45

EFFECTS OF EXERCISE TRAINING ON LEFT VENTRICULAR FUNCTION AND EXERCISE CAPACITY IN PATIENTS WITH CORONARY ARTERY DISEASE AND VARYING DEGREES OF LEFT VENTRICULAR DYSFUNCTION

by

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DECLARATION

I declare that the work reported in this thesis was carried out by myself. However many colleagues have helped me as indicated in the acknowledgements.

This thesis has not previously been submitted for a degree in any university. The work on which it is based was conducted during my employment at the Johannesburg Cardiac Rehabilitation Centre, Department of Health and Scientific Services, Transitional Metropolitan Council (previously Johannesburg City Health Department).

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TABLE OF CONTENTS

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Publications

1) Digenio AG.
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Predictors of exercise capacity and adaptability to training in patients with coronary artery disease.
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Presentations

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- V South African Sports Medicine Association Congress
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Cardiac Rehabilitation in South Africa. Presented at:
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- VI South African Sports Medicine Association Congress
  Durban, South Africa, March 1995. (lecture: presenter)

9) Digenio AG, Slavin A, Daly L, Esser J.
Can patients with myocardial ischaemia benefit from an exercise cardiac rehabilitation programme ? Presented at:
- 9th Annual Meeting of the American Association of Cardiovascular and Pulmonary Rehabilitation
  Portland, Oregon, USA, October 1994. (oral presentation: presenter)

- VI South African Sports Medicine Association Congress
  Durban, South Africa, March 1995. (oral presentation: presenter)

10) Digenio AG, Noakes TD, Daly L, Mavunda D, Esser J
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14) Digenio AG, Noakes TD, Joughin H, Daly L.
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15) Digenio AG, Noakes TD, Joughin H, Daly H.
Exercise training of moderate intensity improves left ventricular diastolic function in coronary patients. Accepted for oral presentation at:
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LIST OF ABBREVIATIONS

Abbreviations appear in a chronological order. The section and the page were they are first defined is described in the parenthesis.

CAD: coronary artery disease (1.1; p1)
LV: left ventricular (1.1; p1)
ECG: electrocardiogram (1.4.1; p13)
VO_2: oxygen uptake (1.4.2.2; p15)
MET: metabolic equivalent (1.4.2.2; p15)
VCO_2 : minute carbon dioxide production (1.4.2.3; p19)
CHF: chronic heart failure (1.4.2.4; p20)
EF: ejection fraction (1.4.3.2; p23)
Tc: technetium (1.4.3.3.2; p24)
Sn: stannous (1.4.3.3.2; p24)
Tl: thallium (1.4.4; p31)
RPE: rating of perceived exertion (1.5.2; p41)
NYHA: New York Heart Association (1.6.3; p50)
PCWP: pulmonary capillary wedge pressure (1.6.5.2; p58)
MI: myocardial infarction (2.1; p79)
CABG: coronary artery bypass surgery (2.1; p79)
PTCA: percutaneous transluminal coronary angioplasty (2.1; p79)
Tc-MIBI: technetium-99m sestamibi (2.2.3; p83)
EDC: end-diastolic counts (2.2.4.3; p85)
ESC: end-systolic counts (2.2.4.3; p85)
SC: stroke counts (2.2.4.3; p85)
T-PER: time to peak ejection rate (2.2.4.3; p85)
PER: peak ejection rate (2.2.4.3; p85)
AV-ER: average ejection rate (2.2.4.3; p86)
T-PFR: time to peak filling rate (2.2.4.3; p86)
PFR: peak filling rate (2.2.4.3; p86)
AV-RFR: average rapid filling rate (2.2.4.3; p86)
G: Group (3.2; p103)
VT: ventilatory threshold (4.2; p124)
VE: minute volume (4.2; p124)
TT: treadmill time (4.2; p124)
FVC: forced vital capacity (4.2; p125)
FEV_1: forced expiratory volume in one second (4.2; p126)
CG-ET: control group for exercise training (6.2; p160)
EG: experimental group (6.2; p160)
CG-LV: control group for measures of resting and exercise LV function (6.2; p165)
ET6: 6 month exercise training programme (8.2; p208)
ET18: 18 month exercise training programme (8.2; p208)
$C1_6$: <40% attendance; $C2_6$: ≥40-<60%; $C3_6$: ≥60-<80%; C_4: ≥80% for cohort ET6 (8.2; p210)
$C1_{18}$: <60%; $C2_{18}$: ≥60-<80%; $C3_{18}$: ≥80% for cohort ET18 (8.2; p210)

LIST OF TABLES, FIGURES & ANNEXURES

ABSTRACT

The medical profession has increased its acceptance of the benefits of exercise training for patients with uncomplicated coronary artery disease. Access to more modern technology and better management of this condition has led to an increase in the number of patients surviving acute coronary episodes. Some of these patients may have developed chronic asymptomatic left ventricular dysfunction and/or residual myocardial ischaemia, and could become potential candidates for cardiac rehabilitation if exercise training could induce physiological benefits without further deteriorating their condition.

Over the last 10 years, several patients at moderate to high risk of future cardiovascular events because of the presence of left ventricular dysfunction and/or myocardial ischaemia have been accepted for cardiac rehabilitation at the Johannesburg Cardiac Rehabilitation Center.

The purpose of the study was to evaluate the effects of exercise training on left ventricular function and exercise capacity in patients with coronary artery disease and varying degrees of left ventricular dysfunction and/or myocardial ischaemia attending the Johannesburg Cardiac Rehabilitation Center.

The degree of left ventricular impairment on admission to the cardiac rehabilitation programme was evaluated in 118 patients with documented coronary artery disease, by comparing the left ventricular function of these patients to that of 31 volunteers without known cardiac disease using resting and exercise radionuclide ventriculography (Chapter 3). Significant alterations in systolic and diastolic left ventricular function were seen both at rest and during exercise in patients compared to controls. Ejection fraction and peak filling rate were significantly reduced at rest (51.2% $\pm$ 1.2 vs 61.1% $\pm$ 2.4, p=0.0004 and 2.04 $\pm$ 0.07 vs 2.39 $\pm$ 0.13, p=0.023, respectively), while peak ejection rate, average ejection rate and peak filling rate had an attenuated increase in response to exercise (p=0.009, p=0.007 and p=0.003 respectively). Sixty two percent of patients had a normal ejection fraction while it was moderately impaired in 23% and severely impaired in 15%. Patients with depressed ejection fraction also had chronic ventricular dilatation at rest whereas they maintained cardiac output during exercise as a result of a greater increase in heart rate rather than an increase in end-

diastolic volume. Even some patients with normal ejection fractions demonstrated alterations in diastolic function suggesting some degree of subclinical myocardial ischemia.

We next evaluated the predictors of exercise capacity in another group of 171 patients with coronary artery disease and various degrees of left ventricular dysfunction (Group 0), with special emphasis on the role of the left ventricular systolic and diastolic dysfunction measured on admission to the programme (Chapter 4). One hundred and six patients had an EF$\geq$50% (Group 1), 38 had and EF$\geq$35% and <50% (Group 2) and 27 had and EF<35% (Group 3). Resting parameters of systolic and diastolic left ventricular function did not predict the exercise capacity of patients with coronary artery disease at any level of left ventricular impairment. Non cardiac factors including age, gender, Broca index, and forced vital capacity explained 50% of the variation in peak oxygen uptake in Group 0 (r^2=0.54, p=0.0001). After exercise training all groups showed a significant increase in peak oxygen uptake (G1: 25.2 $\pm$ 6.1 to 28.7 $\pm$ 7.1 ml/kg/min, p<0.001; G2: 25.1 $\pm$ 6.5 to 30.5 $\pm$ 6.3 ml/kg/min, p<0.001; G3: 20.6 $\pm$ 5.4 to 24.1 $\pm$ 6.9 ml/kg/min, p<0.001) , ventilatory threshold (G1: 17.0 $\pm$ 3.7 to 18.9 $\pm$ 4.4 ml/kg/min, p<0.001; G2: 16.6 $\pm$ 2.9 to 18.8 $\pm$ 3.4 ml/kg/min, p<0.01; G3: 14.3 $\pm$ 3.0 to 16.4 $\pm$ 3.8 ml/kg/min, p<0.001) and treadmill time to exhaustion (G1: 11.3 $\pm$ 3.4 to 13.6 $\pm$ 3.9 minutes, p<0.001; G2: 11.4 $\pm$ 3.5 to 14.7 $\pm$ 3.4 minutes, p<0.001; G3: 9.2 $\pm$ 3.4 to 11.5 $\pm$ 4.0 minutes, p<0.001). The magnitude of the improvement in these variables was the same for all groups.

We analysed more carefully the effects of a 6 month exercise training programme on the physiological status and left ventricular function of twenty eight patients recovering from an acute myocardial infarction and with a left ventricular ejection fraction of 30% or less (Chapter 5). Twenty two patients who completed the exercise training programme showed a significant improvement in maximal exercise capacity and a significant reduction in their cardiovascular demands during submaximal exercise. Peak oxygen consumption was increased by 12% after training (19.4 $\pm$ 3 vs 21.8 $\pm$ 4.8 ml/kg.min, p<0.05) and exercise time to exhaustion by 33% (527 $\pm$ 171 vs 700 $\pm$ 186 seconds, p<0.001). The double product at the same submaximal work load was significantly reduced (214 $\pm$ 52 vs 194 $\pm$ 44 bpm.mmHg x 100, p<0.05). These benefits were achieved without any adverse effects on resting (25.4 $\pm$ 5

vs 28.5 $\pm$ 7.9%, $p<0.05$) or exercise (27.3 $\pm$ 7.7 vs 29.9 $\pm$ 9.5%, p<NS) left ventricular ejection fraction.

We next assessed the effect of myocardial ischaemia developing during exercise on the left ventricular function and adaptability to training of patients with coronary artery disease enrolled into a 6 month exercise training programme (Chapter 6). Twenty two patients with exercise-induced myocardial ischaemia, 10 with symptomatic ischaemia and 12 with silent ischaemia, defined by ST segment depression during maximal exercise testing and by transient perfusion defects during radionuclide perfusion imaging using Tc-MIBI, constituted our experimental group (EG). Fifty patients without evidence of exercise-induced myocardial ischaemia were assigned to the control group for exercise training (CG-ET) and 31 subjects without signs or symptoms of cardiac disease constituted the control group for the measures of left ventricular function (CG-LV). EG had significant abnormalities in systolic and diastolic left ventricular function at rest compared to CG-LV and maintained their cardiac output during exercise through increases in both heart rate and end-diastolic counts. EG showed significant increases in ventilatory threshold (16.8 + 3.0 to 18.7 + 2.6 ml/kg/min, $p<0.003$) and peak oxygen uptake (25.2 + 5.1 to 26.9 + 5.4 ml/kg/min, $p<0.02$) which were of a similar magnitude to the changes in CG-ET, but the latter also showed significant reductions in heart rate (110.7 + 2.5 to 104.5 + 2.0 bpm, $p<0.001$), systolic blood pressure (168.8 + 4.2 to 154.3 + 3.5 mmHg, $p<0.002$) and rate-pressure product (18.9 + 0.7 to 16.3 + 0.5 bpm x mmHg x 10^3, $p<0.001$) at submaximal levels. No significant changes in these measures were found in the subgroups with silent or symptomatic exercise-induced myocardial ischaemia after 6 months. No increase in heart rate or treadmill time at onset of myocardial ischaemia was seen in the EG or in the subgroups with silent or symptomatic ischaemia as a result of training.

We next assessed the ventilatory responses to exercise in a subgroup of 102 patients from the cohort studied in Chapter 4, before and after 6 months of exercise training (Chapter 7). Group 1 (G1) included 63 patients with EF$\geq$50%, Group 2 (G2) included 21 patients with EF$\geq$35 and <50% and Group 3 (G3) included 18 patients with EF<35%. As above all groups showed a significant increase in peak oxygen uptake and treadmill time after training in spite of G3 patients being significantly more deconditioned than G2 and G1 patients on admission to the program (G1: p=0.0001 and p=0.0001; G2: p=0.0001 and p=0.001; G3: p=0.01 and p=0.01;

respectively). Patients in G3 had a significantly higher minute ventilation/carbon dioxide excretion ratio (VE/VCO_2) than patients in G2 and G1 at 9 minutes, at peak exercise, before (9 minutes: p=0.046 and p=0.025, peak: p=0.024 and p=0.002, respectively) and after training (9 minutes: p=0.011 and p=0.005, peak: p=0.001 and p=0.0001, respectively) and also at the point of maximum ventilatory efficiency. The slope of the relation VE to VCO_2 was significantly higher in G3 patients than in those in G2 and G1 (p=0.0001 respectively) and was not reduced by exercise training in any group.

Lastly, we evaluated the effects of 6 and 18 months of exercise training on the left ventricular function of patients with coronary artery disease evaluated in Chapter 3. One hundred and eighteen patients who entered and finished the 6 month training programme (cohort ET6) were divided into 4 categories according to their compliance in terms of attendance to prescribed exercise sessions: <40% attendance – n=16 (C1), ≥40 - <60% - n=23 (C2), ≥60 - <80% - n=33 (C3) and ≥80% - n=46 patients (C4). Forty patients finished the 18 month programme (cohort ET18) and were divided into 3 categories: <60% - n=11 (C1), ≥60 - <80% - n=14 (C2) and ≥80% - n=15 (C3). We found that the most significantly beneficial effects were obtained by those patients who attended more than 80 % of the possible sessions for a period of 6 months. Adaptations at maximal (peak VO_2: 26.1 ± 0.9 to 29.7 ± 1.1 ml/kg/min, p<0.01) and submaximal effort (heart rate: 113.5 ± 3.4 to 108.3 ± 3.1, p<0.01; blood pressure: 156.8 ± 4.4 to 147.8 ± 3.7 mmHg, p<0.05; rate-pressure product: 18.0 ± 0.9 to 16.0 ± 0.6 bpm.mmHgx10^3, p<0.01) were observed as well as a resting bradycardia (75.0 ± 2.4 to 70.8 ± 2.2 bpm, p<0.01) and an improvement in diastolic function as demonstrated by a significantly greater increase in PFR (p=0.037) and AV-RFR (p=0.046) during exercise than in the other groups.

Conclusions

Patients presently accepted for cardiac rehabilitation showed a high incidence of left ventricular function abnormalities emphasizing the need for risk stratification procedures in order to guide the monitoring and supervision of their exercise training sessions.

Non cardiac factors were better predictors of the effort tolerance in these patients than parameters of left ventricular function at entry to an exercise programme or after 6 months of training. A similar degree of adaptation to training was seen in all patients regardless of their degree of left ventricular systolic or diastolic dysfunction on admission to the programme.

After 6 months of exercise training, patients with severe left ventricular dysfunction were able to derive physiological benefits at maximal and submaximal levels of effort without any deleterious effect on their left ventricular function, suggesting that physical training should form part of the comprehensive management of these patients.

In patients with myocardial ischaemia, exercise training produced improvements in maximal exercise capacity but failed to elicit physiologic adaptations at a submaximal workload or to increase the threshold for ischaemia. It is possible that exercise training could have improved cardiovascular efficiency if patients would have been on an aggressive coronary risk factor programme, with particular emphasis to lipid lowering.

Asymptomatic patients in NYHA classes I and II and with an EF below 35% had a greater ventilatory response to effort and lower ventilatory efficiency than patients with moderately impaired or normal left ventricular function. Despite increasing their tolerance to effort, exercise training failed to reduce their ventilatory response to exercise suggesting that mechanisms other than a reduced blood flow or early non-independent metabolism might be implicated in the pathophysiology of this important symptom.

Both groups of patients with left ventricular dysfunction and with myocardial ischaemia maintained their cardiac output by using the Frank Starling mechanism. While patients with left ventricular dysfunction developed a chronic increase in end-diastolic volume at rest, patients with myocardial ischaemia developed an acute increase during exercise.

Improvements in left ventricular diastolic function were observed in patients who attended 80% or more of the possible sessions during the first 6 months. These patients also obtained the greatest benefits from the exercise training programme improving their maximal exercise capacity, reducing their blood pressure and heart rate at submaximal effort and developing a

resting bradycardia. Attendance for a further 12 months produced no additional benefits other than contributing to maintain the maximal exercise capacity reached the year before. However, it is possible that longer participation in a structured cardiac rehabilitation programme could have some effects in promoting better adherence to exercise training and an overall healthier lifestyle.

In summary:

Patients enrolling in contemporary cardiac rehabilitation programmes may have alterations in systolic and/or diastolic left ventricular function as well as residual myocardial ischaemia. Regardless of their degree of left ventricular dysfunction these patients can derive similar beneficial physiological adaptations to those of patients with normal left ventricular function because the effects of exercise training are more manifested in the periphery than in the central circulation. Even patients with ejection fractions of 30% or lower can fully benefit from exercise training during both submaximal and maximal exercise without the risk of further jeopardizing their already severely compromised left ventricular function. On the other hand, exercise training might be marginally important in patients with myocardial ischaemia who only increased their maximal exercise capacity in response to exercise training. Aggressive cholesterol lowering in these patients could be a strategy more relevant than exercise training to reverse the disease process and improve their quality of life. Adherence to 80% or more of the possible exercise sessions is required in order to elicit full training benefits, at rest, during submaximal and during maximal exercise as well as a possible improvement in left ventricular function, in patients participating in moderate intensity exercise training programmes.

CHAPTER 1

INTRODUCTION

1.1 Background

Cardiac rehabilitation is an accepted mode of treatment for patients with coronary artery disease (CAD). Medically supervised exercise conditioning is the focal point of cardiac rehabilitation programmes and it is this, which primarily differentiates such programmes from simple counselling services (1).

Traditionally designed for patients recovering from an acute myocardial infarction, cardiac rehabilitation has been expanded to include patients after revascularization procedures, patients with coronary risk factors, older patients and higher risk patients, that is, subjects with residual myocardial ischaemia and with left ventricular dysfunction.

An improvement in the patient's submaximal and maximal exercise capacity is one of the major end-points of cardiac rehabilitation programmes. This is particularly important in ambulatory patients with chronic heart failure in whom exertional dyspnoea and fatigue are important causes of morbidity and inability to return to work (1).

In patients with CAD, normal or near-normal exercise capacity has generally been thought to reflect normal left ventricular (LV) function. The assumption that exercise capacity relates to the severity of heart disease has formed the basis of the New York Heart Association classification of patients with heart disease, which has become the most commonly used clinical classification for this type of patient (2).

For many years, patients with heart failure were advised to refrain from physical activity and to maintain a sedentary existence, for fear that physical training would result in further deterioration of LV function. It is only in the last decade that some cardiac rehabilitation centres have started accepting this type of patient on their programmes. The Johannesburg Cardiac Rehabilitation Centre, in Johannesburg, South Africa, is one of these centres.

1.2 Cardiac rehabilitation

1.2.1 Introduction

Structured cardiac rehabilitation programmes were developed in the 1960s and their benefits, additional to standard medical care, have been demonstrated. The acknowledgement of these benefits led the World Health Organization Expert Committee on Rehabilitation of Patients with Cardiovascular Diseases (1993) to recommend that cardiac rehabilitation programmes become an essential part of the care that should be available to all cardiac patients worldwide (3). This can only be achieved if such programmes match the needs and resources of each community, and in this way become a component of comprehensive cardiac care integrated into existing health-care delivery systems. Thus it was recommended that basic, intermediate or advanced facilities should be developed according to the needs of different communities (See Annexure 1.1).

1.2.2 Proven benefits of cardiac rehabilitation

Several recent publications confirm that cardiac rehabilitation services are indeed beneficial and cost-effective (4-7).

The "Clinical Practice Guideline: Cardiac Rehabilitation" (4) developed under a contract from the Agency for Health Care Policy and Research with the support of the National Heart, Lung, and Blood Institute, is perhaps the most comprehensive currently available document to address the subject. The contract was awarded in 1992 to the American Association of Cardiovascular and Pulmonary Rehabilitation, which convened a private-sector multidisciplinary panel of experts representing a diversity of health care specialities: cardiology, internal medicine, family medicine, nursing, behavioural science, dietetics, physical therapy and exercise physiology as well as consumer representatives. The panel based its conclusions and recommendations principally on scientific evidence from the

critical review of over 400 original reports published in peer-reviewed medical and health sciences journals. When the scientific literature was incomplete or inconsistent in a particular area, the recommendations reflect the professional judgement of panel members and consultants. The greatest weight of evidence (A) was given to well-designed and well-executed randomized controlled trials, and the least weight was accorded to observational studies (C) (Annexure 1.2).

The most substantial benefits included: improvement in exercise tolerance, improvement in symptoms, improvement in blood lipid concentrations, reduction in cigarette smoking, improvement in psychosocial wellbeing and reduction of stress and reduction in mortality.

Of the 24 randomized and non-randomized controlled trials that reported mortality outcomes only 6 managed to show a reduction in mortality in rehabilitation versus control patients. Two recent meta-analyses of randomized controlled trials (8,9) which included more than 4000 patients with coronary artery disease, confirmed that the lack of consistent results was due to the inability of single studies to enroll adequate numbers of patients in order to be able to measure significant mortality reductions. The meta-analyses were able to show a 25% reduction in mortality at the 3-year follow-up in rehabilitation versus control patients, which is similar to that reported for the use of beta-blocking agents following myocardial infarction or the use of angiotensin converting enzyme inhibitors in patients with left ventricular systolic dysfunction. This beneficial outcome was greater in the trials using the multifactorial components of cardiac rehabilitation than in the trials that used exercise training as the sole intervention.

Information obtained from two large surveys (10,11) showed that exercise cardiac rehabilitation is a safe modality of treatment for cardiac patients as evidenced by a very low rate of myocardial infarctions and cardiovascular complications during exercise training (Annexure 1.3).

Improvement in pathophysiologic measures was also reviewed in the guidelines. Two randomized controlled trials of multifactorial rehabilitation (12,13) including exercise training and intensive dietary intervention, showed less progression and greater regression of the disease in rehabilitation versus control patients, when measured with digitally processed coronary angiography. The Stanford Coronary Risk Intervention Project (14) showed significant improvement in slowing the rate of progression of coronary atherosclerotic lesions over 4 years in individuals with angiographically-defined CAD assigned to a multifactor cardiovascular risk reduction programme versus individuals assigned to usual cardiological care.

The Secondary Prevention Panel of the American Heart Association published their Consensus Statement: "Preventing Heart Attack and Death in Patients with Coronary Disease", with the endorsement of the Board of Trustees of the American College of Cardiology (5). They stated that there is strong scientific evidence that in patients with coronary artery disease, "comprehensive risk factor interventions can extend survival, improve quality of life, decrease the need for interventional procedures such as angioplasty and bypass grafting and reduce the incidence of subsequent myocardial infarction".

