen to the skeletal muscle. Other differing factors that limit exercise in CHF are the inability to increase nutritive blood flow to the exercising muscles (Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000) as well as abnormalities of skeletal muscle (Poole-Wilson 1992). CHF patients have a reduced response to normal exercise induced vasodilation (Keteyian 1997) and increased skeletal muscle atrophy (Harrington, Anker et al. 1997).

#### **2.4.1.1.1 Reduced $VO_{2peak}$ in CHF**

Treatment for patients with CHF should include emphases on improving exercise tolerance, quality of life and clinical outcomes for patients. Modern medicine has improved each in some regard. ACE inhibitors exhibit an increase on exercise capacity of about 10% (Garg 1995). Aerobic exercise training however has been shown to improve exercise tolerance by an average of 20% (Dubach, Sixt et al. 2001) and these improvements may be maintained for over 12 months (Belardinelli, Georgiou et al. 1999; Meyers 2000). Thirty-one of the 40 studies reviewed for Table 2.4, which investigated the effects of aerobic exercise training on CHF studies reported significant improvements in exercise capacity. Coats and coworkers (1994)

reported improvements in measures of fatigue, breathlessness, ability to perform daily activities, and general well being after aerobic exercise training (Coats 1994).

#### **2.4.1.1.2 Reduced Strength in CHF**

Patients with CHF exhibit skeletal muscle atrophy, impaired strength, and abnormal metabolism. Studies have reported muscle histology and biochemical response to exercise in skeletal muscle is abnormal in patients with CHF (Wilson, Fink et al. 1985; Adamopoulos, Coats et al. 1993; Hambrecht 1997). The maximal force generated by the quadriceps is reduced and relates to the intolerance to exercise in CHF (Lipkin 1988). CHF patients have a lower proportion of type I (reduced by 41% (Keteyian 1997)) and a higher proportion of type II muscle fibers, compared with healthy volunteers (Sullivan, Green et al. 1990). Similar findings were reported in rats with CHF (Delp, Duan et al. 1997). These changes require patients with CHF to rely on anaerobic metabolic pathways to produce energy earlier in exercise than in healthy persons. Therefore, patients with CHF exhibit an earlier onset of muscle acidosis and more rapid depletion of phosphocreatine (Chati, Zannad et al. 1994), leading to increased ventilation, carbon dioxide production, and fatigue (Keteyian 1997). Maiorana and coworkers (2000) published the first controlled trial to report generalized improvement in skeletal muscle strength. Seven isolated muscle strength sites were assessed, all showing improvement (Maiorana, O'Driscoll et al. 2000). This research used a circuit weight training regime over an eight week duration. The study results have important implications for CHF patients' capacity to perform daily living tasks, many of which are dependent on muscular strength. Hare and colleagues (1999) showed similar results with the intervention of resistance training (Hare, Ryan et al. 1999).

#### **2.4.1.1.3 Reduced Peripheral blood flow in CHF**

In addition to abnormal cardiopulmonary and muscular function, the impaired nutritive blood flow to the periphery during exercise may be a limiting factor of exercise capacity in CHF (Keteyian 1997). One of the long-term effects of CHF is increased resistance of the vascular bed. Measurements of exercising skeletal muscle blood flow suggest that this resistance is increased 5-fold when compared to healthy volunteers (Poole-Wilson 1992). Exercise is a physiological stimulus that increases both skeletal muscle blood flow and NO release. Exercise training has been shown to improve EDNO-mediated vasodilation in the coronary and peripheral vascular

beds of experimental animals (Bank 1998). Skeletal muscle vasoconstriction impairs vasodilating capacity during exercise in patients with CHF and appears to be a major mechanism contributing to the symptoms of fatigue and exercise intolerance (Love and McMurray 1996). Peripheral abnormalities such as vasoconstriction, have been demonstrated in skeletal muscle histology, mitochondria, oxidative enzyme activities, and high-energy phosphate handling together with early muscle fatigue, sympathetic overactivity, and parasympathetic withdrawal (Poole-Wilson 1992). Several studies have documented that a training program can reverse at least some of the adverse peripheral changes (Drexler 1994; Maiorana, O'Driscoll et al. 2000). Following eight weeks of exercise training, significant increases in blood flow and flow ratio was observed after arterial infusions of ACh (endothelium-dependent) and SNP (endothelium-independent) (Maiorana, O'Driscoll et al. 2000). Peak reactive hyperemia was used to assess vasodilator capacity and resistance vessel structure, results indicate both improved after training. Six months of exercise training (cycling) has shown similar results, with CHF patients improving basal and stimulated endothelium-dependent responses (Hambrecht, Fiehn et al. 1998). Physical training in CHF has been shown to partially reverse the muscle metabolic abnormalities in addition to those of autonomic tone and ventilation but without any detectable effect on central hemodynamics (Poole-Wilson 1992). Thus, the major adaptations to training may be peripheral. Localized forearm training improves both metabolic and functional capacity in CHF patients (Piepoli 1996). The trained forearm demonstrated a greater submaximal endurance without associated changes in blood flow or central hemodynamics. Exercise tolerance improved in both CHF and healthy volunteers (Piepoli 1996). At matched work duration, however (3-minute handgrip), localized forearm exercise reduced systolic and diastolic blood pressures, and nonexercising vascular resistance, consequently raising the blood flow, suggesting a more efficient response to exercise. These results showed that localized exercise training of only the muscles of one forearm brought the responses to exercise of the patient group closer to those of the healthy volunteers. However, it has recently been shown that the vascular improvements are generalized to the circulation rather than specific to the skeletal muscle bed being trained (Maiorana, O'Driscoll et al. 2000). Results showed improvements in forearm vasculature, even though this vascular bed was excluded from the exercise training program. Following six months of aerobic exercise training, peripheral blood flow measured in the superficial femoral artery significantly improved by 187%, from 112 +/-92 to 321 +/-103 mL/min (Hambrecht, Fiehn et al.

1998). Based on the past theoretical (Sullivan, Higginbotham et al. 1988) and present factual considerations (Maiorana, O'Driscoll et al. 2000), physical training has potential to improve the clinical state of patients with CHF. The vascular adaptations associated with physical training are particularly relevant for patients with CHF where peak exercise capacity is partially limited by an impaired vasodilatory response to exercise (Katz 1997). Research consistently documents improvements in exercise performance. Most likely, this improvement occurs due to the training effect on the peripheral vessels (Maiorana, O'Driscoll et al. 2000) since the function of the left ventricle is not improved (Koch 1992). The positive effects on the vascular function probably relate to the effect of increased flow on the endothelium (Maiorana, O'Driscoll et al. 2000). Flow on endothelial cells trigger an increased production of NO that readily moves to the smooth muscle cells, where cyclic guanosine monophosphate (cGMP) is activated initiating relaxation of vascular smooth muscle (as discussed earlier in Section 2.3.3.3) (Dusting 1996). Thus, an increase in shear stress corresponds to increases in NO release (Kingwell, Sherrard et al. 1997) and vasorelaxation. Exercise training, which causes repetitive increases in blood flow, in turn increasing shear stress, results in an increased release of NO (Hornig 1996). Furthermore, if exercise is consistently repeated there is an elevated expression of endothelial constitutive NO synthase, implying that increased blood flow from exercise causes chronic adaptation of the NO vasodilator system (Maiorana, O'Driscoll et al. 2000).

#### **2.4.1.2 Risks of exercise training in CHF**

Exercising above an intensity that may trigger physiological irregularities is the greatest risk in training; prescription of exercise intensity for patients with CHF must be precise. Therefore, the peak heart rate ( $HR_{max}$ ) used in exercise training must be lower than the  $HR_{max}$  at which irregularities begin to show when performing a  $VO_{2peak}$  test. That is assuming the resting HR,  $HR_{max}$ , and rhythm is not affected by medication. Most patients with CHF are on HR-modulating medications that modify the response to exercise. Eston et al. observed that exercise prescription by HR is insensitive to patients taking prescribed medications that blunt the HR response to exercise (Eston R 1996) (e.g. Beta-blockers (ACSM 2000)). This could lead to errors and unsafe exercise prescription in this high-risk population (Samitz 1991). CHF patients that have been sedentary for a long period of time often do not tolerate the first week of exercise very well. Patients may need to be monitored closely and rest often (Keteyian 1997). The Valsalva

maneuver should be avoided due to its increased effects on blood pressure. Studies often eliminate this by requesting the patient to count aloud in rhythm with the repetitions (Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000). Exercising in extreme weather, such as very hot, cold, humid or windy conditions or exposed to poor air quality, should be avoided. In general, there have been almost no reports of adverse events directly attributed to participation in exercise training in patients with CHF (Sullivan 1989; Coats, Adamopoulos et al. 1992; Koch 1992; Kostis, Rosen et al. 1994; Hambrecht 1995; Keteyian 1996; Magnusson, Gordon et al. 1996; Belardinelli 1999; Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000; Pu, Johnson et al. 2001; Tyni-Lenne, Dencker et al. 2001).

#### **2.4.2 Effects of exercise training in CHF**

Patients with CHF have limited exercise tolerance (Coats, Adamopoulos et al. 1992; Willenheimer, Erhardt et al. 1998; Tanabe 2000). Until a few years ago, enrollment of these patients into an exercise training program was uncommon and even considered ill advised. The 1988 edition of Braunwald's "Heart Disease" recommended physical activity be restricted for CHF patients (Braunwald 1988). The basis for this advice centered on two concerns: the perception of risk and no data as to its efficacy. The latter was based on theories that exercise training does not improve cardiac function and central hemodynamics. The reduced exercise capacity and concerns that the stress of exercise would further aggravate heart function (Keteyian 1997) kept physicians from prescribing exercise programs. Recent research has begun to allay the concerns about safety of exercise training for CHF patients, demonstrating that peripheral, rather than central, adaptations are critical to the improvements in exercise capacity and functional status. In fact it has been demonstrated that exercise capacity is poorly correlated to measures of left ventricular function (Hambrecht, Gielen et al. 2000; Karlsdottir 2002). The knowledge that exercise training does not affect the heart itself, but primarily the peripheral vascular and muscular system led to changes in the direction of research toward exercise in CHF. Early studies showed patients were able to safely participate in exercise training after an MI, leading to improvements in their exercise capacity (Giannuzzi, Tavazzi et al. 1993). CHF patients respond positively to exercise training programs (Coats, Adamopoulos et al. 1992; Koch 1992; Shephard 1998; Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000). These programs can induce important adaptations in skeletal muscle, including fibre type alterations, atrophy,

capillary density and blood flow (Drexler 1994; Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000). Belardinelli et al. (1999) randomized 99 CHF patients into either a long-term supervised exercise training program or control for 14 months (Belardinelli 1999). Results of the study demonstrated significant improvements in functional capacity, with an increase of 18% in  $VO_{2peak}$  and 30% in patients ventilatory threshold. Quality of life questionnaires also showed improvement which paralleled  $VO_{2peak}$ . These improvements occurred within the first two months of training and were maintained for 12 months, showing that a long-term exercise program enhances exercise capacity and quality of life in patients with CHF. A plateau in the symptom reduction and exercise capacity was reached following the initial two months, possibly due to the protocol followed in this study where training occurred in two phases. After two months of exercise training three times per week at 60% of  $VO_{2peak}$ , a maintenance phase of 12 months was conducted at the same intensity. Sessions, however, were reduced to twice per week (Belardinelli 1999). This long-term trial showed that all cause mortality was reduced (9 versus 20 deaths for those in training compared to without; risk reduction, -63%; 95% CIs, 16% to 83%;  $P < 0.01$ ) as was the rate of hospital readmissions (5 versus 14; risk reduction, 71%; 95% CIs, 12% to 89%;  $P < 0.02$ ) (Belardinelli, Georgiou et al. 1999). The same research group recently published new data from this experimental cohort providing evidence that exercise training in CHF is cost-effective (Georgiou 2001). Using a cost-benefit analysis of hospitalization fees versus exercise cost and wage loss, it was calculated that US\$1,773 was saved per patient per year. In addition the study estimated that exercising patients prolonged their survival by 1.82 years (Georgiou 2001). Other positive effects of exercise in CHF may be weight loss for obese patients that already have decreased peripheral circulation, improving blood pressure in patients with hypertension, and improving lipid and glucose metabolism (Kostis, Rosen et al. 1994). Prognosis in CHF is related to mood state and psychological well being (Bennett, Pressler et al. 1997). Exercise has been shown to reduce the high level of psychological stress (Kostis, Rosen et al. 1994) and depression found in CHF (Hare and Davis 1996), which contributes positively to enhance quality of life and improve survival. All exercise interventions for CHF, however, have occurred in a supervised, group environment. Social contact and reassurance may have inherently contributed to documented mood improvements. Exercise training did improve exercise capacity in CHF and this is directly associated with better prognosis and inversely related to mortality from cardiovascular causes in healthy individuals (Kostis, Rosen et al. 1994).

The physical inactivity that is consistent with CHF patients can result in a long-term reduction in peripheral blood flow and endothelial shear stress and may change the metabolism or release of endothelial vasodilatory substances (Nakamura 1994). A number of studies indicate that NO release contributes to skeletal muscle vasodilation during exercise (Dyke 1995; Green 1996). NO-mediated responses are improved by exercise training (Koller 1995), which has also been documented to increase NO-synthase expression in animals (Sessa 1994). Exercise training improvements of peak vasodilator function in healthy volunteers have been reported (Green 1996). In CHF patients, improvements of endothelium-dependent and –independent NO function following exercise was more recently reported by the same research group (Maiorana, O'Driscoll et al. 2000). In a separate study of CHF patients, four weeks of handgrip exercise improved radial artery flow-mediated dilation (Hornig 1996), providing further evidence that exercise improves endothelial function.

**Table 2.4** Exercise training studies: CHF patients

Authors	Study Design	Patients Exercise	Patients Control	Healthy Control	Duration (wk)	Intensity (%)	Duration (min)	Frequency (days/wk)	Training (mode)	Results
Adamopoulos et al. 1993	randomized crossover	12	0	15	8				bk	improves skeletal muscle metabolism
Adamopoulos et al. 2002	randomized crossover	24	0	20	12	60-80% MHR	30	5	bk	↑ ET, VO <sub>2</sub> , ↓ TNF-alpha
Ali et al. 1999	no control	15	0	0	12	70-85% MHR	60	3 to 6	bk,wk,hw	↑ ET (NS)
Barlow et al. 1998	Age-matched control	10	0	10	8	70-80% MHR	20	5	bk	↑ VO <sub>2</sub> , ↓ K+ & ventilation
Belardinelli et al. 1992	prospective randomized	10	10	0	8	40% VO <sub>2</sub>		3	bk	↑ VO <sub>2</sub> , AT, peak HR & ↓ resting HR
Belardinelli et al. 1995	Age-matched control	12	0	10	8	40% VO <sub>2</sub>	30	3	bk	
Belardinelli et al. 1999	prospective randomized	50	49	0	60	60% VO <sub>2</sub>	60	3 to 2	bk	↑ QOL, VO <sub>2</sub> , ↓ mortality & readmission
Bertram et al. 2002	no control	25	0	0	15		21	5	bk,wk	↑ VO <sub>2</sub> , & AT
Coats et al. 1990	randomized crossover	11	0	0	8	70-80% MHR	20	5	bk	↑ ET, VO <sub>2</sub> , ↓ Sy
Coats et al. 1992	randomized crossover	17	0	0	8	60-80% MHR	20	5	bk	↑ ET, VO <sub>2</sub> , ↓ VR, ↓ ventilation
Davey et al. 1992	randomized crossover	22	0	0	8	70-80% MHR	20	5	bk	↑ VO <sub>2</sub> , ET, ↓ VCO <sub>2</sub> , ↓ ventilation
Demopoulos et al. 1997	no control	16	0	0	12	50% VO <sub>2</sub>	60	4	ar	↑ VO <sub>2</sub> , PRH

ET: exercise tolerance; AT: anaerobic threshold; NS: not significant; VCO<sub>2</sub>: carbon dioxide excretion; bk: bike; wk: walk; ar: aerobic training; st: stairs; ae: arm ergometer; CWT: circuit weight training; HS: hand squeezing; hw: hand squeezing; ca: callisthenics; r: rowing; RM: repetition maximum; KRT: high intensity knee extensor training; MHR: max heart rate; VO<sub>2</sub>: VO<sub>2peak</sub>; Sy: symptoms; VR: vascular resistance; PRH: peak reactive hyperemia

Authors	Study Design	Patients Exercise	Patients Control	Healthy Control	Duration (wk)	Intensity (%)	Duration (min)	Frequency (days/wk)	Training (mode)	Results
Dubach et al. 1997	prospective randomized	12	13	0	8	70-80% peak capacity	150	7wk/4bk	bk, wk	↑ VO <sub>2</sub> , ET
Dziekan et al. 1998	prospective randomized	10	10	0	8	60-80%HRR	105	7wk/4bk	bk, wk	↑ VO <sub>2</sub> , ET, AT
Gottlieb et al. 1999	prospective randomized	17	16	0	26					↑ VO <sub>2</sub> , ET
Hambrecht et al. 1995	prospective randomized	12	10	0	24	70% VO <sub>2</sub>	60	7	bk	
Hambrecht et al. 1998	prospective randomized	10	10	6	26	70% VO <sub>2</sub>	40	6	bk	↑ VO <sub>2</sub> , ↑ response to ACH
Hambrecht et al. 2000	prospective randomized	36	37	0	28	70% VO <sub>2</sub>	20		bk	↑ VO <sub>2</sub> , ET, ↓ ventilation, ↓ VR
Jette et al. 1991	prospective randomized	7	8	0	4	70-80% MHR	30-60	5	bk, wk, ca	
Kavanagh et al. 1996	non- randomized control	21	9	0	52	50-60% VO <sub>2</sub>	25	5	wk	↑ VO <sub>2</sub> , QOL
Keteyian et al. 1996	prospective randomized	15	14	0	24	60-75% VO <sub>2</sub>	32	3	bk, wk, ae	↑ ET, VO <sub>2</sub> , peak HR, ↓ ventilation
Kiilavuori et al. 1995	prospective randomized	8	12	0	12	50-60% VO <sub>2</sub>	30	3	bk	↑ ET, VO <sub>2peak</sub>
Kiilavuori et al. 1996	prospective randomized	12	15	0	26	50-60% VO <sub>2</sub>	30	3	bk	↑ ET, VO <sub>2</sub> , ↓ ventilation & NYHA class
Kostis et al. 1994	prospective randomized	7	6	0	12	40-60% VO <sub>2</sub>	60	3 to 5	bk, wk, st, r	
Larsen et al. 2002	prospective randomized	15	0	15	12	80% MHR	30	5		↑ ET, ↑ thickness type IIB fibers, ↓ area type I fibers
Linke et al. 2001	prospective randomized	11	11	0	4	70% VO <sub>2</sub>	60	7	bk	↑ response to ACH, ↓ endothelial dysfunction

ET: exercise tolerance; AT: anaerobic threshold; NS: not significant; VCO<sub>2</sub>: carbon dioxide excretion; bk: bike; wk: walk; ar: aerobic training; st: stairs; ae: arm ergometer; CWT: circuit weight training; HS: hand squeezing; hw: small hand weights; ca: callisthenics; r: rowing; RM: repetition maximum; KRT: high intensity knee extensor training; MHR: max heart rate; VO<sub>2</sub>: VO<sub>2peak</sub>; Sy: symptoms; VR: vascular resistance; PRH: peak reactive hyperemia

Authors	Study Design	Patients Exercise	Patients Control	Healthy Control	Duration (wk)	Intensity (%)	Duration (min)	Frequency (days/wk)	Training (mode)	Results
McKelvie et al. 2002	prospective randomized	90	90	0	52	60-70% MHR	30	3	bk, wk, ar	↑ ET, VO <sub>2</sub> , strength
Meyer et al. 1997	randomized crossover	18	0	0	6	50% max work rate	20	3	bk, wk	↑ ET, VO <sub>2</sub>
Parnell et al. 2002	prospective randomized	11	10	0	8	50-60% MHR	30-60	3 to 7	bk, wk, hw	LV function unchanged, ↑ ET, QOL, ↓ Sy
Quitman et al. 1999	prospective randomized	12	13	0	12		60	3	ar	↑ VO <sub>2</sub> , ET
Radaelli et al. 1996	randomized crossover	6	6	0	5	60-70% VO <sub>2</sub>	30	5	bk	↑ VO <sub>2</sub> , ↑ autonomic control
Shephard et al. 1998	no control	17	0	0	16	60-70% VO <sub>2</sub>	~60	5	wk	
Sullivan et al. 1988	no control	12	0	0	16-24	75% VO <sub>2</sub>	60	3 to 5	bk, wk, st	↑ VO <sub>2</sub> , ET, ↑ peak blood flow
Taylor 1999	randomized crossover	8	0	0	16			3	ar	↑ VO <sub>2</sub> , ET, ↓ resting HR
Tokmakova et al. 1999	prospective randomized	15	7	0	8	50% VO <sub>2</sub>			ar	↑ VO <sub>2</sub> , ET, AT, ↑ QOL, ↓ ventilation, ↓ Sy
Wielenga et al. 1998	prospective randomized	35	32		12	60% HRR	30	3	bk, wk	↑ ET, AT, QOL
Willenheimer et al. 1998	prospective randomized	22	27		16	80% max intensity			bk	↑ VO <sub>2</sub> , ET
Willenheimer et al. 2001	prospective randomized	17	20	0	16	80% max intensity		3	bk	↑ ET, Exercise must be continued to maintain benefit

ET: exercise tolerance; AT: anaerobic threshold; NS: not significant; VCO<sub>2</sub>: carbon dioxide excretion; bk: bike; wk: walk; ar: aerobic training; st: stairs; ae: arm ergometer; CWT: circuit weight training; HS: hand squeezing; hw: hand squeezing; ca: calisthenics; r: rowing; RM: repetition maximum; KRT: high intensity knee extensor training; MHR: max heart rate; VO<sub>2</sub>: VO<sub>2peak</sub>; Sy: symptoms; VR: vascular resistance; PRH: peak reactive hyperemia

Authors	Study Design	Patients Exercise	Patients Healthy Control	Duration (wk)	Intensity (%)	Duration (min)	Frequency (days/wk)	Training (mode)	Results
<b>Resistance Training</b>									
Beniaminovitz et al. 2002	randomized active control	17	8	0	12	low-level		bk, wk, ca	↑ VO <sub>2</sub> , ET, ↑ strength & endurance, ↑ QOL
Delagardelle et al. 1999	no control	14	0	0	27	60-75% VO <sub>2</sub>	3 to 4	CWT	↑ VO <sub>2</sub> , ET, ↑ strength & endurance
Delagardelle et al. 2002	randomized active control	10	10	0	13		3	CWT	↑ VO <sub>2</sub> , ET, CWT
Hare et al. 1999	no control	9	0	0	11	RPE 12	3	RT	superior to ar training alone
Koch et al. 1992	prospective randomized	12	13	0	12	% of RM	3 to 4	RT	↑ strength & endurance, ↑ resting FBF
Magnusson et al. 1996	prospective randomized	6	5	0	8		3	KRT	↑ ET and muscular strength & endurance
Maiorana et al. 2000	prospective randomized crossover	12	0	0	8	70-85%MHR 55-65%MVC	3	CWT	↑ ET and muscular strength
Pietilla et al. 2002	no control	13	0	0	26	HR below AT	6	CWT	↑ cardiovascular autonomic nervous control
Pu et al. 2001	Age-matched control	16	0	80	10	80% 1RM	3	RT	↑ ET, strength, muscle endurance, type I fiber area
Radzewitz et al. 2002	no control	88	0	0	4			RT, bk, wk	↑ QOL
Selig et al. 2003	prospective randomized	19	20	0	12	RPE 12	3	RT, bk, st	↑ strength, VO <sub>2</sub> , FBF during exercise and PRH
Tyni-Lenne et al. 2001	prospective randomized	16	8	0	8		3	CWT	

ET: exercise tolerance; AT: anaerobic threshold; NS: not significant; VCO<sub>2</sub>: carbon dioxide excretion; bk: bike; wk: walk; ar: aerobic training; st: stairs; ae: arm ergometer; CWT: circuit weight training; HS: hand squeezing; hw: small hand weights; ca: callisthenics; r: rowing; RM: repetition maximum; KRT: high intensity knee extensor training; MHR: max heart rate; VO<sub>2</sub>: VO<sub>2peak</sub>; Sy: symptoms; VR: vascular resistance; PRH: peak reactive hyperemia

Authors	Study Design	Patients Exercise	Patients Control	Healthy Control	Duration (wk)	Intensity (%)	Duration (min)	Frequency (days/wk)	Training (mode)	Results
<b>Forearm resistance exercise only</b>										
Bank et al. 1998	control	7	0	11	6	30% MVC	30	4	HS	↑ PRH
Hornig et al. 1996	age-matched control	12	0	7	4	70% MVC	30	7	HS	↑ flow dependant dilation
Katz et al. 1997	no control	12	0	0	8	70% MVC	30	7	HS	↑ endothelium-dependant vasodilation
Piepoli et al. 1996	age-matched control	12	0	10	6		5	7	HS	↑ ET of forearm, ↓ reflex excitation
ET: exercise tolerance; AT: anaerobic threshold; NS: not significant; VCO <sub>2</sub> : carbon dioxide excretion; bk: bike; wk: walk; ar: aerobic training; st: stairs; ae: arm ergometer; CWT: circuit weight training; HS: hand squeezing; hw: small hand weights; ca: calisthenics; r: rowing; RM: repetition maximum; KRT: high intensity knee extensor training; MHR: max heart rate; VO <sub>2</sub> : VO <sub>2peak</sub> ; Sy: symptoms; VR: vascular resistance; PRH: peak reactive hyperemia										
(Belardinelli 1992; Adamopoulos, Coats et al. 1993; Belardinelli, Georgiou et al. 1995; Barlow 1998; Belardinelli, Georgiou et al. 1999; Adamopoulos, Parissis et al. 2002) (Coats 1990; Bertram 2002), (Jetté, Heller et al. 1991; Coats, Adamopoulos et al. 1992; Davey 1992; Hambrecht 1995; Kavanagh, Myers et al. 1996; Demopoulos, Bijou et al. 1997; Dubach, Myers et al. 1997; Dziekan 1998; Hambrecht, Fiehn et al. 1998; Gottlieb 1999; Hambrecht, Gielen et al. 2000), (Kostis, Rosen et al. 1994; Kiilavuori, Toivonen et al. 1995; Keteyian 1996; Kiilavuori, Sovijarvi et al. 1996; Radaelli, Coats et al. 1996; Meyer, Samek et al. 1997; Quittan 1999; Linke 2001; Larsen, Lindal et al. 2002; McKelvie 2002; Parnell 2002), (Sullivan, Higginbotham et al. 1988; Shephard 1998; Wielenga 1998; Willenheimer, Erhardt et al. 1998; Delagardelle 1999; Taylor 1999; Tokmakova 1999; Willenheimer 2001; Beniaminovitz 2002; Delagardelle 2002), (Koch 1992; Magnusson, Gordon et al. 1996; Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000; Pu, Johnson et al. 2001; Tyni-Lenne, Dencker et al. 2001; Pietila, Malminiemi et al. 2002; Radzewitz, Miche et al. 2002; Selig 2003), (Hornig 1996; Piepoli 1996; Katz 1997; Bank 1998)										

### 2.4.2.1 Aerobic exercise training in CHF

Published aerobic exercise training studies date back to 1988. Using the first prospective, crossover study in this CHF, Coats et al. (1992) studied eight weeks of aerobic exercise training and demonstrated that training increases exercise tolerance and peak oxygen uptake while reducing systemic vascular resistance and overall symptoms related to CHF (Coats, Adamopoulos et al. 1992). In contrast, during the same period of prolonged immobilization in the control group, oxidative enzymes of skeletal muscle, muscle mass, and capillary density all decreased below baseline values. Since then, 39 other studies investigating the effects of aerobic exercise training on CHF have been published (Table 2.4), 21 of these used a prospective randomized design, eight used a crossover study, seven had no control group, one used a randomized active control, and one other study used a non-randomized control group. Exercise tolerance in CHF patients has been shown to improve as a result of aerobic training (Coats, Adamopoulos et al. 1992; Belardinelli 1999), leading to an improvement of submaximal and peak exercise tolerance. Sullivan and colleagues (Sullivan, Higginbotham et al. 1988) studied responses in CHF patients after 4-6 months of aerobic training. Aerobic training increased exercise capacity and both blood flow and oxygen extraction in the exercising limb. These same researchers later showed that in addition to these benefits, patients were also displaying a rise in oxygen uptake, a decrease in lactate production, and a marked increase in endurance during submaximal exercise after training (Sullivan 1989). Coats et al. showed similar findings, confirming the beneficial effects of aerobic training in CHF (Coats, Adamopoulos et al. 1992). In addition, the effects of long-term moderate aerobic exercise training in CHF have been reported (Belardinelli, Georgiou et al. 1999), showing improvements in both functional capacity and quality of life. It has been well established that regular aerobic exercise reduces the risks of atherosclerotic vascular disease and acute cardiovascular events (Blair, Kohl et al. 1989). The theory that risk reduction caused by aerobic training is a result of improved vascular endothelial function has recently been studied using a cross-sectional design with 68 healthy volunteers (DeSouza, Shapiro et al. 2000). Forearm blood flow and forearm vascular conductance responses to ACh and sodium nitroprusside exhibit greater endothelial vasodilatory capacity in trained compared sedentary volunteers (DeSouza, Shapiro et al. 2000). Although this study does not include patients with CHF, it does show that regular aerobic training is an effective intervention for improving endothelial vasodilatory function in older sedentary individuals. Other studies

have published similar findings. At submaximal exercise, cardiac output remains essentially unchanged compared to healthy age-matched volunteers; improvement of exercise tolerance may have resulted from a decrease of peripheral vascular resistance in the lower limb and a corresponding redistribution of blood flow to the working muscles (Hambrecht, Fiehn et al. 1998). Following six months of exercise training, oxygen uptake at peak exercise was increased by 26%, while in a sedentary control group of untrained CHF patients,  $VO_{2\text{peak}}$  remained virtually unchanged (Hambrecht, Fiehn et al. 1998). Many studies of the effects of aerobic training in CHF patients have described improvements in exercise tolerance attributed to improvements in skeletal muscle structure and metabolism (Adamopoulos, Coats et al. 1993; Belardinelli, Geotgiou et al. 1995), peripheral blood flow (Coats, Adamopoulos et al. 1992), reduced ventilatory drive at submaximal exercise (Coats, Adamopoulos et al. 1992) and recently, a slight improvement in left ventricular (LV) function (Hambrecht, Fiehn et al. 1998).

#### **2.4.2.2 Resistance training in CHF**

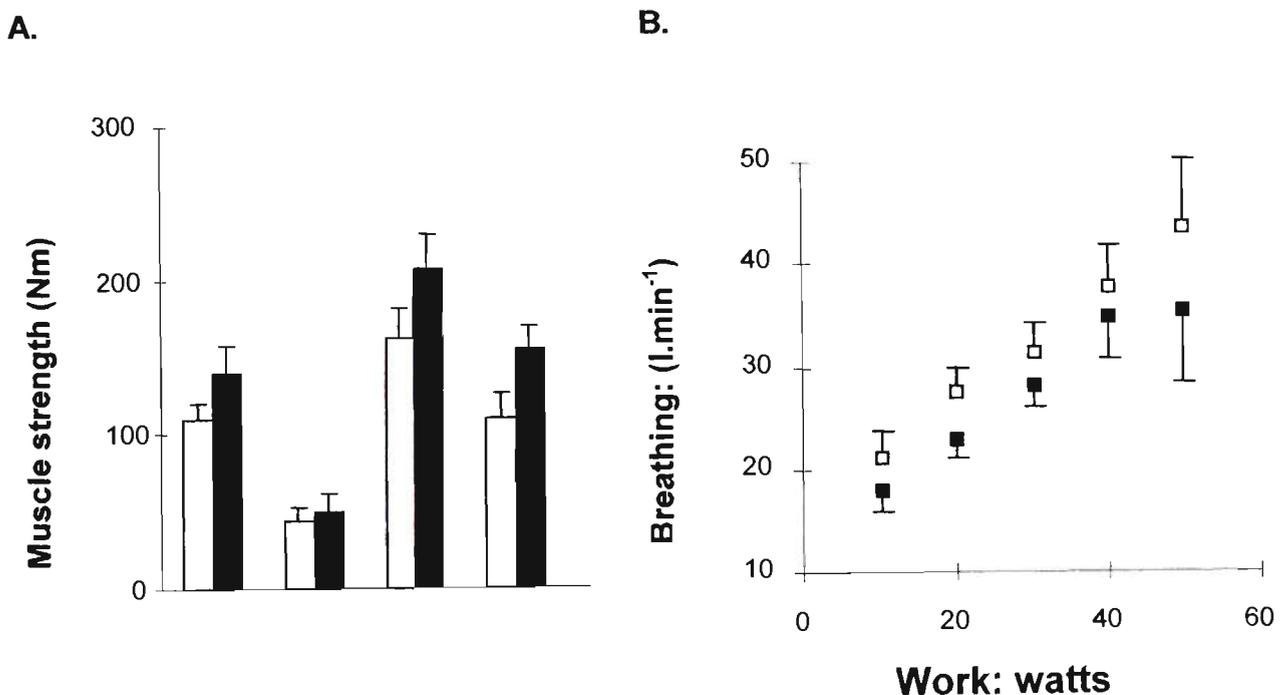
There have been relatively few studies on the effects of resistance training for patients with CHF, in contrast to the numerous investigations of aerobic exercise training, even though there is a sound rationale for including resistance exercises in the physical training of these patients (Clark AL 1996; Anker, Ponikowski et al. 1997). There have been ten studies investigating the effects of resistance exercise training in CHF patients (Table 2.4). Numbers of volunteer patients ranged from 10 to 20 CHF patients with the exception of one study that included 88 patients (Radzewitz, Miche et al. 2002). One study used a randomized crossover design (Maiorana, O'Driscoll et al. 2000) and three used an active control group (Magnusson, Gordon et al. 1996; Pu, Johnson et al. 2001; Delagardelle 2002). Four of these studies were designed to be of mixed (aerobic and resistance) mode (Delagardelle 1999; Maiorana, O'Driscoll et al. 2000; Tyni-Lenne, Dencker et al. 2001) and therefore the effects of the resistance components of the training were difficult to differentiate from the aerobic components. Two studies used high-intensity training (Magnusson, Gordon et al. 1996; Pu, Johnson et al. 2001), which raises concerns with respect to safety, exercise adherence and applicability.

Specific skeletal muscle deficits such as skeletal muscle atrophy (Harrington, Anker et al. 1997), increased type II muscle fibers (Sullivan, Green et al. 1990), and impaired skeletal muscle blood

flow (Hare, Ryan et al. 1999) have been shown to be associated with the symptoms and functional limitations in CHF patients. This suggests that exercise capacity in CHF is affected by peripheral factors that impair oxygen transport and utilization (Harrington, Anker et al. 1997). Activities of daily living, for patients with CHF, are directly hindered by their decreased muscular strength. In the past ten years a number of studies have been published establishing that exercise training can improve  $VO_{2peak}$ , increase peak cardiac output, reverse skeletal muscle abnormalities, increase nutritive blood flow (Hare, Ryan et al. 1999), and improve quality of life and clinical outcomes (Belardinelli, Georgiou et al. 1999). However, nearly all the past studies involving exercise and CHF patients have used aerobic training. The results of aerobic training show vast improvements in cardiorespiratory capacity; the training does not target skeletal muscle. It has therefore been postulated that exercises directed more towards increasing muscle strength would have advantages beyond aerobic training. Resistance training has recently been proposed as a means of partially reversing the skeletal muscle problems associated with CHF, thereby improving exercise tolerance. Resistance training has been used in patients with coronary artery disease (McCartney, McKelvie et al. 1991), but there are very few publications regarding resistance training with CHF. In a study, looking at hemodynamic responses in relation to resistance training versus aerobic training at comparable intensities, the resistance training showed more favorable responses (McKelvie 1995). Safety concerns about recommending resistance exercise to CHF patients have now been allayed, somewhat, by recent experience with resistance training, including that reported by Hare et al. (Hare, Ryan et al. 1999). Rationale for this intervention is that muscle deconditioning is an important factor to exercise intolerance in patients with CHF and resistance training is associated with increased muscle strength, endurance, and mass. Muscle deconditioning causes changes in muscle structure, such as morphology and cellular histochemistry, and is responsible for the significant decrease in muscular performance (Koch 1992). When aerobic training was supplemented with resistance exercise in men with coronary artery disease (CAD), there was a lower incidence of arrhythmias, ischaemia (Daub, Knapik et al. 1996), and LV wall motion abnormalities (Butler, Beierwaltes et al. 1987) during the resistance components of the programs than the aerobic components. Hare and colleagues (1999) conducted a small prospective, uncontrolled observational outcome study of the effects of resistance training in CHF patients (Hare, Ryan et al. 1999). They found that resistance training was effective in increasing muscle strength and endurance (Figure 2.3. A)

whilst reducing the demand for oxygen and ventilation (Figure 2.3. B) at submaximal workloads (Hare, Ryan et al. 1999). Peripheral (forearm) blood flow increased at rest, compared to the pre-training measurement, but the rise during exercise was no greater after training. Other studies have found similar results, showing that CHF patients improve localized skeletal muscle function due to resistance training. Maiorana and coworkers, have documented similar results with aerobic and resistance exercise training over a shorter training period with CHF patients (Maiorana, O'Driscoll et al. 2000). An eight week circuit weight training program increased  $VO_{2peak}$  from  $19.5 \pm 1.2$  to  $22.0 \pm 1.5 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  and exercise test duration improved from  $15.2 \pm 0.9$  to  $18.0 \pm 1.1$  minutes. In addition, muscle strength, capillarization, and oxidative capacity improved in a recently published trial using high-intensity knee extensor exercise (resistance) in CHF patients (Magnusson, Gordon et al. 1996).

**Figure 2.3 A.** Muscle strength (peak torque, Newton-metres) before and after exercise training. Panels from left to right: knee extension, knee flexion, chest pull, chest push.  $\square$  = pre-training;  $\blacksquare$  = post-training. **B.** Breathing ( $\text{l}\cdot\text{min}^{-1}$ ) during the graded exercise test.  $\square$  = pre-training;  $\blacksquare$  = post-training (Hare, Ryan et al. 1999).



## 2.5 Summary and Conclusions

Chronic heart failure is a life-threatening condition characterized by insufficient cardiac performance and is the most common cause of hospitalization in people over 65 years. CHF is a costly syndrome due to low functional status, poor quality of life, frequent hospitalizations and poor prognosis of patients.

CHF causes reduced muscle strength and impaired physical fitness (aerobic capacity). These factors combined render CHF patients unable to perform their usual daily activities. Frequently they have associated poor quality of life. Studies documenting the benefits of exercise for CHF patients are fewer than those demonstrating its benefits for coronary artery disease patients. However, in the past decade, researchers have produced some compelling evidence that training may reverse some of the physiological factors associated with poor exercise tolerance and, more importantly, affect significant improvements in functional capacity and quality of life (Squires 1987; Coats 1990; Kao 1994; Sullivan 1996; Keteyian 1997).

Literature has shown, with a number of short-term (3-12 weeks) and long-term (6-12 months) trials that exercise training results in improvements in exercise tolerance and quality of life. CHF and its responses to exercise have been studied in many scientific disciplines, using aerobic, resistance, and circuit training and even isolating responses of individual muscles. A number of research groups have documented strong evidence that patients with CHF can be safely enrolled into exercise training programs and through measuring exercise heart rate, ventilatory, and peak  $\text{VO}_2$  responses, achieve a favorable training response.

In the absence of effective interventions, CHF is characterized by a marked vasoconstriction at rest, and blunted vasodilatory responses to physical exertion. Recent research has suggested that the impaired vasodilatation is mediated by endothelium-dependent nitric oxide. Exercise training can improve symptoms, exercise performance, hemodynamics, ventilation, and autonomic function in CHF patients. There is general agreement that exercise has shown beneficial effects toward the treatment of CHF, but there is as yet to be a consensus on a specific training regiment that should be followed.

Peripheral abnormalities are now considered to be an important determinant of exercise capacity in this population. Evidence has been reported that vascular dysfunction may be reversed by exercise training, specifically through resistance training. Functional limitations in CHF appear to be defined by skeletal muscle abnormalities, such as a lack of blood flow to exercising muscle and significant decreases in muscle strength. Current treatment or aerobic exercise training does not optimally address these impaired peripheral factors. Therefore, resistance training has been proposed on the basis of its potential to improve peripheral blood flow and reverse skeletal muscle weakness. In addition, the benefits of resistance training on muscle oxidative capacity are greater in deconditioned muscle (Ingemann-Hansen 1984), as characterized by CHF. Increased exercise capacity is negatively correlated with morbidity and mortality in these patients, raising the possibility that increasing and then maintaining functional status might improve long-term outcomes. The literature review presented here could lead to a conclusion that it may be in the best interest of the CHF patients for their physicians to include exercise training in their management.

## Chapter 3 GENERAL METHODS

### 3.1 Study Overview

This chapter provides an overview of the patients tested, data collection, testing procedures and reliability of the protocols common to the four studies in this thesis. Further methodological details are included in the Methods sections of each chapter if the method is specific for that chapter only. (Chapter Five includes descriptions of the healthy age-matched volunteers).

In the first study, reliability was assessed for the methods used in this thesis; forearm blood flow (FBF) by venous occlusion plethysmography, muscle strength and endurance with an isokinetic dynamometer, and aerobic power testing on a braked cycle ergometer, by comparing test and retest results (Chapter Four). The second study utilized a cross-sectional design to compare FBF at rest, during submaximal intermittent exercise, and following brief limb occlusion in patients with chronic heart failure (CHF) and age-matched healthy volunteers (Chapter Five). The third study was a randomized control design investigating the effects of three months of resistance exercise training on peripheral blood flow (Chapter Six).

### 3.2 Test procedures

All patients and healthy age-matched volunteers were tested within the Austin and Repatriation Medical Center. Tests were conducted in the hospitals exercise laboratory ( $VO_{2peak}$ ), Coronary Care Research Facility (FBF) and Physiotherapy Department (muscular strength and endurance) where room temperature was stabilized at 19 to 23 degrees C. and emergency procedures were in place, emergency equipment and trained personnel was present. After written, informed consent was obtained, participants reported to the hospital for three tests: FBF,  $VO_{2peak}$ , and muscular strength and endurance. The study protocol was approved prior to commencement by both the relevant Human Research Ethics Committees (Victoria University and the Austin & Repatriation Medical Centre), and conformed to the National Health and Medical Research Council (Australia) Statement on Ethical Conduct of Research in Humans (1999). During the first week (T0), patients undertook a symptom-limited graded exercise test for the assessment of  $VO_{2peak}$ . This was followed two days later by tests for FBF at rest, during submaximal exercise of the

forearm, and in response to imposed limb ischaemia. On the same day, and following the FBF tests, skeletal muscle strength and endurance were determined. All tests were repeated the following week (T1) in the same order, and again after three months (T2). Healthy age-matched volunteers underwent only one series (T0) of the same three tests.

### 3.2.1. Forearm blood flow

Forearm blood flow (FBF) was assessed by venous occlusion plethysmography (VOP). The scientific principle of VOP is that impeding venous return from the arm while arterial inflow continues results in swelling of the forearm at a rate proportional to the rate of arterial inflow. A Hokanson (Bellevue, WA, USA) mercury-in-silastic strain gauge is connected to a plethysmograph (Hokanson EC4). Strain gauge plethysmography measures the total flow in the forearm from wrist cuff to collecting cuff (Benjamin 1995). The rate of change in circumference in response to venous occlusion is digitally recorded by a Maclab/2E data acquisition system (ADI Instruments, Sydney) for determination of forearm blood flow (FBF). FBF is measured as the slope of the change in forearm circumference. For each measurement, forearm venous blood flow is occluded just proximal to the elbow with rapid inflation of a blood pressure cuff.

**Figure 3.1.** Patient set up for FBF by venous occlusion plethysmography.



### 3.2.1.1 Calibration

A jig has been constructed, especially for calibrating strain gauges. The gauge can be secured at one end while attached to a graduated dial on the other, each full turn of the dial stretches (counter-clockwise) or compresses (clockwise) the gauge by 0.02 cm. The gauges are connected to the plethysmographs, with the range set to 5% and the baseline position dial in the furthest counter-clockwise position and this goes directly into a MacLab. While attached to the jig, a metric tape measure is used to measure the gauges unstretched length. Then the strain gauge is stretched by 4 full turns of the graduated dial. The change in voltage over this stretch is noted, and recorded as the mechanically calculated value of change of output in mV increase in limb volume.

### 3.2.1.2 FBF at rest, exercise and following limb occlusion

Tests were in the morning, with patients arriving at 08:30 to a temperature controlled room (23° C). Participants were asked to eat a light breakfast and refrain from caffeine for 12 hours before the test. Participants rest supine with both arms on a foam support in the same position on each of the three occasions, slightly above the right atrium to ensure venous drainage. Pneumatic pressure cuffs (Hokanson, Bellevue, WA) and strain gauges (Medasonics, Mountain View, CA) were positioned as the patient lay comfortably. Paediatric cuffs (Hokanson), used on the wrists to exclude the hand circulation from the measurements, were connected to a flow-regulated source of compressed air, and arm cuffs to a rapid cuff inflator (Hokanson). A 10 second inflation of the arm cuff, results in a linear increase in forearm volume, then a five second deflation allows forearm veins to empty before the next measurement (Benjamin 1995). Strain gauges two cm shorter than the largest circumference of the forearm were used. The strain gauges were placed at the point of maximum girth on both forearms, and measurements were recorded regularly. Output data from the strain gauges were displayed in real time on a laptop computer (Macintosh), after being calibrated.

Prior to starting, the protocol was explained in detail to the patients. Cuff inflations were also demonstrated, before collecting resting blood flow measurements. The congestion cuff was inflated rapidly to a pressure between venous and arterial (50 mmHg) and deflated in a 15 second cycle, during each measurement. At least six flows were obtained at each measurement time.

Wrist cuffs were inflated to above systolic pressure (200 mmHg) for 1 minute before and during each measurement to exclude the hand circulation from the forearm blood flow determination. After six resting measurements, forearm exercise was started and consisted of an intermittent isometric contraction protocol squeezing the handgrip dynamometer (maintained for 5 seconds and released for 10 seconds). Forearm exercise was performed at 15%, 30%, and 45% of maximum voluntary contraction (MVC) (determined by taking the mean of three MVC attempts) for approximately 3.5 minutes. Exercise intensities were selected to compare against earlier studies which followed a similar (Zelis 1974) or same established protocol (Arnold 1990; Katz 1996). FBF measurements were obtained during the relaxation phase between each isometric contraction for each of the three workloads.

### **3.2.1.3 FBF following limb occlusion: peak reactive hyperemia**

Following a 5-minute recovery period from 45% MVC exercise peak reactive hyperemic (PRH) blood flow was measured. Peak vasodilatory capacity was determined as the first blood flow measurement within five seconds following the release of an occluding arm cuff that had been inflated to a pressure that occluded all arterial inflow (>200 mmHg) for the previous 5 minutes. After 4 minutes of arm occlusion (1 minute before releasing the cuff pressure), wrist cuffs were inflated to exclude blood flow of the hand. Reactive hyperemic blood flow was measured at 5, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 seconds, with upper arm cuffs inflated to 50 mmHg for 8 out of every 15 seconds. The maximal flow determined during this period was deemed to represent peak vasodilatory capacity.

### **3.2.1.4 Blood Pressure**

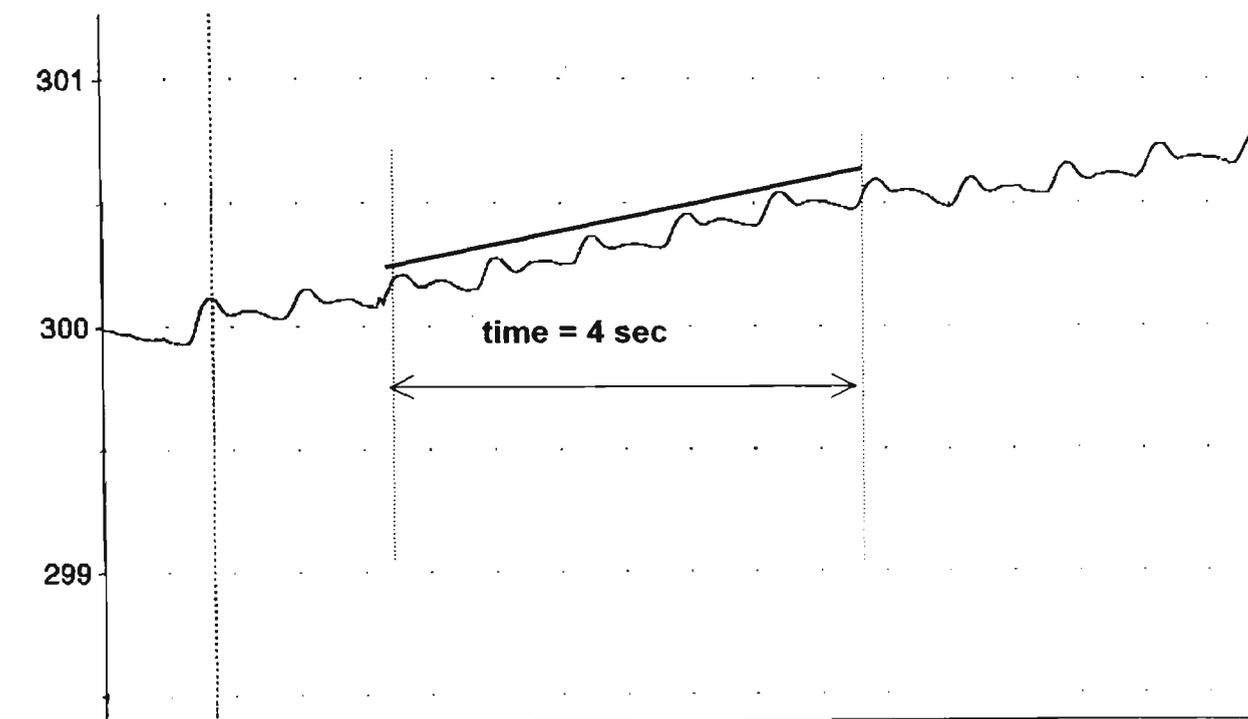
Blood pressure (BP) was measured on the contralateral limb throughout each FBF protocol. The BP did not change in response to either exercise or limb occlusion, demonstrating that central haemodynamics was unaffected by the protocol. This is consistent with previous studies using a similar protocol (Sullivan 1989).

### **3.2.1.5 Calculation of forearm blood flow**

A method of random coding and decoding of files by a neutral third party was developed to insure that the candidate analysed all FBF records while blinded to the identification of the

patientvolunteers and the group allocation of participants. FBF was calculated from the rate of increase in forearm circumference (Flow = 200 x increase in forearm circumference (mm/min) / forearm circumference (mm)) is expressed in units of ml.100 ml<sup>-1</sup>min<sup>-1</sup> (Benjamin 1995) and is determined from the mean slope of each recorded measurement (Figure 3.2). Total test time for the visit was approximately one hour.

**Figure 3.2.** Example of venous occlusion plethysmogram



Tracing shows changes in forearm circumference. Increase in circumference with time is recorded when venous outflow is temporarily occluded.

### 3.2.2. $VO_{2peak}$ tests

Peak total body oxygen consumption ( $VO_{2peak}$ ) tests was determined during a symptom-limited graded exercise test on an electronically-braked bicycle ergometer (Ergomed, Siemens, Erlangen, Germany), commencing at 10 W and increasing by 10 W.min<sup>-1</sup> until the patient could no longer continue to pedal at a minimum cadence of 60 revolutions per minute. Heart rate and ECG was measured by 12-lead electrocardiographic (Marquette, USA) monitoring throughout exercise and recovery. Arterial oxygen saturation was monitored by pulse oximetry

(Oxi-Raiometer, Boulder, Colorado). Blood pressure was measured and recorded by a physician using a mercury sphygmomanometer before exercise, during exercise (every two minutes) at maximum exertion, and several times throughout recovery. The Borg rating of perceived exertion (RPE) (Borg 1973) was recorded at the end of each minute, prior to the increase of resistance (10W). Expired air was collected and analyzed for ventilation, oxygen intake, carbon dioxide output and (more) gas exchange ratio (RER) using a large two-way non-rebreathing valve (Han Rudolph) leading to a mixing chamber (RFU 1975), through an analog-to-digital converter board (Data Translation Inc.) and onto a computer screen (Gateway Computer Corporation, USA E-3000). The software was hand written by technicians at the Austin & Repatriation Medical Center's respiratory laboratory, using standardized physiological equations. The gas analyzer and flow meter (LB2 Medical Gas Analyzer and Hewlett Packard 47304 & Fleisch pneumotach flowmeter) were calibrated according to the manufacturer's recommendations before each test. The gas meters were calibrated against gases of known concentrations before each test. Oxygen uptake ( $\text{VO}_2$ ) and carbon dioxide output ( $\text{VCO}_2$ ) were determined from the measurement of oxygen and carbon dioxide concentration in the inspired and expired air.

### **3.2.3 Muscle strength, power, and endurance**

Unilateral skeletal muscle strength and endurance for knee and elbow extension / flexion were assessed according to methods that have been established in an earlier prospective, uncontrolled observational outcome study (Hare, Ryan et al. 1999) using an isokinetic dynamometer (MERAC<sup>®</sup>; Universal, Cedar Rapids, Iowa, USA) with microprocessor, which had been calibrated for torque and angular velocity according to manufacturer protocols. Limb position and a torque correction for limb weight were calibrated prior to each movement pattern. Limb and torso alignments and machine settings were all recorded at the time of familiarization (T0) and replicated for baseline (T1) and endpoint (T2). Full range of movement within the constraints of the equipment was prescribed for each movement pattern in order to eliminate errors that could be caused by patients who failed to complete full repetitions. Standard instructions were issued with regard to both the technique and the maximal effort required during each test. The patients then practiced the movement patterns just prior to each trial. If smooth curves for torque were not obtained during practice, they were required to repeat these after a brief rest. Strength of the knee extensors and flexors were measured as the peak angular force

(torque, Nm) generated during three maximal continuous repetitions at  $60^{\circ}.\text{sec}^{-1}$  angular velocity. Following three minutes of rest, endurance was determined as the total angular work (joules) achieved during the middle 16 of 20 consecutive maximal repetitions at  $180^{\circ}.\text{sec}^{-1}$ . A similar approach was followed for elbow extension / flexion, except that endurance was measured at  $120^{\circ}.\text{sec}^{-1}$ , as patients were not able to generate sufficient force during the latter repetitions at the higher speed. A recovery period of three minutes was allowed between each of the four (ie knee strength, knee endurance, elbow strength and elbow endurance) maneuvers.

### **3.2.4 Familiarization**

At least one week prior to commencing baseline measurements, each patient was familiarized with the equipment and testing procedures. Each test was performed as if it were the baseline measurement.

### **3.2.5 Resistance training**

Training (three months, 3 sessions per week) was undertaken in a hospital rehabilitation gymnasium using a multi-station hydraulic resistance training system (HydraGym, Belton, USA), arm (RepcO, Australia) and leg cycling (RepcO, Australia) ergometers, and a set of five stairs. Blood pressure and ECG rhythm were recorded after the patients had rested for 10 minutes following arrival. Cardiac rate and rhythm were continuously monitored and recorded during exercise on a four channel (patient) telemetry system (prototype designed and constructed by Victoria University bioengineers, Melbourne, Australia). The graduated resistance training program performed by the Exercise training group in Chapter Six used the following exercises: alternating between upper and lower body: leg cycling (0.5 - 2 minutes), elbow extension / flexion (30 seconds), stair climbing (0.5 - 2 minutes), arm cycling (0.5 - 2 minutes), knee extension / flexion (30 seconds), shoulder press / pull (30 seconds). There were also 5 minute warm-up and cool-down routines including gentle aerobic exercise and stretching. Arm and leg cycling, and stair climbing were each of short duration (0.5 - 2 minutes) and relatively moderate intensity (by heart rate monitoring), the objective being to provide additional strength exercise while minimizing aerobic training effects and to conform to the resistance training format. Recovery intervals between exercises were determined as the period required to return heart rate to within 10 beats of the pre-exercise (rest) recording. This was typically 1-2 minutes between

exercises, and together with the relatively high intensities used, ensured that the training program could be categorized as resistance training. In contrast, circuit training exercises follow continuously without rest intervals to maintain elevated heart rates and are therefore necessarily of lower intensity. Workload intensities were reduced if heart rate responses were in excess of 5  $\text{b}\cdot\text{min}^{-1}$  below the peak heart rate recorded during  $\text{VO}_{2\text{peak}}$  testing. Exercise progressions were introduced gradually either by increasing intensity (resistance) or the number of sets for a given exercise. Refer to Appendix A3 for the training record sheet. Adherence was monitored as attendance and adverse events were recorded wherever they occurred. Training volume (arbitrary units) was estimated as the sum of the product of resistance (derived from the exercise machine settings) and the number of repetitions for each of the exercises.

The hospital based training (11 weeks, 3 sessions per week) program will be performed using hydraulic resistance training equipment (Hydra-Gym, Australia), a stationary bicycle (RepcO, Australia) and an upper limb ergometer (Monark, Sweden). Training intensity will increase gradually as heart rate recovery times fall below pre-set criteria for each patient. Training will be organized as circuits (ie moving smoothly from one exercise to the next) and include seated chest pull/push, seated knee extension/flexion, seated shoulder pull/push, leg cycling, stair climbing and arm cycling, with 5 minute warm-up and cool-down routines. The circuit alternates exercises between the upper and lower body (see Figure 3.3 below). The duration of each resistance exercise is 30 seconds. After each exercise heart rate is monitored with ECG telemetry (computer) until it falls to a pre-determined level.