The above recommendations were again reinforced in September 1995 at the 27th Bethesda Conference of the American College of Cardiology, the theme being "Matching the Intensity of Risk Factor Management with the Hazard for Coronary Disease Events" (6). It was agreed that risk factor management is the cornerstone of the optimal care of patients with cardiovascular disease. It was also recognised that, in spite of the available scientific evidence in support of risk factor management, the proportion of high risk patients receiving appropriate care is alarmingly low.

Similar recommendations were made a year earlier by the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension which were published simultaneously in Atherosclerosis and the European Heart Journal in 1994 (7).

The multidisciplinary team approach was selected as the optimal technique to achieve the risk factor modifications recommended above, reinforcing the role of cardiac rehabilitation in risk factor management.

1.3 Cardiac Rehabilitation in South Africa

1.3.1 Introduction

Despite declining mortality rates from cardiovascular diseases in industrialised countries, such as the United States of America and also Western Europe, Australia, New Zealand and Japan, cardiovascular diseases represent an increasing problem in the developing countries of Latin America, Africa and Asia. Modernisation, control of communicable disease and a resulting increase in life expectancy of people in these countries account for the increased prevalence of these diseases (3).

South Africa is no exception. Increasing urbanisation associated with marginal increases in income result in greater exposure to new consumer opportunities, while poor education results in more vulnerability to mass advertising with a negative impact on recognised risk factors such as smoking and the adoption of high fat diets.

1.3.2 The need

South Africa has one of the highest rates of coronary artery disease in the world, with the Asian population ranking first in terms of mortality and the White population ranking 3rd after Northern Ireland and Scotland (Table 1.1) (15). It was estimated that in 1980 approximately 50 000 South Africans suffer heart attacks every year, 25% of which are probably fatal. This leaves many of the possible 37 000 survivors as well as most people

undergoing revascularization procedures, as future candidates for cardiac rehabilitation (16).

Although there appears to be a downward trend in mortality figures (Table 1.2), there is still a "coronary epidemic" which will remain a problem for many years to come (15).

Chronic diseases which share similar risk factors as a result of an unhealthy lifestyle, such as cerebrovascular accident, myocardial infarction, tobacco and nutrition-induced cancer, chronic obstructive airway disease, diabetes, some liver and renal disease and osteoporosis, accounted for 25% of deaths of all South Africans and 29% of economically active 35 - 64-year-olds whose deaths were reported in 1988. Cerebrovascular disease and coronary artery disease were the two major contributors to these deaths, accounting for 8 % respectively of the overall mortality (17).

Using the South African population aged 15-64 years as determined in the census of 1985 (total population: 18 485 644), it was estimated that 4.9 million Sout Africans were current smokers, that 5.5 million had blood pressure readings above 140/90 mmHg and that 4.8 million had hypercholesterolaemia. Accordingly, approximately 50% of this population was at risk of developing heart disease and thus required lifestyle modification and 17% was at sufficiently high risk to require medication (17).

From the data above it becomes evident that there is a continual loss to commerce and industry as well as a loss to society in the disruption of family life. There is, therefore, an obvious need for the development of primary prevention strategies and for the establishment and acceptance of cardiac rehabilitation programmes in order to conserve much needed manpower.

Table 1.1 Age-standardised mortality rates from Ischaemic Heart Disease in South African populations in 1985 and 1989 compared with rates in other countries in 1985; rates per 100 000 population aged 30-49 years (15).

COUNTRY	MALE		FEMALE	
	1985	1989	1985	1989
SOUTH AFRICA				
Blacks	18	17	11	10
Asians	499	417	234	182
Coloureds	245	198	134	113
Whites	391	257	117	83
NORTHERN IRELAND	406		130	
FINLAND	390		79	
SCOTLAND	398		142	
ENGLAND	318		94	
USA	235		80	
DENMARK	251		69	
AUSTRALIA	247		76	
CANADA	230		66	
ISRAEL	183		73	
SWITZERLAND	40		30	
FRANCE	94		20	
JAPAN	38		13	

Table 1.2 Age-standardised mortality rates per 100 000 (world population, all ages) for total deaths and for Ischaemic Heart Disease deaths in South African populations in 1978 and 1989, with percentage falls in mortality (15).

	BLACKS		ASIANS		COLOUREDS		WHITES	
	M	F	M	F	M	F	M	F
1978								
Total mortality rate	1072	661	1306	980	1691	1108	1002	615
IHD mortality rate	16	9	355	196	171	94	314	133
1989								
Total mortality rate	1068	832	1130	755	1392	911	631	366
IHD mortality rate	11	8	226	113	110	71	139	55
% fall in total mortality rate	-	-	14	23	18	18	37	41
% fall in IHD mortality rate	-	-	36	43	36	25	56	59

1.3.3 The South African Association of Cardiovascular Rehabilitation

The prevalence of cardiovascular diseases in South Africa, the underutilisation of existing cardiac rehabilitation services, the lack of standards and/or guidelines for cardiac rehabilitation, and the lack of an adequate remuneration system for health professionals working in the field created the need for the formation of a body which could co-ordinate and promote cardiac rehabilitation services in South Africa.

The South African Association of Cardiovascular Rehabilitation was created in July 1994. It is controlled by a Board of Directors whose members are all actively involved in cardiac rehabilitation. Multidisciplinary participation as well as geographical representation were assured.

The aim of the Association is to promote and develop the practice of cardiac rehabilitation in South Africa. Specific objectives are:

1- To promote the practice of primary and secondary prevention/rehabilitation through supervised exercise training and lifestyle modification.
2- To promote throughout the public sector an increased awareness and understanding of cardiac rehabilitation services.
3- To provide professional education and to encourage research within cardiovascular rehabilitation through the creation of guidelines, the promotion of educational conferences, scientific meetings and publications.
4- To promote a multidisciplinary approach towards cardiac rehabilitation providing ways and means to enhance career developments for Association members.

1.3.4 Cardiac rehabilitation programmes in South Africa

A preliminary questionnnaire-based survey, performed by the South African Association of Cardiovascular and Pulmonary Rehabilitation in 1994 identified 13 centres where

cardiac rehabilitation played an important part of the services provided. They were all located in the major cities: five in Johannesburg, two in Cape Town, two in Pretoria, one in Bloemfontein, one in Durban, one in Port Elizabeth and one in East London. Although this was probably an underestimation since small programmes unknown to the Board of Directors of the Association were not considered, it shows how underdeveloped cardiac rehabilitation is in South Africa.

According to the World Health Organisation classification of the level of service provided (3), of the 13 programmes identified, one was considered basic, ten intermediate and two advanced. Five programmes were hospital-based and eight community-based. Four programmes offered Phase 1 cardiac rehabilitation, 9 Phase 2, 10 Phase 3 and 8 Phase 4. All programmes required exercise testing before admission onto the programme and in 7 the exercise tests were done at the centre itself. Eleven required also a lipid evaluation at entry. All programmes had an aerobic exercise conditioning component which was complemented by resistance training activities in eight. All programmes required their patients to fill in a log card and only 2 programmes provided telemetric monitoring. Educational sessions were available in 12 out of the 13, psychological counselling in 11, nutritional counselling in 10 and smoking cessation programmes in only 2.

1.3.5 The Johannesburg Cardiac Rehabilitation Programme

The South African Health Act of 1977 decreed that the responsibility for rehabilitation should be taken by the local authorities. As a result, in September 1982, the Health Department of the Johannesburg City Council established a Cardiac Rehabilitation facility at the Civic Centre in Johannesburg. Cardiac rehabilitation was undertaken by the Johannesburg local authority since cardiovascular disease was deemed a priority, certainly for the White, Asian and Coloured groups of the population. Since its inception, the cardiac rehabilitation centre has been entirely non-racial, both in staffing as well as patients. The service is provided free of charge to all appropriate patients referred by

medical practitioners, as the Health Act does not make any provision for charging for health services provided by the local authority. In 1990 the Centre expanded its services by opening a satellite centre in Lenasia, an Asian community.

The Johannesburg Cardiac Rehabilitation Centre has rapidly grown to become the largest rehabilitation centre of its kind in Southern Africa. The facility provides early post-discharge (Phase 2) (Johannesburg Centre only), community-based (Phase 3) (Johannesburg and Lenasia Centres) and maintenance (Phase 4) (Johannesburg and Lenasia Centres) programmes for cardiac sufferers and combines supervised exercise sessions with a lifestyle modification programme aimed a risk factor modification. Two hundred and fifty patients attend the Johannesburg Centre on Mondays, Wednesdays and Fridays between 7.00 am and 7.00 pm and 70 patients attend the Lenasia Centre the same days between 4.00 and 7.00 pm.

The type of patient admitted to the Centre varies from subjects with only coronary risk factors who come for prevention, and low risk patients recovering from an uncomplicated heart attack, to very high risk patients with chronic heart failure.

The Centre's activities are run by a multidisciplinary team which includes doctors with a sports medicine and/or cardiological background, nursing sisters, physiotherapists, biokineticists, dieticians and psychologists.

The exercise sessions consist of a warm-up, walking, walking-jogging, jogging or cycling and a cool-down. Rowing machines and air-dynes are also available. In 1991, resistance training using circuit weight stations was introduced to complement aerobic activities of medically stable patients after 3 months on the programme. All exercise sessions are medically supervised and patients are asked to fill a log card for tracking of their compliance. Patients are individually counselled and group educational sessions on different topics are given on a weekly basis. Various topics are discussed, namely risk factor modification, medication, diet, stress and stress management, symptoms, benefits of

exercise and exercise prescription, as well as basic cardiac life support. Partners are encouraged to come to these discussion sessions. Individual and group psychotherapy sessions including relaxation techniques are also provided. After 18 months on the programme patients can be discharged from the centre or placed on a home programme.

Soon after the Centre was established a group of patients expressed the desire to assist in raising funds. For this purpose they formed the "Superheart" Committee under the auspices of the Southern Transvaal branch of the Heart Foundation. This committee has been very active in the purchasing of equipment, and has contributed a great deal to the success of the unit.

Research and teaching form an integral part of the Centre's activities. The programme and its effects on cardiac patients, with special emphasis on compliance, exercise tolerance, lipid profile, the elderly and patients with chronic heart failure have been described in several papers and presented at local and international conferences. Physiotherapy, biokineticists and community health students spend time at the Centre as part of their training and MSc students from the University of the Witwatersrand attend lectures regularly.

The Centre has organized two consecutive Cardiac Rehabilitation Symposiums in 1993 and 1994 with local and international speakers, and has also been instrumental in the creation of the South African Association of Cardiovascular Rehabilitation where three staff members are on the Board of Directors. In addition to its local role, the Centre has been acknowledged internationally: The Head of the Centre was invited to the USA in October 1994 to deliver a lecture on "Cardiac rehabilitation in South Africa" at the 9th Annual Meeting of the American Association of Cardiovascular and Pulmonary Rehabilitation, the world's largest organisation in this field.

In summary, the Johannesburg Cardiac Rehabilitation Centre is at the forefront of the prevention of cardiac diseases, the rehabilitation of cardiac sufferers, cardiac rehabilitation

research and the education of patients, students and professionals. Based on the World Health Organisation recommendations, the Centre should be considered an advanced facility.

1.4 Medical assessment of patients admitted for cardiac rehabilitation

1.4.1 Introduction

Patients need to be medically evaluated before enrolling in a cardiac rehabilitation programme. Whether patients will be assessed on site or by their referring doctors will depend on the facilities and staff structure of the rehabilitation centre. Ideally, the medical assessment would consist of a complete medical history of the patient, a comprehensive examination, a fasting lipogram and blood glucose determination, a resting electrocardiogram (ECG), lung function testing, anthropometric measurements, a cardiopulmonary exercise test and measurement of LV function. The functional capacity of the patient as well as any abnormal responses to exercise testing including myocardial ischaemia, are determined. In selected cases the diagnosis of ischaemia requires radionuclide perfusion imaging procedures. Through echocardiography or radionuclide ventriculography the left ventricular function of patients is evaluated. An appraisal of the coronary risk profile of patients is performed with a view to lifestyle modification strategies. Patients are subsequently categorized into low, moderate and high risk of exercise-related cardiac events, and the patient's level of risk will determine the extent of the supervision and monitoring of the patient during exercise sessions.

1.4.2 Assessment of exercise capacity

1.4.2.1 Introduction

Most human physiological systems or organs have a large reserve capacity. Disease reduces that reserve capacity, but clinical manifestations may occur only when this capacity is greatly reduced. The general objective of exercise testing is to determine performance characteristics which usually cannot be adequately obtained from either the clinical history or the physical examination of the patient at rest (18). Clinical applications may include diagnostic, functional, and therapeutic objectives (19). Diagnostic and prognostic evaluation of suspected or established cardiovascular disease is the most common clinical application of exercise testing. Functional exercise testing is used in the determination of exercise capacity and cardiopulmonary responses in patients who require exercise prescriptions or occupational activity guidelines. Exercise testing may also be used to optimize medical therapy with certain classes of drugs. Furthermore, since cardiovascular fitness as defined both by submaximal and maximal responses to exercise testing has been inversely associated with cardiovascular disease (20), and all-cause mortality in men (20,21) and women (21), the use of exercise testing to establish cardiovascular fitness becomes an important tool for investigating the role of physical activity in cardiovascular disease.

Of the 3 types of skeletal muscle contractions that stress the cardiovascular system, dynamic stress is preferred for testing over isometric (ie. handgrip) and combination of isometric and dynamic (ie. carrying a heavy object while walking) stresses because it imposes a volume load to the left ventricle producing a cardiovascular response proportional to the severity of the exercise (18).

1.4.2.2 Maximum oxygen uptake

Oxygen uptake by the lungs immediately increases when dynamic exercise is begun. At any intensity of exercise, oxygen uptake will initially increase and then remain relatively stable by the 2nd minute of exercise at the same level, achieving what is called as steady state. At steady state, heart rate, blood pressure, cardiac output and pulmonary ventilation are maintained at reasonably constant levels (18).

Maximal oxygen uptake (VO_2) is the highest level of oxygen uptake that an ambulatory person can achieve by dynamically exercising a large fraction of his or her muscle mass (22,23). By rearrangement of the Fick equation, VO_2 max defines the limits of the circulatory transport of oxygen by the product of the maximal cardiac output (limits of the circulatory pump) and the maximal arteriovenous oxygen difference (limits of extraction from the peripheral circulation by the metabolically active tissues) (22). VO_2 max has a strong genetic component, declines progressively with age, is higher in men than women, varies with physical activity status, averaging 20-30% greater in the well-trained athlete and 20-30% less in the sedentary subject, and is affected by cardiovascular disease (18). Because larger persons have generally more muscle mass and the capability of burning more oxygen per unit of time, aerobic capacity is often expressed relative to body weight as milliliters of oxygen per kilogram of body weight per minute (ml/kg/min) (24). It is convenient also to express oxygen uptake in multiples of metabolic units above resting. The metabolic equivalent (MET) is a unit of sitting resting oxygen uptake: 1 MET=3.5 ml/kg/min.

Because it is easily measured and highly correlated with cardiac output and endurance performance, VO_2 max is being used as the gold standard for assessment of aerobic capacity (24).

1.4.2.3 Equipment and Protocols

Of the numerous devices used to provide dynamic exercise for testing, the cycle ergometer and the treadmill are the most commonly used today (18).

In the USA, exercise testing is mainly performed on a motor driven treadmill while, in European countries, the bicycle ergometer is much more popular, probably because Europeans are more familiar with bicycle riding than are Americans. Cycle ergometer tests provide for stable electrocardiographic and blood pressure recording. Patients not accustomed to cycling will often be unable to reach a maximal heart rate because of premature leg fatigue. Furthermore, the patient controls the rate of cycling and not the ergometer providing less precise control of work than during exercise on the treadmill. Walking on a treadmill seems easier for the vast majority of the population since walking and even running are more natural activities. Exact recordings of the blood pressure and electrocardiogram at near maximal workloads may be difficult to obtain during treadmill exercise. Hand support is common practice among cardiologists leading to an increase in the estimated exercise capacity of the patient (18). The major disadvantage of treadmill exercise is that the workload is difficult to standardise. Factors other than treadmill speed and gradient such as the subject holding on to the rail or walking with long or short strides can affect the final workload achieved.

A maximal exercise test that takes the subject to a level of intensity where fatigue, muscle weakness or other symptoms will prohibit further exercise, is the preferred testing modality.

There are many exercise protocols available. A vigorous exercise protocol may be suitable for the screening of relatively healthy individuals while a less strenuous one may be more adequate for the evaluation of the functional capacity of patients with coronary artery disease.

The Balke treadmill test (25) increases the gradient 1% per minute while holding speed constant at 3.3 mph. This test is too fast for many persons and takes 10 to 18 minutes for many healthy subjects. Measurements of oxygen uptake at any given load are underestimated because oxygen uptake continues to rise for one and a half to two and a half minutes at the same loads even in normals. Another test, developed by Taylor, requires repeated testing over days to define a plateau of the maximal oxygen uptake as the work loads of successive tests are progressively increased (23).

Continuous multistage protocols where time is allowed in order to achieve a steady state are more physiological and adequate for cardiac patients. One of the most commonly used protocols is the Bruce protocol (26) in which both speed and gradient are increased every 3 minutes until exhaustion and/or disabling symptoms are attained. This multistage test provides assessment of both submaximal performance and maximal aerobic power. The metabolic cost of the testing procedure varies directly with body weight and physical intensity and duration of the exertion and indirectly with mechanical efficiency. Because walking and running represent work against gravity, oxygen uptake should have a weight correction. The protocol assumes that all the body weight is supported by the legs, not allowing support from the handrail. Mechanical efficiency is nearly constant for most ambulatory persons and slightly greater in well-coordinated and highly trained runners. In both normals and cardiac patients, mean submaximal VO_2 tends to plateau during the last minutes of stages I and II and thereafter both groups exhibit a nearly linear increase in oxygen uptake with the duration of the exercise. Variance is high during the first minutes because of apprehension in some individuals and diminishes progressively. The Bruce protocol provides an expeditious, safe and reliable method to measure VO_2 max physiologically and to estimate it clinically. Values obtained within minutes are comparable to those obtained by discontinuous methods requiring two or more days (23,26). It has the advantage for normal subjects of being relatively short in duration but the disadvantage for most cardiac patients or elderly individuals of having vigorous exercise workloads with a gradient of 10% from the beginning of the test. In general when any exercise protocol requires speeds beyond 3.4 mph, individuals with shorter stature will

have to jog in order to keep pace. This may result in an awkward physical posture, excessive mental stress for the patient and frequent production of artefacts due to deterioration of the ECG signal.

The Chung protocol (27) overcomes these problems and is closer to the ideal for cardiac patients. The protocol includes seven three minutes stages with approximately increasing intensities for stage of 2 METs or less. The initial speed is 1.7 mph with 0% gradient for 3 minutes during the warming up period. The gradient is increased 4% at each stage and the speed remains constant at 3mph. Most patients with coronary artery disease do not require workloads beyond 8 METs (Stage IV), whereas sedentary healthy subjects can seldom exercise at workloads above 10-11 METs (Stages 6 or 7).

Another type of approach are ramp protocols where work load is continuously increased, gradually causing heart rate to increase in a "ramp" upward. The advantages of such protocols are a constant work rate, decreased exercise time, and accurate determination and possibly estimation of aerobic parameters (28). Computer software has been developed to generate such protocols for a bicycle ergometer or a treadmill (29). The ratio of oxygen uptake to work rate, expressed as a slope has been found higher for the ramp tests than for standard exercise protocols like the Bruce protocol. (30). Ramp protocols have gained more attention recently for their use in defining the intensity for work phases during interval training in patients with chronic heart failure (31).

Taylor and co-workers (23) suggested that if a 2.5 percent increase in treadmill gradient was not accompanied by more than 150 ml O_2/min increase in oxygen uptake this was suggestive of the individual reaching his cardiopulmonary limit. This became the plateau concept and has been widely applied for decades. However disagreement exists today regarding the recognition of maximal cardio-respiratory limits (32). In any case, cardiac patients cannot often achieve those "maximal" levels because of leg fatigue, angina, lack of motivation and discomfort. It is therefore customary to refer to VO_2 max as the peak VO_2 during maximum exercise.

VO_2 max is not routinely measured in clinical practice because it requires relatively expensive equipment, highly trained technicians and time and cooperation from the subject. Since the interindividual variation in mechanical and metabolic efficiency is quite low among adults during activities that do not require much skill such as walking or running on a motor-driven treadmill or cycling on a stationery ergometer, oxygen uptake could be estimated from the rate of work (26,33). However treadmill experience, large standard errors of prediction equations and protocol design suggest that in research in which VO_2 is an important parameter to assess, its direct measurement from expired air will obviously provide the most accurate results (34).

The collection and analysis of an expired gas sample that is taken during the last minute of an exercise test is used to determine VO_2 max directly (35). The ventilatory threshold has been most commonly defined as the first deviation in linearity of the ventilation plotted against the oxygen consumption. This point of hyperventilation was classically labelled the "anaerobic threshold" by Wasserman and colleagues (36,37), who theorized that ventilation was increased due to the increase in carbon dioxide production secondary to the buffering of lactic acid ($H_2CO_3 <=> H_2 + CO_2$). The association between the point of hyperventilation and a turning point in lactic acid is today still controversial (38).

The ventilatory threshold could also be defined as the oxygen uptake before the systematic increase in the ventilatory equivalent for O_2 without a concomitant increase in the ventilatory equivalent for CO_2 (36) or by using the V-slope method introduced in 1986, Beaver and colleagues (39) from the same laboratory as Wasserman. The V-slope method consisted of a computerized regression analysis of the slopes of the CO_2 uptake (VCO_2) vs. VO_2 uptake plot, which detects the beginning of the excess CO_2 output. The authors claimed that this method may have some advantages over others that depend on regular breathing pattern and respiratory chemosensitivity. This method was subsequently simplified by others (40). All three methods discussed above continued to be widely utilized.

1.4.2.4 Exercise testing in patients with chronic heart failure

Since most symptoms in chronic heart failure are manifested on exertion, the assessment of exercise capacity during exercise testing is an important tool for assessing the severity of the disease (41). The evaluation of different drug treatments, the effect of exercise rehabilitation programmes or cardiac transplantation of these patients have made necessary the use of a more objective tool than the clinical examination and the responses to the New York Heart Association questionnaire.