**Figure 3.3.** Progression of Resistance Training circuit utilized for the Exercise training group. ↓ represents the recovery period required to return the exercising heart rate to within 10 beats of the pre-exercise (rest) recording.

Warm-up of five minutes included walking and stretching of large muscle groups



Stationary bike (0.5 to 2 minutes) *Lower Body*



Chest Press (30 seconds) *Upper Body*



Stairs (0.5 to 2 minutes) *Lower Body*



Arm Ergometer (0.5 to 2 minutes) *Upper Body*



Leg Extension/Leg Curl (30 seconds) *Lower Body*



Shoulder Press (30 seconds) *Upper Body*



Stationary bike (0.5 to 2 minutes) *Lower Body*



Cool-down of five minutes included walking and stretching of large muscle groups

# Chapter 4 RELIABILITY OF FBF, STRENGTH, AND $VO_{2peak}$ TESTING FOR PATIENTS WITH CHRONIC HEART FAILURE

## 4.1 Overview

The current study (Chapter Four) is an investigation into the reliability of forearm blood flow (FBF) by venous occlusion plethysmography, muscle strength and endurance, and aerobic power testing by comparing test and retest results. This study focuses on the clinical population of patients with chronic heart failure (CHF) and further examines the repeated measures of  $VO_{2peak}$ .

## 4.2 Abstract

**Purpose:** To assess the reliability of testing forearm blood flow, skeletal muscle strength and peak aerobic power in a clinical population of patients with CHF.

**Method:** This study investigated the reliability of FBF by venous occlusion plethysmography, muscle strength and endurance, and aerobic power in 33 patients with CHF. Each patient underwent two identical series of tests (T0 and T1), one week apart, for strength and endurance of the muscle groups responsible for knee extension / flexion and elbow extension / flexion. FBF was measured by strain gauge venous occlusion plethysmography at rest, during the last minute of each exercise bout and following brief limb occlusion. The patients also underwent two graded exercise tests on a bicycle ergometer to measure peak aerobic power ( $VO_{2peak}$ ). Three months later, 18 of the patients underwent a third test (T2) for each of the measures. Means were compared using MANOVA with repeated measures for strength and endurance, and ANOVA with repeated measures for  $VO_{2peak}$ .

**Results:** After one week there was an increase in strength from T0 to T1 of  $12 \pm 25\%$ . Comparable results were found with endurance, increasing by  $13 \pm 23\%$ . While results for  $VO_{2peak}$  and FBF remained unchanged ( $VO_{2peak}$ :  $16.2 \pm 0.8$  and  $16.1 \pm 0.8$  ml.kg<sup>-1</sup>.min<sup>-1</sup>

for T0 and T1, respectively) (FBF: combined data =  $10.45 \pm 7.1 \text{ ml} \cdot 100\text{mL}^{-1} \cdot \text{min}^{-1}$  for T0 and  $9.8 \pm 5.8 \text{ ml} \cdot 100\text{mL}^{-1} \cdot \text{min}^{-1}$  for T1). Three months later, re-testing (T2) showed no significant changes between T1 and T2 for muscular strength and endurance or FBF, but  $VO_{2peak}$  decreased from  $16.7 \pm 1.2$  to  $14.9 \pm 0.9 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ( $-10 \pm 18\%$ ;  $P=0.021$ ;  $ICC = 0.89$ ).

**Conclusion:** When testing patients with CHF, a familiarization trial for skeletal muscle strength testing is necessary. Whilst familiarization is not required for assessing FBF or aerobic power as a single measurement,  $VO_{2peak}$  declined markedly in the three month period for which these patients were followed.

### 4.3 Introduction

In the past ten years a number of studies have been published establishing that exercise training can improve  $VO_{2peak}$ , increase peak cardiac output, reverse skeletal muscle abnormalities, increase nutritive blood flow (Hare, Ryan et al. 1999), improve quality of life and clinical outcomes (Belardinelli, Georgiou et al. 1999). However, nearly all the past studies with exercise and CHF patients have used aerobic training, although this shows vast improvements in cardiorespiratory capacity, it does not target skeletal muscle. It has therefore been postulated that exercises directed more towards increasing muscle strength would have advantages over and above aerobic training. Therefore resistance training has recently been proposed as a means of partially reversing the skeletal muscle problems and abnormal blood flow, thereby improving exercise tolerance. This form of training has been used in patients with coronary artery disease (CAD) (McCartney, McKelvie et al. 1991), but there are very few publications regarding resistance training with CHF. Traditionally, there was concern about recommending resistance exercise to cardiac patients due to possible compromise of LV function, increase hemodynamic burden, cause abnormal wall motions, arrhythmias and other safety factors. In a study, which looked at hemodynamic responses in relation to resistance training versus aerobic training, at comparable intensities, the resistance training showed more favorable responses (McKelvie 1995). Concerns have now been allayed, somewhat, by recent experience with resistance training, including that reported by Hare et al. (Hare, Ryan et al. 1999). Rationale for this intervention include the goals to increase peripheral blood flow and skeletal muscle strength and endurance, to partly reverse skeletal muscle atrophy and metabolic deficits that are common in

these patients. In addition, to provide interesting, alternative forms of exercise training to aerobic training, and to enable activities of daily living to be performed at lower and therefore safer levels of intensity than prior to the exercise training.

Information as to the efficacy of resistance training programs in CHF populations is limited and there is no published data on the need to familiarize these patients with strength testing protocols prior to them being tested for strength. Following a single bout of resistance exercise training a learning effect may occur (Rutherford 1986) suggesting that a true measurement of strength is not observed on initial testing. Evidence-based practice depends on reliable efficacy data and thus it is important to establish the reliability of testing both skeletal muscle strength and endurance in these patients. Thus the objective of this study was to assess the reliability of strength and musculoskeletal endurance testing in a group of patients with stable CHF. Most investigators who have studied the effects of resistance training in cardiovascular patients have also evaluated the effects on peak aerobic power ( $VO_{2peak}$ ) and forearm blood flow (FBF).  $VO_{2peak}$  is a very important prognostic indicator for CHF patients (Pilote L 1989), and although the absolute changes in  $VO_{2peak}$  are low in CHF patients, any small improvements may be of clinical significance. In addition to hemodynamic modifications that reduce cardiac output in patients with CHF (Katz 2002), peripheral factors such as blood flow may contribute to exercise intolerance. Therefore accurate measures of  $VO_{2peak}$  and FBF are essential. Although many investigators have previously included familiarization protocols for the assessment of  $VO_{2peak}$  in cardiovascular patients (Sullivan, Higginbotham et al. 1988; Coats, Adamopoulos et al. 1992; Adamopoulos, Coats et al. 1993; Belardinelli, Geotgiou et al. 1995; Ades, Waldmann et al. 1996; Kavanagh, Myers et al. 1996; Keteyian 1996; Ferketich, Kirby et al. 1998; Maiorana, O'Driscoll et al. 2000), there is no published data on the reliability of  $VO_{2peak}$  testing in these patients. Therefore, the current study will also assess the test-retest reliability of  $VO_{2peak}$  in CHF patients.

## Hypotheses

1. In CHF patients, a familiarization trial is necessary when measuring skeletal muscle strength and endurance testing using an isokinetic apparatus.

In CHF patients, a familiarization trial is not necessary when measuring;

2. peak aerobic power ( $VO_{2peak}$ ) determined by a symptom-limited graded exercise test on an electronically-braked bicycle ergometer.
3. forearm blood flow by venous occlusion plethysmography.

## 4.4 Methods

### 4.4.1 Participants

The cohort consisted of 33 patients with stable CHF (28 male, 5 female) of mean age  $65 \pm 9$  years (SD), mean New York Functional Class  $2.5 \pm 0.5$ , mean left ventricular ejection fraction (LVEF%)  $27 \pm 7\%$ . Nineteen patients (60%) had ischaemic cardiomyopathy and the remainder (40%) had dilated cardiomyopathy. Most were on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and a diuretic. These and other medications that patients were taking at Entry and Exit are summarized in Table 4.1.

Participants were informed of all test procedures and associated risks (Appendix A1) before completing a detailed medical questionnaire and given written informed consent (Appendix A2) prior to commencing the study. Prior to the recruitment of participants, ethics approval was obtained from the Victoria University Human Research Ethics Committee and the Austin and Repatriation Medical Center. The project complied with the NHMRC Statement on Human Experimentation.

Inclusion criteria to the study was as follows; (i) male and female adults were included without specific restriction because of their age; (ii) any aetiology of left ventricular systolic failure; (iii) a left ventricular ejection fraction below 40%; (iv) and stable pharmacological therapy with a minimum of two weeks unaltered drug therapy at entry.

Exclusion criteria to the study was as follows; (i) NYHA Class IV patients that had symptoms at rest or during minimal activity; (ii) cardiovascular limitations that would prevent taking part in the exercise program such as previous cardiac arrest, recent surgery, aortic stenosis, symptomatic or sustained ventricular tachycardia or current exercise limitation because of angina; (iii) musculo-skeletal or respiratory problems that would prevent appropriate exercise; (iv) metabolic diseases such as diabetes.

#### **4.4.2 Design**

##### **4.4.2.1 Overview**

For each patient, all testing was conducted at the same time of day in the same order in temperature controlled hospital laboratories, where emergency equipment and trained personnel was present. During the first week (T0), patients undertook a graded exercise test for the assessment of aerobic power ( $VO_{2peak}$ ), followed two days later by tests for skeletal muscle strength and endurance. All tests were repeated the following week (T1) and, for a subgroup of 18 patients, again after three months (T2). The subgroup of 18 was requested to maintain their previous activity levels (before T0) and this was monitored. The remaining 15 patients were not tested at T2 because they were prospectively randomized to exercise training after T1 as part of a larger study (Chapter Six).

**Table 4.1.** Descriptive characteristics of the 33 patients who underwent T0 and T1, and the corresponding data for the 18 patients who also underwent T2.

	Whole group (n=33)		Subgroup (n=18)	
	Entry	Exit	Entry	Exit
Age, yrs	65 ± 9		64 ± 9	
Male / Female	28 / 5		16 / 2	
Height (cm)	170 ± 8		170 ± 7	
LVEF%	27 ± 7		28 ± 6	
NYHA	2.3 ± 0.5		2.3 ± 0.5	
Weight	80 ± 13	82 ± 13	80 ± 12	82 ± 11
<b>CHF diagnosis</b>				
Ischemic heart disease	19 (58%)		11 (61%)	
Dilated cardiomyopathy	14 (42%)		7 (39%)	
<b>Medications</b>				
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	29 (88%)	29 (88%)	16 (89%)	16 (89%)
Diuretic	28 (85%)	28 (85%)	15 (83%)	15 (83%)
Beta-blocker	14 (42%)	14 (42%)	8 (44%)	8 (44%)
Digoxin	12 (36%)	12 (36%)	7 (39%)	7 (39%)
Aspirin	19 (58%)	18 (55%)	10 (55%)	9 (50%)
Warfarin	13 (39%)	12 (36%)	8 (44%)	8 (44%)
<b>Amiodarone</b>	5 (15%)	6 (18%)	4 (22%)	3 (17%)
Nitrates	3 (9%)	3 (9%)	2 (11%)	2 (11%)
Calcium channel antagonist	2 (6%)	2 (6%)	2 (11%)	2 (11%)

#### 4.4.2.2 Exercise testing protocols

All experimental procedures and equipment for FBF measurement using strain gauge venous occlusion plethysmography have been fully described earlier (Chapter Three). Briefly, unilateral skeletal muscle strength and endurance for knee and elbow extension / flexion were assessed using an isokinetic dynamometer (MERAC®; Universal, Cedar Rapids, Iowa, U.S.). Limb position and a torque correction for limb weight were calibrated prior to each movement pattern. Limb and torso alignments and machine settings were all recorded at the time of T0 and replicated for T1 and T2. Full range of movement within the constraints of the equipment was prescribed for each movement pattern in order to eliminate errors that could be caused by patients who failed to complete full repetitions. Standard instructions were issued with regard to both the technique and the maximal effort required during each test. The patients then practiced the movement patterns just prior to each trial. If smooth curves for torque were not obtained during practice, they were required to repeat these after a brief rest.

Exercise testing was performed while seated on an electronically-braked cycle ergometer (Ergomed, Siemens, Erlangen, Germany), with a workload commencing at 10 W and increasing  $10 \text{ W}\cdot\text{min}^{-1}$  until the patient could no longer continue to pedal at a minimum cadence of 60 revolutions per minute. Heart rate and ECG was measured by 12-lead electrocardiographic (Marquette, USA) monitoring throughout exercise and recovery. Oxygen uptake ( $\text{VO}_2$ ) and carbon dioxide output ( $\text{VCO}_2$ ) were determined from the measurement of oxygen and carbon dioxide concentration in the inspired and expired air.

FBF was measured with a mercury-in-Silastic rubber strain gauge placed at the maximum girth of the dominant forearm. Pressure cuffs were applied to the wrist (inflated to 200 mm HG 1 minute prior to recording) and upper arm (inflated to 50 mm HG for 5 to 7 seconds for each flow recording).

### 4.4.2.3 Testing measures

#### 4.4.2.3.1 Forearm blood flow

FBF was calculated from the rate of increase in forearm circumference (Flow =  $200 \times$  increase in forearm circumference (mm/min) / forearm circumference (mm)) expressed in units of  $ml \cdot 100mL^{-1} \cdot min^{-1}$  and is determined from the mean slope of each recorded measurement.

#### 4.4.2.3.2 Muscle strength and endurance test

Strength of the knee extensors and flexors were measured as the peak angular force (torque, Nm) generated during three maximal continuous repetitions at  $60^\circ \cdot sec^{-1}$  angular velocity. Following three minutes rest, endurance was determined as the total angular work achieved during the middle 16 of 20 consecutive maximal repetitions at  $180^\circ \cdot sec^{-1}$ . A similar approach was followed for elbow extension / flexion, except that endurance was measured at  $120^\circ \cdot sec^{-1}$ , as patients were not able to generate sufficient force during the early repetitions at the higher speed. A recovery period of three minutes was allowed between each of the four (ie knee strength, knee endurance, elbow strength and elbow endurance) maneuvers.

#### 4.4.2.3.3 $VO_{2peak}$

Measurements were made each minute of  $VO_2$  (OM-11 Medical Gas Analyser, Beckman, Fullerton, CA, U.S.),  $VCO_2$  (LB2 Medical Gas Analyser, Beckman, Fullerton, CA, U.S.), minute ventilation ( $V_E$  (BTPS), 47304A respiratory flow transducer with Fleisch pneumotach, Hewlett Packard, U.S.), heart rate (EK43 Multiscriptor 12 lead ECG, Hellige, Belgium), arterial oxygen saturation (Biox 3700 Pulse Oximeter, Oxi-Radiometer, Boulder, Colorado, U.S.) and self-ratings of perceived exertion. (Borg 1973) Respiratory exchange ratio (RER) was measured each minute and  $RER_{peak}$  and  $HR_{peak}$  were used as indices of metabolic stress at the end of the  $VO_{2peak}$  test. All instrumentation used in the measurement of  $VO_{2peak}$  was calibrated using standard methods before and immediately after each test

### 4.4.3 Statistical Analyses

FBF and  $VO_{2peak}$  data were compared for T0, T1, and T2, where applicable, using one-way ANOVA with repeated measures. Similarly, skeletal muscle strength and endurance for each of the four movement patterns were compared using MANOVA with repeated measures. Consistency of values within cases is presented using four approaches: (i) Scatterplots, with the line of equality (Bland 1986); (ii) Bland-Altman plots to graph the measurement errors against the true values (Bland 1986); (iii) calculation of the intraclass correlation coefficient for each variable; (iv) estimation of the 95% confidence intervals (CI) (Bland 1996). The statistical analyses were performed using SPSS (version 10.0.5; SPSS Inc. Headquarters, Chicago, Illinois, U.S.). Data is expressed as mean  $\pm$  SD and the level of significance was set at  $P < 0.05$  for all variables.

## 4.5 Results

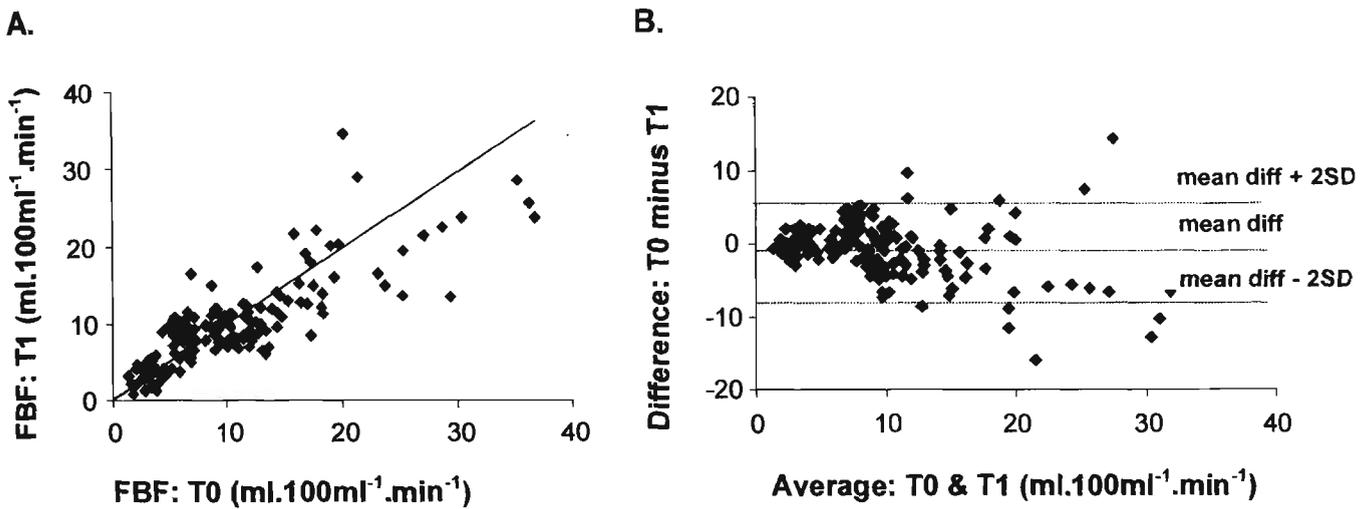
### 4.5.1 Forearm blood flow

The consistency of values within cases for FBF at T0 and T1 for the five test situations are displayed in Figure 4.4. Combining data for all five, FBF did not change significantly between the first and second tests (combined data =  $10.45 \pm 7.1 \text{ ml} \cdot 100\text{mL}^{-1} \cdot \text{min}^{-1}$  for T0 and  $9.8 \pm 5.8 \text{ ml} \cdot 100\text{mL}^{-1} \cdot \text{min}^{-1}$  for T1;  $P = 0.827$ ,  $\text{ICC} = 0.83$ , Figure 4.4). After the three months, 18 of the patients underwent a third test (T2) for each of the five test situations. There were no significant differences between T1 and T2 for any of the five FBF measures (combined difference for FBF was  $4\% \pm 23\%$ ;  $95\% \text{ CI} = -2\% \text{ to } +3.3\%$ ;  $P = 0.595$ ;  $\text{ICC} = 0.76$ ; Table 4.4 and Figure 4.4). To assess that no change in central hemodynamic occurred during the forearm exercise protocol, blood pressure was repeatedly measured. There was no significant change in blood pressure, suggesting forearm exercise produced local vascular changes only (Figure 4.5 A and B)

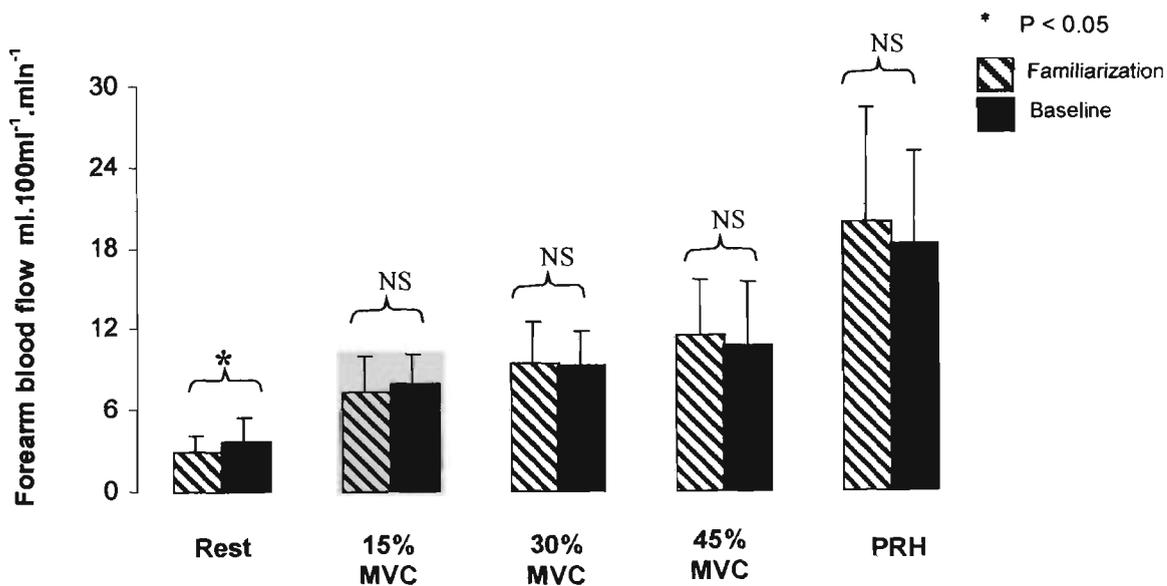
**Table 4.2.** FBF testing, for the 33 patients who underwent T0 and T1, and the corresponding data for the 18 patients who also underwent T2. Units for FBF are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD.

Test	FBFrest	15% MVC	30% MVC	45% MVC	PRH	All movements
<b>FBF testing for 33 patients who underwent T0 and T1</b>						
T0	$3.2 \pm 1.1$	$7.8 \pm 2.8$	$9.5 \pm 2.9$	$11.3 \pm 3.9$	$20.0 \pm 8.2$	$10.5 \pm 7.1$
T1	$3.5 \pm 1.5$	$7.8 \pm 1.9$	$8.7 \pm 2.1$	$10.0 \pm 2.6$	$17.2 \pm 6.1$	$9.8 \pm 5.8$
ICC	0.78	0.94	0.81	0.70	0.63	0.83
<b>FBF testing for 18 patients who underwent T1 and T2</b>						
T1	$3.3 \pm 1.4$	$7.8 \pm 1.5$	$8.8 \pm 2.0$	$10.3 \pm 2.6$	$17.2 \pm 7.1$	$9.7 \pm 5.9$
T2	$3.2 \pm 1.7$	$7.3 \pm 3.2$	$8.7 \pm 3.2$	$9.8 \pm 5.0$	$15.9 \pm 6.5$	$9.3 \pm 5.8$
ICC	0.74	0.93	0.87	0.69	0.60	0.76

**Figure 4.1.** Left Panel (A) (Scatterplot): Test-retest data (n=33 patients) for the first (T0, horizontal axis) and second (T1, vertical axis) tests for FBF. The dashed line is the line of identity. Right Panel (B) (Bland-Altman plot): Average of T0 and T1 (horizontal axis) versus Difference of T1 and T0 (vertical axis). Dashed lines represent mean difference and the mean difference plus or minus 2SD's of the mean difference.

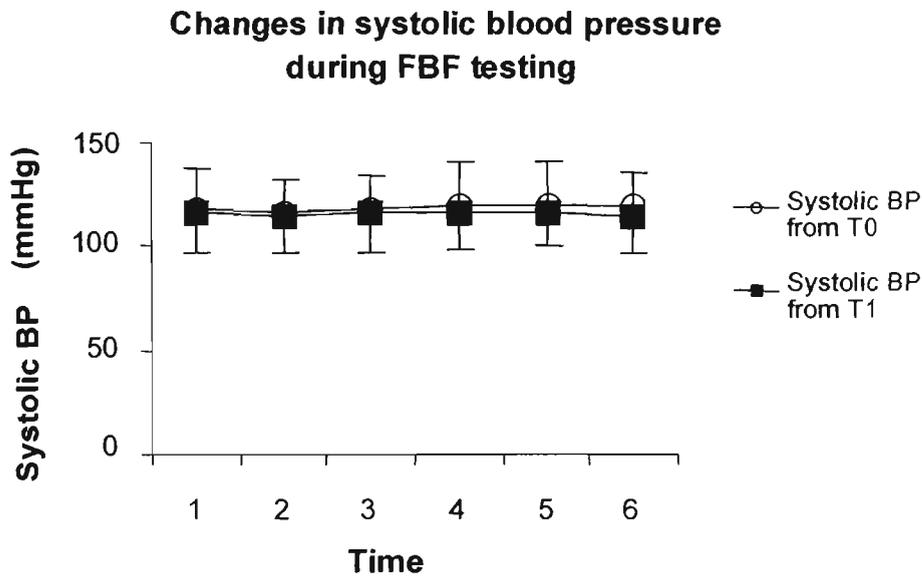


**Figure 4.2.** Effects of familiarization on FBF in CHF patients. Units for FBF are ml·100mL<sup>-1</sup>·min<sup>-1</sup>. Data are presented as mean ± SD. \* P < 0.05.

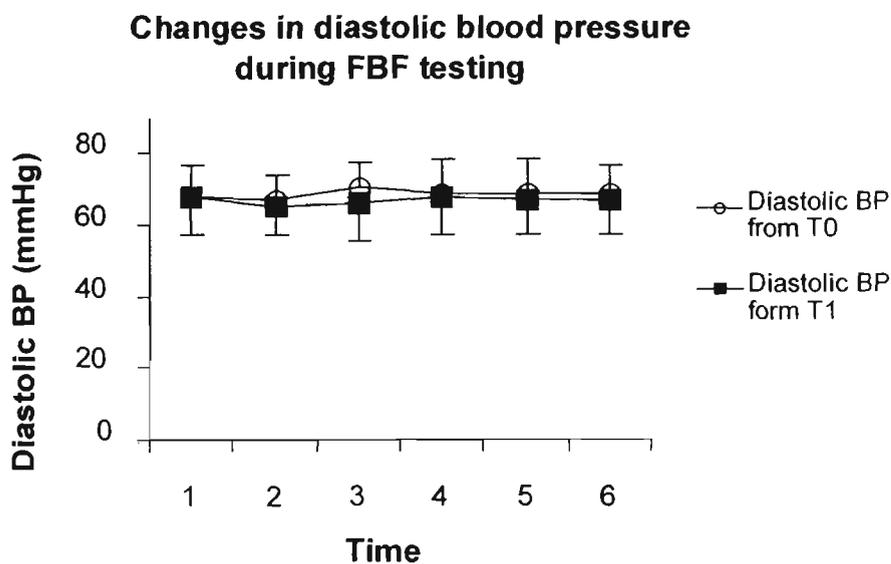


**Figure 4.3.** Systolic (A.) and diastolic (B.) blood pressure data (n=33 patients) during FBF testing at rest, during exercise, and following brief limb occlusion for the first (T0) and second (T1) tests for FBF. Units for BP are mmHg. Data are presented as mean  $\pm$  SD.

A.



B.



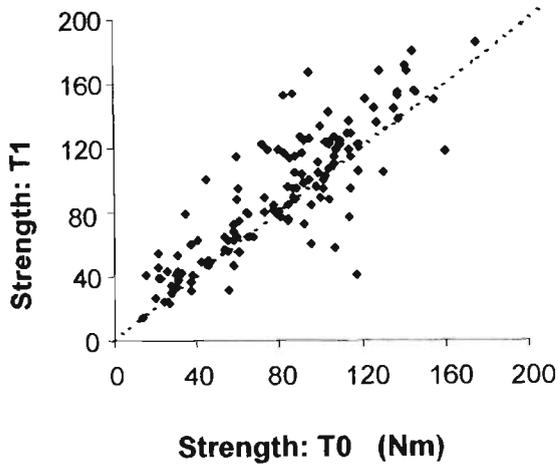
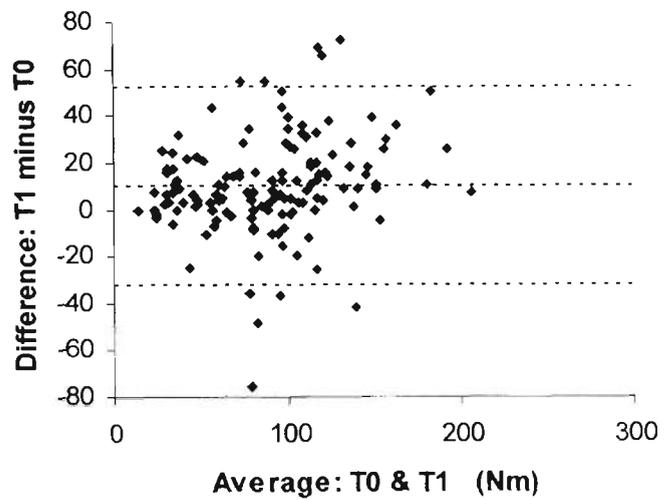
### 4.5.2 Strength and endurance

The consistency of values within cases for strength at T0 and T1 for the four movement patterns are displayed in Figure 4.1. Combining data for all four movement patterns, strength increased from T0 to T1 by  $12 \pm 25\%$  (95% confidence interval (CI) =  $-38\%$  to  $+62\%$ ;  $P < 0.001$ ; ICC = 0.89). The expression of strength for the knee extensors increased by  $13 \pm 21\%$  (ICC = 0.88; Table 4.2). The corresponding increases for knee flexors, elbow extensors and elbow flexors were  $27 \pm 38\%$  (ICC = 0.75),  $6 \pm 24\%$  (ICC = 0.89) and  $15 \pm 28\%$  (ICC = 0.81), respectively (as shown in Table 4.2).

Correspondingly, the expression of endurance increased by  $13 \pm 64\%$  (95% CI =  $-58\%$  to  $+84\%$ ;  $P = 0.004$ ; ICC = 0.87). The gains in strength and endurance were correlated ( $R^2 = 0.155$ ;  $P = 0.010$ ). Endurance increased for the knee extensors by  $9 \pm 64\%$  (ICC = 0.89; Table 4.2). The corresponding increases for knee flexors, elbow extensors and elbow flexors were  $10 \pm 77\%$  (ICC = 0.84),  $13 \pm 96\%$  (ICC = 0.84) and  $20 \pm 77\%$  (ICC = 0.88), respectively.

Three months later, 18 of the patients underwent a third test (T2) for each of the measures. There were no significant differences between T1 and T2 for any of the four strength or endurance measures (combined difference for strength was  $2\% \pm 23\%$ ; 95% CI =  $-43\%$  to  $+47\%$ ;  $P = 0.736$ ; ICC = 0.92; Figure 4.2, and for endurance was  $-1 \pm 54\%$ ; 95% CI =  $-59\%$  to  $+58\%$ ;  $P = 0.812$ ; ICC = 0.96; Table 4.2).

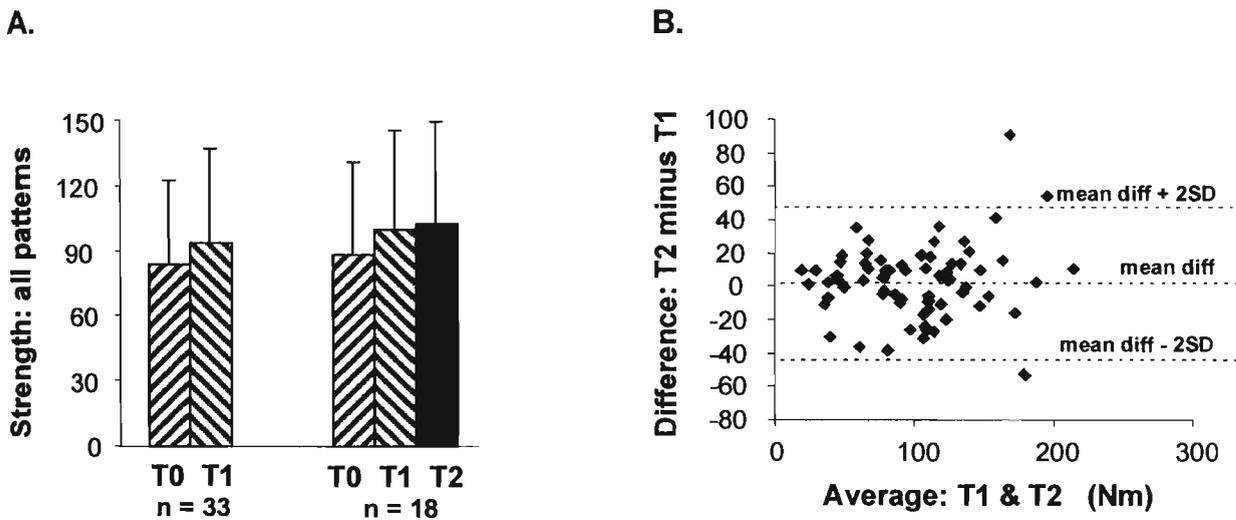
**Figure 4.4. A.** (Scatterplot): Test-retest data (n=33 patients) for the first (T0, horizontal axis) and second (T1, vertical axis) tests for strength. The dashed line is the line of identity. **B.** (Bland-Altman plot): Average of T0 and T1 (horizontal axis) versus Difference of T1 and T0 (vertical axis). Dashed lines represent mean difference and the mean difference plus or minus 2SDs of the mean difference. For both panels, each data point represents the T0-T1 comparison for one of the four movement patterns (knee extension / flexion, elbow extension / flexion) in an individual patient.

**A.****B.**

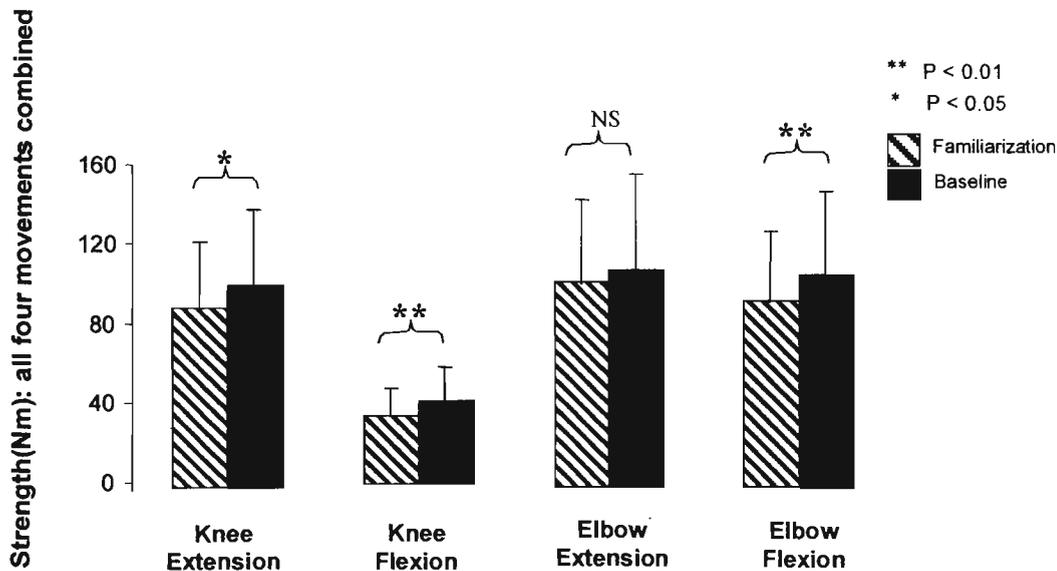
**Table 4.3.** Skeletal muscle strength and endurance, for the 33 patients who underwent T0 and T1, and the corresponding data for the 18 patients who also underwent T2. Units for skeletal muscle strength and endurance are Nm. Data are presented as mean  $\pm$  SD.

<b>Test</b>	<b>Knee Extension</b>	<b>Knee Flexion</b>	<b>Elbow Extension</b>	<b>Elbow Flexion</b>	<b>All movements</b>
<b>Skeletal muscle strength for 33 patients who underwent T0 and T1</b>					
T0	88 $\pm$ 33	33 $\pm$ 14	101 $\pm$ 41	91 $\pm$ 35	83 $\pm$ 39
T1	99 $\pm$ 38	41 $\pm$ 17	106 $\pm$ 49	104 $\pm$ 42	94 $\pm$ 43
ICC	0.88	0.75	0.89	0.81	0.89
<b>Skeletal muscle endurance for 33 patients who underwent T0 and T1</b>					
T0	986 $\pm$ 419	408 $\pm$ 208	640 $\pm$ 266	710 $\pm$ 379	686 $\pm$ 386
T1	1071 $\pm$ 424	449 $\pm$ 220	722 $\pm$ 399	853 $\pm$ 497	774 $\pm$ 454
ICC	0.89	0.84	0.84	0.88	0.87
<b>Skeletal muscle strength for 18 patients who underwent T1 and T2</b>					
T1	111 $\pm$ 30	46 $\pm$ 17	121 $\pm$ 46	122 $\pm$ 34	100 $\pm$ 46
T2	112 $\pm$ 32	48 $\pm$ 20	121 $\pm$ 38	127 $\pm$ 45	102 $\pm$ 47
ICC	0.94	0.78	0.92	0.76	0.91
<b>Skeletal muscle endurance for 18 patients who underwent T1 and T2</b>					
T1	1111 $\pm$ 420	489 $\pm$ 215	808 $\pm$ 460	1008 $\pm$ 519	854 $\pm$ 474
T2	1068 $\pm$ 367	532 $\pm$ 293	773 $\pm$ 298	1016 $\pm$ 491	847 $\pm$ 421
ICC	0.88	0.65	0.90	0.92	0.96

**Figure 4.5.** Left panel (A.): test-retest data (n=33 patients), combined for all four movement patterns, for the first (T0) and second (T1) tests for strength, and test-retest data for the group of 18 patients who underwent all three tests (T0,T1,T2). Right panel (B.): (Bland-Altman plot): Average of T1 and T2 (horizontal axis) versus Difference of T2 and T1 (vertical axis). Dashed lines represent mean difference and the mean difference plus or minus 2SDs of the mean difference. Each data point represents the T1-T2 comparison for one of the four movement patterns (knee extension / flexion, elbow extension / flexion) in an individual patient.



**Figure 4.6.** Effects of familiarization on strength in CHF patients. Units measured in Nm. Data are presented as mean ± SD. \* P < 0.05 and \*\* P < 0.01.



**4.5.3.  $VO_{2peak}$** 

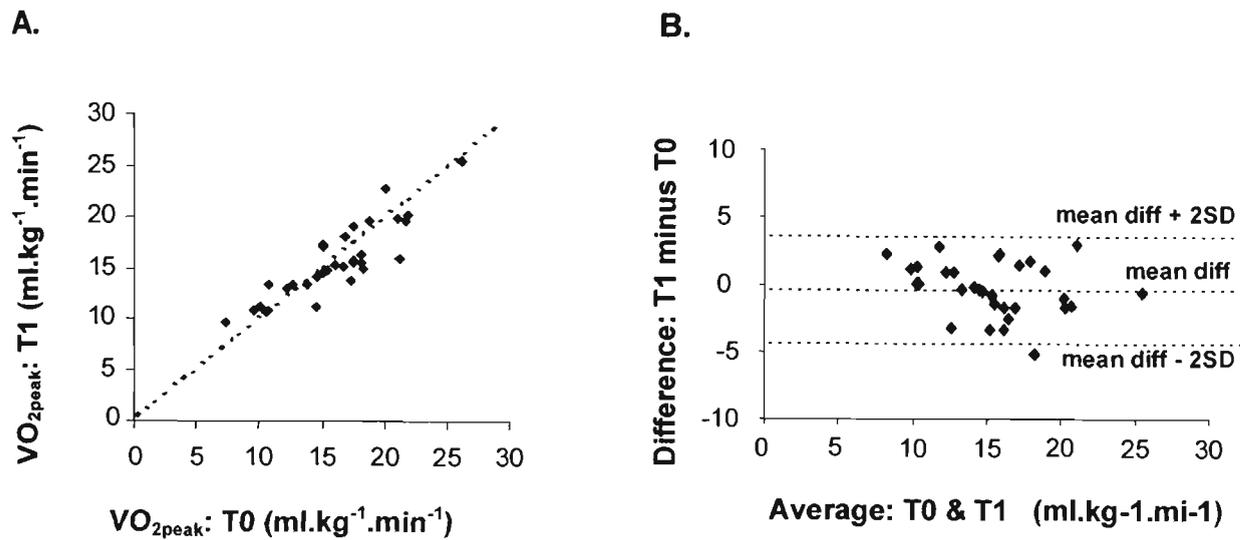
$VO_{2peak}$  did not change significantly between the first and second tests ( $16.2 \pm 0.8 \text{ ml.kg}^{-1}.\text{min}^{-1}$  for T0 and T1  $16.1 \pm 0.8 \text{ ml.kg}^{-1}.\text{min}^{-1}$  for T1;  $P=0.686$ ;  $ICC = 0.91$ , Figure 4.4).

However,  $VO_{2peak}$  decreased from  $16.7 \pm 1.2 \text{ ml.kg}^{-1}.\text{min}^{-1}$  to  $14.9 \pm 0.9 \text{ ml.kg}^{-1}.\text{min}^{-1}$  ( $-10 \pm 18\%$ ;  $95\% \text{ CI} = -46\% \text{ to } 25\%$ ;  $P=0.021$ ;  $ICC = 0.89$ ; Table 4.3). This fall was accompanied by a small rise in mean  $RER_{peak}$  (not significant) and no change in  $HR_{peak}$  (Table 4.3).

**Table 4.4.**  $VO_{2peak}$  for the 33 patients who underwent T0 and T1, and the corresponding data for the 18 patients who also underwent T2. Units  $VO_{2peak}$  are  $\text{ml.kg}^{-1}.\text{min}^{-1}$ . Data are presented as mean  $\pm$  SD.

Test	$VO_{2peak}$	$RER_{peak}$	$HR_{peak}$
<b>Data for 33 patients who underwent T0 and T1</b>			
T0	$16.2 \pm 4.3$	$1.12 \pm 0.22$	$126 \pm 23$
T1	$16.1 \pm 4.7$	$1.17 \pm 0.15$	$127 \pm 25$
ICC	0.91	0.76	0.96
<b>Data for 18 patients who underwent T1 and T2</b>			
T1	$16.7 \pm 5.3$	$1.18 \pm 0.14$	$133 \pm 25$
T2	$14.9 \pm 4.0$	$1.23 \pm 0.19$	$129 \pm 26$
ICC	0.89	0.75	0.96

**Figure 4.7.** Left Panel (A.) (Scatterplot): Test-retest data (n=33 patients) for the first (T0, horizontal axis) and second (T1, vertical axis) tests for  $VO_{2peak}$ . The dashed line is the line of identity. Right Panel (B.) (Bland-Altman plot): Average of T0 and T1 (horizontal axis) versus Difference of T1 and T0 (vertical axis). Dashed lines represent mean difference and the mean difference plus or minus 2SD's of the mean difference.



## 4.6 Discussion

By comparing test and retest results the outcome measures in this study are reproducible, though some training or learning may be required. Whilst familiarization is not required for assessing FBF or aerobic power as a single measurement,  $VO_{2peak}$  declined markedly in the three month period for which these patients were followed. When testing patients with CHF, a familiarization trial for skeletal muscle strength testing is necessary.

In the 50 years since strain gauge venous occlusion plethysmography was established (Whitney 1953), there have been several studies of its reproducibility (Roberts 1986; Wiener DH 1986; Benjamin 1995; Petrie 1998). Earlier studies have observed acceptable within-subject reproducibility for unilateral FBF measures varying in healthy volunteers by  $9.2 \pm 7.2\%$  (Wiener DH 1986) and others showing a coefficient of variation of 10.5% (Roberts 1986). Other investigators have reported poor reproducibility with the unilateral method (Altenkirch 1990; Cooke 1997). Petrie et al. studied the within-subject variability of bilateral FBF and reported a coefficient of variation of 31-39% for unilateral flows at rest and a more acceptable 19% when FBF ratios were used (Petrie 1998). Their data also included intra-arterial infusion studies and similar results were reported. Reproducibility while infusing vasoconstrictors noradrenaline and angiotensin II was improved by assessing the measurements as percentage change in FBF ratio. However, the intra-subject variability of the response to exercise induced vasodilation was less when reported as absolute values of FBF than as FBF ratios (Petrie 1998). When assessing vasodilation, (such as exercise) presenting data as absolute values are recommended rather than in FBF ratios (Walker 1999). One of the explanations for this is that small blood flow changes in the control (non-exercising) arm can influence the percentage of change in FBF ratio, thereby confounding any localized effects of the exercise on the test arm when reporting data as ratios. Thus data throughout the thesis is presented as absolute values for the test arm only (except where noted otherwise).

The FBF protocol used in this thesis is a well-established and accepted method, enabling direct comparison of data with that of earlier studies (Zelis 1974; Arnold 1990; Katz 1996). In addition, the exercise protocols used in this thesis (15%, 30%, and 45% of MVC) were deliberately identical to earlier studies of FBF in CHF patients (Arnold 1990; Katz 1996). This assisted in

discussing the potential benefits of resistance exercise training, a relatively new mode of exercise training for CHF patients (see Chapter Six). FBF data from this study suggests that familiarization with strain gauge venous occlusion plethysmography at rest, during intermittent forearm exercise, and following brief limb occlusion in CHF patients is unnecessary and that internal consistency within patients is high for FBF. Resting blood flow measures in this study were shown to be reliable with no significant change between tests ( $ICC = 0.76$ ), however it is acknowledged that other researchers who have used this technique [Welsch, 2002 #205], indicate that resting flow measures are not very reproducible.

Strength training is now recommended for people with cardiovascular disease (NIH 1995; Pollock 2000), including recent recommendations for patients with CHF (Maiorana, O'Driscoll et al. 2000; Pu, Johnson et al. 2001). For this reason, both the test-retest reliability and the effects of familiarization should be established in order to test the efficacy of interventions in research protocols and the effectiveness of clinical training in these patients. There are no previous reports of test-retest data for strength testing in patients with cardiovascular disease. Although several studies have included familiarization trials before baseline testing (Hurley 1988; Haennel 1991; Fragnoli-Munn 1998; Beniamini 1999; Maiorana, O'Driscoll et al. 2000), in each case this data was not reported. Several of these studies used the isotonic one-repetition maximum test (1-RM) (Hurley 1988; Fragnoli-Munn 1998; Beniamini 1999), with familiarization of the 1-RM test being included in these trials after 1-2 weeks of aerobic training (Beniamini 1999), resistance training (Hurley 1988) or a combination of both (Fragnoli-Munn 1998).

Patients with CHF exhibited increases of the order of an average of 12% in the expression of skeletal muscle strength and endurance in the second of two tests conducted one week following the first. At the same time, there were no corresponding changes in aerobic power. The increase in strength was unlikely to be due to lower motivation or effort of the participants at the first test, as the protocols and instructions were identical and the participants were advised that all results were to be recorded for analysis. The increases in endurance paralleled the increases in strength, as the former was calculated as total work for 16 repetitions, rather than an index of fatigue.

One possible explanation for the increase in the expression of strength observed in the second week of testing (T1) is that neural adaptations (Sale 1988; Kraemer 1996) occurred in response to the onset of exercise, following prolonged periods of disuse. There have been many reports of increased strength in the absence of hypertrophy (Moritani 1979). Most of the patients in this study were unaccustomed to activity of any modality for many months or, in some cases years, prior to T0, but none was immobilized and all were ambulatory. As a result of T0, the muscles may have undergone a form of neural “awakening” which was manifested at T1. These neural adaptations may have resulted in increased activation of the agonists (Moritani 1979; Hakkinen 1998), encompassing increased recruitment of individual motor units (Sale 1988) and/or increased firing rate of the motor units (Grimby 1981). Co-contraction of antagonists occurs in people who are unaccustomed to the task (Person 1958) and therefore decreased co-activation of antagonists (Carolan 1992) may also have contributed to the improvement at T1. The effects of learning from T0 to T1 (Rutherford 1986) may have also have played a role. It is likely that the strength and endurance testing conducted in the present work using an isokinetic dynamometer required some learning in order to achieve maximum results. Although patients were not questioned as to their past experience with the various tests, it may be implied that many have undergone some level of exercise test on treadmills or cycle ergometers with ECG and blood pressure cuffs, thus establishing a level of comfort. However, it is likely that few, if any, would be familiar with an isokinetic dynamometer and the detailed protocol for testing. This introduction to new testing equipment requires some level of learning. This is probably less so in the FBF protocol as it was passive and non-invasive. Taken together, it is possible that the increases in strength were the result of a combination of neural adaptations and learning.

It was interesting that strength did not change from T1 to T2 in the 18 patients who underwent all three trials. Since three months of inactivity elapsed between these, this supports the notion that a learning effect was responsible for at least some of the early gains (T0 to T1) in strength and that this was retained three months later. This is supported by the work of Rutherford and Jones (1986)(Rutherford 1986), who found that when participants were followed during a prolonged detraining period of 20-24 weeks following a 12 week resistance training program, strength was maintained at a much higher proportion of that during training for the more complex movement

patterns, compared to simple patterns. They concluded that learning effects are retained for a significant period following resistance training.

There have been at least three prospective randomized studies (Kelemen 1986; Haennel 1991; Ferketich, Kirby et al. 1998) that provide some data indicating increased expression of strength in the non-exercising control group at a second test. Two of these studies were of patients with cardiovascular disease (Kelemen 1986; Haennel 1991) and the other was of elderly women (Ferketich, Kirby et al. 1998). Although none of these investigators reported the increases as being statistically significant, the effect sizes were in each case substantial, ranging from an average effect of 7% across eight different strength exercises in patients with a history of coronary artery disease (CAD)(Kelemen 1986) to about 15% for leg extension in elderly women (Ferketich, Kirby et al. 1998). In two of these studies, the lack of statistical significance was probably attributable to the low sample sizes ( $n=6$  for Ferketich et al. (1998)(Ferketich, Kirby et al. 1998) and  $n=8$  for Haennel et al. (1991)(Haennel 1991)), compared to the present study ( $n=33$ ). In the work of Kelemen et al. (1986)(Kelemen 1986), the control group increased strength for the leg curl exercise by 19% ( $P<0.01$ ), and there were strong trends in four other exercises (7-13%). Two of the eight exercises exhibited small decreases (-2%, -4%) and one remained unchanged (Kelemen 1986). These increases in strength in the control groups were not discussed by these investigators, probably because the effects of the exercise training interventions were the main focus of these studies.

However, where exercise training may produce relatively small gains in strength, such as in patients with CHF who may also have been sedentary for some time, it is important to account for these very early gains in strength in the control group that are not attributable to training. In studies of the effects of resistance training in CHF patients, Hare et al. (1999)(Hare, Ryan et al. 1999) did not include familiarization in the protocol, while Maiorana et al. (2000)(Maiorana, O'Driscoll et al. 2000) included familiarization trials in their prospective randomized crossover study, but only reported the effects of detraining, rather than familiarization.

Familiarization for  $VO_{2peak}$  testing is commonplace in studies of exercise training in CHF patients (Sullivan, Higginbotham et al. 1988; Coats, Adamopoulos et al. 1992; Adamopoulos,

Coats et al. 1993; Belardinelli, Geotgiou et al. 1995; Ades, Waldmann et al. 1996; Kavanagh, Myers et al. 1996; Keteyian 1996; Ferketich, Kirby et al. 1998; Maiorana, O'Driscoll et al. 2000). While the effects of any habituation were not documented by these investigators, several claimed that reproducibility of  $VO_{2peak}$  was evident during the familiarization phase (Adamopoulos, Coats et al. 1993; Keteyian 1996). The current work suggests that familiarization with incremental cycle ergometer protocols in CHF patients is unnecessary and that internal consistency within patients is high for  $VO_{2peak}$ . However, this consistency is in contrast to the treadmill ergometer data obtained from a group of 23 elderly patients with coronary artery disease (CAD) (Gardner 1993).  $VO_{2peak}$  was 5.6% higher for the second of two tests conducted within one week, leading to the conclusion that familiarization was necessary for treadmill testing in these patients (Gardner 1993). Apart from one study from the same group of investigators (Ades, Waldmann et al. 1996), all others were conducted using cycle ergometer protocols (Sullivan, Higginbotham et al. 1988; Coats, Adamopoulos et al. 1992; Adamopoulos, Coats et al. 1993; Belardinelli, Geotgiou et al. 1995; Kavanagh, Myers et al. 1996; Keteyian 1996; Ferketich, Kirby et al. 1998; Maiorana, O'Driscoll et al. 2000).

The decrease in  $VO_{2peak}$  after three months was surprising. The possible explanations for this fall include worsening heart failure, decreased aerobic power due to continued deconditioning of these otherwise sedentary patients, decreased effort on the part of the participants for T2, or technical problems with the accuracy or reliability of the cardiorespiratory data measurements. The last is unlikely, given that patients were enrolled sequentially; that is some patients were commencing with data collection, while others were completing T2. Furthermore, all instrumentation used in the measurement of  $VO_{2peak}$  was calibrated before and immediately after each test and was found to maintain very high levels of precision and accuracy. No tests needed to be repeated on account of technical problems. There was little evidence of changed clinical condition; most of the 18 patients who were studied over the three month period maintained stable medication regimes, and none was withdrawn. It is unlikely that the lower  $VO_{2peak}$  for T2 was due to reduced effort or motivation, as mean  $RER_{peak}$  actually increased, albeit not significantly, while the small fall in  $HR_{peak}$  for T2 was also not significant. Therefore, the 10% fall in  $VO_{2peak}$  from T1 to T2 was probably attributed to deterioration of aerobic power due to continuation of inactivity.

## 4.7 Conclusion

These data suggest that in a clinical population of CHF patients, a single familiarization trial for skeletal muscle strength and endurance using isokinetic apparatus is necessary. Whilst familiarization appears not to be required for assessing aerobic power as a single measurement,  $VO_{2peak}$  declined markedly in the three month period, probably due to deconditioning. In addition, FBF data suggest that it is not necessary to perform familiarization testing. Internal consistency within patients was high for the second and third strength trials, the first and second tests of  $VO_{2peak}$  and all three FBF tests.

# Chapter 5 PERIPHERAL BLOOD FLOW IN PATIENTS WITH CHRONIC HEART FAILURE AND AGE-MATCHED HEALTHY VOLUNTEERS

## 5.1 Overview

The current study (Chapter Five) is the first of two studies investigating peripheral (forearm) blood flow (FBF) at rest, and activated by submaximal exercise or limb occlusion. This study focuses on whether local blood flow to the forearm is altered in patients with chronic heart failure (CHF) when compared to healthy age-matched volunteers. This is the sixth cross-sectional study during the last 35 years to compare FBF in patients with CHF to healthy volunteers, the third to include patients on angiotensin-converting enzyme (ACE) inhibitors, and the first to compare the effects of exercise on FBF in CHF patients prescribed ACE inhibitors with healthy volunteers. Patients not on ACE inhibitors were not excluded, but 89% of the patients in this study were prescribed ACE inhibitors (77%) or angiotensin receptor blockers (12%).

## 5.2 Abstract

**Purpose:** To measure forearm blood flow at rest in CHF patients, and when activated submaximally by moderate exercise and maximally in response to limb occlusion. These were then compared to age-matched healthy volunteers.

**Methods:** FBF was measured by strain gauge venous occlusion plethysmography in 43 CHF patients and 8 healthy age-matched volunteers at rest and during the last minute of each exercise bout. Exercise consisted of intermittent hand dynamometer squeezing for five seconds then ten seconds rest for three minutes at 15%, 30%, and 45% of maximum voluntary contraction (MVC). Peak vasodilatory capacity was measured following five minutes of limb occlusion. Each patient and healthy volunteer underwent a single test to measure forearm blood flow. Means were compared using MANOVA.

**Results:** FBF was lower in CHF patients at 15%, 30%, and 45% of MVC and during peak reactive hyperemia (PRH) compared to healthy volunteers, but there was no significant difference at rest between the two groups. Peak vasodilatory capacity was significantly higher in healthy volunteers' ( $30.6 \pm 8.6 \text{ ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ ) than the CHF group ( $18.3 \pm 6.9 \text{ ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ ).

**Conclusion:** Local blood flow stimulation in response to exercise or five minutes of limb occlusion is reduced in patients with CHF when compared to healthy age-matched volunteers. There was no difference at rest between the two groups.

### 5.3 Introduction

Patients living with CHF have significantly impaired tolerance to exercise (Wilson 1984; Coats, Adamopoulos et al. 1992) and the factors that limit this are not fully understood. Since the introduction of angiotensin-converting enzyme (ACE) inhibitors, the duration of exercise capacity has improved (ACC 1999). However patients continue to show a state of exercise intolerance (Barlow 1998). Several peripheral factors such as reduced arteriole vasodilatory capacity (Zelis 1974), skeletal muscle atrophy (Anker, Swan et al. 1997), and muscle oxidative ability (Hayoz 1993) may contribute to this dysfunction. Reduced blood flow to the limbs has been documented in CHF (Zelis 1974; Poole-Wilson 1992) and is associated with decreased exercise tolerance (Wilson 1984; Sullivan, Higginbotham et al. 1988), but a cause and effect relationship has not been established. It has been suggested, however, that the more severe the degree of CHF, the more severe is the exercise intolerance, associated with a greater impairment of blood flow (Wilson 1984). Low exercise tolerance is independently correlated with morbidity and mortality in CHF patients (Bittner, Weiner et al. 1993). If this limitation is linked to the impairment of peripheral blood flow, as suggested by Wilson et al., then it is a worthwhile topic of investigation. The pathophysiological cause of this reduction of blood flow after the development of heart failure has not been clearly defined. Recent observations concerning impaired peripheral blood flow suggest that it is not a result of reduced cardiac output or other central hemodynamic factors. (1) Forearm resistance is increased following heart transplantation and does not return to normal for four weeks (Sinoway 1988) although cardiac output improves

immediately. (2) ACE inhibitors cause rapid improvements in central hemodynamics (Enseleit F 2001), however, improvements to exercise tolerance are delayed (Wilson 1984; ACC 1999), sometimes for months. In a trial on ACE inhibitors an increase in lower limb blood flow was observed with a delayed increase in exercise capacity (Drexler 1989).