The safety of a graded maximal exercise test has been established in a group of 607 stable patients participating in the Veterans Administration Cooperative Heart Failure Trial (42). Exercise protocols must allow patients to exercise long enough in order to acquire sufficient data to discriminate for different grades of exercise limitation. Furthermore, stages must be long enough to allow patients with chronic heart failure (CHF) to reach steady state; very often haemodynamic and metabolic responses to exercise are delayed when cardiac output is reduced (41). The Chung protocol has all the necessary requirements for the accurate and reproducible testing of this type of patient.

Recent studies have suggested that adding respiratory gas analysis to the exercise test provides a more objective assessment (41). Although exercise duration correlates significantly with oxygen uptake, the relationship between the two variables is not sufficiently strong. Furthermore, repeated tests may improve exercise duration by improving the efficiency (the individual walks better), without a corresponding increase in VO_2 (41). Although patients with CHF may never achieve a true VO_2 max, the measurement of oxygen consumption at peak exercise, peak VO_2, is reproducible and permits classification of patients into subgroups according to the level of functional impairment. The ideal index of exercise capacity would be one that is independent of the patient's motivation, that is one that is totally objective. Since the onset of acidosis is independent of the patient's motivation, the anaerobic threshold could provide an objective means of assessing the exercise capacity of these patients. In spite of the anaerobic

threshold concept having being challenged, measurement of the ventilatory threshold could provide information regarding the general motivation of patients. For example changes in maximum oxygen consumption in the absence of a change in ventilatory threshold, could suggest an alteration in the patient's motivation rather than a change in functional capacity (41). Submaximal tests such as the 6 minute walking test (43) could be used to assess the exercise capacity of patients with CHF in centres that do not have access to gas analysis equipment. These tests are better tolerated and closer to the daily activities of patients.

1.4.3 Assessment of left ventricular function

1.4.3.1 Background

The evaluation of LV function by noninvasive methods is an important part of the study of cardiac patients attending cardiac rehabilitation programmes.

The ability of the myocardium to contract, a direct consequence of the balance between myocardial oxygen supply and demand provides a useful functional measure of the importance of coronary lesions. Since narrowed coronary arteries may carry sufficient oxygenated blood to supply myocardium oxygen demands at rest, complete assessment of the physiologic importance of the coronary artery lesion will require some type of intervention like physical exertion that will test the functional reserve capacity of the coronary arteries. Hence abnormalities of left ventricular function during exercise may reflect myocardial ischaemia (44).

The identification and quantification of LV dysfunction can be done either by echocardiography (45) or radionuclide studies (46).

1.4.3.2 Echocardiography

Echocardiography involves the method of transmitting ultrasound waves and of receiving and recording those waves that have been reflected by cardiac structures. It also includes the art of analysing and interpreting the patterns recorded. The echocardiographic examination has become part of the routine examination of cardiac patients by cardiologists. The quality of the examination is highly dependent on the expertise of the technician involved. The primary usefulness of routine LV recordings lies in the detection of wall motion abnormalities, the measurement of chamber size and the determination of circumferential muscle fibre shortening velocity. It also has the ability of providing serial measurements of certain parameters of left ventricular function (45).

M-mode and two-dimensional echocardiographic techniques are frequently employed to assess cardiac structure and performance. They both demonstrate cardiac anatomy by detecting echoes reflected from large interfaces, such as those that occur between myocardium and blood. M-mode echocardiography offers an extremely high sampling rate and is thus most helpful for recording rapidly moving structures such as valve leaflets. Two-dimension echocardiography provides more complete spatial sampling and correct anatomic orientation and thus provides a more comprehensive overview of cardiac anatomy. New developments in technique have permitted the evaluation of blood flow through Doppler echocardiography including color flow Doppler and the obtainment of higher quality imaging through trans-oesophageal echocardiography (45).

The following applications in patients with coronary artery disease have been identified (39):

1- Detection of ischaemic muscle: When a muscle becomes ischaemic, its motion is altered almost immediately. Two-dimension echocardiography is now the principal ultrasonic technique for detecting regional wall motion abnormalities in patients with coronary artery disease.

2- Assessment of overall performance: The global ejection fraction (EF) as well as regional LV function can be predicted fairly well using 2-dimension echocardiography.

3- Detection of reversible ischaemia

Any form of stress such as pharmacological, using a vasodilator like dipyridamol or an adrenergic stimulating drug like dobutamine, or physical exercise, can be monitored by echocardiography. With bicycle exercise it is possible to perform the echocardiographic examination during effort whereas with treadmill testing one must rely on an immediate post-exercise examination. It is the introduction of digital echocardiographic recording that has made stress echocardiography a practical examination. The digital technique permits elimination of the respiratory artifact that occurs with the hyperventilation that accompanies exercise, allowing recording only of the cardiac cycles that are not obscured by inspiration. Furthermore, the digital technique allows one to display the resting and exercise images side by side for a better comparison. The sensitivity and specificity of stress echocardiography appears to be comparable to that of stress nuclear testing.

One of the principal reasons for the popularity of and interest in echocardiography is that the examination is presumed to pose no hazard to the patient. Furthermore, no ionizing radiation is involved.

1.4.3.3 Radionuclide methods

1.4.3.3.1 Contrast left ventriculography vs radionuclide ventriculography

Contrast left ventriculography was routinely used to assess regional and global left ventricular function (47) but offered several disadvantages over radionuclide studies (44):

- its invasive nature and the exposure to radiation made the procedure impractical for repeated studies as would be desirable in order to assess the effects of cardiac rehabilitation programmes.

- the contrast medium could affect ventricular function directly and by production of ventricular premature contractions. On the other hand, exposure to radiation by radionuclide ventriculography is minimal, 160 mrad for 10-mCi dose of 99mTechnetium, and the technique itself does not influence left ventricular function.

1.4.3.3.2 Equilibrium vs first-pass radionuclide ventriculography

Radionuclide techniques to assess left ventricular function use two types of methods, equilibrium or first pass.

Equilibrium radionuclide angiocardiography was initially proposed in 1971 (48) and has been widely applied since then. It is based on an imaging agent remaining in the intravascular space. ^{99m}Technetium (Tc)-labelled red blood cells are currently the agent of choice for blood pool imaging. While Technetium as pertechnetate moves freely in and out of the red blood cell and does not bind firmly to the cells in this chemical form, reduced Technetium species do not generally cross the cell membrane (49). Stannous compounds were found to be excellent reducing agents allowing the administered pertechnetate, after finding entry into the cells, to be reduced and become firmly bound to cell components (50). High labelling efficiency is achieved by consecutive treatment of the red cells with stannous ion and ^{99m}Tc pertechnetate. The technetium is bound to the beta chain of the haemoglobin molecule without altering the physical or biochemical property of the red cell, either in vivo or in vitro (51). The optimal stannous (Sn) ion concentration for maximal erythrocyte tagging was found to be between 10 and 30 μg Sn^{+2}/kg body weight (50). Labelling may be done in vitro, in vivo or by a combined in vivo/in vitro technique. Despite the widespread use of in vivo labeling, especially for cardiac studies, variable labelling efficiency and urinary activity were reported. It seems that the Tc amount injected exceeds the binding capacity of the Sn-red blood cells, permitting the uptake of the excess by the thyroid and the gastric mucosa. This can obviously cause a deterioration in the quality of imaging. A slower

injection of pertechnetate and a higher amount of stannous, from 0.6 to 1.1 mgSn^{+2} can improve the quality of the image (51).

Scintigraphic images can be acquired with conventional scintillation cameras, either a single crystal standard Anger camera or with a multiple, small-crystal camera. The technique is based on the use of a physiological indicator such as the ECG to "gate", or physiologically synchronize, serial static imaging of the cardiac blood pool in relation to the cardiac cycle. The ECG is used to define the temporal relation between the acquired nuclear data and different phases of the cardiac cycle (ie. end-systole and end-diastole). Data acquisition depends upon an ECG signal being fed into a minicomputer, which uses the R-wave as a signal to begin acquiring scintigraphic events. Each cardiac cycle is sequenced into 30 to 50 msec segments beginning with the R-wave of the ECG. All the count data occurring within a given segment are then summed for all cardiac cycles and a composite image frame formed for that segment. These images represent the activity acquired over 200 or more cardiac cycles at rest, so that there is sufficient count density to allow meaningful quantitative analysis (44,52,53). Current computer techniques are automated or semi-automated to allow rapid and routine data computation and analysis. A region of interest can be defined over either ventricle and time-activity curves can be generated from each region.

The first transit technique (46,54) involves analysing the initial transit of an intravenously administered radionuclide bolus as it traverses the central circulation. It requires an imaging agent that is rapidly cleared from the intravascular space. Technetium-labeled sulfur colloid or technetium pertechnetate are those most commonly used. The multicrystal scintillation camera is preferred over the single crystal because of a higher count-rate acquisition capability. Duration of imaging is limited to the transit time of the bolus of activity through the heart and involves sampling for only the first 15 to 30 seconds after the injection. Frames acquired during activity transit through the cardiac chamber being studied are then summed to produce a cineventriculogram which usually consists of only 5 or 6 cardiac cycles. During first-pass transit the radioactive bolus is temporally and anatomically separated in each ventricle, allowing for separate measurement of the performance of left and right ventricle by

selecting the appropriate region of interest. First pass studies are not widely used because the technique has specific instrumentation and radiopharmaceutical requirements. However, new technetium-99m-labeled perfusion tracers now make it possible to measure ventricular function by the first-pass technique when the radionuclide is injected primarily for myocardial perfusion imaging (55).

Both first-pass and equilibrium evaluations can also be performed during exercise. Available exercise protocols such as the Bruce protocol which uses treadmill exercise are unsuitable for gamma camera studies, which require that the heart remain in a fixed position during acquisition of data, close to the camera's detector crystal. A cycle ergometer is usually employed, with the patient in a supine or erect seated position which allows for leg motion but no thoracic movement. With the equilibrium technique, this is most often done with supine bicycle ergometry (44) and with the first-pass, upright exercise can be performed (54,56). Borer and co-workers (44) first demonstrated the feasibility of radionuclide determination of EF during supine bicycle exercise using the equilibrium technique. Subsequent reports documented the possibility of multistage exercise tests with as little as 2-minutes acquisition at each step (57). The first pass method is not amenable to multistage protocols as a new injection needs to be given for each determination and time is required for the background resulting from previous studies to stabilize and to be substracted (58).

Measurements of regional and global systolic function expressed as EF as well as ventricular volumes and diastolic filling can be routinely derived. The EF is the number of stroke-volume radionuclide counts divided by the number of end-diastolic counts times 100, with appropriate correction for background counts. The normal left ventricular EF is considered as 50% or higher. In the analysis of diastolic function, the filling portion of the time-activity curve is assessed. Peak filling rate and the time required to attain the peak filling rate are the most common parameters used for this purpose. The normal peak filling rate is 2.50 or more end-diastolic volumes per second. Since radioactivity is in equilibrium with the blood, count rates are directly proportional to the volume of blood in any given area of the blood pool sampled externally with the scintillation camera. Measuring ventricular volume on the basis

of count rates of radioactivity presents a substantial advantage over conventional area-length geometric methods, because the count-based methods do not depend on geometric assumptions about the shape of the left ventricle (44).

The equilibrium method has several advantages over the first pass method (59):

1) The equilibrium method allows for multiple, sequential studies at rest, during and post exercise while the first transit method is restricted to a single measurement at rest and maximal exercise.
2) It allows for better wall motion analysis because of the statistically superior images.
3) The results or the quality of the image are minimally affected by the presence of arrhythmias, which could be excluded by the ECG gating mechanism or averaged as part of the longer imaging period. This is not the case in the first transit method where just a few cardiac cycles are acquired.
4) It uses standard gamma cameras as found in most nuclear medicine departments which can also be portable.

Disadvantages of the equilibrium method are:

1) Relatively long acquisition times - 1 to 2 minutes.
2) Use of only the left anterior oblique projection for quantitative analysis since it is the only one that effectively isolates the left ventricle from the right ventricle and right atrium.
3) The spleen receives a relatively high radiation dose of 0.16 rad/mCi.

1.4.3.3.3 Clinical applications in cardiac rehabilitation

Radionuclide ventriculography allows for the simultaneous assessment of systolic and diastolic dysfunction. The latter is much more common than normally thought and about 30% of patients admitted with congestive heart failure may have this abnormality (60). Its importance also increases with increasing age since diastolic filling declines with age (61).

Through serial studies, radionuclide determinations could be extremely valuable in assessing the haemodynamic response to exercise training in patients with coronary artery disease. Analysis of left ventricular volumes adds substantially to the evaluation of the effects of training in patients with LV dysfunction

1.4.3.3.4 Accuracy

1.4.3.3.4.1 At rest

Radionuclide measured ejection fraction compares favourably in most studies with biplane cineangiographic volumes (57,62,63). The range of correlation coefficients has been between 0.80 and 0.95, and the standard error of the estimate has been in the range of $\pm$ 0.10 ejection fraction units for both methods. Most laboratories found that the first pass method has a slightly better correlation with the contrast angiogram than does the equilibrium study, but this difference was not statistically significant.

1.4.3.3.4.2 During exercise

A good correlation between ejection fraction generated from time-activity curves and ejection fraction determined by X-ray contrast left ventricular cineangiography indicates the validity of the count-volume proportionality assumptions upon which radionuclide angiography is based. It would therefore be logical to expect that if count data provide a good measure of EF, these data should also provide an adequate measure of ventricular volumes and cardiac output.

Sorensen and co-workers (64) validated the assumption that radionuclide count data closely reflect cardiac chamber volumes by showing parallel changes with the Fick cardiac output during exercise. Agreement between count and Fick methods persisted in the individuals

tested, without drugs, after reducing preload with nitroglycerine and after reducing heart rate with propranolol. Although their results applied only to normal subjects they support the feasibility of quantitatively evaluating changes in ventricular volumes during exercise to define mechanisms of ventricular dysfunction more accurately in patients with coronary artery disease.

1.4.3.3.5 Reproducibility

1.4.3.3.5.1 At rest

Reproducibility is very important in a longitudinal study aimed at evaluating an intervention such as cardiac rehabilitation. Previous reports have suggested that for a single study done at rest, the intraobserver variability is in the range of 1 to 3 % for equilibrium studies and 2 to 7 % for first transit, and the interobserver variability is 3 to 5 % and 2 to 9% for equilibrium and first transit respectively (65,66). For serial studies done either hours or days apart the variability has been in the 3 to 5 % range for both methods (67,68).

1.4.3.3.5.2 During and post-effort

Using the equilibrium method during exercise, Okada et al. (69) showed that both intraobserver and interobserver variability was in the range of 4 to 6 % with serial variability in the range of 5 to 7 %. Pfisterer et al (70) studied the reproducibility of ejection fraction determinations by equilibrium radionuclide angiography in response to supine bicycle exercise. All 16 patients with chronic stable CAD were studied on two separate occasions averaging 14.5 days apart. On each occasion the patients were studied first at rest, during a graded supine bicycle exercise with up to three levels of increasing work, and during the initial 10 minutes of the recovery period. Recordings were made at rest (5 min), and continuously throughout the entire exercise and recovery periods. The data were

subsequently divided into serial 2-min periods: exercise (2+3, 5+6, 8+9) and recovery (rec1=2+3, 4+5, rec2=9+10). Each patient reached similar rate-pressure products in the 2 studies. Mean EFs for the first and second studies were: at rest: 53.0 ± 10.8% vs 52.5 ± 10.4%, r=0.95; submaximal exercise: 51.4 ± 12.0% vs 52.1 ± 12.8%, r=0.91; maximal exercise: 50.6 ± 12.6% vs 51.6 ± 12.9%, r=0.97; rec1: 62.7 ± 11.6 vs 62.4 ± 12.2%, r=0.95; rec2: 55.5 ± 10.8% vs 57.2 ± 11.7%, r=0.91. They concluded that EF determined by equilibrium radionuclide ventriculography provided reproducible results in clinically stable individuals at rest, during peak supine bicycle exercise and during the early recovery period. The increase in EF to greater than the resting EF in the early recovery period (minutes 2 and 3) is called the overshoot phenomenon and shows the importance of using the ejection fraction during maximal exercise for diagnostic purposes rather than a post-exercise value. The best correlation coefficient between the two tests was seen at peak exercise where the patients reached their maximal tolerable work limit, at rest and during the early recovery period at the time of the "overshoot" EF increase. Poorer correlations were found during the early, submaximal exercise level (minutes 2 and 3) and in the later recovery period (minutes 9 and 10 post-exercise).

Little information is available on the variability of the first transit technique during exercise.

Since cardiac output, stroke volume, heart rate and blood pressure responses to exercise are dependent upon body position, the relative merits of supine versus upright exercise positions need to be addressed when left ventricular function is evaluated. The sensitivity of the technique for the diagnosis of coronary artery disease has been reported as equal for the two exercise positions (44,54).

1.4.4 Myocardial perfusion imaging

Myocardial perfusion imaging is based upon obtaining images of radioactivity emanating from radioactive tracers whose uptake in myocardial cells is proportional to blood flow

and myocyte integrity (71). When administered intravenously, their uptake by the myocardium approximates the fraction of the cardiac output perfusing the heart. Thallium (Tl)-201 became the most clinically used radiopharmaceutical for myocardial perfusion imaging with a conventional gamma scintillation camera since it offered superior physical properties for imaging with a scintillation camera than previous potassium analogs such as potassium-43 and rubidium-86 (71). In the 1980s, however, technetium-99m labelled myocardial perfusion agents with superior physical characteristics to Thallium were developed (72). These were the Tc-99m-labelled isonitrile compounds of which Tc-99m methoxyisobutylisonitrile (sestamibi) is the most applicable for clinical use. The high photon energy of Tc-99m sestamibi is optimal for gamma camera imaging and can produce higher quality images than those produced by Tl-201. Because of its short half-life (6 hours), approximately 10 to 20 times larger doses can be administered than are feasible with Tl-201, yielding a higher count density in both planar and SPECT images. Furthermore, Tc-99m sestamibi produces less scatter and attenuation than Tl-201 and gated planar imaging can be performed using available multiple-gated acquisition software and hardware (71).

Myocardial uptake of Tc-99m sestamibi is proportional to regional blood flow and non-viable cells cannot concentrate the tracer. Since Tc-99m does not redistribute over time after intravenous injection, separate injections of the radionuclide have to be administered during stress and resting states. These separate injections are required to differentiate defects that represent stress-induced ischaemia from those that represent myocardial scarring. The most optimal protocol at present using this radionuclide agent could be performed over 2 days with performance of the exercise study first and the resting study 24 hours later. Each imaging procedure employs 20 to 30 mCi of Tc-99m sestamibi. However in clinical practice this type of protocol is not very practical and same-day rest-stress imaging procedures have been developed. An injection of 8 to 10 mCi is administered for the rest procedure with imaging performed 60 minutes later. A dose of 22 to 30 mCi is then injected at peak exercise and images acquired 30 to 45 minutes post-injection. The exercise injection should be administered at least 4 hours after the rest

injection. Like Tl-201, Tc-99m sestamibi is injected at symptom-limited endpoints, and exercise is encouraged for at least another minute. Some have advocated continuing exercise for another 1 to 2 minutes at a rate several stages lower than the stage that corresponds to the peak exercise to allow more complete initial uptake in the myocardium. Some laboratories require the patient to drink a glass of whole milk or eat a fatty meal 15 minutes before commencing image acquisition, to stimulate enhanced Tc-99m sestamibi clearance from the gallbladder.

Tc-99m sestamibi imaging showed good correlation to Tl-201 for detection of CAD using the planar approach and both procedures were concordant in differentiating ischaemia from scar (71). An overall sensitivity of 90% and overall specificity of 83% have been determined for Tc-99m sestamibi (71). As observed with planar imaging, both Tl-201 and Tc-99m sestamibi have comparable sensitivity and specificity for CAD detection. However, the SPECT technique was more sensitive than planar imaging in detecting stress-induced ischaemia but had lower specificity. Of 1285 segments that showed perfusion abnormalities following exercise stress by both agents, 84% were concordant for differentiating between ischaemia and scar (71).

The higher photon energy, enhanced count rate, and decreased attenuation and scatter compared with Tl-201 make Tc-99m sestamibi most suitable for SPECT imaging.

1.4.5 Risk stratification

Admission of patients at higher risk of sudden death has made necessary the development of a risk stratification system to identify the patient's risk for an early recurrent coronary event and long-term prognosis, and to guide the duration and extent of his/her supervision and monitoring during exercise. The risk stratification process should form part of the routine assessment of patients admitted for cardiac rehabilitation.

Guidelines for risk stratification are based on assessment of the extent of myocardial damage, left ventricular dysfunction, and presence or absence of residual myocardial ischaemia and ventricular arrhythmias. Although desirable, it is not always necessary to send patients for sophisticated and expensive studies since there is good correlation between the clinical and high-tech assessment of some of the above variables. Guidelines for risk stratification have been developed by the American Association of Cardiovascular and Pulmonary Rehabilitation (73) (Annexure 1.4).

1.5 Exercise prescription and exercise training

1.5.1 Introduction

Aerobic exercise is the key element in all cardiac rehabilitation programmes. It not only has the effect of enhancing physical and psychological wellbeing, but also provides the basis for other health activities and changes in lifestyle (74).

The fundamental objective of exercise prescription is to aid participants in increasing their habitual physical activity.

The exercise recommendation should be treated with the same seriousness and caution which is used in prescribing drug therapy and should always be under the control of the medical health care team. It should take into consideration several factors such as age, gender, medical status, previous physical activity, orthopaedic and musculoskeletal integrity and should be based on the physiological responses to a symptom-limited graded exercise test.

The important parameters determined from the test are peak heart rate and oxygen uptake (either measured directly or estimated from the exercise load), ventilatory threshold, rating

of perceived exertion, limiting signs or symptoms, any ischaemic ST-segment displacement, dysrrhythmias and an abnormal blood pressure response.

A balance must be achieved between the patient's optimal improvement and his cardiac and orthopaedic safety, while the activity is made enjoyable enough for him to want to continue.

1.5.2 The prescription

The format for the exercise session should include a warm-up period (10 minutes), a conditioning phase which should involve aerobic exercise (30-45 minutes), an optional muscle-conditioning programme and a cool-down period (5 minutes).

The warm-up facilitates the transition from rest to aerobic-endurance training and reduces the risk of cardiovascular and musculo-skeletal injuries (75-77). It should include musculo-skeletal exercises such as stretching and flexibility movements and cardio-respiratory exercise, preferably the actual prescribed activity performed at a lower intensity. The cool-down involves slow walking or low intensity exercise and provides a gradual recovery from the conditioning phase. It allows for appropriate circulatory adjustments and return of the heart rate and blood pressure to near resting values, enhances venous return, reduces the potential for post-exercise hypotension, facilitates the dissipation of body heat and combats the deleterious effects of the post-exercise rise in plasma catecholamines (76,77). Of 61 cardiovascular complications reported during exercise training of cardiac patients, at least 72% occurred either during the warm-up or cool-down phases (10).