Recent reports on FBF show basal blood flow measurements that are similar to healthy volunteers in CHF suggesting resting FBF ( $FBF_{rest}$ ) may be restored (Hayoz 1993; Welsch 2002). In earlier studies that were conducted prior to the widespread prescription of ACE inhibitors in CHF,  $FBF_{rest}$  was reported to be reduced in CHF patients compared to healthy volunteers (Zelis 1968; Zelis 1974; Leithe 1984; Arnold 1990). This disparity cannot be explained by a change or improvement of methods as strain gauge venous occlusion plethysmography is an established technique of more than 50 years (Whitney 1953), conducted now as it was then and is considered reliable (Wilkinson 2001). Thus, ACE inhibitors which assist in maintaining peripheral blood flow at rest (Enseleit F 2001; Joannides R 2001) are probably the main factor explaining the maintenance of satisfactory blood flow in the resting condition.

These recent findings of normal  $FBF_{rest}$  suggest that a state of partial vasodilation is present in CHF patients in spite of central hypoperfusion that is characteristic of this syndrome. If vasodilation at rest in CHF patients exceeds that of healthy age-matched controls, then this suggests that further vasodilation in response to either an exercise stimulation or a brief period of limb occlusion may result in blunted vasodilation. Therefore, this chapter studied patients under current best practice of medical management for CHF in relation to  $FBF_{rest}$ , and in conditions of submaximal vasodilation (in response to moderate intensity exercise) and maximally activated peripheral vasodilation (in response to brief limb occlusion, PRH).

## Hypotheses

1. FBF at rest is similar in patients with CHF and age-matched healthy volunteers, probably due to improved medical management of patients.
2. As FBF at rest in the patients reflects some basal vasodilation, further vasodilation is present but blunted in response to intermittent, submaximal isometric exercise.
3. For reasons similar to 2, above, peak vasodilatory capacity in response to brief limb occlusion is blunted in patients with CHF, compared to age-matched healthy volunteers.

## 5.4 Methods

### 5.4.1 Patient Group (n = 44)

Most patients were on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and a diuretic. These and other medications that patients were taking at Entry and Exit are summarized in Table 5.1.

Participants were informed of all test procedures and associated risks (Appendix A1) before completing a detailed medical questionnaire and given written informed consent (Appendix A2) prior to commencing the study. Prior to the recruitment of participants, ethics approval was obtained from the Victoria University Human Research Ethics Committee and the Austin and Repatriation Medical Center. The project complied with the NHMRC Statement on Human Experimentation.

Inclusion criteria to the study was as follows; (i) male and female adults were included without specific restriction because of their age; (ii) any aetiology of left ventricular systolic failure; (iii) a left ventricular ejection fraction below 40%; (iv) and stable pharmacological therapy with a minimum of two weeks unaltered drug therapy at entry.

Exclusion criteria to the study was as follows; (i) NYHA Class IV patients that had symptoms at rest or during minimal activity; (ii) cardiovascular limitations that would prevent taking part in

the exercise program such as previous cardiac arrest, recent surgery, aortic stenosis, symptomatic or sustained ventricular tachycardia or current exercise limitation because of angina; (iii) musculo-skeletal or respiratory problems that would prevent appropriate exercise; (iv) metabolic diseases such as diabetes.

#### **5.4.2 Healthy volunteers (n = 8)**

Eight healthy sedentary subjects (7 male/1 female;  $63 \pm 11$  years,  $78 \pm 8$  kg, body mass index  $26 \pm 3$  kg.m<sup>-2</sup>) participated in this study. Participants were healthy with no history of cardiovascular disease or other limiting non-cardiac disorders. None was taking medication that had an inotropic or chronotropic effect. All volunteers were of similar age to the patient group and lead a sedentary lifestyle. Participants underwent an incremental cycle ergometer exercise test. The volunteers would have been excluded if they had exhibited any signs or symptoms of cardiovascular disease during or after the exercise test.

**Table 5.1.** Descriptive characteristics of the 43 patients with CHF who completed FBF testing. Mean  $\pm$  SD. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

<b>CHF patients (n=43)</b>	<b>Characteristics</b>
Age, yrs	64 $\pm$ 13
Male / Female	38 / 5
Height (cm)	170 $\pm$ 8
LVEF%	27 $\pm$ 7
NYHA	2.4 $\pm$ 0.5
Weight (kg)	80 $\pm$ 13
<b>CHF diagnosis</b>	
Ischemic heart disease	27 (63%)
Dilated cardiomyopathy	15 (35%)
Valvular	1 (2%)
<b>Medications</b>	
Angiotensin converting enzyme inhibitor	33 (77%)
Angiotensin receptor blocker	5 (12%)
Diuretic	36 (84%)
<b>Beta-blocker</b>	19 (44%)
Digoxin	17 (40%)
Aspirin	26 (60%)
Warfarin	19 (44%)
Amiodarone	6 (14%)
Nitrates	6 (14%)
Calcium channel antagonist	4 (9%)

### 5.4.3 Design

A cross-sectional design was used in this study. FBF measurements were obtained at rest, during isometric exercise, recovery, and during peak reactive hyperemia in patients with CHF and compared against age-matched healthy volunteers. All experimental procedures and equipment for FBF measurement using strain gauge venous occlusion plethysmography have been fully described earlier (Chapter Three). Briefly, FBF was measured with a mercury-in-Silastic rubber

strain gauge placed at the maximum girth of the dominant forearm. Pressure cuffs were applied to the wrist (inflated to 200 mm HG 1 minute prior to recording) and upper arm (inflated to 50 mm HG for 5 to 7 seconds for each flow recording). FBF was calculated from the rate of increase in forearm circumference (Flow =  $200 \times$  increase in forearm circumference (mm/min) / forearm circumference (mm)) and expressed in units of  $\text{ml} \cdot 100\text{mL}^{-1} \cdot \text{min}^{-1}$ .

#### 5.4.4 Statistical Analyses

Data from patients and control subjects were compared using unpaired Student's *t* tests for independent variables. Data are expressed as means  $\pm$  S.E. A *p* value of less than 0.05 was considered significant. The statistical analyses were performed using SPSS (version 10.0.5; SPSS Inc. Headquarters, Chicago, Illinois, U.S.).

### 5.5 Results

Of the 44 patients, only one did not complete the testing. One patient was unable to squeeze the hand dynamometer due to arthritis. The effects of forearm isometric exercise at 15, 30, and 45% of MVC in the healthy volunteers and patients with CHF are shown in Table 5.2 and displayed as a graph in Figure 5.1. Resting values were similar in both groups. As each stage of exercise increased in intensity, there was a progressive increase in FBF in both groups, although the rates were significantly lower in the CHF patients. FBF was reduced in the CHF patients compared with the healthy participants at 15%, 30%, and 45% of MVC and during PRH. However, there was no significant difference at rest between the two groups. With isometric exercise, the rate of increase in FBF was also decreased in patients. FBF responses to PRH in healthy volunteers ( $30.6 \pm 8.6 \text{ ml} \cdot 100\text{mL}^{-1} \cdot \text{min}^{-1}$ ) were significantly higher than the CHF group ( $18.3 \pm 6.9 \text{ ml} \cdot 100\text{mL}^{-1} \cdot \text{min}^{-1}$ ).

Effects of submaximal isometric hand squeezing on CHF patient group caused local vascular changes only. Forearm exercise in CHF patients resulted in no significant changes in mean blood pressure (Chapter Four).

**Table 5.2** Forearm Blood Flow (FBF) at rest, for 15%, 30% and 45% of maximal voluntary contraction (MVC), and for max peak reactive hyperemia (PRH). Units for forearm blood flow are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD. \*  $P < 0.05$  and \*\*  $P < 0.01$ .

Group	n	Forearm Circumference at max (mm)	FBF <sub>rest</sub>	FBF <sub>15%MVC</sub>	FBF <sub>30%MVC</sub>	FBF <sub>45%MVC</sub>	FBF <sub>PRH</sub>
Healthy Volunteers	8	266 $\pm$ 21.7	3.4 $\pm$ .9	9.5 $\pm$ 2.8	12.8 $\pm$ 4.3	15.8 $\pm$ 3.2	30.6 $\pm$ 8.6
Chronic Heart Failure	43	270 $\pm$ 23.7	3.7 $\pm$ 1.7	8.0 $\pm$ 2.2	9.2 $\pm$ 2.5*	10.8 $\pm$ 4.6*	18.3 $\pm$ 6.9**

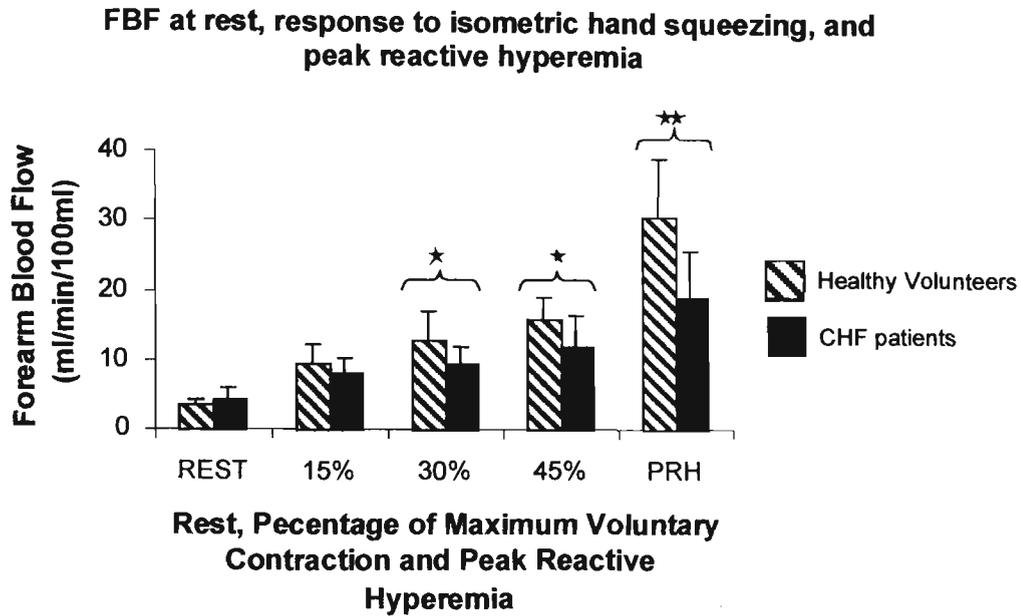
**Table 5.3.** Blood pressure and heart rate characteristics of CHF patients and healthy volunteers. Data are presented as mean  $\pm$  SD. \*  $P < 0.05$

	Healthy Volunteers		CHF patients		P
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range	
Resting systolic blood pressure (mmHg)	128.0 $\pm$ 10.5	115 - 145	116 $\pm$ 19.3	84 - 164	.044*
Resting diastolic blood pressure (mmHg)	78.8 $\pm$ 7.9	60 - 90	67.28 $\pm$ 7.5	50 - 86	.018*
Resting heart rate (beats/min)	77.5 $\pm$ 17.6	62 - 97	73 $\pm$ 14	50 - 105	.665

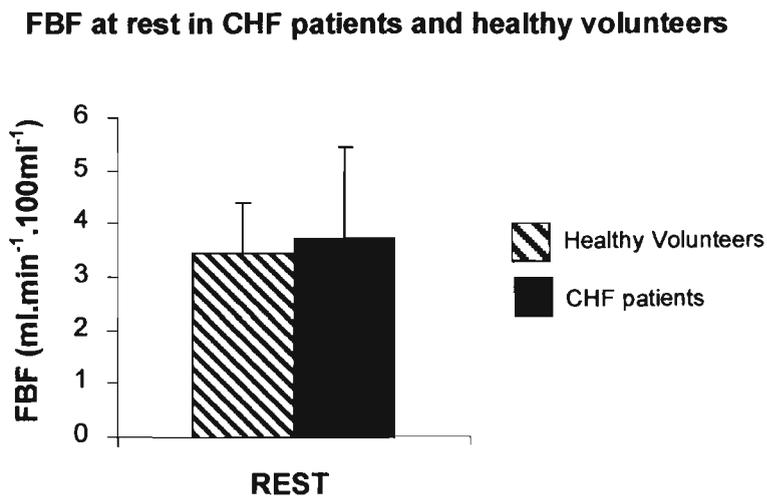
**Table 5.4.** Comparison of FBF ratios from Rest to increases of FBF during 15%, 30%, and 45% MVC. Data are presented as mean  $\pm$  SD. \*  $P < 0.05$

FBF Ratios	Healthy Volunteers	CHF patients	P
Rest to 15% MVC	2.8 $\pm$ 0.7	2.5 $\pm$ 1.2	.197
Rest to 30% MVC	3.7 $\pm$ 1.1	3.1 $\pm$ 1.9	.055
Rest to 45% MVC	4.7 $\pm$ 0.8	3.7 $\pm$ 2.6	.038*

**Figure 5.1.** Forearm blood flow at rest, responses to submaximal isometric hand squeezing, and peak vasodilatory capacity in patients with CHF and healthy age-matched volunteers. Units for FBF are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD. \*  $P < 0.05$  and \*\*  $P < 0.01$ .

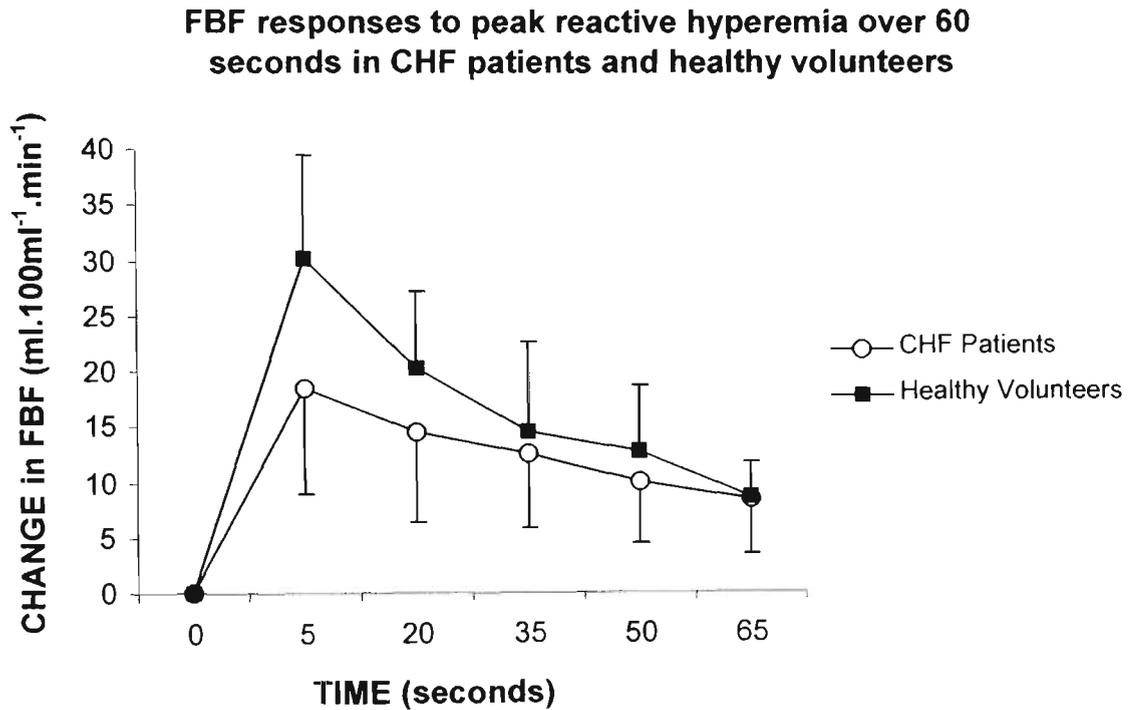


**Figure 5.2** FBF at rest in CHF patients compared to age-matched healthy volunteers. Units for forearm blood flow are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD.



Peak reactive hyperemic flows were decreased in the CHF patient group compared to the healthy volunteers (Figure 5.3).

**Figure 5.3** Forearm blood flow responses to peak reactive hyperemia over 60 seconds in patients with CHF compared to age-matched healthy volunteers. Data are presented as mean  $\pm$  SD.

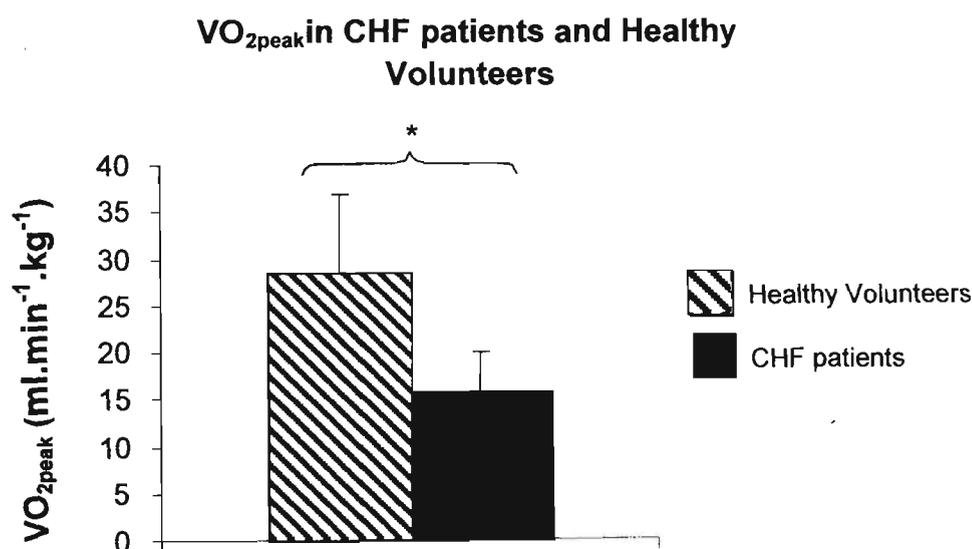


A significant difference was observed between groups in  $VO_{2peak}$ , results are shown in Table 5.5 and displayed as a graph in Figure 5.4. CHF patients showed a significant reduction in  $VO_{2peak}$  compared to healthy volunteers.

**Table 5.5.**  $VO_{2peak}$  data for CHF patients and healthy age-matched volunteers. Units of  $VO_{2peak}$  are  $ml \cdot min^{-1} \cdot kg^{-1}$ . Data are presented as mean  $\pm$  SD. \*  $P < 0.05$

	Healthy Volunteers	CHF patients	<i>P</i>
$VO_{2peak}$ ( $ml \cdot min^{-1} \cdot kg^{-1}$ )	28.5 $\pm$ 8.5	15.7 $\pm$ 4.3	.001*

**Figure 5.4.** Comparison of  $VO_{2peak}$  in CHF patients and healthy age-matched volunteers. Data are presented as mean  $\pm$  SD. \*  $P < 0.05$

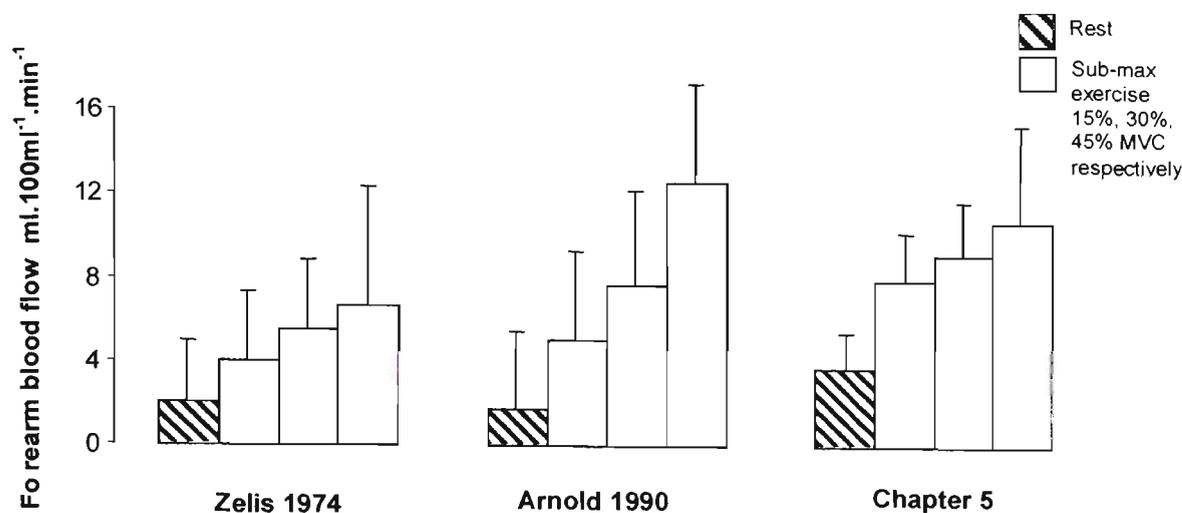


## 5.6 Discussion

There are only five previous cross-sectional studies that have compared the function of forearm resistance vessels in CHF patients with healthy age-matched volunteers (Zelis 1968; Zelis 1974; Leithe 1984; Arnold 1990; Welsch 2002). One additional study (Hayoz 1993) used the method of A-mode ultrasound device for the measurement of flow-mediated dilation of conduit vessels of the upper limb. This study and the other five used venous occlusion plethysmography. Four of these previous studies were conducted before the widespread use of ACE inhibitors (Zelis 1968; Zelis 1974; Leithe 1984; Arnold 1990). These other studies used significantly smaller numbers of heart failure patients ( $n=9$  (Hayoz 1993),  $n=13$  (Arnold 1990),  $n=7$  (Zelis 1974)) than the 43 patients with CHF used in this study, or the older studies used patients who exhibited decompensated heart failure and fluid retention (Zelis 1968; Zelis 1974). Arnold et al. investigated  $FBF_{rest}$  and FBF during exercise, but did not assess peak vasodilatory capacity. In addition, nine of the 13 severe left ventricular dysfunction ( $EF 13.7 \pm 1.5\%$ ) patients used in their cross-sectional study were in NYHA functional class IV, and all patients were reported to be receiving digoxin and diuretics, but no ACE inhibitors (Arnold 1990). Recently, Welsch and colleagues examined  $FBF_{rest}$  and PRH, but did not measure FBF during exercise (Welsch 2002). The CHF population in this study included NYHA functional class I and displayed a higher resting blood pressure than their healthy volunteers and 75% had a history of hypertension as the cause of heart failure. In contrast, CHF patients in this study had a significantly lower resting blood pressure compared to healthy volunteers (Table 5.3) and 65% had ischemic heart disease as the cause of heart failure.

$FBF_{rest}$  was not reduced in CHF patients compared to healthy age-matched volunteers, in contrast to earlier findings (Figure 5.5) (Zelis 1968; Zelis 1974; Leithe 1984; Arnold 1990). The trend (albeit not significant) to higher  $FBF_{rest}$  in the CHF patients compared to the controls (Figure 5.2) may be attributed in part to the widespread prescription of vasodilators, such as ACE inhibitors, which assist in maintaining peripheral blood flow at rest (Enseleit F 2001; Joannides R 2001).

**Figure 5.5** Historical data comparing FBF at rest and during submaximal isometric exercise in CHF patients. Units for FBF are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD.



Studies in which the patient groups were observed to have a reduced  $\text{FBF}_{\text{rest}}$  compared to healthy age-matched volunteers were not taking ACE inhibitors (Zelis 1968; Zelis 1974; Leithe 1984; Arnold 1990). This suggests that  $\text{FBF}_{\text{rest}}$  in the patients may reflect some pharmacologic vasodilation at rest, resulting in a lower capacity for further vasodilation in response to the other maneuvers (exercise and re-perfusion following brief occlusion). Recently two studies showed no significant difference in  $\text{FBF}_{\text{rest}}$  between CHF patients and healthy volunteers (Hayoz 1993; Welsch 2002).  $\text{FBF}_{\text{rest}}$  values in this study and Welsch et al. included patients prescribed ACE inhibitors showed very comparable figures ( $3.7 \pm 1.7 \text{ ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$  vs  $3.4 \pm .95 \text{ ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$  present study;  $3.2 \pm 1.2 \text{ ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$  vs  $3.5 \pm 1.2 \text{ ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$  (Welsch 2002)). One other study found no significant difference in  $\text{FBF}_{\text{rest}}$  between CHF patients and healthy volunteers (Wiener DH 1986). Interestingly, they included CHF patients receiving vasodilator medication, however measurements were recorded in an upright position (Wiener DH 1986). Sixty percent of the patient population in the Welsch et al. study and all patients in the Hayoz et al. were receiving ACE inhibitors. Interestingly, these combined results also depict a heart failure population through a range of severities (NYHA class I, II, and III) with the same  $\text{FBF}_{\text{rest}}$  measurement. In a much earlier study, Leithe and colleagues who examined FBF in three groups of CHF patients that were classified as NYHA class II, III, or IV and reported that blood flow became attenuated as the severity of the heart failure progressed (Leithe 1984). Patients in the Leithe et al. study were before the widespread prescription of ACE inhibitors. These findings

on  $FBF_{rest}$  can also be seen in resting leg blood flow ( $LBF_{rest}$ ). Sullivan et al. studied 30 CHF patients which were not receiving ACE inhibitors and found  $LBF_{rest}$  was significantly reduced in CHF patients compared with healthy volunteers (Sullivan 1989). More recently, Barlow et al. and Piepoli et al. using mostly patients on ACE inhibitors (83% and 90% respectively) showed no difference in  $LBF_{rest}$  between patients with CHF and healthy volunteers (Piepoli 1996; Barlow 1998).

During exercise, FBF progressively increased in both groups, but the rises in CHF patients were significantly lower than the corresponding rises in normal volunteers during 45% MVC. These results are consistent with previous observations (Zelis 1974; Wilson 1984; Sullivan 1989). There was no significant difference between the two groups at 15%MVC in absolute blood flows, but there was a difference observed in the percentage of change relative to the respective resting values; this relative value represents the vasodilatory response. Healthy volunteers showed an increase of 64% from  $FBF_{rest}$  to 15% MVC, whilst the CHF patients increased by just 54%. The percentage of change in FBF from rest to 30% MVC in the healthy volunteers (74%) was increased compared to the percentage of change in the CHF patients (60%), although these differences were not statistically significant ( $p = .197$  and  $.055$  respectively) they are able to show a progressive vasodilatory impairment in CHF patients. At 45% MVC there was significant difference ( $p = .038$ ) in the percentage of change relative to  $FBF_{rest}$  in the CHF patients (66%) compared to healthy volunteers (82%). Vasodilatory response to exercise becomes more impaired as the intensity of exercise increases compared to healthy volunteers. These findings are inconsistent with other studies (Wiener DH 1986; Arnold 1990), which reported no difference between healthy volunteers and CHF patients in the ability to vasodilate and increase blood flow during exercise. Both studies showed lower  $FBF_{rest}$  in CHF patients and healthy volunteers than recorded in this study and others (Zelis 1968; Zelis 1974; Welsch 2002). This may partially be explained by the method of collecting data in these studies. Patients were in a seated recumbent position (Arnold 1990) or upright position (Wiener DH 1986) rather than supine which was used in this study and most others (Zelis 1968; Zelis 1974; Hayoz 1993; Welsch 2002). Body posture has been shown to have a direct influence on peripheral blood flow. In an upright position FBF is reduced in healthy volunteers but not in CHF patients (Goldsmith 1983). Although it is not fully understood it has been suggested that the differences may be associated with abnormalities in

reflex control of the circulation in CHF patients (Goldsmith 1983). Thus any difference between the two groups in supine would be reduced in the upright position. It has also been suggested that this FBF variation between healthy volunteers and CHF patients occurs during exercise (Wiener DH 1986).

Peak reactive hyperemia (PRH) was used to assess the maximal vasodilatory capacity of forearm vasculature. There was a large disparity between the two groups. PRH in the CHF group was reduced by 39% when compared against the healthy volunteers. Peak vasodilatory capacity documented over a period of one minute was also significantly reduced in the patients with CHF compared to normal volunteers. This is consistent with other studies (Zelis 1968; Hayoz 1993) that found reactive hyperemic blood flow to be lower in patients with CHF compared with healthy subjects. These findings support the hypotheses of this chapter, suggesting that the pharmacologically-induced vasodilation at rest in the patients blunts the further capacity to vasodilate in response to the other maneuvers. Several previous studies which included  $FBF_{rest}$ , during exercise, and/or following brief limb occlusion measured blood flow in the leg (Sullivan 1989; Reading 1993; Hambrecht 1997; Barlow 1998; Dziekan 1998; Taylor 1999). Reactive hyperemic blood flow to the legs has been shown to be reduced in CHF patients by up to 25% to 50% compared to healthy volunteers (Zelis 1968; Arnold 1990; Reading 1993). It has been suggested that the reduced blood flow shown in this patient population affect large muscle mass, as opposed to small muscle mass such as the forearm (Squires 1998). The results of this study and those reported by Welsch et al. suggest that the impaired vasodilatory capacity observed in the leg is also found in the smaller muscle mass of the forearm (Welsch 2002).