The prescription of endurance exercise should take into account the type of activity, intensity, duration, frequency and progression.

In order to achieve a training effect the exercise must be continuous, rhythmical and involve large muscle groups. Of the numerous activities which involve large groups of muscles, walking, jogging and cycling seem to be the most suitable because of the relative consistency of energy expenditure. In other activities like swimming, the energy expenditure is highly dependent on skill. Activities such as volleyball, basketball, etc are highly variable in intensity but can be useful when played non-competitively because of the enjoyment they provide (19).

The exercise intensity is expressed as a percentage of the maximum heart rate achieved during the exercise test and should be above a certain level in order to induce a training effect and below the load that could evoke symptoms, ST segment or blood pressure abnormalities and orthopaedic injury (77). The optimal intensity occurs between 70 and 85% of the maximal heart rate (77). If ST segment depression develops during the exercise test, the intensity must be set 10 to 15 beats per minute below the ischaemic threshold (19). Once the actual training heart rate has been established, the speed of walking or jogging must be calculated. Because various activities have been previously related to oxygen consumption and extensive data are available on these relationships, it becomes practical to state the training exercise loads in terms of oxygen consumption as opposed to heart rate. The oxygen consumption level for training can either be measured directly from the exercise test data, or estimated from the work rate of the protocol, at the appropriate training heart rate. The optimal level of intensity for exercise when related to oxygen consumption occurs at a level which lies between 57 and 78% of the maximal oxygen uptake. The relationship between training at a heart rate intensity between 70 and 85% of the maximum heart rate and training at an oxygen uptake betwen 57 and 78% of the maximal oxygen uptake can be seen in Figure 1.1. There appears to be little additional training benefit at intensities above 78% of the maximal oxygen uptake, but a well-defined increased risk of cardiovascular complications (Figure 1.2).

Figure 1.1 Relationship between % maximal heart rate, % maximal oxygen uptake and rate of perceived exertion (185)

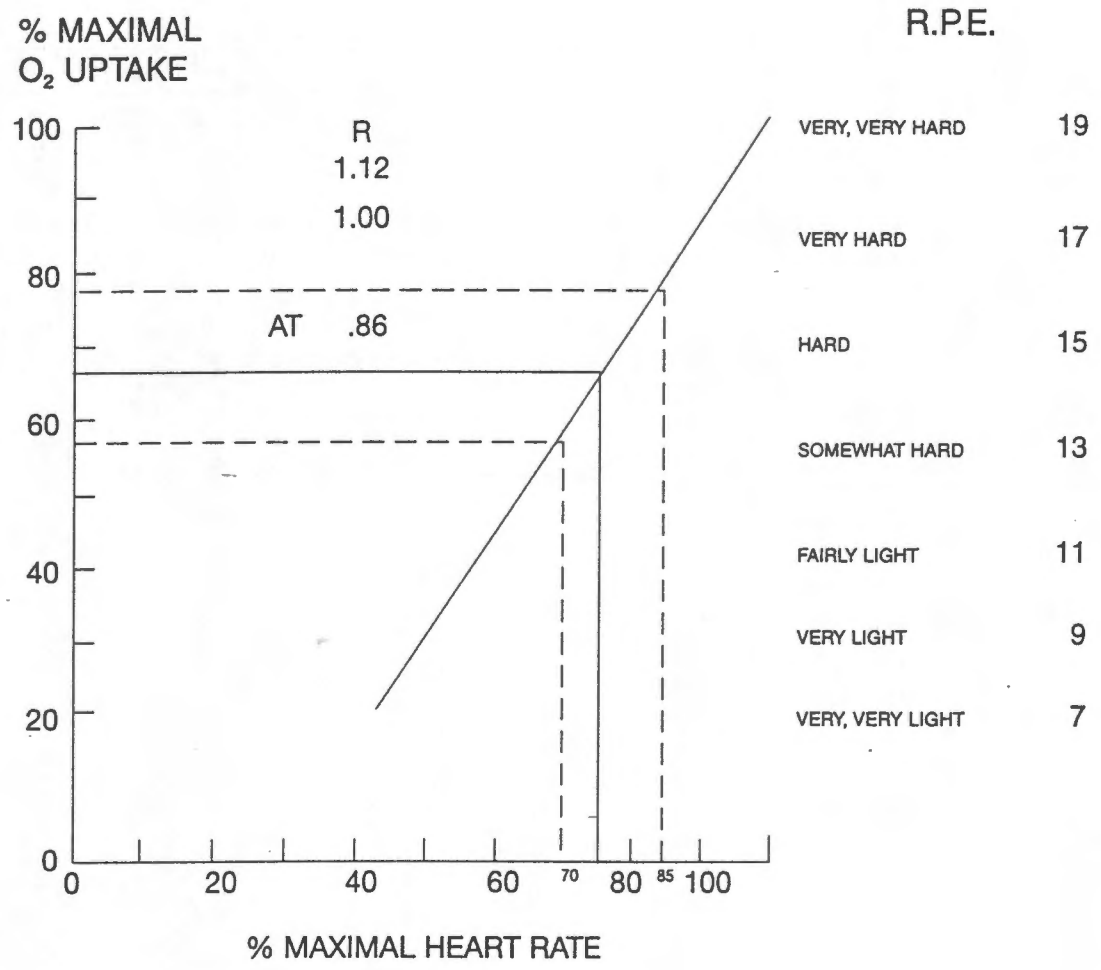
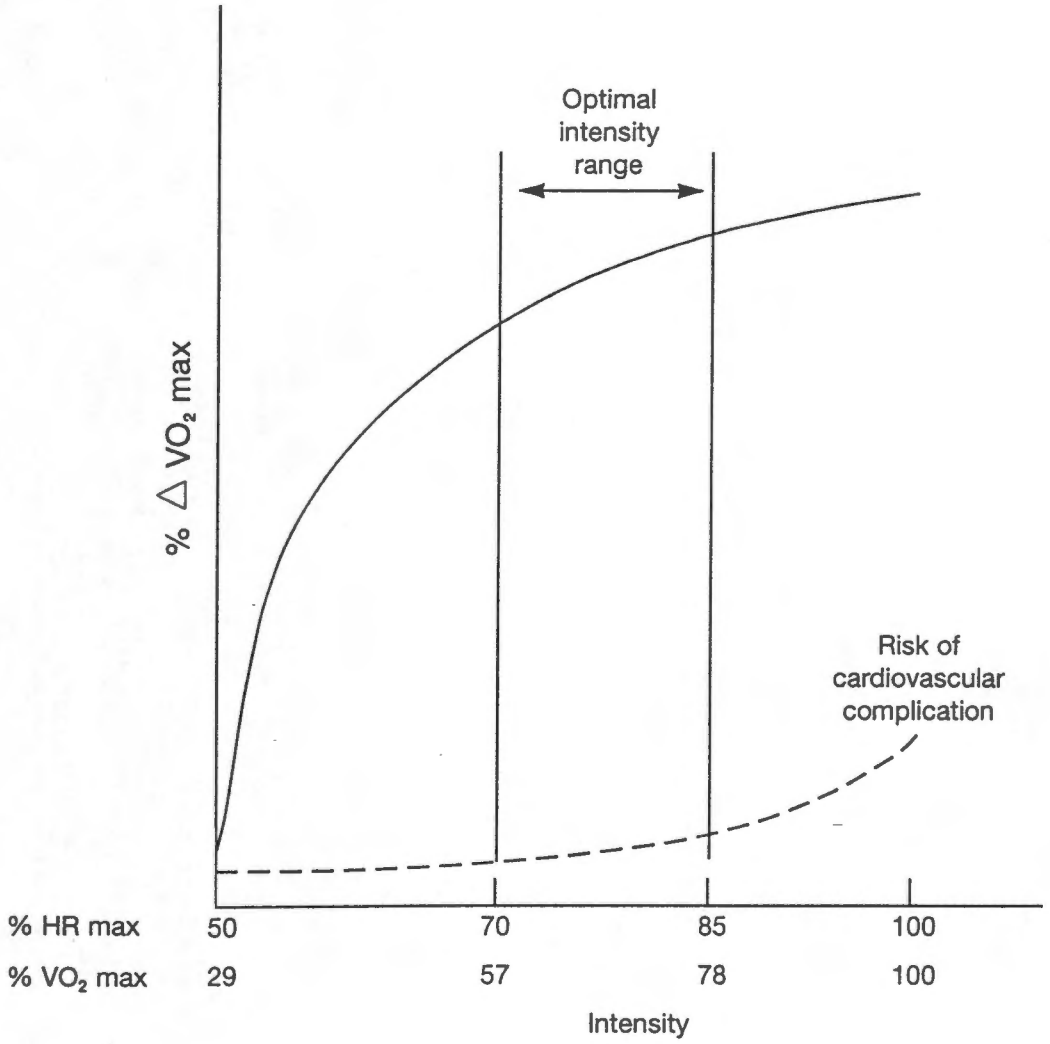


Figure 1.2 Relationship between gain in aerobic capacity (expressed as VO_2 max, % $\triangle$) and intensity of exercise (expressed as % HR max or % VO_2 max). (185)



Once the training level is expressed in terms of oxygen consumption, standard tables such as those developed by Kavanagh (74) can be used to set an appropriate walking, walk/jog or jogging programme. These tables usually express the energy requirements of activities in terms of the basal oxygen uptake by giving a MET rating. Each patient is given his/her training heart rate and the speed and distance which he/she should walk, walk/jog or jog. Both patients and staff must monitor heart rate, speed and distance (19). Patients exercising on a bicycle ergometer should also be given the load for the bicycle expressed in Watts. The load is calculated according to the following formula:

$$\text{Watts} = \frac{VO_2 \text{ (ml/min)} - (5.8 \times \text{body mass (kg)}) - 151}{10.5}$$

Patients should be encouraged to pedal at 60 revolutions per minute.

Another way of prescribing the intensity of the exercise is to set the heart rate slightly below the ventilatory threshold which is defined as the point at which during incremental exercise the subject's ventilation deviates from linearity. The threshold usually occurs close to the middle of the prescribed range of optimal intensity for exercise training: 67 - 70% in the range of 57 to 78% of maximal oxygen uptake and about 75% in the range of 70 to 85% of maximal heart rate (77). It is our experience at the Johannesburg Cardiac Rehabilitation Centre that exercise done at this level is well tolerated and still enhances fitness.

The rating of perceived exertion (RPE) could also be a useful adjunct to the heart rate to guide the intensity of training (19). The RPE response to graded exercise correlates highly with cardio-respiratory and metabolic variables such as oxygen uptake, heart rate and ventilation. Using the 15-point scale which ranges from 6 to 20, a perceived exertion rating of 12 to 13 corresponds to approximately 60% of the heart rate range. A rating of 16 corresponds to approximately 85% of heart rate range. Consequently most participants should exercise within the RPE range of 12 and 16 ("somewhat hard" to "hard"). Corresponding ratings using the 10-point RPE scale would be between 4 and 6.

Duration interacts with intensity, total energy expenditure being the result of the product of the intensity and duration of exercise. Thirty to 45 minutes will be adequate to produce a training effect at the intensity prescribed. Three to four evenly spaced workouts a week appear to be the optimal frequency. When doing weight bearing exercise it is desirable to alternate a day of exercise with a day of rest.

Each patient should progress slowly over a number of weeks up to his ultimately required duration and intensity of exercise. This allows the patient to become accustomed gradually to an increasing work rate.

1.5.3 Role of resistance training

Resistance training could complement traditional aerobic-only conditioning programmes. It is recommended that low-risk patients participate in this type of exercise. The contraindications for aerobic training also apply to resistance training. Patients with poor left ventricular function and/or residual myocardial ischaemia should be considered ineligible for resistance training (until proven otherwise) (78). Weight stations are preferred to free weights because they are safer and more time-efficient. The prescription with regard to weights is set between 30 and 50% of the maximum weight load. The latter is based on a test which assumes the maximum weight that the patients can lift at least twice but not three times to be 90% of his "one repetition maximum". Eight to ten weight stations are recommended. Patients should perform 10 to 15 repetitions in 1-3 sets. The improvement in muscle strength and endurance can be assessed by retesting for one repetition maximum on the circuit or by isokinetic testing.

1.5.4 Interval training

Meyer et al. (79) have recently introduced a new exercise training procedure for patients with chronic heart failure. The procedure includes interval exercise training for 3 weeks on a cycle ergometer (30s work phases alternating with 60s recovery phases) and on a treadmill (60s work alternating with 60s recovery phases). The authors designed a specific steep ramp test to derive exercise intensity for the work phases. The rationale behind this new training modality is that short bouts of exercise allowed for intense stimuli of 50% of maximum work rate achieved during the steep ramp test to be applied to the working muscles with minimal cardiac strain. The authors stated that it is possible that the intermittent nature of the interval training allows the left ventricle to accommodate to an enhanced venous return associated with the high muscle work rates. This new training modality proved safe since no ST segment depression or serious ventricular arrhythmias occurred during testing or training and the clinical results suggested that there is no worsening of heart failure. The authors observed that higher work rates with significantly lower cardiac stress were achieved during interval training than during conventional steady-state exercise training at intensity levels of 75% of peak VO_2 and ventilatory threshold (79,80). A higher intensity stimulus might be more beneficial in reversing the alterations in skeletal muscle ultrastructure, biochemistry and fibre type as well as in peripheral perfusion that occurred in patients with heart failure.

1.5.5 Contraindications for exercise training

The following contraindications for participation in physical exercise have been suggested by the American Association of Cardiovascular and Pulmonary Rehabilitation Guidelines for Cardiac Rehabilitation Programmes (73):

* Unstable angina
* Resting systolic blood pressure over 200 mm Hg or resting diastolic blood pressure over 110 mm Hg

* Moderate to severe aortic stenosis
* Acute systemic illness or fever
* Uncontrolled atrial or ventricular arrhythmias
* Acute/uncompensated heart failure
* Third-degree heart block without pacemaker
* Active pericarditis or myocarditis
* Recent embolism
* Thrombophlebitis
* Uncontrolled diabetes or other metabolic conditions
* Orthopaedic problems that would prohibit exercise

1.6 The Physiological Effects of Physical Training

1.6.1 The cardiovascular effects of physical training in normal subjects

In healthy subjects exercise training increases VO_2 max by increasing both cardiac output and maximal arteriovenous oxygen difference (35,81). However cardiac output seems to contribute more to the increase in VO_2 max than does the increase in arteriovenous oxygen difference. The increase in cardiac output is mediated by an increase in stroke volume since maximal heart rate does not increase in trained healthy subjects (24,82,83). The increase in stroke volume at maximal exercise after training in the absence of an increase in ejection fraction is predominantly due to a better utilisation of the Frank-Starling mechanism leading to an increase in LV end-diastolic volume. This can lead in some (84,85) to training-induced volume overload left ventricular hypertrophy with proportional increase in left ventricular end-diastolic diameter and wall thickness, and without changes in the wall thickness-radius ratio, but this is not universally accepted (86). An increased left ventricular diastolic performance facilitating the filling during exercise may also contribute (84,87).

At any given submaximal workload, heart rate is usually reduced as a result of training (24) and this is compensated by an increase in stroke volume and/or arteriovenous oxygen difference. Both adaptive mechanisms may be operative since the submaximal stroke volume has been reported to be increased (88,89) or unchanged (90-92).

In addition to its cardiovascular effects, aerobic training induces an increase in mitochondrial size and number as well as in the activity of aerobic enzymes, increased capillarization of the trained muscle, and enhanced oxidation of lipids and carbohydrates, adaptations which are geared to a greater aerobic production of ATP (93).

1.6.2 The effects of physical training in patients with coronary artery disease

Exercise training also produces an increase in peak VO_2 after training in patients with coronary artery disease (91,92,94,95). Most of the increase in peak VO_2 in these patients is mediated by an increase in the arteriovenous oxygen difference since most studies have not demonstrated an increase in stroke volume or ejection fraction in these patients (94-99). These peripheral adaptations include an increase in peak muscle blood flow (97), an increase in capillary density, mitochondrial volumes and their aerobic enzyme content in skeletal muscle (100). The natural process of recovery after a myocardial infarction and the resumption of usual activities explains a major part of the improvement in VO_2 even in the absence of formal training (101-103). However studies have shown that patients randomly assigned to a programme of supervised physical activity could increase their exercise capacity by an average of 15-25% more than that which occurred spontaneously in a control group (104,105). The increase in peak VO_2 in patients post-myocardial infarction ranges from 11 to 56% and post-CABG patients from 14 to 66% after 3-6 months of exercise training (106). The greatest improvement can be expected in those patients with the lowest initial VO_2 max values.

A lower heart rate at submaximal exercise is also seen in these patients, but unlike healthy subjects, they compensate for their lower post-training heart rate by an increased arteriovenous oxygen difference rather than by an increased stroke volume (94,96). However Frick and Katila and Clausen (107,108) reported an unchanged submaximal cardiac output with an increased stroke volume after physical training. At a submaximal workload and as a result of training, the blood pressure is unchanged or slightly reduced (81) resulting in a reduced double product which reflects a reduction in myocardial oxygen demand and an improvement in cardiovascular efficiency (109). Some of the largest increases in effort tolerance have been reported in patients with angina pectoris since exercise training delays the onset of symptoms by reducing the submaximal double product, so that some patients will no longer experience angina after physical training (110).

Another possible explanation suggested by Franklin (111) is that exercise training could increase myocardial oxygen supply by promoting transient episodes of myocardial ischaemia which is the best stimulus for collateral development. Although animal studies have produced positive results (81), there is as yet no direct evidence that exercise stimulates development of coronary collaterals in humans (111-114).

In contrast, high intensity, long-term training (1 year at an intensity between 70 - 90 % VO_2 max) can elicit central adaptations in selected patients with CAD, which result in the ability to reach a higher double product before the onset of significant ST depression. These adaptations are characterized by an increase in stroke volume by means of an increase in end-diastolic volume as in healthy subjects as well as an increase in ejection fraction. (115).

1.6.3 The rationale for considering exercise training of patients with left ventricular dysfunction

Congestive heart failure has been defined by Braunwald (2) as "the pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or to be able to do so only from an elevated filling pressure". The definition implies that there is an alteration in the pumping function of the muscle of the heart. As a result there is a combination of underperfusion of vital organs, increased filling pressures of the left ventricle and fluid accumulation in the lungs and venous system. Typical signs and symptoms of congestive heart failure are generalized fatigue, pulmonary congestion, shortness of breath, oedema, fluid retention, elevation in venous pressure and liver enlargement.

The most common cause of chronic left ventricular dysfunction particularly in older patients is loss of heart muscle due to myocardial infarction secondary to coronary artery disease. Three other important conditions leading to heart failure are cardiomyopathies of known or unknown origin, valvular heart disease and poorly-controlled systemic hypertension.

While the mortality from stroke and heart attack is declining in industrialised countries, the incidence and prevalence of heart failure is growing dramatically without reduction in annual mortality (116,117). This increase in incidence and prevalence probably reflects an improved survival of patients with angina, hypertension and acute myocardial infarction, better reporting and recognition of heart failure, and the progressive ageing of the population.

Subjects with heart failure are at high risk for sudden death, mainly due to ventricular arrhythmias (118). Once the diagnosis of congestive heart failure has been established, even in the outpatient setting, the prognosis is ominous: 60% of men and 40% of women

died within 4 years of the diagnosis of congestive heart failure in the Framingham population (118). Survivors of acute myocardial infarction with a left ventricular ejection fraction of less than 40% had a 26% one year mortality if they showed clinical signs of heart failure while in the coronary unit, compared with 12% if they did not manifest such clinical signs (119).

Patients with severe ventricular dysfunction may also experience greater psychological and emotional stress than other survivors of myocardial infarction (120).

All these factors suggest that subjects with left ventricular dysfunction are a particular group of patients who require more intensive rehabilitative efforts and specialized monitoring. However, patients with left ventricular dysfunction were traditionally excluded from formal cardiac rehabilitation programmes on the basis that they were at a much higher risk of sudden death during exercise activity, even though supervised, and that exertion could adversely affect the natural history of ventricular dysfunction precipitating or accelerating the decompensation of the left ventricle.

Rest is an essential component in the management of an acute episode of heart failure, but once the heart failure has been stabilized and the fluid overload and oedema have been adequately controlled, the patient should be mobilized (121).

Any potentially deleterious role of exercise training for patients with heart failure has not been substantiated. Basic exercise physiology principles suggest that the physiologic adaptations seen after training could be beneficial to this type of patient, rather than harmful: Exercise involving large muscle groups is associated with a reduction in peripheral vascular resistance (95). This reduction in afterload could allow some patients with abnormal ventricular function to increase their cardiac output and tolerate some degree of physical activity. The biochemical and morphological alterations that occur in the skeletal muscle (100) suggest that even patients with cardiac failure may be able to increase their maximal oxygen consumption and maximal work capacity through exercise

training. Improvements in cardiovascular efficiency, that is the ability to perform daily activities at a lower percentage of the peak oxygen consumption and lower myocardial oxygen consumption, seen in normal subjects and patients with coronary artery disease and normal left ventricular function (96) could be expected to offer physiological advantages especially to persons with heart failure. A small increase in exercise performance in these patients may have a profound effect on their quality of life. In animal models, physical training has been shown to increase the threshold for ventricular fibrillation (122) and may protect patients with heart failure from fatal ventricular arrhythmias and sudden death. Psychological benefits noted in patients participating in group rehabilitation exercise programmes (123,124) could favourably improve the well-being of patients with heart failure. These patients could also benefit from the favourable changes in blood lipid profiles induced by exercise training and counselling and education in cardiac rehabilitation programmes (13,14).

If we follow this line of reasoning, we could expect exercise training to be relatively safe for patients with left ventricular dysfunction and to produce favourable physiological and psychological adaptations. Extra benefit could be derived in these patients from the close medical surveillance available in the context of a formal rehabilitation programme and from the lifestyle changes normally induced by these programmes.