The present study also found a reduction in  $VO_{2peak}$  in the CHF patients compared to healthy volunteers, which may attribute to the explanation of the reduced FBF during exercise and following limb occlusion compared to healthy volunteers. Lactate concentration during exercise in CHF patients is increased compared to healthy volunteers (Wilson 1984). The increased lactate production to exercising muscle may be attributed to a reduction of blood flow (Bylund-Fellenius 1981). It has been suggested that the level of exercise capacity in patients with CHF is closely related to the adequacy of blood flow to the exercising muscle (Wilson 1984). Wilson et al. studied aerobic capacity, cardiac output, femoral blood flow, and leg metabolism in 23 CHF

patients with a range of severities and 23 healthy volunteers (Wilson 1984). Their results suggest that the exercise intolerance observed with CHF is directly linked to reduced peripheral blood flow and primary cause of fatigue. However, this study needs to be updated with patients under current medical management. Patients in this study were not receiving ACE inhibitors or any other medication that may assist in vasodilation as it was conducted prior to the widespread prescription of these drugs.

Although this study primarily focused on advances in vasodilatory therapy to explain why the findings of this study differ from earlier observations, the condition of the patient populations may also be a factor. This study used CHF patients with a less severe classification of heart failure compared to earlier studies. As mentioned above,  $FBF_{rest}$  is directly related to the severity of heart failure (Leithe 1984). CHF patients in this study were considered stable and in NYHA function class II and III, whereas all patients studied by Zelis et al. were decompensated, edematous and in NYHA function class III and IV (Zelis 1968; Zelis 1974). Arnold et al. also used CHF patients that were NYHA function class III and IV (nine of the 13 were class IV) and had severe left ventricular dysfunction with a mean left ventricular ejection fraction of  $13.7 \pm 1.5\%$  (Arnold 1990) compared to  $27 \pm 7\%$  in this study. This issue of population difference may also be extended to the recent study by Welsch et al. who observed no significant difference in  $FBF_{rest}$  between CHF patients and healthy volunteers in a patient group primarily made up of NYHA function class I patients (Welsch 2002). In addition age matching between CHF patients and healthy volunteers in earlier studies showed large disparities between groups, with the control group being younger (Zelis 1974). Zelis et al. showed significant differences between CHF patients and healthy volunteers at rest, during exercise, and following brief limb occlusion matching older patient groups ( $43.8 \pm 6.5$  years) against younger healthy volunteers ( $27.3 \pm 6.9$  years) (Zelis 1968; Zelis 1974) whereas this study used an age-matched study population. This disparity between ages in the two groups may attribute to the significant differences in blood flows as FBF has been shown to reduce with age (Hellon 1959).

A limitation of the study was that not all, but most (91%) of the patients were taking at least one vasodilator (ACE inhibitor, angiotensin receptor blocker, or nitrates). A further limitation of the

study was the low number of healthy age-matched volunteers that were studied, compared to the number of patients.

## **5.7 Conclusion**

The findings of this study, although limited by a small number of healthy volunteers, show that forearm vasodilation during exercise and peak vasodilatory capacity is significantly impaired in patients with CHF compared to healthy age-matched volunteers. However, basal blood flow in patients with CHF and healthy volunteers were similar and may be attributed to current best practice of medical management of these patients.

# Chapter 6 PERIPHERAL BLOOD FLOW IN PATIENTS WITH CHRONIC HEART FAILURE: RESPONSES TO RESISTANCE EXERCISE TRAINING

## 6.1 Overview

The previous chapter showed that chronic heart failure (CHF) patients have satisfactory forearm blood flows at rest, but impaired vasodilatory responses to graded stimuli capacity beyond rest such as during exercise. The purpose of the current chapter is to investigate whether exercise training is effective in improving vasodilatory responsiveness part of this vasodilatory impairment. Previous studies of aerobic training have shown this form of training to be beneficial, little is known about the potential benefits of resistance exercise training. Thus the objective of the current chapter was to investigate the effects of three months of hydraulic resistance exercise training (RT) in patients with chronic heart failure (CHF) on local blood flow regulation of the forearm. A combination of pharmacologic (ACE inhibitors) and nonpharmacologic therapy (RT) may provide the optimal management to rectify functional capacity in patients with CHF. This was the first prospective randomized study in CHF patients using an inactive control group to examine the effects of resistance exercise as the predominant modality.

## 6.2 Abstract

**Purpose:** To investigate the potential benefits of resistance exercise training in patients with CHF. With main objectives of examining the effects of a three-month resistance exercise training program on peripheral blood flow in a clinical population of patients with CHF. The significance of this is that if forearm blood flow improves with this form of exercise training, which is novel in this population of patients, then this may provide a very important mechanism by which their exercise tolerance and quality of life are improved.

**Method:** Thirty-nine patients with CHF (New York Heart Association Functional Class (NYHA) =  $2.3 \pm 0.5$ ; left ventricular ejection fraction (LVEF%)  $27\% \pm 7\%$ ; age  $65 \pm 9$  years; 32:5 male:female) initially underwent two identical series of tests (T0 for familiarization; T1 for baseline), one week apart, for strength and endurance of the knee and elbow extensors and flexors, and  $VO_{2peak}$ . Each patient also underwent a single test (T1) to measure forearm blood flow (FBF) at rest, and FBF activated by exercise and limb occlusion. Following T1, all patients were randomized to either three months of resistance training (EX,  $n = 17$ ) or continuance with usual care (CON,  $n = 20$ ), at which time they underwent endpoint (T2) testing.

**Results:** FBF increased at rest by  $20 \pm 32\%$  ( $P < 0.01$ ), and when stimulated by submaximal exercise ( $24 \pm 32\%$ ,  $P < 0.01$ ), or limb occlusion ( $26 \pm 45\%$ ,  $P < 0.01$ ) in EX, but not in CON ( $P < 0.01$  EX vs CON). Combining all four movement patterns, strength increased for EX by  $21 \pm 30\%$  (mean  $\pm$  SD,  $P < 0.01$ ) following training, whilst endurance improved  $21 \pm 21\%$  ( $P < 0.01$ ). Corresponding data for CON remained almost unchanged ( $P < 0.005$  EX vs CON).  $VO_{2peak}$  improved in EX by  $11 \pm 15\%$  ( $P < 0.05$ ), while it decreased by  $10 \pm 18\%$  ( $P < 0.05$ ) in CON ( $P < 0.05$  EX vs CON). There were three patient withdrawals, all from EX, but none of these was attributed to their participation in the exercise training program.

**Conclusion:** Moderate-intensity resistance exercise training in CHF patients is safe, and produces favorable changes to forearm blood flow, skeletal muscle strength and endurance, and  $VO_{2peak}$ .

### 6.3 Introduction

Chronic heart failure (CHF) is a multifaceted syndrome, which includes alterations or irregularities of nearly all organ systems. Exertional dyspnea appears to be due to increased respiratory muscle work stimulated by excessive ventilation and decreased lung compliance [Wilson, 1993 #221]. Excessive carbon dioxide production, secondary to increased muscle lactate release, and increased lung dead space contribute to the excessive ventilation and decreased lung compliance is caused by chronic pulmonary congestion and fibrosis. Fatigability is likely caused by muscle underperfusion and deconditioning, whilst the underperfusion is largely due to impaired arteriolar vasodilation within exercising muscle [Wilson, 1984 #212]. It

is the combination of all these factors that contribute to the clinical status of the patients. The primary parameter measured in this study was peripheral blood flow. Generally, CHF is categorized by inadequate cardiac function, and associated with reduced exercise tolerance which is attributed in part to peripheral maladaptations as mentioned above, in skeletal muscle, including fibre type alterations, atrophy, capillary density and reduced blood flow (Drexler and Coats 1996). This research investigates whether resistance training will increase local blood flow which has been attributed to an impaired exercise capacity (Wilson 1984) thereby improving a patient's quality of life. Exercise training programs are now thought to be safe for CHF patients (Hare, Ryan et al. 1999; Karlsdottir 2002) and may partially reverse some of these problems (Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000). There is now good evidence that many patients with stable CHF respond well to long-term programs of progressive aerobic training (Shephard 1998; Delagardelle 1999). The effects of exercise training on exercise-induced local blood flow are not fully understood in the treatment of CHF, although CHF patients have displayed improvements in blood flow and exercise tolerance with the use of aerobic exercise (Hornig 1996; Katz 1997; Hambrecht, Fiehn et al. 1998), the effects of resistance training are not well understood and is the focus of this chapter. The objectives are to assess the effects of resistance exercise training on local blood flow to the periphery and any associations with exercise tolerance. There has been only one study reporting the effects of resistance exercise training on FBF (Maiorana, O'Driscoll et al. 2000). Until now, there have been no prospective randomized studies in CHF patients using an inactive control group to examine the effects of resistance exercise as the predominant modality.

## **Hypotheses**

As a result of three months of moderate intensity resistance exercise training in patients with CHF,

1. FBF increases at rest
2. FBF increases in response to submaximal, isometric, intermittent exercise (submaximal vasodilatory capacity)
3. FBF increases in response to brief limb occlusion (peak vasodilatory capacity)

4.  $\text{VO}_{2\text{peak}}$  increases
5. Strength and endurance increase

## 6.4 Methods

### 6.4.1 Participants

Thirty-nine patients with CHF consented to participate in this study. Most were on an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker, and a diuretic. These and other medications that patients were taking at Entry and Exit are summarized in Table 6.1.

Participants were informed of all test procedures and associated risks (Appendix A1) before completing a detailed medical questionnaire and given written informed consent (Appendix A2) prior to commencing the study. Prior to the recruitment of participants, ethics approval was obtained from the Victoria University Human Research Ethics Committee and the Austin and Repatriation Medical Center. The project complied with the NHMRC Statement on Human Experimentation.

Inclusion criteria to the study was as follows; (i) male and female adults were included without specific restriction because of their age; (ii) any aetiology of left ventricular systolic failure; (iii) a left ventricular ejection fraction below 40%; (iv) and stable pharmacological therapy with a minimum of two weeks unaltered drug therapy at entry.

Exclusion criteria to the study was as follows; (i) NYHA Class IV patients that had symptoms at rest or during minimal activity; (ii) cardiovascular limitations that would prevent taking part in the exercise program such as previous cardiac arrest, recent surgery, aortic stenosis, symptomatic or sustained ventricular tachycardia or current exercise limitation because of angina; (iii) musculo-skeletal or respiratory problems that would prevent appropriate exercise; (iv) metabolic diseases such as diabetes.

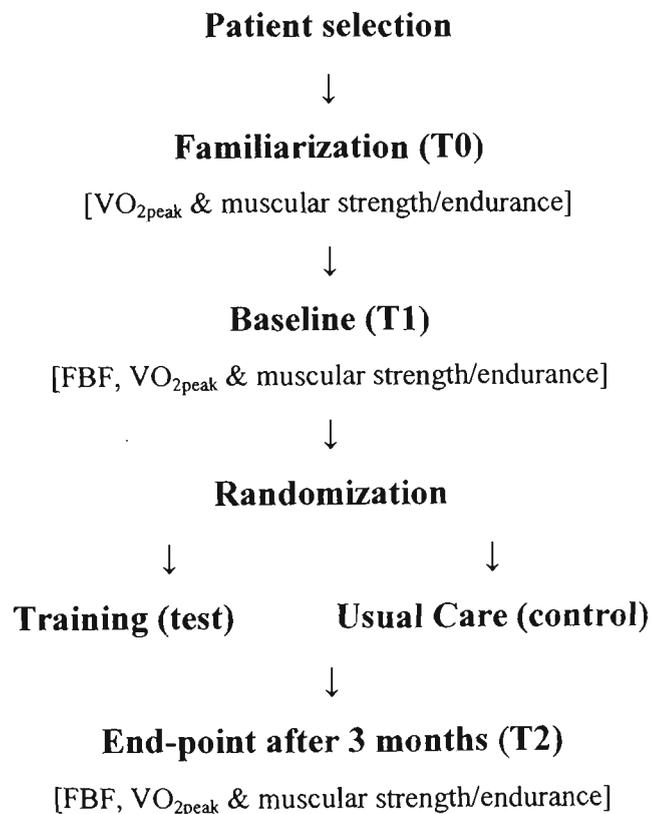
**Table 6.1.** Descriptive characteristics of the 39 patients who underwent the series of tests comprising skeletal muscle strength and endurance, symptom-limited graded exercise test for the assessment of aerobic power ( $VO_{2peak}$ ), and forearm blood flow. Withdrawals refers to patients who did not complete at least one of the assessment tasks.

	Exercise group (n=19)		Control group(n=20)	
	Entry	Exit	Entry	Exit
Age, yrs	65 ± 13		64 ± 9	
Male / Female	15 / 4		18 / 2	
Height (cm)	171 ± 9		171 ± 7	
LVEF%	27 ± 7		28 ± 6	
NYHA	2.4 ± 0.5		2.3 ± 0.4	
Weight	84 ± 19	82 ± 13	79 ± 12	81 ± 12
<b>CHF diagnosis</b>				
Ischemic heart disease	11 (58%)		12 (60%)	
Dilated cardiomyopathy	8 (42%)		8 (40%)	
<b>Medications</b>	<b>n=19</b>	<b>n=16</b>	<b>n=20</b>	<b>n=19</b>
ACE inhibitor or angiotensin receptor blocker	17 (89%)	15 (94%)	17 (85%)	17 (89%)
Diuretic	17 (89%)	14 (88%)	16 (80%)	15 (79%)
Beta-blocker	9 (47%)	5 (31%)	8 (40%)	8 (42%)
Digoxin	8 (42%)	6 (38%)	8 (44%)	8 (42%)
Aspirin	11 (58%)	10 (63%)	12 (60%)	10 (53%)
Warfarin	8 (42%)	5 (31%)	8 (40%)	8 (42%)
Amiodarone	2 (11%)	4 (25%)	4 (20%)	3 (16%)
Nitrates	6 (32%)	3 (19%)	7 (35%)	6 (32%)
Calcium channel antagonist	1 (5%)	1 (6%)	2 (10%)	2 (11%)
<b>Withdrawals</b>	<b>n =3</b>		<b>n =0</b>	
Sudden death at home	1		0	
Other (non-cardiac) illness	1		0	
Non-compliant	1		0	
<b>Missing Data</b>	<b>n</b>		<b>n</b>	
Medications	0		1	
Strength and endurance	1		3	
$VO_{2peak}$	2		1	
FBF	2		2	

### 6.4.2 Design

The design was a prospective randomized study, with two series of tests one week apart (Familiarization = T0, and Baseline = T1). Following T1, they were randomly allocated to either an exercise group (EX) or a usual care group (CON). EX undertook three months of resistance exercise training, while CON continued with usual care. After three months, a third series of tests (Endpoint = T2) was conducted. During the first week (T0), patients undertook a symptom-limited graded exercise test for the assessment of aerobic power ( $VO_{2peak}$ ). This was followed two days later by tests of skeletal muscle strength and endurance. Protocol for skeletal muscle strength and endurance, and  $VO_{2peak}$  have previously been described (Chapter Three). These tests were repeated the following week (T1) and in addition forearm blood flow (FBF) was measured at rest, during submaximal exercise of the forearm, and in response to imposed limb ischaemia and again after three months (T2). The control group was requested to maintain previous activity levels and this was monitored.

**Figure 6.1.** Chapter Six study design



## Testing protocols

All experimental procedures and equipment for FBF, muscular strength and endurance, and  $\text{VO}_{2\text{peak}}$  measurements have been fully described earlier (Chapters Three & Four).

### 6.4.3 Resistance exercise training

Training (three months, 3 sessions per week) was undertaken in a hospital rehabilitation gymnasium using a multi-station hydraulic resistance training system (HydraGym, Belton, U.S.), arm (RepcO, Australia) and leg cycling (RepcO, Australia) ergometers, and a set of five stairs. Blood pressure and ECG rhythm were recorded after the patients had rested for 10 minutes following arrival. Cardiac rate and rhythm were continuously monitored and recorded during exercise on a four channel (patient) telemetry system (prototype designed and constructed by Victoria University bioengineers, Melbourne, Australia). The graduated resistance training program performed by the Exercise training group used the following exercises: alternating between upper and lower body: leg cycling (0.5 - 2 minutes), elbow extension / flexion (30 seconds), stair climbing (0.5 - 2 minutes), arm cycling (0.5 - 2 minutes), knee extension / flexion (30 seconds), shoulder press / pull (30 seconds). There were also 5 minute warm-up and cool-down routines including gentle aerobic exercise and stretching. Arm and leg cycling, and stair climbing were each of short duration (0.5 - 2 minutes) and relatively high intensity to conform to the resistance training format. Recovery intervals between exercises were determined as the period required to return heart rate to within 10 beats of the pre-exercise (rest) recording. This was typically 1-2 minutes between exercises, and together with the relatively high intensities used, ensured that the training program could be categorized as resistance training. In contrast, circuit training exercises follow continuously without rest intervals to maintain elevated heart rates and are therefore necessarily of lower intensity. Workload intensities were reduced if heart rate responses were in excess of  $5 \text{ b}\cdot\text{min}^{-1}$  below the peak heart rate recorded during  $\text{VO}_{2\text{peak}}$  testing. Exercise progressions were introduced gradually either by increasing intensity (resistance) or the number of sets for a given exercise. Refer to Appendix A3 for the training record sheet. Adherence was monitored as attendance and adverse events were recorded wherever they occurred. Training volume (arbitrary units) was estimated as the sum of the product of resistance (derived from the exercise machine settings) and the number of repetitions for each of the exercises.

The hospital based training (11 weeks, 3 sessions per week) program will be performed using hydraulic resistance training equipment (Hydra-Gym, Australia), a stationary bicycle (Repcos, Australia) and an upper limb ergometer (Monark, Sweden). Training intensity will increase gradually as heart rate recovery times fall below pre-set criteria for each patient. Training will be organized as circuits (ie moving smoothly from one exercise to the next) and include seated chest pull/push, seated knee extension/flexion, seated shoulder pull/push, leg cycling, stair climbing and arm cycling, with 5 minute warm-up and cool-down routines. The circuit alternates exercises between the upper and lower body. The duration of each resistance exercise is 30 seconds. After each exercise heart rate is monitored with ECG telemetry (computer) until it falls to a pre-determined level.

#### **6.4.4 Statistical Analyses**

MANOVA's with repeated measures (T1 and T2) were applied to the forearm blood flow measures (rest, submaximal exercise, PRH). Where significant interactions (time x group) were found for any of the above measures, post-hoc analyses were conducted using the Studentized Newman-Keuls (S-N-K) method to locate the means that were significantly different. This included within subject comparisons of T0 to T1 (effects of familiarization on muscular strength and endurance testing and  $VO_{2peak}$  testing), within subject comparisons of T1 to T2 (effects of exercise training or continuance with usual care) and between subject comparisons of the effects of group participation (T2 for EX versus T2 for CON). The repeated measures MANOVA's and ANOVA's were performed using SPSS (version 10.0.5; SPSS Inc. Headquarters, Chicago, Illinois, U.S.). S-N-K analyses were set up on spreadsheets. Data is expressed as mean  $\pm$  SD and the level of significance was set at  $P < 0.05$  for all variables.

## 6.5 Results

### 6.5.1 Clinical factors

Patients ( $n = 39$ ; NYHA =  $2.3 \pm 0.5$ ; left LVEF% =  $28 \pm 7\%$ ; age =  $65 \pm 11$  years; 33:6 male:female) were included with either ischemic cardiomyopathy (59%) or dilated cardiomyopathy (41%). Most were on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and a diuretic. These, and other medications that patients were taking at Entry and Exit are summarized in Table 6.1. Withdrawals ( $n = 3$ , all in the exercise group, Table 6.1) were due to sudden death at home three days after the most recent exercise training session ( $n = 1$ ), other (non-cardiac) illness ( $n = 1$ ), and non-compliance ( $n = 1$ ). Other sources of missing data are also identified in Table 6.1. The patient groups were well-matched for age, height, weight, functional class, diagnosis, and medications (Table 6.1).

### 6.5.2 Muscle strength and endurance

Combining all four movement patterns for strength, average torque in both groups increased as a result of familiarization ( $77 \pm 20$  Nm at T0 to  $85 \pm 24$  Nm at T1 for EX,  $P < 0.05$ ;  $86 \pm 19$  Nm at T0 to  $99 \pm 28$  Nm at T1 for CON,  $P < 0.05$ ; Table 6.2A; Fig 6.2). As a result of resistance exercise training, there were further substantial increases in strength in the EX group to  $103 \pm 30$  Nm ( $P < 0.01$ ), whilst CON remained at  $99 \pm 29$  Nm after three months of inactivity, with a significant time  $\times$  group interaction ( $P < 0.005$ ). The corresponding changes to individual muscle groups are tabulated in Table 6.2A.

Similarly for skeletal muscle endurance, work increased as a result of familiarization for both groups ( $631 \pm 233$  J to  $683 \pm 283$  J for EX,  $P < 0.05$ ;  $683 \pm 298$  J to  $775 \pm 351$  J for CON,  $P < 0.05$ ; Table 6.2B). Following exercise training, EX improved endurance further to  $830 \pm 275$  J ( $P < 0.01$ ), whilst CON remained almost unchanged ( $768 \pm 334$  J), with a significant time  $\times$  group interaction ( $P < 0.003$ ).

**Table 6.2.** Skeletal muscle strength (A. upper panels) and endurance (B. lower panels). T0, T1 and T2 represent the Familiarization, Baseline and Endpoint tests, respectively. Units for skeletal muscle strength and endurance are Nm and joules, respectively. Data are presented as mean  $\pm$  SD. \*  $P < 0.05$  and \*\*  $P < 0.01$  are for within subject comparisons of T0 and T1. #  $P < 0.05$  and ##  $P < 0.01$  are for within subject comparisons of T2 with T1. &  $P < 0.05$  is for between subject comparisons for T2 for the exercise and control groups. See Methods for more detail on the statistical analyses.

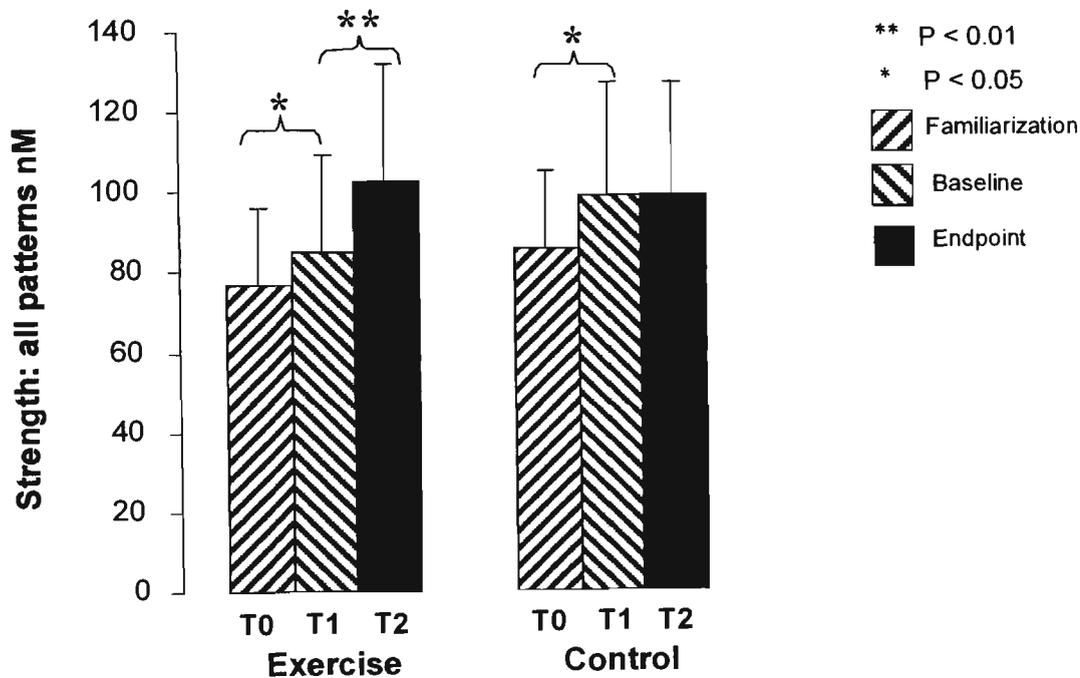
### A. Skeletal muscle strength (Nm)

Group	n	Test	Knee Extension	Knee Flexion	Elbow Extension	Elbow Flexion	Combined movements
Exercise	15	T0	89 $\pm$ 28	36 $\pm$ 13	96 $\pm$ 31	85 $\pm$ 23	77 $\pm$ 20
		T1	99 $\pm$ 32*	41 $\pm$ 12	102 $\pm$ 41	99 $\pm$ 34 *	85 $\pm$ 24*
		T2	111 $\pm$ 37	58 $\pm$ 32 <sup>#</sup>	121 $\pm$ 43 <sup>#</sup>	121 $\pm$ 38 <sup>#</sup>	103 $\pm$ 30 <sup>#</sup>
Control	17	T0	96 $\pm$ 28	31 $\pm$ 12	114 $\pm$ 36	104 $\pm$ 28	86 $\pm$ 19
		T1	110 $\pm$ 31*	45 $\pm$ 17*	120 $\pm$ 47	122 $\pm$ 35*	99 $\pm$ 28*
		T2	110 $\pm$ 32	46 $\pm$ 18 <sup>&amp;</sup>	119 $\pm$ 39	122 $\pm$ 41	99 $\pm$ 29

### B. Skeletal muscle endurance (joules)

Group	n	Test	Knee Extension	Knee Flexion	Elbow Extension	Elbow Flexion	Combined movements
Exercise	15	T0	973 $\pm$ 477	366 $\pm$ 153	596 $\pm$ 254	589 $\pm$ 330	631 $\pm$ 233
		T1	1025 $\pm$ 439	405 $\pm$ 223	625 $\pm$ 302	678 $\pm$ 421*	683 $\pm$ 283*
		T2	1153 $\pm$ 495 <sup>#</sup>	530 $\pm$ 238 <sup>#</sup>	716 $\pm$ 178 <sup>#</sup>	919 $\pm$ 440 <sup>#</sup>	830 $\pm$ 275 <sup>#</sup>
Control	17	T0	1011 $\pm$ 384	453 $\pm$ 253	667 $\pm$ 282	780 $\pm$ 380	683 $\pm$ 298
		T1	1112 $\pm$ 433	488 $\pm$ 222	746 $\pm$ 395*	945 $\pm$ 466**	775 $\pm$ 351*
		T2	1047 $\pm$ 368	514 $\pm$ 293	753 $\pm$ 295	948 $\pm$ 417	768 $\pm$ 334

**Figure 6.2.** Skeletal muscle strength for the combined data of knee extension/flexion and elbow extension/flexion. Left bars are for the Exercise group; right bars are for the non-exercise Control group. T0, T1, and T2 represent data for familiarization, baseline and endpoint, respectively. Data are represented as mean  $\pm$  SD. \* $P < 0.05$ . \*\* $P < 0.01$ .



### 6.5.3 $VO_{2peak}$

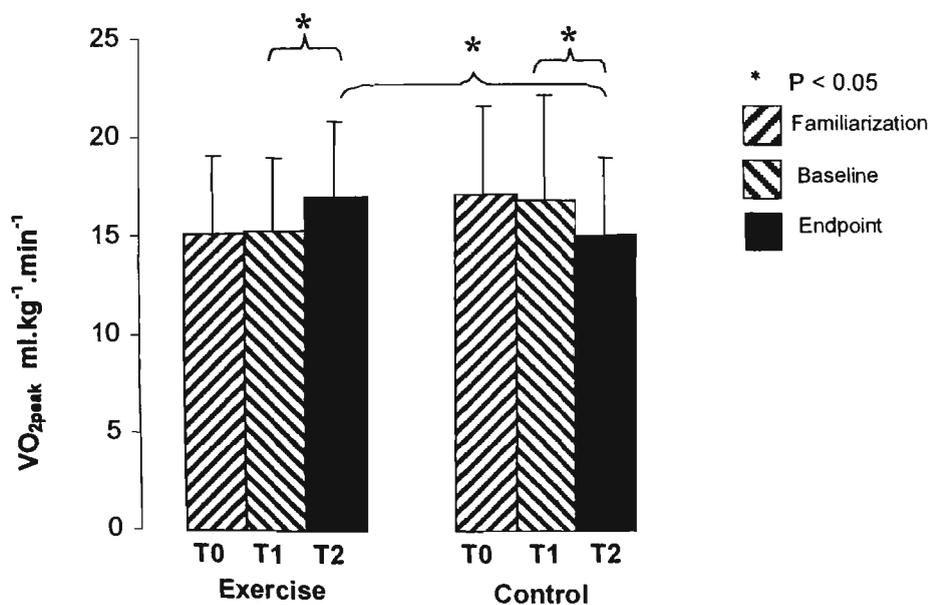
There were no significant effects of familiarization for any of the variables observed during the symptom-limited graded exercise tests for the assessment of aerobic power ( $VO_{2peak}$ ; Table 6.3; Fig 6.3). Following training, there were improvements in  $VO_{2peak}$  ( $15.3 \pm 3.7$  to  $16.9 \pm 3.8$   $ml \cdot min^{-1} \cdot kg^{-1}$ ,  $P < 0.05$ ; Table 6.3; Fig 6.2) and power at  $VO_{2peak}$  ( $67 \pm 23$  to  $80 \pm 23$  W,  $P < 0.01$ ; Table 6.3) in EX, while  $VO_{2peak}$  fell during the corresponding period in CON ( $16.7 \pm 5.3$  to  $14.9 \pm 4.0$   $ml \cdot min^{-1} \cdot kg^{-1}$ ,  $P < 0.05$ ; Table 6.3; Fig 6.3).  $VO_{2peak}$  ( $P < 0.05$ ) and power at  $VO_{2peak}$  ( $P < 0.01$ ) were significantly higher at T2 in EX compared to CON (Table 6.3). Peak lactate increased in EX from familiarization to endpoint ( $4.2 \pm 1.4$  at T0 to  $5.5 \pm 1.8$   $mmol \cdot l^{-1}$  at T2,  $P < 0.01$ ; Table 6.3), but the changes from T1 to T2 in both EX and CON were not significant. None of the other variables ( $RER_{peak}$ ,  $HR_{peak}$ , and  $RPE_{peak}$ ) changed significantly during any of the three tests (Table 6.3).