All this is reinforced by the fact that, presently, patients with heart failure have fewer signs and symptoms of heart failure and better functional capacity due to the advent of new pharmacologic agents. One of the most significant developments in the management of heart failure has come from the angiotensin converting enzyme inhibitors, mainly captopril and enalapril which have improved signs and symptoms of congestive heart failure, but which have also reduced mortality as shown in placebo-controlled trials. In patients with severe heart failure, captopril treatment resulted in a 17% higher survival compared to the placebo group (125). The CONSENSUS study (126) also demonstrated a survival benefit favouring enalapril over placebo in 253 patients with Class IV congestive heart failure. The addition of enalapril to standard regimens was associated with a 31% reduction in

mortality at 1 year. Additional recent findings in 2569 patients with symptomatically milder degrees of heart failure (Class II) who were followed for approximately 3.5 years showed that treatment with enalapril reduced total mortality by 16% and cardiovascular mortality by 18% (127). The risk of progressive heart failure was reduced by 22% with a favourable downward trend in the risk of fatal myocardial infarction (28%). Furthermore, enalapril showed better survival statistics than the direct-acting vasodilators isosorbide nitrate and hydralazine (128).

Over the last few years there has also been considerably interest in the use of beta-adrenergic blocking agents for the treatment of heart failure, because such agents may prevent the adverse effects of sympathetic stimulation on the failing heart (129). A recent meta-analysis of double-blind, placebo-controlled, randomized trials concluded that there is persuasive evidence supporting a more favorable effect of beta-blockade on ejection fraction and the combined risk of death and hospitalization for heart failure than on the improvement on the New York Heart Association (NYHA) class (130).

Digitalis remains an effective, safe, and inexpensive choice of therapy for the relief of symptoms of patients with heart failure. However, its inability to substantially influence morbidity and mortality relegates it to be prescribed for the treatment of persistent symptoms after the administration of drugs that do reduce the risk of death and hospitalization such as angiotensin converting enzyme inhibitors and beta-adrenergic blockers (131).

Exercise training could therefore complement the presently limited therapeutic options available for patients with heart failure.

1.6.4 The effects of physical training in patients with left ventricular dysfunction: current knowledge

Several studies have now suggested possible benefits of exercise training in patients with moderate or even severe left ventricular dysfunction without evidence of clinically manifest congestive heart failure.

Letac and colleagues (98) were the first to report the effects of exercise training in patients with some degree of left ventricular dysfunction due to coronary artery disease. They evaluated the effects of 2 months of exercise training in 15 patients, 12 convalescent from a myocardial infarction and 3 suffering from angina. Only 8 of those patients had an ejection fraction below 45%. In the total group and in those patients with moderately depressed systolic function, they found an improvement in maximal exercise capacity, a reduction in heart rate, blood pressure and rate-pressure product at submaximal exercise and no changes in left ventricular end-diastolic pressure, ventricular volume and ejection fraction. They concluded that training had no direct influence on the myocardium, either beneficial or detrimental.

In 1979 Lee and associates (132) performed symptom-limited exercise testing and cardiac catheterization studies before and after 12 to 42 months of exercise training in 18 patients with left ventricular ejection fractions of 40 percent or less. As a result of training, there was a significant reduction in the mean functional aerobic impairment which decreased from 32% to 23% ($p<0.01$) and resting and submaximal heart rates were significantly lower ($p<0.01$ and 0.05 respectively). Similar to the previous study, there were no changes in resting left ventricular ejection fraction, left ventricular dimensions or intracardiac pressures after exercise training.

In 1982 Cohn and co-workers (133) evaluated the effects of an exercise training programme with a follow-up duration of 4 to 37 months (mean 13 months) in 10 patients with a prior myocardial infarction and severely depressed left ventricular function with a

resting left ventricular ejection fraction of less than 27 % (range 13 to 26) determined by radionuclide ventriculography. Maximal exercise capacity improved in 6 of the patients after exercise training, while 4 patients showed no changes. Overall, maximum exercise capacity increased significantly from 7 to 8.5 METs ($p=0.05$) and oxygen pulse showed an almost uniform increase from 12.8 to 15.7 ml/beat ($p<0.01$). No correlation was found between left ventricular ejection fraction at rest and exercise capacity. No adverse effects occurred during exercise testing or training sessions, although 2 patients died suddenly during the period of observation.

While the studies of Letac et al. (98) and Lee et al. (132) demonstrated an improvement in maximal exercise capacity and a reduction in submaximal heart rates in patients with modest left ventricular impairment at rest, the study of Cohn et al. (133) showed that even patients with severely impaired left ventricular function at rest can achieve significant training effects.

It was not until 1988 that investigators published the results of a more intensive evaluation of the role of exercise training in patients with chronic heart failure. Sullivan and colleagues (134) examined the effects of 4 to 6 months of exercise training in 16 patients with Class I-III chronic heart failure due to systolic left ventricular dysfunction. Mean left ventricular ejection fraction in this group was $24\pm10\%$. In 9 of the patients the heart failure was due to coronary artery disease and in seven it was idiopathic. Before and after training, patients underwent maximal bicycle exercise testing and direct measurement of central haemodynamic, leg blood flow and metabolic responses. Four patients dropped out of the programme prior to completion and were excluded from the analysis. One had an orthopaedic injury, two developed increasing symtoms of congestive heart failure and one died suddenly, unrelated to exercise. They demonstrated that exercise training significantly increased peak oxygen consumption from 16.8 ± 3.8 to 20.6 ± 4.7 ml/kg.min ($p<0.01$), peak leg blood flow from 2.5 ± 0.7 to 3.0 ± 0.8 l/min ($p<0.01$) and peak central arteriovenous oxygen difference from 13.1 ± 1.4 to 14.6 ± 2.3 ml/dl ($p<0.05$). There was a trend for an increase in cardiac output and stroke volume at maximal exercise ($p=0.13$ and

p=0.12 respectively). Heart rate was reduced at rest and during submaximal exercise but did not change at maximal exercise. Resting and exercise arterial, right atrial, pulmonary capillary wedge and pulmonary artery pressures were unchanged after training. Resting and exercise left ventricular ejection fraction and left ventricular volumes were not significantly altered by training. Arterial and femoral venous lactate levels and leg lactate production were markedly reduced during submaximal exercise after training but were unchanged at rest or maximal exercise. The ventilatory threshold occurred at an increased oxygen consumption (10±1.2 vs 12±2.6 ml/kg.min, $p<0.01$). There was no correlation between the change in peak VO_2 after training and baseline haemodynamic variables.

This study showed that exercise training can improve submaximal and maximal exercise capacity in patients with severely depressed left ventricular function. Peripheral adaptations played a major role in the training effect measured in these patients. However in some patients, increased peak cardiac output also contributed to improved exercise performance.

The first controlled comparison of exercise training and restriction of physical activity in patients with stable heart failure secondary to coronary artery disease was reported by Coats and colleagues in a preliminary study in 1990 (135). Eleven patients with a mean left ventricular ejection fraction of 19±8% underwent a random-order, crossover comparison of 8 weeks of exercise training and 8 weeks of restriction of physical activity. Patients exercised at home on a stationary bicycle ergometer for 20 minutes 5 days a week at a training heart rate between 60 and 80% of their previously determined maximum. Training increased exercise duration from 14.8±1 to 16.8±1.3 minutes ($p<0.01$) and peak oxygen consumption from 13.5±1.1 to 16.7±1.3 ml/kg/min ($p<0.01$). Heart rate at submaximal work loads and rate-pressure products were significantly reduced by training and there was also a significant improvement in patient rated symptom-scores. This study showed once again but in a controlled manner, that patients with severely depressed left ventricular dysfunction can improve submaximal and maximal exercise performance and

symptoms after physical training. This was in addition the first report of an entirely outpatient exercise training programme for this type of patient.

Coats and co-workers extended their preliminary study and published a more comprehensive evaluation two years later (136). Nineteen patients entered the trial and two failed to complete the programme. Cardiac failure worsened in both dropouts while they were in the rest phase; one died and the other underwent cardiac transplantation. Seventeen patients completed the trial without complications. Similar improvements to those described in the preliminary report were seen in peak oxygen uptake and exercise duration after training. Training produced a significant vasodilatation associated with an increased cardiac output at submaximal and maximal exercise (5.9 vs 6.7 l/min, $p<0.05$ and 6.3 vs7.1 l/min, $p<0.05$ respectively). Minute ventilation and the slope relating minute ventilation to carbon dioxide production were significantly reduced after training. Autonomic function was evaluated by three methods: heart rate variability assessed by 24 hours Holter monitoring, power spectral analysis and norepinephrine kinetics. Exercise training produced changes in autonomic balance shifting away from sympathetic toward enhanced vagal activity. They concluded that carefully selected patients with moderate to severe chronic cardiac failure can achieve significant improvements in exercise capacity, haemodynamics, ventilation and autonomic function.

Other randomized studies followed Coat's research. They contributed to provide a better understanding of the effects of aerobic exercise training in reverting intrinsic muscle abnormalities produced by heart failure and showed that the improvement in functional capacity can lead to an improvement in quality of life and other outcomes like hospital readmission and mortality rate. (137-142)

In 1995, Hambrecht et al. (137) evaluated the effects of a combined hospital and home-based 6 month exercise training programme on the oxidative capacity and ultrastructural morphology of skeletal muscle and its relation to central and perifpheral hemodynamic variables in 22 patients with stable chronic heart failure in NYHA class II and III. Twelve

patients (EF = 26 ± 9%) were randomized to the training group and ten patients (EF = 27 ± 10%) to a physically inactive control group. Patients in the training group showed a significant increase in ventilatory threshold (23%: 0.86 ± 0.2 to 1.07 ± 0.2 L/min, $p<0.05$), in peak oxygen uptake (33%: 1.49 ± 0.4 to 1.95 ± 0.4 L/min, $p<0.01$), in total volume density of mitochondria (19%: 4.7 ± 1.5 to 5.6 ± 1.5 vol%, $p<0.05$) and in volume density of cytochrome c oxidase-positive mitochondria (41%: 2.2 ± 1.0 to 3.1 ± 1.0 vol%, $p<0.01$), while there were no changes for those parameters in the control group. Cardiac output did not change at rest or during submaximal exercise but increased at peak exercise (11.9 ± 4.0 to 14.1 ± 3.3 L/min, $p<0.05$). Peak leg oxygen consumption also showed a significant increase as a result of training (510 ± 172 to 740 ± 254 ml/min, $p<0.01$). An important finding was that the significant increase in oxidative capacity of skeletal muscle after exercise training was significantly correlated with ventilatory threshold ($r=0.82$, $p<0.00001$) and with peak oxygen uptake ($r=0.87$, $p<0.00001$). The mechanism for the intrinsic muscle alterations remains unclear. Deconditioning appears to be a strong determinant, however it is not the only factor since muscle dysfunction can also occur in small hand muscles not expected to become deconditioned.

In 1996, Kiilavuori et al. (138) showed a greater increase in exercise endurance at a submaximal workload (14.7 ± 2.0 to 27.8 ± 2.7 minutes, $p<0.01$) than in peak exercise capacity (19.3 ± 1.6 to 21.7 ± 2.3 ml/kg/min, $p=0.09$) in 12 patients with symptomatic congestive heart failure (NYHA Class II and III, EF<40%) randomized to training (n=12). The training program consisted of 3 month supervised exercise of moderate intensity (50-60% of peak VO_2) and 3 months unsupervised activity at home. This study was novel in the sense that their program had one of the lowest intensity used so far in the training of CHF patients and that by using a separate control group they could overcome the problem of the possible training effect of repeated exercise tests which could overestimate the effect of the intervention.

In the same year, Keteyian et al. (139) compared the physiological adaptations of 21 men with compensated heart failure and LV dysfunction (NYHA class II or III, EF<35%)

randomized to a 6 month exercise training program of moderate to high intensity to those of 19 patients randomized to a non-exercise control group. Exercise training increased peak VO_2 (+231 ± 54 ml/min vs. +58 ± 38 ml/min), peak heart rate (+10 ± 4 vs. –2 ± 4 bpm), peak ventilation (+12 ± 3 L/min vs. –4 ± 3 L/min), peak power output (+20 ± 6 vs. +2 ± 5 Watts) and exercise duration (+2.8 ± 0.6 min vs. +0.5 ± 0.5 min) over time compared to the control group, but failed to increase the ventilatory threshold which translates in the ability to perform standard or routine daily activities with fewer or less severe symptoms.

In 1997, Dubach et al. (140) evaluated the effects of a 2 month high-intensity exercise residential exercise training program in men with reduced LV function post-MI or CABG (NYHA class II and III, EF<40%) randomized to a training. Peak oxygen uptake increased significantly (19.4 ± 3.0 to 25.1 ± 4.8 ml/kg/min, $p<0.05$) in the intervention group only, by way of an increase in maximal cardiac output (12.0 ± 1.8 L/min to 13.7 ± 2.5 L/min, $p<0.05$) and a widening of maximal arteriovenous oxygen difference (13.1 ± 1.3 to 14.8 ± 1.6 O_2/100 ml, $p<0.05$).

In 1997 as well, Hambrecht et al. (141) in an expansion of their previous study published in 1995, demonstrated that a 6 month aerobic endurance training programme can correct the ultrastructural abnormalities found in the skeletal muscle of patients with chronic congestive heart failure and can also reshift the muscle fiber type distribution from type II to type I fibers. The improvement in peak oxygen uptake was positively correlated to the increase in the surface density of cytochrome c oxidase-positive mitochondria ($r=0.66$, $p<0.01$). They also demonstrated that femoral venous lactate accumulation during submaximal exercise was inversely related to changes in oxidative capacity of skeletal muscle assessed by volume density of mitochondria ($r=-0.66$, $p<0.01$) and by surface density of the mitochondrial inner border membrane ($r=-0.5$, $p<0.05$). However venous lactate accumulation was not related to changes in submaximal leg blood flow ($r=-0.4$, p=NS).

In 1999, Belardinalli et al. (142) made a significant contribution by demonstrating that long-term moderate exercise training can improve the functional capacity and quality of life of 50 patients with chronic heart failure randomized to exercise training when compared to 49 patients receiving usual treatment. Exercise training was performed at 60% of peak VO_2, three times a week during the first 2 months and thereafter twice a week for 12 months. Both benefits were observed immediately after 2 months of physical training but more importantly and more novel they were maintained at 1 year with a programme of the same intensity but of a lower frequency. The other important finding of this study is that the improvement in functional capacity translated into a lower rate of hospital readmission for heart failure (RR=0.29, p=0.02) and a lower mortality rate (RR=0.37, p=0.01). Thallium activity scores improved by 2 months (24%, $p<0.01$) and were maintained for one year, partially explaining why an increased functional capacity could lead to improved outcomes. Peripheral factors may have also contributed to better the outcomes but were not assessed in this study.

1.6.5 Physiological determinants of the impaired exercise tolerance of patients with left ventricular dysfunction

1.6.5.1 Introduction

A number of factors may contribute to exercise intolerance in chronic heart failure, including an increased pulmonary capillary wedge pressure, a reduction in cardiac output, decreased skeletal muscle blood flow, early altered cellular metabolism in muscle and excess pulmonary dead space and ventilation (143).

1.6.5.2 An increase in pulmonary capillary wedge pressure

Since pulmonary capillary wedge pressure (PCWP) is an important cause of dyspnoea in patients with acute congestive heart failure and it increases in some of these patients during exercise, it has been postulated that dyspnoea produced by pulmonary vascular congestion may be the factor limiting the exercise tolerance of patients congestive heart failure (144). Increased PCWP during exercise stimulates pulmonary J-receptors causing reflex hyperventilation and hypoxia which in turn causes dyspnoea (145).

However several findings are against this postulated mechanism of exercise intolerance. Some patients with chronic congestive heart failure reach the point of fatigue during a symptom-limited exercise test without an increase in the pulmonary capillary wedge pressure above resting values, but still demonstrate major reductions in peak VO_2 (146). The greater ventilatory response to exercise seen in patients with chronic heart failure is associated with an increase in pulmonary dead space probably caused by ventilation-perfusion mismatching, resulting from pulmonary hypoperfusion due to a decreased cardiac output and not increased pulmonary wedge pressures (146). While resting pulmonary capillary wedge pressure is inversely associated to peak oxygen consumption (147), peak exercise pulmonary capillary wedge pressure is not related to peak oxygen uptake (148,149).

1.6.5.3 Central haemodynamic factors

Several investigators demonstrated a reduction in cardiac output during exercise in patients with LV dysfunction and a significant correlation between cardiac output and oxygen uptake at peak (148-151) and submaximal (152) exercise levels.

Diastolic left ventricular dysfunction, even in the presence of normal systolic left ventricular function may lead to significant reductions in exercise tolerance due to a

decrease in the submaximal cardiac output (153). These authors compared the haemodynamic response to exercise of 7 patients with chronic heart failure to that of 10 age-matched normal subjects. They found that although left ventricular end-diastolic volume was not different at rest in the two groups, it was lower in the patients during exercise and did not increase in this group from rest to exercise. However, this response was accompanied by a marked increase in left ventricular filling pressures in the patients suggesting left ventricular diastolic dysfunction with reduced left ventricular compliance. Because left ventricular end-diastolic volume did not change during exercise despite elevated left ventricular filling pressures, stroke volume failed to increase during exercise in the patients.

Some patients with left ventricular dysfunction may develop secondary mitral regurgitation due to progressive ventricular dilatation. This condition may play an important role in determining the forward stroke volume response to exercise in some patients (143) and could be treated with vasodilator therapy (154).

In spite of the above results, the lack of correlation between exercise left ventricular ejection fraction and peak VO_2 in patients with left ventricular dysfunction has been considered to show that abnormalities in cardiac function were not important in determining exercise tolerance. A possible explanation is that ejection fraction plays a small role in determining cardiac output in patients with low left ventricular ejection fractions (143). Cardiac output is the product of heart rate and stroke volume and is determined not only by LV contractility but by several other factors such as the end-diastolic volume and the mitral regurgitation fraction as seen above: Cardiac Output = Heart Rate x End-Diastolic Volume x EF x (1-Mitral Regurgitation Fraction). The contribution of end-diastolic volume and mitral regurgitation fraction to the determination of cardiac output are accentuated in patients with chronic heart failure.

1.6.5.4 Chronotropic incompetence

Szlachcic and co-workers (155) found a good correlation between maximal oxygen consumption and maximal cardiac index ($r=0.82$, $p<0.001$) in patients with CHF. Since stroke volume did not change, oxygen consumption correlated significantly with the exercise-induced increment in heart rate ($r=0.77$, $p<0.001$). However, Sullivan (150) showed that the heart rate response to exercise is much higher in normal subjects suggesting some degree of chronotropic incompetence in patients with CHF. Abnormalities of cardiocirculatory reflexes, lower catecholamine concentrations in the heart with congestive failure and a reduced sensitivity to beta-adrenergic receptor stimulation could explain the heart rate incompetence of these patients (149).

1.6.5.5 Peripheral adaptations

Recent studies have demonstrated that chronic peripheral adaptations play an important role in the exercise intolerance of patients with chronic heart failure.

The findings that improvements in exercise performance do not accompany immediate improvements in central haemodynamics after inotropic (156) or vasodilator therapy (157) and that exercise capacity is increased over 3 to 6 months only after long-term therapy with angiotensin converting enzyme inhibition (158-160) suggest that chronic peripheral adaptations are responsible for this response.

The earlier studies of Weber and Janicki (161) demonstrated that the onset of lactate accumulation is an important predictor of submaximal exercise tolerance in chronic heart failure. Subsequent studies showed that exercise intolerance in patients with chronic heart failure is associated with an early increase in blood lactate concentrations in skeletal muscle. Two factors that could contribute to this response in patients are reduced muscle perfusion during exercise (150,162,163), and reduced aerobic enzyme content in skeletal

muscle (164,165). However it is interesting to note that many of these alterations are consistent with the effects of exercise deconditioning and could be partly attributable to muscle wasting secondary to prolonged inactivity (136).

Peak leg blood flow and peak cardiac output, both showed a good correlation with peak oxygen consumption in patients with this disorder (134). Several studies showed that skeletal muscle perfusion was reduced in patients with CHF compared with normal subjects (150,162,163). A reduced cardiac output during exercise reduces the perfusion of working skeletal muscle which in turn is a potent stimulus for increased oxygen independent metabolism in muscle. In contrast, others (166,167) reported abnormalities of high-energy phosphate metabolism in congestive heart failure without blood flow changes. Massie et al. (149) demonstrated that patients with CHF show greater declines in pH and a higher rate of lactate production and ATP consumption than normal subjects at comparable submaximal workloads, during exercise performed with the brachial artery occluded by a cuff inflated to a pressure exceeding systolic blood pressure. Their study strongly suggested the existence of intrinsic skeletal muscle abnormalities in patients with CHF, unrelated to altered skeletal muscle perfusion during exercise.

These abnormalities were more directly confirmed by muscle biopsy studies which showed decreases in skeletal muscle aerobic enzyme activity, muscle fibre changes and alterations in the vasodilator capacity of peripheral vessels (164,165). Mitochondrial enzymes involved in terminal oxidation such as enzymes mediating beta-oxidation of fatty acids, as well as glycogen content were also reduced. There was a decrease in slow twitch type 1 fibers which have a high potential for aerobic oxidation and an increase in fast twitch type 2b fibers (164,165). These biochemical and histological alterations in skeletal muscle are likely to modify exercise tolerance in these patients.

1.6.5.6 Neurohormonal activation

Congestive heart failure promotes the activation of several neuroendocrine mechanisms largely in order to compensate for reduced flow. Alterations in the reflex control of the circulation are also seen (168).

The sympathetic nervous system is uniformly activated while the renin-angiotensin system is variably activated in chronic heart failure (169). Both systems are potent vasoconstrictor stimuli which can increase the impedance to left ventricular ejection and influence the peripheral distribution of blood flow. In addition arginine vasopressin (170) and plasma atrial natriuretic peptide (171) levels are often increased in these patients. Vasopressin also has a vasoconstrictor effect, but this effect may be manifested only under the unusual circumstances when the circulating hormone level is very high (172). Atrial natriuretic peptide may exert a modulating effect on vasoconstrictor tone and on neurohormonal stimulation in heart failure (173).

Activation of these neurohomonal systems relates to the severity of the clinical syndrome (169). Plasma norepinephrine, plasma arginine vasopressin and plasma atrial natriuretic peptide levels are increased even in patients with asymptomatic LV dysfunction while the renin-angiotensin system is activated only in symptomatic patients requiring treatment for heart failure (168).

Furthermore, an impaired reflex responsiveness to baroreceptor and mechanoreceptor unloading is frequently seen in these patients, blunting the usual rise in plasma norepinephrine and renin activity in response to orthostasis (174) and vasodilator drug infusion (175).

The activation of these systems could impact directly on exercise tolerance by limiting exercise-induced vasodilation or by contributing to maldistribution of peripheral blood flow.

1.6.5.6.1 Role of resting neurohormonal activity

Francis et al (176) have demonstrated an inverse relationship between resting plasma norepinephrine levels and peak exercise capacity in subjects with heart failure. On the other hand, other authors found a very weak correlation between peak oxygen consumption measured during a progressive bicycle ergometer test and blood hormone levels (177).