**Table 6.3.** Symptom-limited graded exercise test for the assessment of aerobic power ( $VO_{2peak}$ ,  $ml.kg^{-1}.min^{-1}$ ) and the related variables of power at  $VO_{2peak}$  ( $Power_{peak}$ , watts),  $RER_{peak}$  ( $VCO_2/VO_2$  ratio),  $HR_{peak}$  ( $b.min^{-1}$ ) and peak self-rating of perceived exertion ( $RPE_{peak}$ , Borg 6-20 point scale (Borg 1973)). T0, T1 and T2 are as for Table 6.2. Data are presented as mean  $\pm$  SD. \*\*  $P < 0.01$  is for within subject comparisons of T2 with T0. #  $P < 0.05$  and ##  $P < 0.01$  are for within subject comparisons of T2 with T1. &  $P < 0.05$  and &&  $P < 0.01$  are for between subject comparisons for T2 for the exercise and control groups.

### Symptom-limited graded exercise test

Group	n	Test	$VO_{2peak}$	$Power_{peak}$	$RER_{peak}$	$HR_{peak}$	$RPE_{peak}$
Exercise	14	T0	$15.1 \pm 3.9$	$65 \pm 19$	$1.2 \pm 0.1$	$117 \pm 21$	$16.2 \pm 2.0$
		T1	$15.3 \pm 3.7$	$67 \pm 23$	$1.2 \pm 0.2$	$117 \pm 23$	$16.6 \pm 1.7$
		T2	$16.9 \pm 3.8$ #	$80 \pm 23$ ##	$1.2 \pm 0.1$	$121 \pm 21$	$16.6 \pm 1.9$
Control	19	T0	$17.0 \pm 4.5$	$69 \pm 24$	$1.2 \pm 0.2$	$130 \pm 25$	$15.6 \pm 2.1$
		T1	$16.7 \pm 5.3$	$69 \pm 26$	$1.2 \pm 0.1$	$133 \pm 26$	$16.7 \pm 1.4$
		T2	$14.9 \pm 4.0$ # &	$67 \pm 29$ &&	$1.2 \pm 0.2$	$129 \pm 27$	$16.6 \pm 0.9$

**Figure 6.3.** Aerobic Power ( $VO_{2peak}$ ) determined during the symptom-limited graded exercise test. Left bars are for the Exercise group; right bars are for the non-exercise Control group. T0, T1 and T2 as for Figure 6.2. Data are presented as mean  $\pm$  SD. \*  $P < 0.05$ .



### 6.5.4 Forearm blood flow

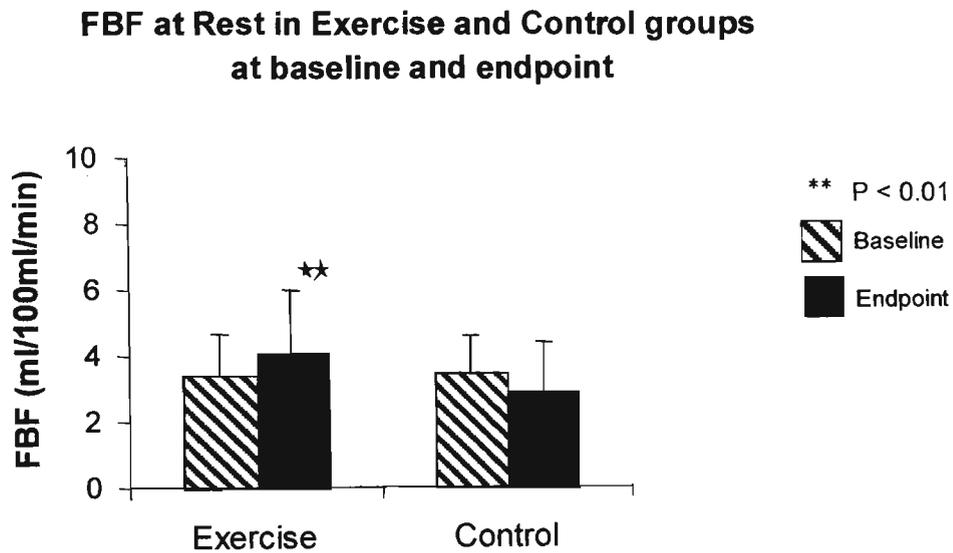
FBF at rest showed a trend (not significant) of increasing from T1 to T2 in EX ( $3.4 \pm 1.3$  to  $4.1 \pm 1.1$  ml.min<sup>-1</sup>.100 ml<sup>-1</sup>, Table 6.4). In CON, there were no significant changes to resting FBF during three months of inactivity, whilst FBF was lower at T2 in CON ( $2.9 \pm 1.5$  ml.min<sup>-1</sup>.100 ml<sup>-1</sup>), compared to EX ( $P < 0.01$ ; Table 6.4). Three months of resistance training (EX) resulted in improvements in activated FBF in response to all three intensities of isometric exercise of the forearm (Table 6.4), whilst there were no corresponding changes in FBF in response to acute exercise in CON. Similarly, FBF activation in response to limb occlusion improved after exercise training, with no significant changes in CON (Table 6.4). FBF was significantly higher in EX compared to CON at T2 for all three voluntary exercise intensities, as well as in response to limb occlusion (Table 6.4).

**Table 6.4.** Forearm Blood Flow (FBF) at rest, for 15%, 30% and 45% of maximal voluntary contraction (MVC), and for peak reactive hyperemia (PRH). T1 and T2 represent Baseline and Endpoint tests, respectively. Units for forearm blood flow are ml.min<sup>-1</sup>.100 ml<sup>-1</sup>. Data are presented as mean  $\pm$  SD. #  $P < 0.05$  and ##  $P < 0.01$  are for within subject comparisons of T2 with T1. \*  $P < 0.05$  and \*\*  $P < 0.01$  are for between subject comparisons for T2 for the exercise and control groups.). Total  $n = 32$  due to seven withdraws and five cases with missing data see Appendix B Table B2 for collected data on all 44 patients.

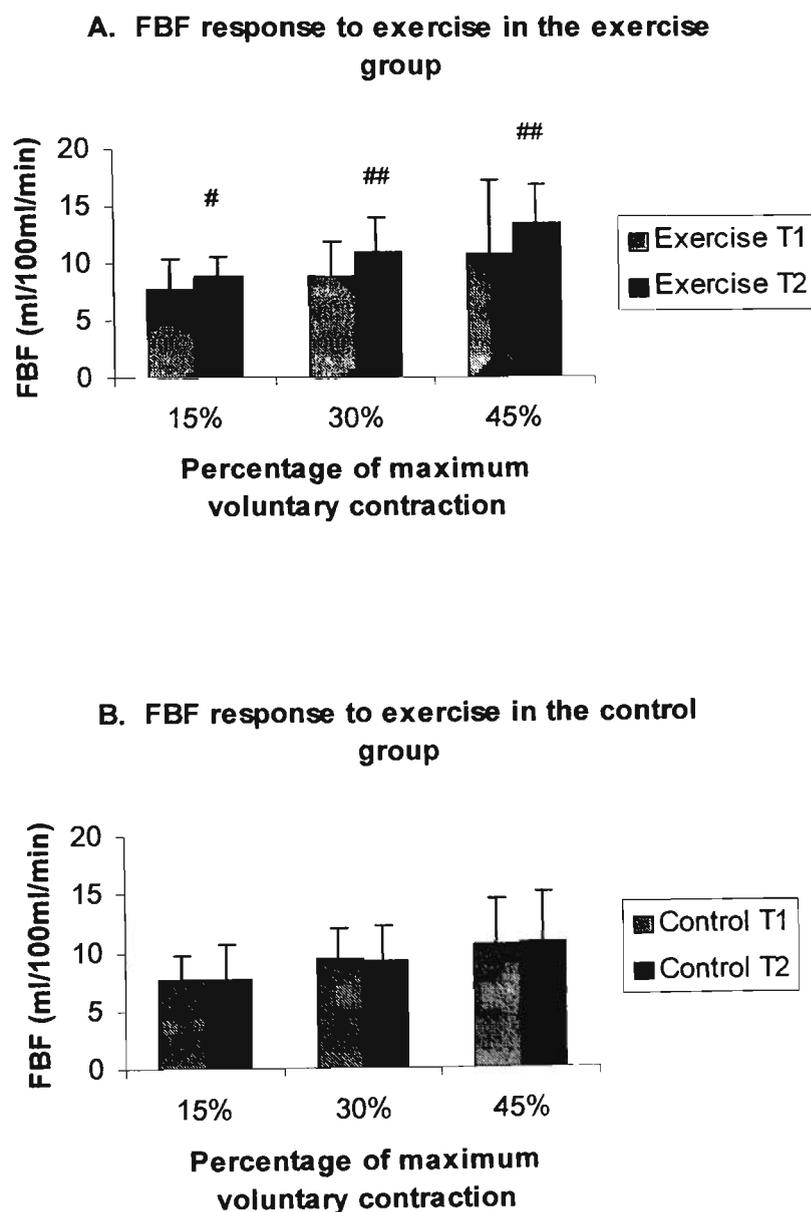
#### FBF by venous occlusion plethysmography

Group	n	Test	FBF <sub>rest</sub>	FBF <sub>15%MVC</sub>	FBF <sub>30%MVC</sub>	FBF <sub>45%MVC</sub>	FBF <sub>PRH</sub>
Exercise	14	T1	$3.4 \pm 1.3$	$7.7 \pm 2.7$	$8.9 \pm 3.1$	$10.8 \pm 6.6$	$18.9 \pm 7.2$
		T2	$4.1 \pm 1.1$	$8.9 \pm 1.7$ #	$10.9 \pm 3.2$ ##	$13.4 \pm 3.5$ ##	$23.8 \pm 8.6$ ##
Control	18	T1	$3.5 \pm 1.9$	$7.6 \pm 2.1$	$9.3 \pm 2.7$	$10.5 \pm 3.9$	$18.3 \pm 8.0$
		T2	$2.9 \pm 1.5$ **	$7.7 \pm 2.9$ *	$9.2 \pm 3.0$ **	$10.6 \pm 4.5$ **	$17.2 \pm 7.1$ **

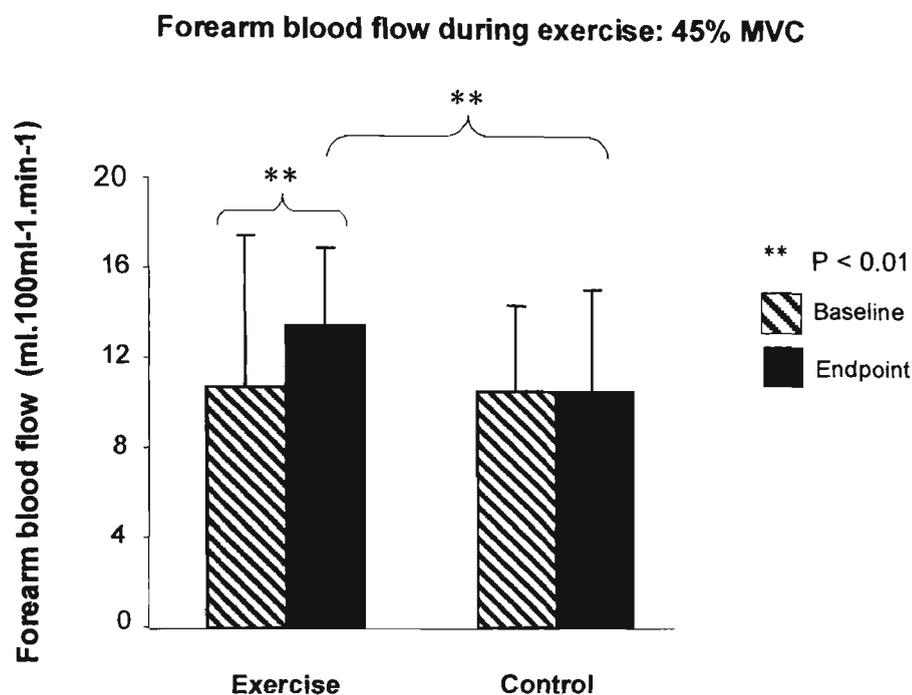
**Figure 6.4.**  $FBF_{rest}$  in EX and CON groups at baseline and endpoint following 3 months resistance training in patients with CHF. Units for forearm blood flow are  $ml \cdot 100ml^{-1} \cdot min^{-1}$ . Data are presented as mean  $\pm$  SD. **\*\*** $P < 0.01$  for between subject comparisons for T2 for the exercise and control groups.



**Figure 6.5 A and B.** FBF response to moderate intensity hand squeezing exercise in EX (A) and CON (B) groups at baseline (T1) and endpoint (T2) following 3 months resistance training in patients with CHF. Units for forearm blood flow are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD. #  $P < 0.05$  and ##  $P < 0.01$  are for within subject comparisons of T2 with T1.

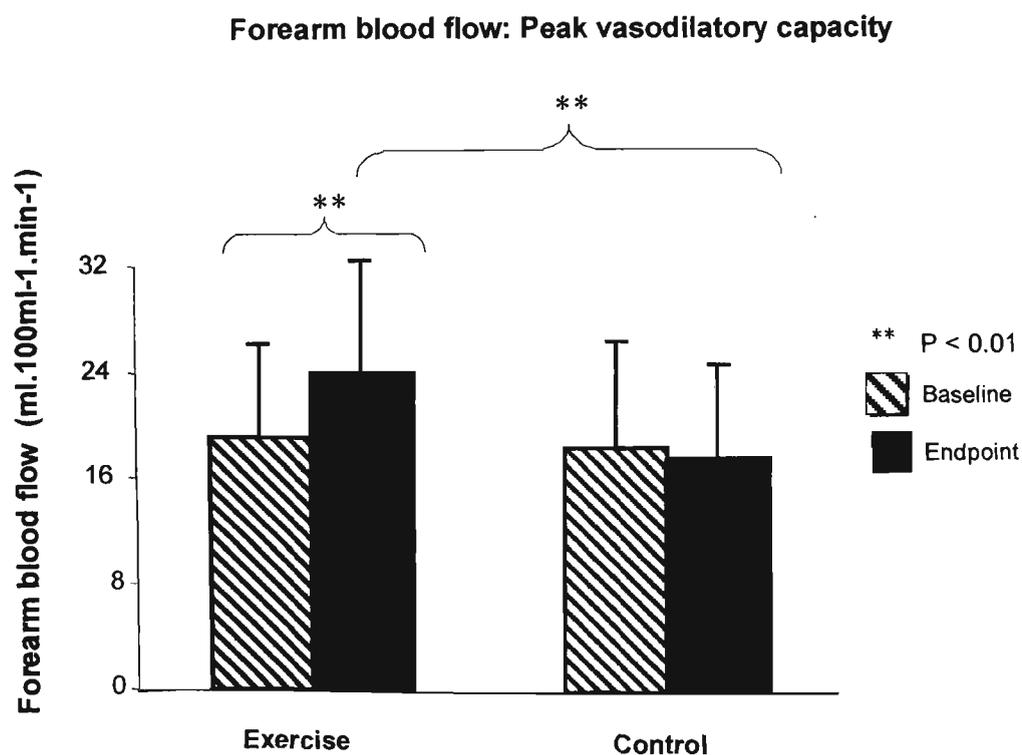


**Figure 6.6** FBF response to submaximal isometric hand squeezing at 45% MVC in the EX and CON groups at baseline and endpoint following 3 months resistance training in patients with CHF. Units for forearm blood flow are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD.

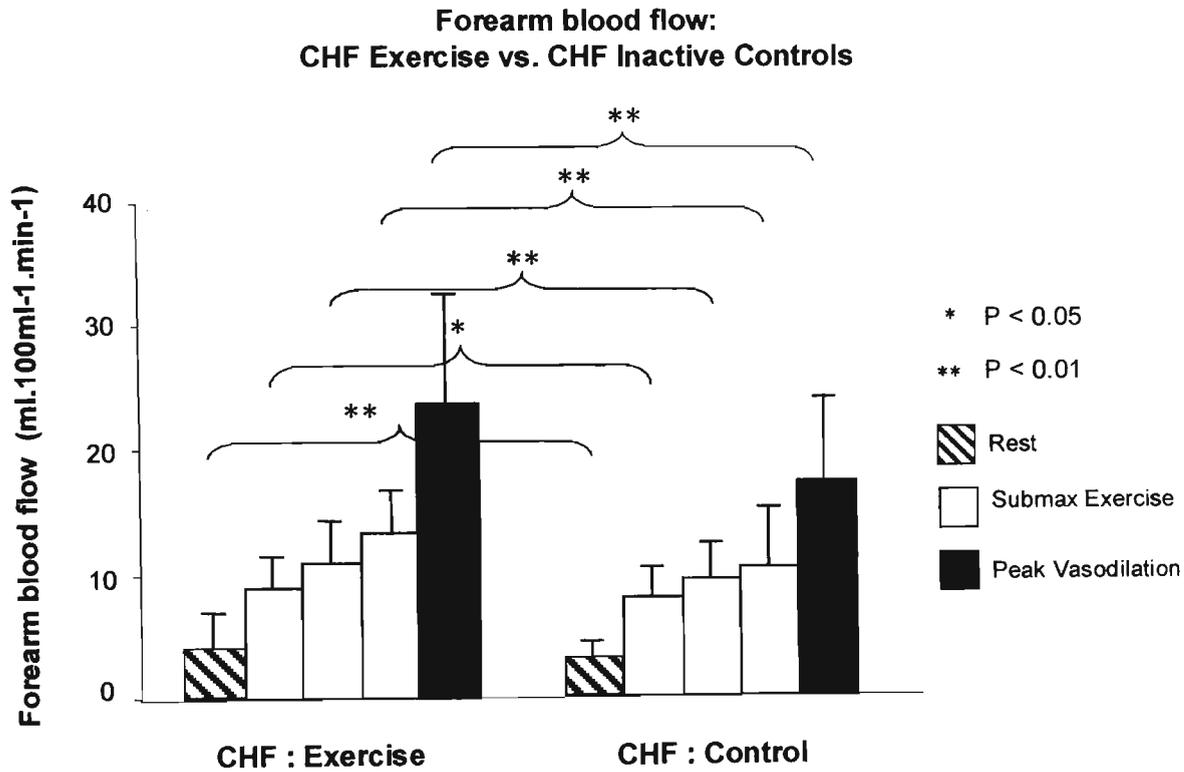


**Figure 6.7.** Peak reactive hyperemia blood flow after release of 5 min of arterial occlusion in the EX and CON groups at baseline and endpoint following 3 months resistance training in patients with CHF. Units for forearm blood flow are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD.

## P < 0.01 is for within subject comparisons of T2 with T1.

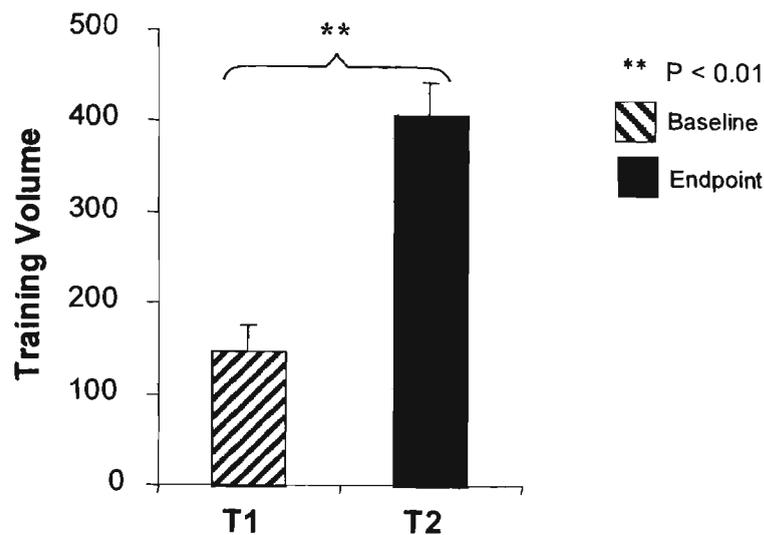


**Figure 6.8** Endpoint data of forearm blood flow at rest, responses to submaximal isometric hand squeezing, and peak vasodilatory capacity in patients with CHF. Resistance exercise training group compared to inactive control group. Units for FBF are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD. \*  $P < 0.05$  and \*\*  $P < 0.01$ .



The patients randomized to EX were able to increase their training volumes from an average of  $148 \pm 27$  to  $408 \pm 37$  arbitrary units ( $P < 0.001$ ; Figure 6.9).

**Figure 6.9.** Training volumes for patients at the commencement (T1 = Wk 1, left bar) and the conclusion (T2 = Wk 11, right bar). Volume (arb. units) was estimated as the sum of the product of resistance (machine settings) and number of repetitions for each of the exercises. Data are presented as mean  $\pm$  SD. \*\*  $P < 0.001$ .



## 6.6 Discussion

There have been relatively few studies on the effects of resistance training for patients with CHF, in contrast to the numerous investigations of aerobic exercise training, even though there is a sound rationale for including resistance exercises in the physical training of these patients (Clark AL 1996; Anker, Ponikowski et al. 1997). This was the first prospective randomized study in CHF patients using an usual care group to examine the effects of resistance exercise as the predominant modality. Previous studies used significantly smaller numbers of volunteer patients ( $n = 12$  (Maiorana, O'Driscoll et al. 2000),  $n = 12$  (Koch 1992),  $n = 13$  (Maiorana, O'Driscoll et al. 2000),  $n = 16$  (Pu, Johnson et al. 2001),  $n = 17$  (Benjaminovitz 2002)) than the 39 patients studied here, or used a randomized crossover design (Maiorana, O'Driscoll et al. 2000), an active control group (Magnusson, Gordon et al. 1996; Pu, Johnson et al. 2001; Benjaminovitz 2002; Delagardelle 2002) or randomizations that were skewed in the number of participants towards the exercise group (Tyni-Lenne, Dencker et al. 2001) (Benjaminovitz 2002). Four of these

studies were designed to be of mixed (aerobic and resistance) mode (Maiorana, O'Driscoll et al. 2000; Maiorana, O'Driscoll et al. 2000; Tyni-Lenne, Dencker et al. 2001; Beniaminovitz 2002) and therefore the effects of the resistance components of the training were difficult to differentiate from the aerobic components. Two studies used high-intensity training (Magnusson, Gordon et al. 1996; Pu, Johnson et al. 2001), which raises concerns with respect to safety, exercise adherence and applicability.

The patients in this study are older than those in previous studies of exercise training. This increases the generalizability of the results, given that the prevalence of heart failure in the community increases steeply with increasing age. In an Australian population over 60 years of age, 13% of 22,060 consecutive patients attending primary care physicians have heart failure (Krum 2001). The average age of volunteers in the current study (65 years) was at the upper end of the range of comparable investigations (Magnusson, Gordon et al. 1996; Bank 1998; Maiorana, O'Driscoll et al. 2000; Maiorana, O'Driscoll et al. 2000; Pu, Johnson et al. 2001; Tyni-Lenne, Dencker et al. 2001; Beniaminovitz 2002). In these other studies, the average ages of heart failure patients were 40 years (Bank 1998), 49 years (Beniaminovitz 2002), 56 years (Magnusson, Gordon et al. 1996), 60 years (Maiorana, O'Driscoll et al. 2000; Maiorana, O'Driscoll et al. 2000), and 63 years (Tyni-Lenne, Dencker et al. 2001). Another investigation (Pu, Johnson et al. 2001) used a substantially older cohort (77 years) than all of these, but this was a study restricted to women only. The elderly cohort in the current investigation increases its validity, as 13% of all Australians over the age of 60 years who consult their general practitioners have heart failure.

In the present study, moderate-intensity resistance exercise with prolonged recovery intervals was the centerpiece of the training program, while aerobic exercise on leg and arm cycle ergometers were both brief and of low intensity. The program was well-tolerated in CHF patients, resulting in improvements in skeletal muscle strength and endurance,  $VO_{2peak}$ , and FBF. Patients were able to increase their training volumes threefold during the three month period (Figure 6.9). Skeletal muscle strength and endurance increased by an average of 21% each.  $VO_{2peak}$  also improved (by 10%) in the training group, while it fell by a similar amount in the non-exercise control group. These results may indicate that muscle mass plays an important role

in exercise capacity in this population. FBF showed an increasing trend ( $p = \text{NS}$ ) at rest in EX after training, but was unchanged in CON, and vascular responsiveness improved in response to both submaximal exercise and brief limb occlusion in the trained volunteers.

The current moderate-intensity exercise program yielded similar magnitude improvements in skeletal muscle strength to that for circuit weight training (Maiorana, O'Driscoll et al. 2000) and low-level leg endurance and resistance training (Benjaminovitz 2002), while high-intensity resistance training produced higher order improvements of 40-45% (Magnusson, Gordon et al. 1996; Pu, Johnson et al. 2001). However, high-intensity training is neither warranted nor suitable for home-based maintenance programs for these patients, with respect to both safety and compliance considerations. The exercise program utilized in this study emphasized brief bouts of moderate-intensity exercise, which may have prevented many patients from reaching a "symptom threshold". Although the duration of the training sessions (approximately one hour) was similar in all of these studies [(Magnusson, Gordon et al. 1996); Maiorana, 2000 #94; Tyni-Lenne, 2001 #124; Pu, 2001 #112; Benjaminovitz, 2002 #150], the work:rest ratio was lower in the present study ( $< 1:4$ ), which should make the program more adaptable for home- or fitness facility-based training in CHF patients. Importantly, the present study is only the second to report improvements in skeletal muscle endurance following resistance training, with the only other report of improved endurance being in response to high-intensity training (Pu, Johnson et al. 2001). Endurance improved by similar magnitude to strength, and was consistent with the increases in training volumes apparent after three months of exercise training.

$\text{VO}_{2\text{peak}}$  increased in the resistance training group by about 10%. By comparison,  $\text{VO}_{2\text{peak}}$  improved in CHF patients by 8% for combined aerobic and resistance training (Tyni-Lenne, Dencker et al. 2001), 13% for circuit weight training (Maiorana, O'Driscoll et al. 2000) and by 16% for lower limb aerobic and resistance training (Benjaminovitz 2002), but all of these studies were designed to improve  $\text{VO}_{2\text{peak}}$  by emphasizing or including aerobic training. In contrast to this previous research (Maiorana, O'Driscoll et al. 2000; Tyni-Lenne, Dencker et al. 2001; Benjaminovitz 2002), moderate-intensity resistance exercise was emphasized in the training regime of the current study, with the only aerobic exercises being of short duration and low intensity. Furthermore, there were prolonged rest intervals between each exercise to enable heart

rate to return to within  $10 \text{ b}\cdot\text{min}^{-1}$  of the pre-exercise (rest) level. In contrast, single-mode high-intensity resistance training was shown to have no effect on  $\text{VO}_{2\text{peak}}$  (Pu, Johnson et al. 2001) or treadmill time-to-fatigue, but 6 min walk distance improved by 13%. It is not currently known whether improvements in  $\text{VO}_{2\text{peak}}$  contribute to better survival in CHF, but there is sound evidence from large studies that exercise capacity is a strong prognostic indicator in CHF patients (Bittner, Weiner et al. 1993) and those undergoing cardiac rehabilitation (Kavanagh, Mertens et al. 2002).

Surprisingly,  $\text{VO}_{2\text{peak}}$  decreased in the inactive control group of CHF patients. Although a similar finding was reported recently (Tyni-Lenne, Dencker et al. 2001), most prospective randomized studies of aerobic and/or resistance training in CHF patients have reported no deterioration in  $\text{VO}_{2\text{peak}}$  in the non-exercise control groups (Hambrecht 1995; Callaerts-Vegh Z 1998; Belardinelli 1999; Pu, Johnson et al. 2001; Beniaminovitz 2002). Possible explanations for the decrease include clinical deterioration, onset of cardiac cachexia, decreased aerobic power due to continued deconditioning of these otherwise sedentary patients, less interaction with testers resulting in a decreased level of comfort (as compared to the exercise group), decreased effort on the part of the participants at endpoint, or technical problems with the accuracy or reliability of the cardiorespiratory data measurements. The latter two explanations have previously been discounted (Selig 2002). Although the exercise training group may have had an increased comfort level with testers due to the time spent together during training sessions, the  $\text{VO}_{2\text{peak}}$  testing followed strict protocol to insure that each test replicated the one before it. There was little evidence of changed clinical condition: most of the 39 patients studied over the three-month period maintained stable medication regimes, with all patients in the control group undergoing endpoint testing. Mean weight of the control group increased by 2 kg, arguing against a cachexia mechanism. Therefore, the 10% fall in  $\text{VO}_{2\text{peak}}$  from T1 to T2 in the control patients was probably due to deterioration of aerobic power due to prolongation of inactivity.