1.6.5.6.2 Role of neurohormonal response to exercise

During exercise all the neurohormonal vasoconstrictor systems are activated.
In normal subjects, plasma norepinephrine levels rise modestly during exercise below the so-called "anaerobic" threshold but rise rapidly above this threshold (176), while in patients with chronic heart failure even modest workloads cause a substantial increase in the plasma norepinephrine level (178). When plasma norepinephrine levels were compared at the same relative work intensity expressed as a percentage of peak VO_2, patients with heart failure demonstrated a slower rate of rise of plasma norepinephrine suggesting an attenuated sympathetic response to exercise (178). Pharmacologic blockade of these systems by inhibition of alpha-receptor function or the formation of angiotensin II was unable to acutely improve the exercise tolerance of these patients (168).

1.6.5.6.3 Role of cardiac innervation

Resting plasma norepinephrine levels and reflex responses to orthostasis and nitroprusside infusion returned toward normal in patients with congestive heart failure after cardiac transplantation (179) . However, peak exercise performance usually remains impaired in these patients after a heart transplant (180). One possible explanation for this is the immunosupressive therapy that these patients receive, but another possibility is the loss of

neural cardiac control since the donor heart is denervated. In this regard, there is evidence to suggest that gradual reinnervation of the heart occurs two or more years after orthotopic cardiac transplantation in some patients (181). However, maximal exercise capacity was not greater in these patients than in those who have not developed reinnervation.

There is therefore no evidence to support the concept that neurohormonal activation is a factor limiting the exercise tolerance of patients with chronic heart failure (168). These abnormalities may however contribute to some of the signs and symptoms of the disease and retain an important role in its prognosis.

1.7 The aim of the study

1.7.1 Background

In 1988 we started assessing left ventricular function in all patients enrolling into our programme at the Johannesburg Cardiac Rehabilitation Center in order to stratify them according to the risk of an exercise-cardiac related event and to establish the degree of their monitoring during exercise. We began to realise that many patients with low ejection fractions could actually perform very well from a functional point of view and lead an active and normal life.

The subject of this thesis was conceptualised as a result of these personal observations at the Johannesburg Cardiac Rehabilitation Centre. However, it did not take long for our observations to be partially substantiated by studies done at large University Centres around the world. These studies showed that selected patients with depressed left ventricular systolic function following acute myocardial infarction could safely participate in supervised exercise training programmes and significantly improve their effort tolerance (134,135). In an attempt to understand the nature of these beneficial effects, researchers were also prompted to investigate the precise mechanism for the exercise intolerance of these patients (143) and the accumulated evidence started to suggest that it is multi-factorial. Of special interest for cardiac rehabilitation practitioners was the finding that measurements of systolic left ventricular function could not predict the exercise tolerance of these patients (147,182).

We were disappointed when some of these data were published before we could finish our studies and realized that our observations were no longer absolutely unique. Although some of the questions were answered we could identify several important methodological limitations in those studies. As a result, our studies compliment a growing literature showing that exercise training should play an important role in the management of patients with left ventricular dysfunction.

1.7.2 Limitations of previous studies

Non-cardiac factors which could have had a confounding effect on effort tolerance were not considered when correlating measures of left ventricular dysfunction to measures of exercise tolerance.

Only impairments in left ventricular systolic function have been related to exercise capacity even though it is known that congestive heart failure can exist in the presence of preserved systolic function and that left ventricular diastolic dysfunction may be a major determinant of effort intolerance in these patients (183,184).

Most patients were accepted on these trials on the basis of their New York Heart Association (NYHA) functional class and left ventricular ejection fraction. The limitations of the use of the NYHA class have been demonstrated (185). Most studies categorized patients into two categories, one with an EF less than, and one with more than a certain value. But no study has yet evaluated a complete spectrum of patients with various degrees of left ventricular dysfunction. The majority were on NYHA classes III and IV and on treatment with diuretics and digitalis.

Most patients enrolled into the studies have been evaluated while in hospital for an acute event, whether due to ischaemia or congestive heart failure and the reported left ventricular dysfunction was rarely a true reflection of their status during exposure to daily activities. The criteria for admission into these studies has been very restricted in terms of the patient's medical condition since only patients post-MI and patients with non-ischaemic cardiomyopathies have been enrolled.

Since most cardiac rehabilitation programmes utilise exercise as their main instrument of therapy, measurement of changes in LV function during exercise rather than at rest, at entry to the programme, could provide information more representative of the adaptations that are likely to occur as a result of training.

Because of its prognostic value, resting ejection fraction has been widely utilised as an end-point to describe improvement or deterioration of function in this population group (186). It is possible that the poor correlation between EF and exercise tolerance is due to the lack of sensitivity of EF in estimating cardiac output. There is therefore a need to evaluate other parameters of systolic and diastolic LV function, as predictors of exercise tolerance.

Patients joining a cardiac rehabilitation programme may not only have varying degrees of left ventricular dysfunction but also demonstrable myocardial ischaemia (187-189). It is well known that an imbalance between myocardial oxygen supply and demand can significantly affect the left ventricular function of patients but little is known about how exercise training can affect the association between ischaemia and left ventricular function. It has been suggested that patients with low EFs and associated myocardial ischaemia may not show improvements in maximal oxygen uptake as a result of exercise training (190). Furthermore, most studies including these type of patients utilised an electrocardiographic criterion of evaluation. The sensitivity of the use of the treadmill test as a measurement of myocardial ischaemia has been reported as 68% in a population with angiographically demonstrated coronary artery disease (191) and could be greatly enhanced with myocardial perfusion imaging techniques (192-194).

The effects of exercise rehabilitation on the left ventricular performance of patients with coronary artery disease remain controversial. Most studies have shown little change in LV systolic function in patients undergoing conventional exercise training programmes (98,99,103,134,195-198) while others have reported training-induced central adaptations after high-intensity and prolonged endurance training programmes (115,196,197,199,200).

Although it is well known that poor compliance with the exercise programme can lead to an inadequate training stimulus, researchers very seldom adjusted their data according to this important variable. Age-related deterioration in left ventricular function could have been another contributory factor to the lack of improvement in cardiac function seen by

some authors after training (201,202-204). Furthermore, little attention has been given to changes in diastolic function as a result of exercise training especially in this patient group. Most exercise rehabilitation programmes recommend that their cardiac patients exercise 3 times a week for 30 to 45 minutes at an intensity between 70 to 85% of maximal heart rate, which corresponds to between 50 and 70% of VO_2 max, for a period of 3 to 6 months. In the USA the duration of the post-discharge exercise programme (Phase 2) is dictated by the patient's medical insurance company and never exceeds 3 months duration. Since patients are responsible of the programme costs thereafter, only a small percentage of these patients will continue exercising into a Phase 3 exercise cardiac rehabilitation programme. The progamme run by the Johannesburg Cardiac Rehabilitation Centre is fully sponsored by the Johannesburg City Council. Exercise is prescribed in the same way but since costs are not an issue most patients will remain on the programme for a duration of 6 months and 50% for 18 months. We are therefore in a unique position to assess the effects on long term exercise training in these patients.

1.7.3 The need for and the purpose of the study

Based on the above studies, we can conclude that the left ventricular functional profile of patients admitted to community-based cardiac rehabilitation programmes as well as the physiological adaptations to exercise training of patients with various degrees of left ventricular dysfunction remain to be fully established.

Accordingly, the following needs for research of this topic were identified:

1- To assess the left ventricular profile of a wider spectrum of patients with coronary artery disease enrolling into an outpatient cardiac rehabilitation programme.
2- To use a method of evaluation of left ventricular function that accurately measures diastolic as well as systolic function at rest and during exercise.
3- To include non-cardiac factors and parameters other than EF when correlating left ventricular function parameters to exercise tolerance.

4- To evaluate the physiological adaptations to exercise training in a wider spectrum of patients with LV dysfunction.
5- To establish the impact of myocardial ischaemia on left ventricular function and adaptability to training by selecting patients on the basis of their ischaemic response to exercise testing and myocardial perfusion imaging studies.
6- To evaluate the effects of exercise training of short and long term duration on the systolic and diastolic left ventricular function of patients with coronary artery disease, adjusting the results to the patient's adherence to the training regime.

It is the purpose of this thesis to address the methodological limitations seen in the above studies and to evaluate the relationship between left ventricular function and exercise tolerance in a wide range of patients with coronary artery disease and with different levels of impairment in left ventricular function, before and after short and long term exercise training. The thesis is based on the hypothesis that if peripheral mechanisms play a major role in limiting the exercise tolerance of patients with left ventricular dysfunction, exercise training that enhances skeletal muscle function could improve their exercise tolerance, regardless of their initial limitations in myocardial function.

Point 1 is addressed in Chapter 3 which reports an evaluation of the degree of left ventricular impairment of a wide variety of patients with coronary artery disease on admission to an outpatient community-based cardiac rehabilitation programme. Their data for left ventricular function were compared to those of a group of individuals without known cardiovascular disease.

Point 2 is addressed throughout the different studies by using radionuclide ventriculography at rest and during exercise as the method for assessing systolic and diastolic left ventricular function in these patients.

Point 3 is addressed in Chapter 4 using a multiple regression analysis that includes non-cardiac as well as cardiac factors other than EF as possible predictors of the exercise capacity of these patients.

Point 4 is addressed in Chapters 4, 5 and 7. In Chapters 4 the physiological and cardiovascular responses to exercise training are compared between patients with various degrees of asymptomatic left ventricular dysfunction. In Chapter 5 the effects of exercise training on the exercise capacity, cardiovascular efficiency and left ventricular function of a group of patients with more severe left ventricular dysfunction is reported. In Chapter 7 the ventilatory responses to exercise are compared between patients with various degrees of left ventricular dysfunction.

Point 5, the effect of myocardial ischaemia on left ventricular function and adaptability to training, is addressed in Chapter 4 in which the adaptations to training of patients with left ventricular dysfunction and myocardial ischaemia are reported and more selectively in Chapter 6 in which a population with myocardial ischaemia documented by radionuclide imaging and normal left ventricular function was evaluated.

Point 6 is addressed in Chapter 8 by evaluating the effects of 6 and 18 months of exercise training on physiological variables and left ventricular function, categorizing patients according to compliance categories.

In sumary, this thesis will:

1) Establish the prevalence of systolic and diastolic LV function abnormalities in patients with coronary artery disease joining a cardiac rehabilitation programme;

2) Identify predictors of exercise capacity in the patients above and evaluate their adaptability to training by comparing the physiological adaptations between categories of LV impairment;

3) Evaluate the feasibility of exercise training in patients with severely depressed systolic LV function in South Africa, in terms of physiological adaptations and possible deleterious effects on LV function;

4) Investigate the effects of exercise training on LV function and maximal and submaximal exercise capacity in patients with myocardial ischaemia with or without LV dysfunction;

5) Study the mechanisms involved in the maintenance of cardiac output in patients with left ventricular dysfunction and/or myocardial ischaemia;

6) Assess the ventilatory responses to effort in patients with depressed LV function as well as the effects of exercise training on these responses;

7) Evaluate the effects of adherence to exercise training on the above adaptations.

Annexure 1.1 Levels of Cardiac Rehabilitation Requirements according to the World Health Organization Expert Committee (3).

In establishing a cardiac rehabilitation programme, the following needs should be considered (3):

- trained personnel
- physical facilities, equipment, and educational materials
- financial resources (within the context of the community and existing health care system)
- programme of exercise and patient education

These four elements are discussed below for each of the three possible levels of cardiac rehabilitation. The simplest level delivers cardiac rehabilitation at the local community level (basic facility). At the second level cardiac rehabilitation is developed within a local town or city hospital (intermediate facility). The third level is the establishment of a major cardiac rehabilitation centre (advanced facility).

A basic facility would be situated in a community and run by a part-time community health care worker trained in cardiac rehabilitation. The physical facility would require an exercise or walking area, with equipment limited to a sphygmomanometer and stethoscope, plus educational material. Low to moderate intensity exercise would be prescribed, requiring minimal or no supervision. This type of facility would be adequate for the provision of Phase III and IV services in a disadvantaged area, and could be run at a minimal cost.

An intermediate facility would be located within or close to a hospital where general medical services are available. The services of a doctor trained in cardiology, cardiac rehabilitation or exercise physiology, and of health professionals trained in exercise prescription, monitoring and patient education would be required. The personnel would usually work part-time and have other responsibilities within the hospital. Facilities required would be an office, an area for exercise testing, an area for exercise classes and monitoring and an area for group discussions. Equipment would consist of an electrocardiograph and monitor, a bicycle ergometer or treadmill, and aerobic, resistance training and resuscitation equipment. The exercise programme would include

low to moderate intensity exercise under supervision. Muscle strengthening would also be encouraged according to patients' specific requirements. Basic information and long-term compliance support would be provided. A small budget would cover the costs of equipment and consumables as well as the health professionals' time. This type of facility would be adequate for the provision of Phase I and II services.

An advanced facility would be situated in a major city and have a cardiovascular disease referral system. Such a centre could be developed in a university teaching hospital or a private institution. Personnel would consist of a multidisciplinary team, including a medical director with experience in cardiac rehabilitation; nursing sisters; exercise specialists, such as physiotherapists or biokineticists; a dietician; a psychologist; and an occupational therapist or social worker. . The physical facilities would be similar to, but more extensive than, the intermediate centre. Doctors' consulting rooms would be required in addition to the administration office.

Desirable equipment includes exercise testing equipment with treadmill or bicycle ergometer, 12 lead electrocardiograph and monitor; optional metabolic cart for gas exchange measurements; exercise training equipment such as treadmills, bicycle ergometers, combined arm and leg ergometers, circuit weight stations and free-standing weights; monitoring equipment such as blood pressure sets, time-clocks, telemetry and Holter. Resuscitation equipment, including oxygen, defibrillator and drugs would be on site. If the facility is located within a hospital it would be ideal for the provision of Phase I, II and III services, while if it is located within a community it would be more suitable for the provision of Phase III and IV services.

Supervised moderate to high intensity exercise would be prescribed, and a more complete educational programme would be delivered in keeping with the greater expertise available. Advanced facilities have other important responsibilities, such as teaching and training, and should have sufficient expertise to undertake research and evaluation of the effects of rehabilitation programmes.

Annexure 1.2 Summary Of Evidence For Cardiac Rehabilitation Outcomes: Effects Of Exercise Training (ET) and Education, Counselling And Behavioral Interventions (E,C & BI).

	STUDIES (ET / E,C & BI)				
OUTCOME	**NUMBER**	**RANDOMIZED**	**NON RANDOMIZED**	**OBSERVATIONAL**	**STRENGTH OF EVIDENCE**
Exercise tolerance	114 / 3	46 / 1	25 / 1	43 / 1	A / C
Exercise tolerance (strength training)	7	4	3	0	B
Exercise habits	15	10	2	3	B
Symptoms	26 / 4	12 / 2	7 / 1	7 / 1	B / B
Smoking	24 / 7	12 / 5	8 / 1	4 / 1	B / B
Lipids	37 / 18	18 / 12	6 / 3	13 / 3	B / B
Body weight	34 / 5	11 / 3	7 / 1	16 / 1	C / B
Blood pressure	18 / 2	9 / 0	6 / 2	3 / 0	B / B
Psychosocial Wellbeing	20 / 14	9 / 6	8 / 6	3 / 2	B / A
Social adjustment and functioning	6	2	2	2	B
Return to work	28 / 3	10 / 2	9 / 0	9 / 1	A / C
Morbidity	42 / 3+2	15 / 3	14 / 0	13 / 0	A / B
Mortality	30 / 8+2	16 / 8	8 / 0	6 / 0	B

Annexure 1.2 (Cont.) Effects of Exercise Training.

	STUDIES				
OUTCOME	**NUMBER**	**RANDOMIZED**	**NON RANDOMIZED**	**OBSERVATIONAL**	**STRENGTH OF EVIDENCE**
Changes in atherosclerosis	9	5	1	3	A - B
Changes in haemodynamic measurements	5	0	0	5	B
Changes in myocardial perfusion/ myocardial ischaemia	11	6	2	3	B
Changes in myocardial contractility, ventricular wall motion abnormalities, and/or ventricular ejection fraction	22	9	5	8	B
Changes in cardiac arrhythmias	5	4	0	1	B
Heart Failure patients	12	5	3	4	A
Cardiac transplantation patients	5	0	1	4	B
Elderly patients	7	0	1	4	B

Annexure 1.3 Risk of cardiovascular complications during the exercise Training of cardiac patients.

	HASKELL et al. (10)	VAN CAMP et al. (11)
Years of study	1960 -1977	1980 - 1984
Number of programmes	30	167
Number of patients	13 750	51 303
Number of patient-hours of training (p/h)	1 629 634	2 361 916
Cardiac arrests (Number (p/h))	50 (1 / 32 593)	21 (1 / 111 996)
Successful resuscitations (Number (%))	42 (84)%	18 (86)
Myocardial infarctions (Number (p/h))	7 (1 / 232 805)	8 (1 / 293 990)
Mortality (Number (h/p))	14 (1 / 116 402)	3 (1 / 783 972)
Number and Type of Complications	8 - cardiac arrests 2 - myocardial infarctions 2 - pulmonary embolisms 1 - pulmonary oedema 1 - cardiogenic shock	3 - cardiac arrests

Annexure 1.4 GUIDELINES FOR RISK STRATIFICATION (73)

Low Risk

1. No significant left ventricular dysrfunction (ie. Ejection fraction $\geq$ 50%)
2. No resting or exercise-induced myocardial ischaemia manifested as angina and/or ST-segment displacement
3. No resting or exercise-induced complex arrhythmias
4. Uncomplicated myocardial infarction, coronary artery bypass surgery, angioplasty, or arthrectomy
5. Functional capacity $\geq$ 6 METs on graded exercise test 3 or more weeks after clinical event

Moderate Risk

1. Mild to moderately depressed left ventricular function (Ejection fraction 31%-49%)
2. Functional capacity < 5-6 METs on graded exercise test 3 or more weeks after clinical event
3. Failure to comply with exercise intensity prescription
4. Exercise-induced myocardial ischaemia (1-2 mm ST-segment depression) or reversible ischaemic defects (echocardiographic or nuclear cardiology)

High Risk

1. Severely depressed left ventricular function (Ejection fraction $\leq$ 30%)
2. Complex ventricular arrhythmias at rest or appearing or increasing with exercise
3. Decrease in systolic blood pressure of > 15 mm Hg during exercise or failure to rise with increasing workloads
4. Survivor of sudden cardiac death
5. Myocardial infarction complicated by congestive heart failure, cardiogenic shock, and/or complex ventricular arrhythmias
6. Severe coronary artery disease and marked exercise-induced myocardial ischaemia (>2 mm ST-segment depression)

CHAPTER 2

MATERIAL AND METHODS

2.1 Patient population

Of patients admitted to the Johannesburg Cardiac Rehabilitation Centre, only patients with CAD were selected, thus excluding patients with other forms of heart disease or who were at risk for its development. Because of methodological problems during radionuclide ventriculography determinations, patients with CAD and atrial fibrillation or significant ventricular arrhythmias, or both were also excluded from our studies. Patients with handicaps unable to walk on a treadmill were also excluded.

The subjects were admitted 12 weeks after myocardial infarction (MI) or coronary artery bypass surgery (CABG) and 4 weeks after percutaneous transluminal coronary angioplasty (PTCA) in order to reduce the effect of spontaneous recovery in the measures of left ventricular dysfunction.

Several cohorts of patients were studied in chronological order between 1989 and 1993 on the basis of the subjects' consent and availability to the performance of radionuclide ventriculography and radionuclide myocardial imaging studies (Annexure 2.1):

1- Cohort 1 included 171 patients with CAD consecutively referred to the Johannesburg Cardiac Rehabilitation Center who had their left ventricular function measured at rest on admission. These patients were enrolled into the studies described in Chapters 4 and 7.

2- Cohort 2 included 118 consecutive patients with CAD who had their left ventricular function assessed at rest and during exercise, on admission and after 6 months of exercise training. Some of these patients also belonged to cohort 1. These patients were enrolled into the studies described in Chapters 3 and 8. Forty patients from this cohort had also left ventricular function studies at rest and during exercise after 6 months of exercise training.

3- Cohort 3 included 28 consecutive patients recovering from an acute MI and with a LVEF of 30% or less. Some of these patients were also part of cohort 1. The results of this study are reported in Chapter 5.

4- Cohort 4 included 22 patients with planar or downsloping ST segment depression $\geq$ 1mm during exercise testing who underwent radionuclide imaging studies. Some of these patients were also part of cohorts 1 and 2. These patients were enrolled into the study reported in Chapter 6.

Two control groups were used (Annexure 2.2):

1- Thirty one volunteers without any history, signs or symptoms of cardiac disease and with normal results for an exercise test, were prospectively evaluated and selected as a control group for the measures of left ventricular function for the studies in Chapters 3, 4 and 7.

2- Fifty consecutive patients with CAD without signs and/or symptoms of myocardial ischaemia during exercise testing were selected as a control group for cohort 4 which consisted of patients with demonstrable myocardial ischaemia during exercise testing and radionuclide perfusion imaging. This group was used as a control group in Chapter 6 only.

All studies were approved by the Ethics Committee of the Johannesburg City Council's City Health Department and by the Research and Ethics Committee of the Faculty of Medicine of the University of Cape Town Medical School. Informed consent was obtained from all participants.

The characteristics of patients and controls are described in the individual studies.

2.2 Medical assessment of patients admitted at the Johannesburg Cardiac Rehabilitation Centre

2.2.1 Introduction

Patients were fully assessed on admission to the programme, and again after 6 and 18 months and at regular intervals thereafter. The assessment includes a full medical history and examination, full fasting lipogram, anthropometric evaluation (height and weight, skinfolds, body pletismography), lung function test, resting ECG, stress ECG including expiratory gas analysis, and a dietary and psychological profile. Patients are subsequently stratified according to risk and exercise is individually prescribed.

2.2.2 Exercise testing at the Johannesburg Cardiac Rehabilitation Centre

A full cardiopulmonary exercise test with expiratory gas analysis is performed at the Centre. In spite of being considered a safe procedure (18), the exercise test is always performed under the supervision of a doctor appropriately trained to conduct these tests and emergency equipment is always available. The author has personally supervised the majority of tests whose data has been used for the different studies. Patients are instructed not to eat for 3 hours prior to the test and to dress appropriately for exercise. A thorough physical examination is performed in all and contraindications for exercise testing (18) are ruled out. Patients are tested while taking their usual medications. They have the testing procedure explained to them and a demonstration of treadmill walking is performed. The areas for electrode placement are shaved and rubbed with alcohol-saturated gauze in order to lower the resistance of the skin, reducing the signal-to-noise ratio. Silver plate electrodes are used. A standard 12 lead ECG with the limb electrodes placed on wrists and ankles is performed at rest in the supine position and a Mason-Likar placement is used during exercise testing bringing the wrist and ankle electrodes to the base of the limbs (173).

The Chung protocol has been adopted for the testing of cardiac patients admitted to the Johannesburg Cardiac Rehabilitation Centre (27). Its reproducibility has been validated against the Bruce protocol in a previous report (205) and its metabolic requirements have been described in Chapter 1.

The exercise test was performed on a motorized treadmill according to the Chung protocol. Leads SII, V2 and V5 are continuously recorded during exercise and blood pressure was continuously monitored at each stage of the exercise test and during the recovery phase.

Expired air was analysed throughout exercise using a metabolic cart (EOS-Sprint, Erich JAEGER GmbH&CoKG, Wurzburg, Federal Republic of Germany). Metabolic, ventilatory and haemodynamic variables were determined at rest, at submaximal (6 minutes on the treadmill according to the Chung protocol) and maximal levels. As previously discussed in Chapter 1, peak oxygen uptake rather than VO_2 max was determined.

The ventilatory threshold, expressed as absolute oxygen uptake, is defined as the first deviation in linearity of the ventilation plotted against the oxygen consumption. The limitations of this visually-determined technique are appreciated (206); these are less important in a longitudinal training study in which subjects act as their own controls. The accuracy in determining the ventilatory threshold as the point at which there is a non-linear increase in minute ventilation has been questioned by some due to a large inter observer variability (207). Others have reported that intraobserver and interobserver variation were very small for visual inspection in normal subjects and cardiac patients (208). This is in agreement with our experience (unpublished results) that the ventilatory threshold can be determined accurately from gas exchange variables.

The ventilatory threshold was determined by the physician supervising the test, who had experience in performing such determinations. The author was the physician during most

tests. The graph relating minute volume to peak VO_2 was printed and the value obtained for ventilatory threshold was checked again by the physiotherapist or biokineticist responsible for the exercise prescription of the patient. In the very few occasions when there was a discrepancy between observers the graph was plotted again on computer and the point re-evaluated by a third person. Physicians were generally blinded to whether the patient was a compliant or a not-compliant, however knew when the test was a pre or a post-test.

The end-points for fatigue during maximal exercise were one or more of the following: physical exhaustion, development of marked angina pectoris, ST segment depression of more than 3mm, sustained ventricular tachyarrhythmias or a drop in systolic blood pressure of more than 10 mm Hg. The test was considered positive for ischaemia if 1mm horizontal or downsloping ST segment depression, persisting 80 msec after the J point, was observed (173). The limitations of ST segment analysis alone in predicting ischaemia are appreciated. The sensitivity of the method was enhanced by including in the model the ST segment time course in the post-effort period. The sensitivity of the exercise test in detecting myocardial ischaemia was further increased in selected patients by the addition of myocardial perfusion imaging.

2.2.3 Resting and exercise myocardial perfusion imaging: method used in this study

Myocardial perfusion imaging with Tc-99m sestamibi (Tc-MIBI) superceded the use of Thallium-201 in Johannesburg and was the method of choice.

Myocardial perfusion studies were performed first at rest and then during exercise according to the protocol set by the Department of Nuclear Medicine of the Johannesburg Hospital, University of the Witwatersrand. Twenty to 30 mCi of Tc-MIBI per average 70 kg patients were injected in an antecubital vein at rest, after four hours of fasting. Imaging was started not earlier than one hour from the time of the injection. On a separate day patients underwent

symptom-limited exercise testing and at peak exercise, 10 to 30 mCi of Tc-MIBI were injected intravenously. After the injection the patient was encouraged to exercise for another 30 to 45 seconds. Imaging began not earlier than half an hour from the time of the injection and 15 minutes after patients had taken a fatty drink. Data were acquired at rest and post-exercise both by ECG gated planar and SPECT methods on an Anger scintillation camera. The author personally conducted all exercise tests for this study and injected the radiotracer in the patients' veins.

2.2.4 Method used in this study for the assessment of left ventricular function

2.2.4.1 Introduction

At the time the study was initiated, resting and exercise radionuclide techniques were fully developed in Johannesburg while stress echocardiography was not yet perfected so that very few technicians were fully trained in its use. Furthermore the interpretation of the results is a very subjective exercise.

It was therefore concluded that radionuclide ventriculography should be selected as the method of evaluation of left ventricular function and that the equilibrium method should be the method of choice because of its advantages over the first transit method. It was felt that this method could provide an excellent noninvasive means of serially assessing the effects of a cardiac rehabilitation programme on left ventricular systolic and diastolic function.

2.2.4.2 Resting radionuclide ventriculography

Radionuclide ventriculography, using the equilibrium multi-gated blood pool technique (44) was performed at rest in all patients (Department of Nuclear Medicine of the Johannesburg Hospital, University of the Witwatersrand). Red blood cells were labelled in vivo by

injecting unlabelled stannous pyrophosphate in an antecubital vein, followed by injection of 15 to 25 mCi of Technetium 99m 15 to 20 minutes later. A mobile scintillation camera (Elscint Apex 409M, Haifa, Israel) equipped with a low energy, medium resolution and medium sensitivity collimator (Elscint APC 3) was used to determine the number of counts during each phase of the cardiac cycle. Cardiac images were acquired in a modified left anterior oblique position to allow for good separation between right and left ventricles. Acquisitions were gated to the R wave of the ECG and collected at 24 frames per cardiac cycle. The left ventricular region of interest in each frame was identified using a second derivative technique and time-activity curves were generated from these regions.

2.2.4.3 Exercise radionuclide ventriculography

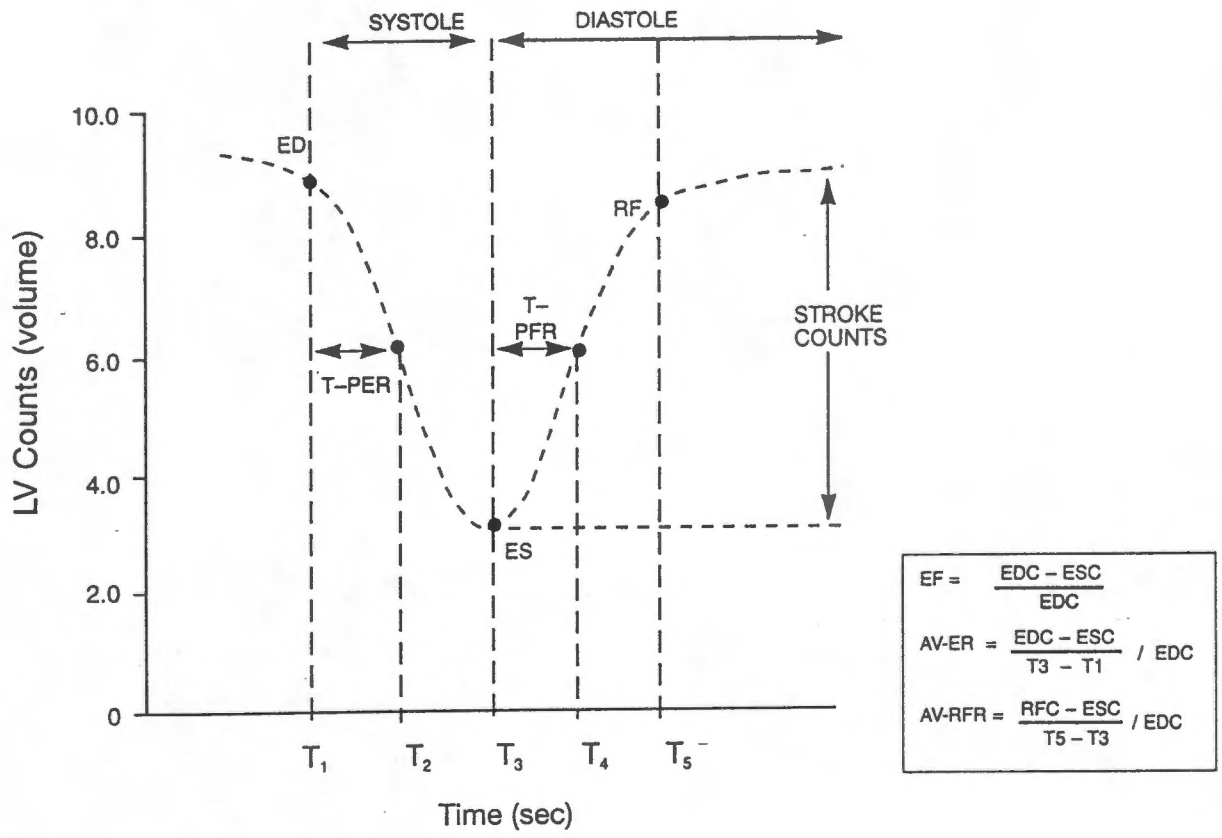
After a radionuclide ventriculogram performed at rest, selected patients were exercised in the supine position on a Quinton 845T bicycle ergometer table. They were instructed to minimize upper body motion whilst under the camera and a Technetium marker was placed on the chest during exercise to detect excessive movement. The exercise protocol began at a work rate of 200 kg.m/min. Patients were asked to pedal in the range of 50 to 70 rpm. Exercise work rates were increased by 100 kg.m/min every minute until 85% of the patient's maximal heart rate obtained on the symptom limited exercise test, had been reached. Patients then exercised for 3 minutes at that work rate. The test was stopped prematurely if any of the other end-points, previously described, were also reached. Radionuclide scanning was performed in the last 3 minutes of exercise and during the early (0 to 5 minutes) and late (5 to 10 minutes) post-exercise periods. The author personally conducted all exercise radionuclide ventriculography studies at the Johannesburg Hospital with the help of a technician.

Indices of systolic and diastolic left ventricular function were derived from the time-activity curves (Fig 2.1): end-diastolic counts (EDC), end-systolic counts (ESC), stroke counts (SC), EF, time to peak ejection rate (T-PER), peak ejection rate (PER), average

ejection rate (AV-ER), time to peak filling rate (T-PFR), peak filling rate (PFR) and average rapid filling rate (AV-RFR) (46). Ejection fraction was calculated according to the formula: EDC - ESC / EDC after substraction for background activity. Average ejection rate was calculated after substraction of background activity by dividing the stroke volume (EDC - ESC) by the ejection time (T3 - T1), and normalizing for EDC. Average rapid filling rate was calculated after substraction of background activity by dividing the rapid filling volume (RFC - ESC) by the rapid filling time (T5 - T3) and normalizing for EDC.

Radionuclide measurements using the gated equilibrium approach rely on the well established proportionality between ventricular counts and volume. As previously reported in Chapter 1, Borer and co-workers (44) demonstrated the feasibility of radionuclide determination of ejection fraction during supine bicycle exercise using the equilibrium technique and Sorensen and co-workers (64) validated the use of count-derived changes in cardiac output as accurately reflecting true haemodynamic changes determined by the Fick technique. Count-volume relationships are linear for a given subject but discordant when comparisons are made between subjects because of inter-individual differences in attenuation, scatter, radioisotope dosage and timing of study. Furthermore counts are a relative rather than an absolute manifestation of volume changes. Therefore, because of these reasons, comparison of radionuclide data using counts is best made using percentage changes from baseline (64). We evaluated the change from rest to exercise by the use of the percentage change from rest to exercise, calculated as the value during exercise minus the value at rest divided by the value at rest x 100. A computer algorhythm reduced inter and intraobserver variability, but to minimize this factor even more, all studies were processed by one observer.

Figure 2.1 Schematic left ventricular time-activity curve



ED = end-diastolic counts measured at time T1; ES = end-systolic counts measured at time T3 and RF = rapid filling counts measured at time T5.

T3 – T1 defines the ejection period and T5 – T3 the rapid filling period.
T2 = time at which peak ejection rate occurs; T4: time at which peak filling rate occurs

2.3 Exercise prescription and exercise training at the Johannesburg Cardiac Rehabilitation Centre

After the initial assessment, all patients underwent a 6 month medically supervised programme of aerobic exercise and attended weekly discussion sessions about lifestyle modification. Some of these patients continued exercising at the centre for 18 months. The exercise prescription and monitoring of patients was controlled by a physiotherapist or a biokineticist with the help of other members of the health care team.

The intensity of exercise was set using the heart rate achieved at the ventilatory threshold identified in the initial exercise test. Typically this occurred at 70-85% of the maximal heart rate. Patients were required to exercise at their prescribed heart rates three times per week continuously for 30-45 minutes.

Exercise sessions consisted of a warm-up period, aerobic exercise and a cool-down period.

Prescribed activities were aerobic and emphasized walking, walking-jogging and cycling. Stationary cycling was prescribed for high risk patients or in those for whom weight-bearing exercise was contraindicated. The exercise intensity for each patient was progressed gradually over a number of weeks until the required intensity of exercise was achieved (Table 2.1). Patients were given a training heart rate and the speed and distance which they had to walk or walk/jog. For instance, starting with 2 km of walking at a pace aimed at 10 minutes per km, the distance was increased to 3.5 km after 2 weeks and to 5 km after a further 2 weeks. Once up to 5 km, the pace was increased by means of a faster walking speed or the addition of brief periods of jogging. Depending on their conditions, patients on the bicycle ergometer were asked to cycle between 5 and 15 minutes at their prescribed load calculated using the formula described in the previous Chapter. They were progressed by 1 minute per session until they were able to cycle for 30 minutes. Further increases in load were achieved via 5 watt increments every week until they reached an appropriate level. Patients were not allowed to exceed 85% of their maximal heart rates.

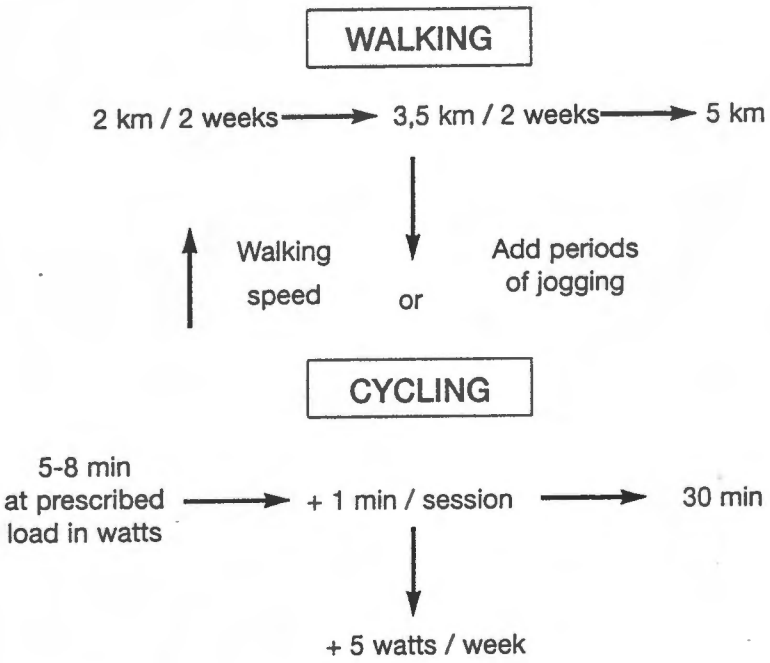
Patients were carefully monitored by the staff during their exercise sessions. The patients' compliance with the programme was monitored on a daily basis in terms of attendance at exercise sessions and the intensity of their training programmes. The day they attended as well as their maximal heart rate, wattage on the bicycle ergometer or distance walked or walked/jogged and duration of the effort were all recorded by the patients on a log card (Table 2.2). The information on the log card was captured on a computer. Reasons for dropout were obtained telephonically. Unless stated otherwise, compliance was monitored to ensure that subjects completed at least 60% of the exercise sessions during the 6-month period. We (209) and others (24) have previously found that a compliance of 60% or higher provides an adequate stimulus for a training effect in patients with cardiac diagnoses and in healthy subjects.

The exercise protocol was the same for patients with or without left ventricular dysfunction and/or myocardial ischaemia. Patients developing ST segment depression during exercise testing had their intensity set 10 to 15 beats per minute below the ischaemic threshold as previously described.

Our protocol for conditioning differs from a number which have been used by others in that the conditioning period was of 6 or 18 months rather than the usual 3 or 4 months. This is an important consideration because the cardiovascular effects of training in any subject are related to the intensity of the programme and its duration. Because patients with coronary disease are very deconditioned and have to be advanced slowly, the duration of a conditioning programme is an important factor in determining the cardiovascular response. In the design of a study to test the effects of exercise conditioning, it is important to allow time for the patient to achieve a near maximal benefit from training, and this is a matter of months or even a year in subjects with coronary artery disease.

Although resistance training activities were started in 1992 for selected patients, patients enrolled in this study participated only in aerobic activities.

Table 2.1 Progression of exercise



WALKING PRESCRIPTION: Patients started by walking 2 km at a prescribed speed. Progression was achieved by increasing distance after 2 weeks to 3.5 km and after a further 2 weeks to 5 km. Further progression took the form of an increase in the speed of walking or by the addition of brief periods of jogging.

CYCLING PRESCRIPTION: Patients started by cycling 5 to 8 minutes, depending on their physical status, at a load determined by the formula: Watts = (VO_2 ml / min – (5.8 x Weight in kg) – 151)/10.5. Duration was progressed one minute per session until they reached 30 minutes. Further increases in load were achieved by increasing 5 Watts per week until an appropriate exercise intensity was reached.

Table 2.2 Johannesburg Cardiac Rehabilitation Centre's log card

Johannesburg Cardiac Rehabilitation Unit																								
NAME				NUMBER						EXERCISE PRESCRIPTION														
TEL. NO.				CODE																				
D.O.B. AGE				PROGRAMME																				
STRESS TEST DUE				THR																				
DIAGNOSIS				B BLOCKER																				
DATE																								
B.P.																								
WEIGHT																								
RESTING H.R.																								
WARM-UP H.R.																								
WALK – JOG																								
TIME																								
DISTANCE																								
MAX H.R.																								
RPE																								
CYCLE AND/OR ROW (ADD TIMES FOR THESE ACTIVITIES TOGETHER)																								
TIME																								
LOAD (WATTS)																								
MAX H.R.																								
RPE																								
COOL-DOWN H.R.																								

2.4 Statistical methods

All the studies were done prospectively. Except for the study described in Chapter 3 which was an observational cross-sectional study, all other studies were experimental and tested the intervention exercise training on different variables.

The study lacks a control study of patients not undergoing exercise training because, based on our knowledge at the time the study was conceptualized, it would have been unethical not to accept a patient for cardiac rehabilitation.

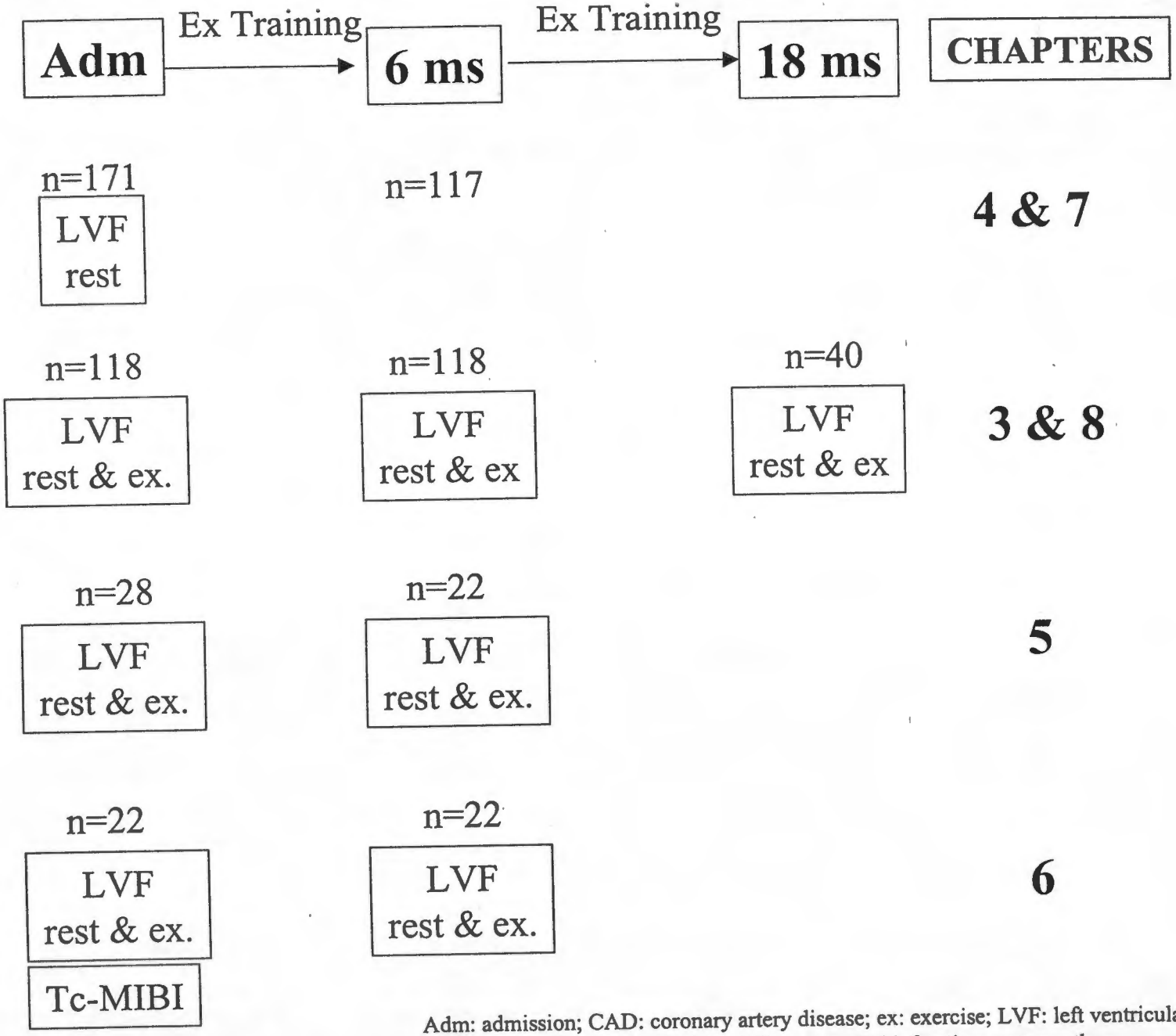
One major source of bias is the selection of the patient population. Only a small percentage of the population suffering from coronary artery disease in Johannesburg is actually referred to the Centre for cardiac rehabilitation. The referral pattern reflects the doctor's perception that a particular patient could benefit more from cardiac rehabilitation than another. Subjects were included into the studies not only on the basis of their personal consent, but also their doctor's consent and their availability for radionuclide studies.