There have been several previous investigations of the effects of exercise training on forearm blood flow in CHF patients (Hornig 1996; Katz 1997; Bank 1998; Dziekan 1998; Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000). This is one of the first randomized studies on the effects of resistance exercise training in patients with CHF and the second to report on FBF

(Maiorana, O'Driscoll et al. 2000). Three studies followed a forearm exercise training protocol consisting of hand squeezing only (Hornig 1996; Katz 1997; Bank 1998) and most others consisted of aerobic exercise training or a high intensity aerobic rehabilitation program (Dziekan 1998). One study used Doppler ultrasound for the measurement of flow-mediated dilation of conduit vessels of the upper limb. In contrast, venous occlusion plethysmography measures flow through resistance vessels and was used in this study and most others (Katz 1997; Bank 1998; Dziekan 1998; Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000). Studies assessing the effects of exercise on peripheral blood flow reporting data measured in the leg (Sullivan, Higginbotham et al. 1988; Piepoli 1996; Barlow 1998; Hambrecht, Fiehn et al. 1998; Taylor 1999) was not considered in the comparison of data, as absolute values in the lower limb are much higher than those measured in the forearm and most used a technique other than venous occlusion plethysmography. The major findings in this study were that moderate-intensity resistance training showed a trend, albeit not significant, to increase  $FBF_{rest}$ , confirming previous findings in an observational outcome study (Hare, Ryan et al. 1999) and supported by a non-significant trend of similar magnitude for a training program in CHF patients which combined aerobic and resistance exercises (Maiorana, O'Driscoll et al. 2000). The present exercise program also resulted in improved vascular responsiveness to intermittent, submaximal isometric exercise, and to five minutes of limb occlusion that was used to determine peak vasodilatory capacity. Aerobic training has been shown to improve endothelium-dependent but not endothelium-independent vasodilation in CHF patients (Hambrecht, Fiehn et al. 1998), possibly due to repeated flow stimulus of exercise training which is thought to assist in vasodilation by triggering the release of NO (Miller 1988). However, little is known about the effects of resistance training on peripheral blood flow. In a non-randomized study of 12 patients with heart failure, eight weeks of resistance training confined to handgrip exercise resulted in improvements in endothelium-dependent, but not endothelium-independent, FBF (Katz 1997). Surprisingly, Maiorana and colleagues provided evidence indicating improvements in both endothelium-dependent and endothelium-independent FBF following lower body exercise training in CHF patients that excluded upper limb exercise (Maiorana, O'Driscoll et al. 2000), although the endothelium-independent improvements could only be demonstrated with complicated statistical analyses. In contrast to these findings and the present study, 4-6 wk of local forearm muscle training in CHF patients (Bank 1998) did not result in improvements in

basal FBF, or FBF stimulated by exercise, limb occlusion, or vasoactive substances. However, their healthy control volunteers who also underwent the exercise training program exhibited improvements in endothelium-dependent vasodilation and peak hyperemic FBF. The 24% increase in peak reactive hyperemic flow that their healthy control group exhibited, is consistent with the present study which used patients with CHF and showed a 20% increase in the exercise group (Bank 1998).

Resistance exercise training causes an additional increase in vasodilatory responses to exercise and limb occlusion which has been shown to be blunted in patients with CHF compared to healthy volunteers (Chapter Five). It is acknowledged, however, that there could have been an overlapping aerobic effect due to inclusion of arm and leg cycling. The objective was to minimize this by using prolonged rest intervals between each exercise to enable heart rate to return to within  $10 \text{ b}\cdot\text{min}^{-1}$  of the pre-exercise (rest) level. Other studies concentrated the exercise stimulus to the forearm only and showed no change in resting blood flow (Katz 1997), but partial restoration of vasodilatory capacity (Katz 1997) (Hornig 1996). Findings of this study and the recent publication by Maiorana et al. (Maiorana, O'Driscoll et al. 2000) suggest that significant improvements may be due to the training stimuli. The resistance exercise training program used in this study emphasized muscular strengthening at a moderate intensity using large muscle mass compared to hand squeezing (Katz 1997).

## **6.7 Conclusion**

In summary, three months of resistance training in patients with CHF resulted in favorable changes to forearm blood flow. This data extends on previous aerobic training studies, which showed benefits of exercise on impaired vasodilatory response in CHF patients. The improved vasodilatory capacity shown in this study helps to explain how training increases exercise capacity in these patients.

## **Chapter 7 GENERAL DISCUSSION AND CONCLUSIONS**

### **7.1 Overview**

The body of research comprising this thesis focussed on peripheral blood flow adaptations to resistance exercise training in patients with chronic heart failure. Supporting research included a cross-sectional comparison study of patients with CHF and age-matched normal volunteers with respect to peripheral blood flow, and a reliability study of the main outcome measures. Specifically the study found that resistance training is not only safe, but also effective in increasing peripheral blood flow during submaximal exercise and peak reactive hyperemia, muscular strength and endurance whilst reducing the demand for oxygen and ventilation at submaximal workloads (Chapter Six). Supporting research confirmed that (1) peripheral blood flow is reduced in patients with CHF when compared to age-matched healthy volunteers during submaximal hand squeezing exercise and peak reactive hyperemia but not at rest (Chapter Five). (2) a familiarization trial for skeletal muscle strength testing is necessary for test reliability when using an isokinetic dynamometer, but familiarization is not required for assessing  $\text{VO}_{2\text{peak}}$  or forearm blood flow (Chapter Four). The following discussion examines these findings. Section 7.3 examines the evidence for resistance exercise training in the population of chronic heart failure and its possible implications for this patient group, and the relationship between increasing exercise tolerance and quality of life. A summary of the main conclusions of this research is included.

### **7.2 Major Findings**

#### **7.2.1 Established reliability of strength and endurance testing, aerobic power and FBF in patients with CHF**

Information as to the efficacy of resistance training programs in CHF populations is limited and there is no published data on the need to familiarize these patients with strength testing protocols prior to them being tested for strength. Evidence-based practice depends on reliable efficacy data and thus it is important to establish the reliability of testing both skeletal muscle strength and endurance in these patients. Thus one of supporting objectives of this thesis (Chapter Four) was to assess the reliability of strength and musculoskeletal endurance testing in a group of patients with stable CHF. Investigators have previously included familiarization protocols for the

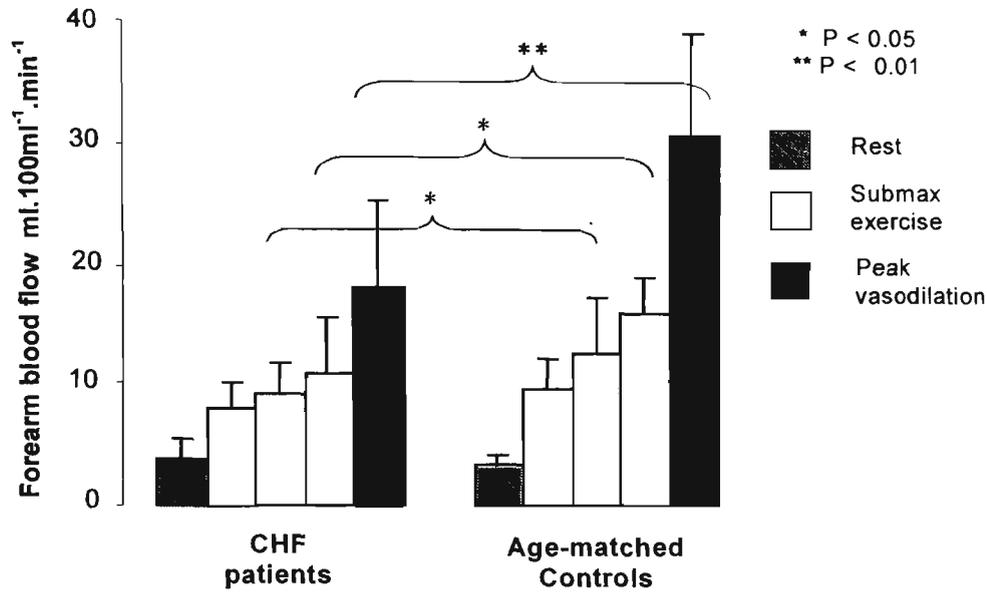
assessment of  $VO_{2peak}$  in cardiovascular patients (Sullivan, Higginbotham et al. 1988; Adamopoulos, Coats et al. 1993; Maiorana, O'Driscoll et al. 2000), but there is no published data on the reliability of  $VO_{2peak}$  testing in these patients. There have been several studies of FBF reproducibility (Roberts 1986; Wiener DH 1986; Benjamin 1995; Petrie 1998). It has been demonstrated that there is good within-subject reproducibility by some researchers whilst others have reported otherwise.

Patients with CHF exhibited increases by an average of 12% in the expression of skeletal muscle strength and endurance in the second of two tests conducted one week following the first. The effects of learning from the first test to the second seem to help explain the difference exhibited between the two tests. Strength and endurance testing conducted in the present work using an isokinetic dynamometer required some learning in order to achieve maximum results showing that familiarization testing is necessary for reliability. However, the same cannot be said about  $VO_{2peak}$  and FBF testing. The current work in Chapter Four suggests that internal consistency within patients was high for the first and second tests of  $VO_{2peak}$  and FBF. Familiarization with incremental cycle ergometer protocols to measure aerobic capacity and venous occlusion plethysmography to determine FBF in CHF patients is unnecessary.

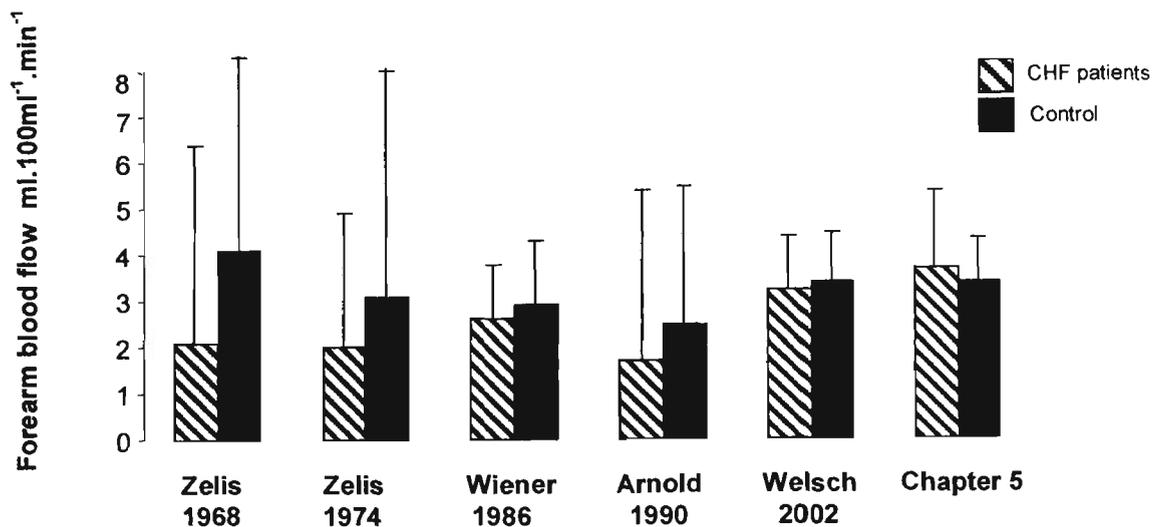
### **7.2.2 Peripheral blood flow in CHF is reduced during exercise and peak vasodilation and not at rest compared to healthy age-matched volunteers**

Evidence that patients with CHF have reduced blood flow responses to isometric exercise and reactive hyperemia compared to healthy age-matched volunteers is further supported by this thesis. However, resting FBF was not reduced in the CHF patients compared to the healthy age-matched volunteers (Figure 7.1) as others have previously reported (Figure 7.2). This may be explained by their prescription to vasodilators, such as ACE Inhibitors, which assist in peripheral blood flow (Drexler 1992) and/or patient selection. During exercise, FBF progressively increased in both groups, but the rises in CHF patients were significantly lower than the corresponding rises in normal volunteers.

**Figure 7.1** FBF at rest, during exercise, and following brief limb occlusion in patients with CHF compared to healthy age-matched volunteers. Units for FBF are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD. \*  $P < 0.05$  and \*\*  $P < 0.01$ .



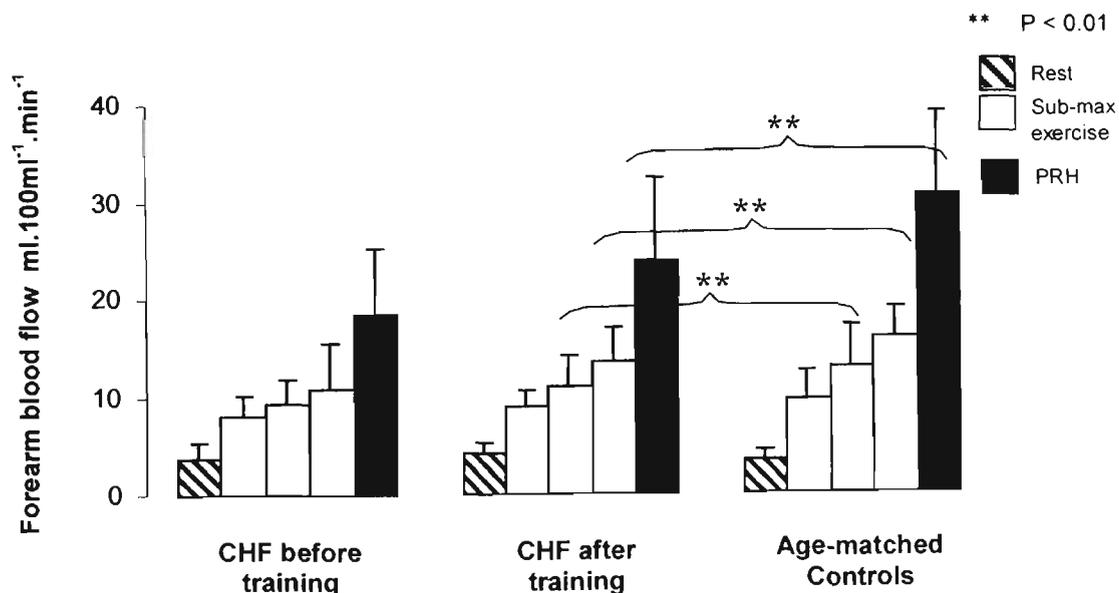
**Figure 7.2** Historical data on FBF at rest in patients with CHF compared to healthy controls. Units for FBF are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD.



### 7.2.3 Moderate resistance training improves FBF in CHF patients

The major findings of the primary study in this thesis were that moderate-intensity resistance training improved FBF at rest, confirming previous results from an observational pilot study (Hare, Ryan et al. 1999). This is supported by a non-significant trend of similar magnitude for a training program in CHF patients which combined aerobic and resistance exercises (Maiorana, O'Driscoll et al. 2000). The present exercise program also resulted in improved vascular responsiveness to intermittent, submaximal isometric exercise, and to five minutes of limb occlusion that was used to determine peak vasodilatory capacity. These findings differ, however, from those reported in the pilot study (Hare, Ryan et al. 1999) which showed no significant vasodilatory responses to handgrip exercises or limb occlusion. This may be explained by the small number of participants used in the pilot study ( $n = 9$ ). Although CHF patients showed a significant improvement in FBF measures following three months of resistance training, absolute values were still significantly reduced compared to healthy age-matched volunteers measured for Chapter Five (Figure 7.3).

**Figure 7.3** FBF before and after 3 months of resistance exercise training (Chapter Six) compared to healthy age-matched volunteers (Chapter Five). Units for FBF are  $\text{ml}\cdot 100\text{mL}^{-1}\cdot \text{min}^{-1}$ . Data are presented as mean  $\pm$  SD. \*\*  $P < 0.01$ .



#### 7.2.3.1 Exercise training as an adjunct treatment to CHF is safe and effective

Whilst measuring testing reliability and local blood regulation to skeletal muscle is important to better understand effects of exercise in CHF, a goal for such research is to determine how these

findings can assist in establishing recommended guidelines. The significance of the present studies is that they provide general evidence that patients with severe CHF benefit from strength training, and do so without hazard. Three months of strength training resulted in significant increases in skeletal muscle strength and endurance, aerobic power associated with increases in peak lactate, and forearm blood flow. Patients randomized to exercise increased their training volumes by 64% (Figure 6.9) without a single adverse event caused by the exercise. This is consistent with an overview of recent studies. A literature review covering 1966 to 2000 has been recently published and 31 studies were identified that investigated the effects of exercise training on patients with CHF (Lloyd-Williams F 2002). Beneficial findings were reported on physical performance in 27 of the 31 studies. Of the 16 studies that measured quality of life 11 showed positive results. The number of patients with CHF that have participated in a randomized study has increased significantly in the past few years. A review of randomized controlled trials was undertaken by the European Heart Failure Training Group (European 1998), showing 134 patients with CHF had completed an exercise training study with an overall increase of 13% in  $VO_{2peak}$  and 17% in exercise duration. From the time of its publication to present (2003) a further 22 trials have occurred, 14 of them randomized, adding 627 CHF patients which have participated in exercise training. More than 900 patients in all have safely participated in exercise training, 570 of those in randomized controlled trials from various research centers around the world. There are very few accounts of patients who were unable to tolerate the training and even less who documented adverse effects from exercise. Most studies show improvements in exercise capacity or tolerance, which includes duration of exercise and  $VO_{2peak}$ . In most studies both are reported to increase from exercise (+17% exercise duration; +13%  $VO_{2peak}$  (European 1998)). In the present study the increase in  $VO_{2peak}$  is slightly less than other trials, at +10%. A couple of factors may account for this. Most studies investigating the effects of exercise in CHF used predominately aerobic training with the bicycle ergometer as the most common mode of exercise. The primary mode of exercise used in this study was hydraulic resistance exercise training. Patients' heart rate had to recover to within 10 beats of the pre-exercise rest before changing exercise stations. Arm and leg cycling, and stair climbing were each of short duration (0.5 - 2 minutes) and relatively high intensity to conform to the resistance training format. This was typically 1-2 minutes between exercises, and together with the relatively high intensities used, ensured that the training program could be categorized as resistance training. In contrast,

circuit training exercises follow continuously without rest intervals to maintain elevated heart rates and are therefore necessarily of lower intensity and aerobic in nature. A recent study investigating the effects of circuit training exercises on CHF patients showed a +12% increase in  $VO_{2peak}$  (Maiorana, O'Driscoll et al. 2000). A second consideration to the lower rise in  $VO_{2peak}$  is the duration of the training was only three months. Studies lasting 6 to 12 months have shown a greater percent of change in  $VO_{2peak}$  (Hambrecht 1995; Kavanagh, Myers et al. 1996; Keteyian, Levine et al. 1996) thus an extended training period may show greater results. Although  $VO_{2peak}$  results rose slightly there were significant increases in exercise duration, peak lactate levels, skeletal muscle strength and endurance, and forearm blood flow suggesting an improvement in the transportation of oxygen to skeletal muscle and its utilization.

### **7.3 Utilization of resistance training as a recommended therapy in patients with CHF**

Chronic heart failure (CHF), a syndrome categorized by inadequate cardiac function, is associated with reduced exercise tolerance which is attributed mainly to peripheral maladaptations in skeletal muscle, including fibre type alterations, atrophy, reduced blood flow and capillary density (AACPR 1999). The major symptoms of CHF are fatigue and breathlessness. Often, the first thing a patient notices is that they are less able to cope with physical effort. Acute exacerbations of CHF is the most common cause of hospitalization in people over 65 years (Sharpe 1998). On both human and economic scales, CHF is costly due to low functional status, poor quality of life, frequent hospitalizations and poor prognosis of patients. Standard therapy to CHF did not include the prescription of exercise until recently because it was felt that the acute and chronic risks of exercise training outweighed the potential benefits. However, a number of recent publications indicate that patient-specific exercise training programs are not only safe, but highly desirable in relation to improved quality of life and survival.

For too many patients with CHF, aerobic exercise training is not appropriate. CHF often coexists with other severe exercise limitations, such as COPD, neurological disorders, osteoarthritis, perform less than four minutes on their exercise test. Patients in this state are more suited to resistance exercise training or circuit weight training, both have been shown to be safe and

provide beneficial effects (Hare, Ryan et al. 1999; Maiorana, O'Driscoll et al. 2000). Recent research has allayed many concerns regarding resistance training and the benefits of training are accomplished without any impact on left ventricular systolic function (Karlsdottir 2002). The present study accumulated more than 700 hours of supervised resistance training without an adverse effect as a result of exercise.

Low exercise tolerance (Bittner, Weiner et al. 1993), and loss of skeletal muscle mass leading to a cachectic state (Anker, Swan et al. 1997), are independently correlated with morbidity and mortality in CHF patients and are therefore worthwhile targets for intervention. Aerobic exercise training by patients with CHF produce favorable outcomes in aerobic power ( $VO_{2peak}$ ) (Belardinelli 1999), skeletal muscle metabolism (Adamopoulos, Coats et al. 1993), autonomic function (Coats, Adamopoulos et al. 1992), peripheral hemodynamics (Hambrecht, Fiehn et al. 1998), central hemodynamics and functional class (Hambrecht, Gielen et al. 2000), exercise tolerance (Coats, Adamopoulos et al. 1992) (Hambrecht, Gielen et al. 2000), and quality of life (Belardinelli 1999). Improvements in  $VO_{2peak}$  are associated with lower rates of morbidity and mortality for patients with coronary artery disease (Kavanagh, Mertens et al. 2002) and CHF (Belardinelli 1999), underlining the value of exercise training for these patients. However there is no published data showing reversal of skeletal muscle atrophy or cachexia with aerobic exercise training.

Resistance (strength) training has recently been recommended for trial in CHF patients, because this form of exercise training may be more effective in reversing skeletal muscle atrophy than aerobic training. There is some preliminary evidence supporting this contention (Magnusson, Gordon et al. 1996). To date, there have been very few studies of resistance training in CHF patients. Exercise programs that incorporate resistance training in CHF patients have been shown to improve  $VO_{2peak}$  (Maiorana, O'Driscoll et al. 2000) (Tyni-Lenne, Dencker et al. 2001), skeletal muscle strength (Magnusson, Gordon et al. 1996) (Maiorana, O'Driscoll et al. 2000) (Pu, Johnson et al. 2001), skeletal muscle structure (Magnusson, Gordon et al. 1996; Pu, Johnson et al. 2001), and forearm blood flow (FBF) (Maiorana, O'Driscoll et al. 2000). Until now, there have been no prospective randomized studies in CHF patients using an inactive control group to examine the effects of resistance exercise as the predominant modality.

Rationale to support resistance exercise training comes from several points. It is widely accepted that maintaining two to three sessions of resistance exercise training per week increases muscular strength and endurance by 25% to 100%, while aerobic exercise has only minimal effects (Pollock 2000). An increase in muscular strength and endurance promotes independence, prevents falls, and improves physical work capacity for occupational and leisure-time. Resistance exercise training develops upper and lower body segments rather than only leg exercises commonly concentrated on by aerobic training programs. This is significant for the elderly and frail CHF patients whom have difficulty in their activities of daily living. Furthermore, the ACSM, AHA, CDC, Surgeon General's Report, and AACVPR recommend resistance training as an integral part of any fitness program due to its associated benefits of increased lean body mass, metabolic rate, reduces risk of orthopaedic injury, low back pain, osteoporosis, and diabetes mellitus (Pollock 2000). Recently, investigators examined the effects of combined aerobic and resistance training versus aerobic training alone in twenty patients with cardiac disease over a six month duration (Pierson 2001). The training program involved three 30 minutes sessions per week of aerobic exercise at an intensity of 65% to 80% of their maximum HR. Following each of the aerobic training sessions, ten of the patients continued with resistance training. Seven resistance exercises were set at 40% of one repetition maximum (1RM) and performed in two sets of 12 to 15 repetitions. Muscular strength gains were significant in the combined aerobic and resistance training group for all seven movements, with an average percentage change of 63%, while the aerobic training group improved by an average of 22% and two of the seven were insignificant. Increases in  $VO_{2peak}$  were evident in both groups, 10% in the combined aerobic and resistance training group and 18% for the aerobic training group. Although patients with CHF were excluded from this study, the results reciprocate those of the present study, that a moderate resistance exercise training program will enhance exercise tolerance and improve the muscular deconditioning that debilitates this population.

A significant amount of research has been collected to support the recommendation of aerobic and resistance exercise training programs to patients with severe CHF. It has been the contention of this study that CHF patients lack the physical strength to perform common activities of daily living and few patients have the exercise tolerance to return to employment. This study provides

further evidence that resistance training does not adversely effect the health and well being of patients with heart failure. These patients can participate in this form of exercise training without the development of adverse cardiovascular responses. There are many arguments for the contention that aerobic training alone is sub-optimal in terms of restoring skeletal muscle, therefore guidelines should include the prescription of resistance exercise training as for healthy persons of all ages and many patients with chronic diseases, including cardiovascular disease. Orientation to resistance exercise training to establish loads and technique, and use of ECG telemetry, were supervised by an exercise physiologist and nurse in this study. In addition to an easy warm up, basic stretches and short bouts of aerobic exercise, a resistance training circuit of 7 to 10 different pinned weighted exercises can be recommended. The present three month study demonstrated the safety and efficacy of isokinetic (hydraulic resistance) muscle strengthening exercise in CHF patients.

## **7.4 Conclusions**

The following summarizes the main conclusions found in this research.

1. Local blood regulation to skeletal muscle of the forearm is improved in patients with chronic heart failure following three months of hydraulic resistance exercise training.
2. Local blood regulation to skeletal muscle of the forearm is reduced in patients with chronic heart failure when compared to healthy individuals.
3. Familiarization testing for skeletal muscle strength testing with an isokinetic dynamometer in CHF patients is necessary.
4. Familiarization testing is not required for assessing aerobic power as a single measurement.
5. Moderate-intensity resistance exercise training in patients with heart failure is safe and effective.

## **Chapter 8 RECOMMENDATIONS FOR FURTHER RESEARCH**

Studies conducted in this thesis have raised many further questions regarding the effects of resistance exercise training on the clinical population of patients with chronic heart failure. The important problems that remain unresolved are analyses of the potential benefits of this form of exercise training on quality of life, morbidity and mortality. In relation to morbidity and mortality, the relatively low number of CHF patient volunteers ( $n = 45$ ), the exclusion of NYHA Class IV patients, and the relatively short duration of the exercise intervention (3 months) would not have provided enough statistical power to answer any of these important questions. Quality of life was not the focus of the thesis but is of importance in assessing the applicability of the exercise. Use of a longer time course would help to answer some of these questions. Relatively little is known about the cost effectiveness of resistance exercise training programs. On both human and economic criteria, CHF is costly due to low functional status, frequent hospitalizations and poor prognosis of patients. Exercise training is a relatively new form of therapy for CHF patients and recommended programs with specific guidelines for each of the four New York Heart Association classifications need to be investigated for optimal safety and efficacy. The exercise program in this thesis was applied as an intensely supervised hospital program. It proved to be safe for this cohort, and it is now important to assess the safety and efficacy of similar programs in home- and community-based facilities.

Use of strain gauge venous occlusion plethysmography to measure forearm blood flow is non-invasive, reliable and relatively simple to perform for the measurement of peripheral blood flow. Future research might focus on the inter-relationships between current medication management and benefits of exercise training in relation to peripheral blood flow.

Resistance exercise training equipment used in this thesis (Chapter Six) was isokinetic, concentric (hydraulic) exercise and had previously been demonstrated to be safe for patients with CHF (Hare, Ryan et al. 1999). Further improvement in strength, endurance and FBF may be possible with the introduction of eccentric exercise. Eccentric exercise will potentially have even

greater effect on increasing skeletal muscle strength with increased ability to reverse the skeletal muscle abnormalities that limit CHF patients. Pinned weight machines can be adapted for most patients, progression of overload can be easily monitored, safe for patients that have balance or vision problems, and the range of movements can be full or limited. It will also increase the generalizability of the results because eccentric exercise is more generally undertaken in daily living and programs including eccentric exercise could be made more widely available. Although this study extends existing support to the beneficial effects of exercise in patients with CHF, further randomized studies are required to evaluate the long-term effects of resistance training as an adjunct treatment to patients living with heart failure.

The relative lack of studies investigating on resistance exercise training effects on blood flow in CHF patients indicates a need for further exploration of an important area of research. Research in this area can expect to have considerable impact on understanding the mechanisms of fatigue and the effective management of CHF patients with exercise intolerance.

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