Another source of bias is the fact that those who adhered better to the programme may represent a subgroup of the self-selected small group of patients who join exercise programmes and who are perhaps more committed to long term lifestyle changes.

The statistical tests performed are described in detail within each study for better understanding and in order to avoid duplications.

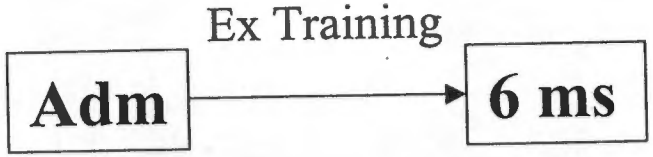
The studies will be presented in a logical order and not necessarily in the chronological order in which they were originally performed.

Annexure 2.1
Patient cohorts & Design



Adm: admission; CAD: coronary artery disease; ex: exercise; LVF: left ventricular function; LVEF: ejection fraction;MI: myocardial infarction; ms: months.

Annexure 2.2 Control Groups



CHAPTERS

Healthy Controls	n=31 LVF rest & ex.		*Control group for measures of LVF only*	**3, 4 & 7**
CAD Controls without ischaemia	n=50	n=50	*Control group for exercise training only*	**6**

Adm: admission; CAD: coronary artery disease; ex: exercise; LVF: left ventricular; function; ms: months.

CHAPTER 3

DIFFERENCES IN LEFT VENTRICULAR FUNCTION BETWEEN PATIENTS WITH CORONARY ARTERY DISEASE AT ENTRY TO A CARDIAC REHABILITATION PROGRAMME, AND NORMAL SUBJECTS

3.1 Introduction

Since patients with more severe degrees of heart disease are presently being accepted to current cardiac rehabilitation programmes, it would be expected that these patients would have various degrees of systolic and/or diastolic left ventricular dysfunction. However, little information is available on the range of left ventricular impairments in patients at entry to a community-based cardiac rehabilitation programme. Most of the available data describing the left ventricular function of cardiac patients comes from measurements obtained at rest, in hospital, at the time of the acute event. Most measurements evaluated only systolic function and had little value in predicting the patient's status during an exercise training programme which commenced some time later when some degree of left ventricular functional recovery might have been expected.

Radionuclide ventriculography has proved to be an effective tool in the noninvasive evaluation of systolic and diastolic left ventricular function at rest and during exercise in both patients with coronary artery disease and in normal subjects (44,210,211). Since the hemodynamic adaptations to exercise could be masked by an increase in heart rate during exercise, the evaluation of left ventricular function in the recovery period as heart rate decreases could provide additional insight into the mechanisms by which the healthy and diseased hearts adapt to exercise (211-213).

The aim of this study was therefore to evaluate the systolic and diastolic left ventricular function of patients with coronary artery disease at entry to a Phase III cardiac rehabilitation program, at rest, during exercise in the supine position and after exercise. We wished to compare cardiac function in that group to that of a group of normal subjects without known heart disease to test the hypothesis that patients admitted for cardiac rehabilitation at present have a high incidence of left ventricular abnormalities.

3.2 Methods

One hundred and eighteen patients, 110 males and 8 females with documented coronary artery disease consecutively referred to the Johannesburg Cardiac Rehabilitation Center were included in this study. Fifty four patients were post-myocardial infarction, 36 post-coronary artery bypass surgery, 19 post-percutaneous transluminal coronary angioplasty and 9 had chronic stable angina. The infarct was located in the anterior wall in 51% and in the inferior wall in 49%.

In addition 31 men matched for age, without any history, signs or symptoms of cardiac disease and with normal results for an exercise test, were selected as a control group for the measures of left ventricular function. Their coronary risk profile was as follows: none of the subjects were smokers; none had a history or were on treatment for a high cholesterol; two subjects suffered from hypertension and were on treatment for it: one was on enalapril and the other on amlodipine; none of the subjects had diabetes; eleven subjects exercised regularly at least 3 times per week, including those who were hypertensives; all had a Broca index within normal limits; 5 had a family history of coronary artery disease.

The age of the patient group ranged from 36 to 85 years with a mean of 63 $\pm$ 7.5 years, and that of the control group from 42 to 64 years with a mean of 52 $\pm$ 8.1 years ($p=0.001$). Eighty percent of patients were of Caucasian origin, 19% Asian and 1% African. Subjects in the control group were all of Caucasian origin. Twenty five % of patients were on angiotensin converting enzyme inhibitors, 26% on beta-blockers, 32% on calcium channel blockers, 18% on nitrates, 13 % on diuretics, 1% on digitalis and 87% on aspirin.

All patients underwent a treadmill symptom-limited exercise test according to the Chung protocol before being accepted onto the exercise cardiac rehabilitation program. The test was considered positive for ischaemia in 9 patients who showed 1 mm or more horizontal or

downsloping ST depression, 80 milliseconds after the J point. Seven patients showed an upward ST segment displacement in the area of previous infarction.

Radionuclide ventriculography, using the equilibrium multi-gated blood pool technique (44) was performed at rest in all patients and controls and during exercise in the supine position in 93 patients and all controls. Radionuclide scanning was performed at rest, during the last 3 minutes of exercise and during the early (0 to 5 minutes) and late (5 to 10 minutes) post-effort periods. As previously described in the Methods section, we derived the following indices from time activity curves: EDC, ESC, SC, EF, T-PER, PER, AV-ER, T-PFR, PFR and AV-RFR. We evaluated the change from rest to exercise by the use of the percentage change from rest to exercise, calculated as the value during exercise minus the value at rest divided by the value at rest x 100. A computer algorithm reduced inter and intraobserver variability, but to minimize this factor even more, all studies were processed by one observer.

Statistical analysis

The entire cohort of patients studied was divided into 3 groups for additional analysis so that, in total, four population groups were evaluated: Group 0 (G0) included all 118 patients irrespective of their left ventricular systolic function; Group 1 (G1) included 73 patients with normal left ventricular systolic function (EF≥50%); Group 2 (G2) included 27 patients with moderately depressed systolic function (EF≥35 and <50%) and Group 3 (G3) included 18 patients with severely depressed systolic function (EF<35%).

Patients and normal subjects were compared with respect to their systolic and diastolic left ventricular function at rest and during exercise.

A mixed model ANOVA and Fisher's LSD tests were used to assess the significance of the differences between groups. Significance at the 5% level or lower is reported.

3.3 Results

Significant differences in left ventricular hemodynamics and systolic and diastolic function were seen between patients and controls.

3.3.1 In all patients with coronary artery disease irrespective of degree of left ventricular dysfunction

3.3.1.1 At rest. (Table 3.1)

There was no difference in heart rate between patients and controls. ESC were significantly increased in the patients (p=0.019) and SC significantly decreased (p=0.0006), while there were no differences in EDC between the two groups. EF, PER, AV-ER, PFR and AV-RFR were significantly reduced in patients compared to controls (p=0.0004, p=0.006, p=0.0004, p=0.023 and p=0.0001 respectively).

3.3.1.2 During exercise. (Table 3.1)

Heart rate increased significantly during exercise in patients and controls but the percentage increase was significantly higher in the control group (98.7% vs 62.7%, p=0.0001). EDC and ESC were significantly increased during exercise in the control group, without significant changes in SC; while in the patients group, only ESC increased significantly during exercise. There were no significant differences in the volume changes from rest to exercise between both groups. EF was significantly reduced in patients during exercise while it did not change in the control group. The percentage change in EF from rest to exercise was not significantly different between the groups. T-PER was significantly shortened in both groups, the change being of a similar magnitude. PER, AV-ER, PFR and AV-RFR were significantly increased during exercise in both groups, while

T-PFR was significantly reduced during exercise only in the control group. PER, AV-ER, and PFR increased significantly more in controls than in patients ($p=0.0001$, $p=0.007$ and $p=0.003$ respectively).

Table 3.1 Differences in resting and exercise left ventricular function between patients with coronary artery disease and healthy individuals without known cardiac disease.

	CAD			CONTROL			CONTROL vs CAD p VALUE
VARIABLES	Rest n=118	Exercise n=93 *	Δ R-E n=93	Rest n=31	Exercise n=31 *	Δ R-E n=31	Rest Exercise Δ R-E
HEART RATE (bpm)	66.1 (1.2)	104.7 (1.7) p=0.0001	-62.7 (3.2)	62.4 (2.4)	121.9 (2.5) p=0.0001	-98.7 (5.5)	NS 0.00001 0.0001
EDC	496969 (16840)	507217 (31203) p=NS	-4.5 (5.5)	454895 (32856)	541477 (52420) p=0.034	-20.4 (9.5)	NS NS NS
ESC	263663 (16049)	303999 (26179) p=0.002	-21.6 (6.8)	180400 (31312)	244226 (26493) p=0.001	-40.9 (11.8)	0.019 NS NS
SC	233305 (5320)	203218 (13475) p=NS	10.0 (5.9)	274494 (10379)	297251 (30211) p=NS	-10.0 (10.2)	0.0006 0.002 NS
EF %	51.2 (1.2)	45.6 (1.6) p=0.0001	10.0 (2.0)	61.1 (2.4)	58.4 (1.6) p=NS	3.8 (3.4)	0.0004 0.0001 NS
T-PER (sec)	0.15 (0.00)	0.08 (0.00) p=0.0001	46.1 (2.6)	0.15 (0.00)	0.07 (0.00) p=0.0001	50.1 (4.5)	NS NS NS
PER (EDV/sec)	2.44 (0.07)	3.43 (0.12) p=0.0001	-44.5 (4.1)	2.86 (0.13)	5.00 (0.21) p=0.0001	-77.4 (7.2)	0.006 0.00001 0.0001
AV-ER (EDV/sec)	1.53 (0.04)	1.73 (0.08) p=0.0001	-14.6 (4.2)	1.86 (0.08)	2.53 (0.11) p=0.0001	-37.8 (7.3)	0.0004 0.00001 0.007
T-PFR (sec)	0.18 (0.01)	0.13 (0.01) p=0.0001	20.3 (5.1)	0.16 (0.01)	0.10 (0.01) p=0.0001	37.2 (8.8)	NS 0.0008 NS
PFR (EDV/sec)	2.04 (0.07)	4.05 (0.17) p=0.0001	-116.7 (8.4)	2.39 (0.13)	6.27 (0.28) p=0.0001	-167.3 (14.6)	0.023 0.00001 0.003
AV-RFR (EDV/sec)	1.37 (0.05)	2.80 (0.13) p=0.0001	-124.9 (10.9)	1.81 (0.09)	4.46 (0.27) p=0.0001	-157.7 (18.8)	0.0001 0.00001 NS

Values are expressed as Mean (Standard Error). * p values: rest vs exercise.Δ R-E: % change from rest to exercise; AV-ER: average ejection rate; AV-RFR: average rapid filling rate; CAD: coronary artery disease; EDC: end-diastolic counts; EDV/sec: end-diastolic volumes per second; EF: ejection fraction; ESC: end-systolic counts; PER: peak ejection rate; PFR: peak filling rate; SC: stroke counts; T-PER: time to peak ejection rate; T-PFR: time to peak filling rate.

3.3.1.3 Post-effort. (Tables 3.2 and 3.3)

Heart rate was still significantly increased compared to the resting period in both groups, being higher in the control group for both post-effort periods ($p=0.001$ and $p=0.0001$, respectively). There was a significant increase in EDC and SC which was greater in controls than in patients (Post-Effort 1: $p=0.04$ and $p=0.041$ respectively; Post-Effort 2: $p=0.023$ and $p=0.028$ respectively) . ESC were lower than during exercise in both groups. A greater increase in SC than EDC led to a significant and similar increase in EF in both groups. Similarly, PER and AV-ER were significantly higher post-effort than during exercise and rest, the magnitude of the change in PER being greater for the control group in the immediate post-effort period ($p=0.004$). PFR and AV-RFR although higher than at rest, were lower than during exercise in both groups.

Table 3.2 Differences in left ventricular function at rest and post-effort between patients with coronary artery disease and healthy individuals without known cardiac disease.

	CAD			CONTROL			CAD vs CONTROL p value	
VARIABLES	Rest n=118	Post-E1 n=93 *	Post-E2 n=93 *	Rest n=31	Post-E1 n=31 *	Post-E2 n=31 *	Post-E1	Post-E2
HEART RATE (bpm)	66.1 (1.2)	103.1 (1.9) p=0.0001	83.7 (92.4) p=0.0001	62.4 (2.4)	112.8 (3.2) p=0.0001	92.4 (2.5) p=0.0001	0.01	0.003
EDC	496969 (16840)	611242 (32981) p=0.0001	508153 (25891) p=NS	454895 (32856)	666223 (57124) p=0.0001	551219 (44845) p=0.002	NS	NS
ESC	263663 (16049)	297929 (25886) p=0.023	253393 (20329) p=NS	180400 (31312)	210477 (44836) p=0.048	180772 (35211) p=NS	NS	NS
SC	233305 (5320)	313312 (14658) p=0.0001	254761 (11953) p=0.006	274494 (10379)	455746 (25388) p=0.0001	370447 (20703) p=0.0001	0.0001	0.0001
EF %	51.2 (1.2)	56.5 (1.4) p=0.0001	54.6 (1.5) p=0.0001	61.1 (2.4)	70.1 (2.5) p=0.0001	67.3 (2.5) p=0.0001	0.0001	0.0001
T-PER (sec)	0.15 (0.00)	0.11 (0.00) p=0.0001	0.13 (0.00) p=0.003	0.15 (0.00)	0.10 (0.01) p=0.0001	0.12 (0.01) p=0.013	NS	NS
PER (EDV/sec)	2.44 (0.07)	3.68 (0.13) p=0.0001	3.04 (0.09) p=0.0001	2.86 (0.13)	5.13 (0.22) p=0.0001	3.89 (0.16) p=0.0001	0.0001	0.0001
AV-ER (EDV/sec)	1.53 (0.04)	2.09 (0.07) p=0.0001	1.78 (0.06) p=0.0001	1.86 (0.08)	2.63 (0.12) p=0.0001	2.37 (0.10) p=0.0001	0.0002	0.0001
T-PFR (sec)	0.18 (0.01)	0.17 (0.01) p=NS	0.18 (0.01) p=0.032	0.16 (0.01)	0.15 (0.01) p=NS	0.19 (0.01) p=0.023	NS	NS
PFR (EDV/sec)	2.04 (0.07)	3.25 (0.12) p=0.0001	2.78 (0.09) p=0.0001	2.39 (0.13)	4.32 (0.21) p=0.0001	3.53 (0.16) p=0.0001	0.0001	0.0001
AV-RFR (EDV/sec)	1.37 (0.05)	1.82 (0.07) p=0.0001	1.64 (0.06) p=0.0001	1.81 (0.09)	2.32 (0.12) p=0.003	2.07 (0.11) p=0.038	0.0005	0.001

Values are expressed as Mean (Standard Error). * p values: rest vs post-effort.
Post-E1: 1st post-effort period; Post-E2: 2nd post-effort period. Other abbreviations as per Table I.

Table 3.3 Differences in left ventricular function response post-effort between patients with coronary artery disease and healthy individuals without known cardiac disease.

	CAD n=93		CONTROL n=31		CAD vs CONTROL p VALUE	
VARIABLES	Δ R-Post-E1	Δ R-Post-E2	Δ R-Post-E1	Δ R-Post-E2	Post-E1	Post-E2
HEART RATE (bpm)	-60.2 (3.6)	-28.7 (2.0)	-84.2 (6.2)	-50.4 (3.5)	0.001	0.0001
EDC	-25.5 (5.3)	-3.9 (3.8)	-47.7 (9.2)	-21.5 (6.6)	0.04	0.023
ESC	-12.2 (5.3)	4.3 (3.6)	-18.4 (9.2)	-2.7 (6.2)	NS	NS
SC	-40.3 (6.3)	-13.1 (4.7)	-66.5 (11.0)	-34.0 (8.1)	0.041	0.028
EF %	-12.7 (1.7)	-8.0 (1.5)	-15.4 (3.0)	-10.7 (2.6)	NS	NS
T-PER (sec)	26.0 (3.5)	11.3 (3.0)	33.4 (6.1)	13.2 (5.2)	NS	NS
PER (EDV/sec)	-54.9 (4.4)	-28.4 (3.1)	-81.1 (7.7)	-37.6 (5.4)	0.004	NS
AV-ER (EDV/sec)	-39.5 (3.7)	-19.8 (2.8)	-42.7 (6.4)	-28.4 (4.8)	NS	NS
T-PFR (sec)	-1.3 (4.4)	-10.0 (4.6)	0.9 (7.6)	-18.3 (8.0)	NS	NS
PFR (EDV/sec)	-74.6 (6.2)	-48.9 (4.6)	-83.8 (10.7)	-50.1 (7.9)	NS	NS
AV-RFR (EDV/sec)	-50.5 (6.6)	-32.7 (5.3)	-34.9 (11.5)	-19.3 (9.2)	NS	NS

Values are expressed as Mean (Standard Error).
Δ R-Post-E1: % change from rest to 1st period post-effort; Δ R-Post-E2: % change from rest to 2nd period post-effort; Post-E1: 1st period post-effort; Post-E2: 2nd period post-effort. Other abbreviations as per Table I.

3.3.2 In patients with coronary artery disease according to degree of left ventricular dysfunction

An example of the differences in the time-activity curve between patients is shown in Figures 3.1-3.3.

3.3.2.1 At rest

G1 differed from the control group only in EDC and SC which were significantly lower ($p=0.017$ and $p=0.0174$ respectively).

In G2, EDC and ESC were significantly higher ($p=0.03$ and $p=0.00001$ respectively) and SC significantly lower ($p=0.0061$) than in the control group. EF, PER, AV-ER, PFR and AV-RFR were all significantly lower in G2 than controls ($p=0.0001$, $p=0.00001$, $p=0.0001$, $p=0.00001$, $p=0.0001$ respectively).

In G3, heart rate, EDC and ESC were significantly higher ($p=0.012$, $p=0.0001$ and $p=0.0001$ respectively) and SC significantly lower ($p=0.00001$) than in the control group. As in G2, EF, PER, AV-ER, PFR and AV-RFR were all significantly reduced when compared to the control group ($p=0.00001$, $p=0.0001$, $p=0.0001$, $p=0.00001$ and $p=0.0001$ respectively).

End-diastolic and end-systolic counts were significantly higher in Group 3 compared to Groups 2 and 1 ($p<0.001$ respectively) and in Group 2 compared to Group 1 ($p<0.01$ and $p<0.001$ respectively). Stroke counts were significantly lower in Groups 3 and 2 when compared to Group 1 ($p<0.01$ and $p<0.05$ respectively). The time to peak ejection rate and the time to peak filling rate were not different between the three groups. Ejection fraction, peak ejection rate, average ejection rate, peak filling rate and average rapid filling rate were significantly lower in Group 3 compared to Group 2 ($p<0.001$, $p<0.001$, $p<0.001$,

$p<0.01$ and $p<0.001$ respectively) and Group 1 ($p<0.001$ respectively) and in Group 2 compared to Group 1 ($p<0.001$ respectively).

3.3.2.2 During exercise

In G1, all parameters had a similar trend in the change from rest to exercise to that in the control group except for EDC which did not increase significantly during exercise and EF which fell significantly ($p=0.0001$). However, the magnitude of the change during exercise was greater in controls, who achieved higher heart rates ($p=0.0001$), PER ($p=0.0001$), AV-ER ($p=0.004$), PFR ($p=0.0002$) and AV-RFR ($p=0.02$) than the patient's group.

In G2, left ventricular parameters changed also in the same direction as in the control group during exercise, except for EDC and ESC which failed to increase. The magnitude of the change was greater for controls than patients for heart rate ($p=0.0001$) and PER ($p=0.027$).

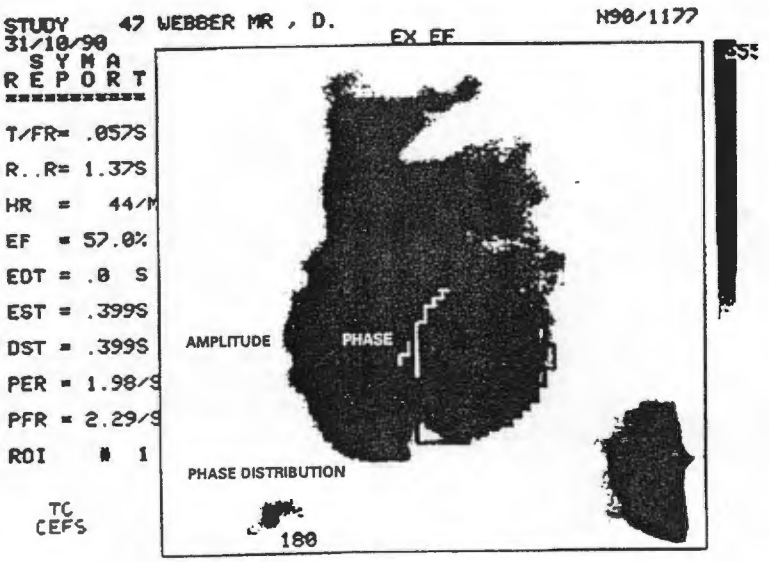
In G3, similarly to G2, apart from EDC and ESC which failed to increase significantly during exercise, and AV-ER that did not change, all the other variables moved in a direction similar to that of controls. The magnitude of the change was only greater for heart rate ($p=0.0004$) and AV-ER ($p=0.005$) in controls versus patients.

Table 3.4 Differences in resting and exercise left ventricular function between patients with coronary artery disease and healthy individuals according to ejection fraction category.

	CAD (Group 1)			CAD (Group 2)			CAD (Group 3)			CONTROL VS CAD p value		
										G1	G2	G3
VARIABLES	Rest n=73	Exercise n=56 *	Δ R-E n=56	Rest n=27	Exercise n=23 *	Δ R-E n=23	Rest n=18	Exercise n=14 *	Δ R-E n=14	Rest Exercise Δ R-E	Rest Exercise Δ R-E	Rest Exercise Δ R-E
HEART RATE (bpm)	64.9 (1.6)	105.9 (2.1) p=0.0001	-64.9 (4.2)	66.8 (3.4)	99.1 (3.8) p=0.0001	-58.4 (6.7)	69.9 (2.5)	108.6 (3.2) p=0.0001	-60.9 (8.2)	NS 0.00001 0.0001	NS 0.00001 0.0001	0.012 0.003 0.0004
EDC	403603 (10702)	421189 (27205) p=NS	-6.5 (7.3)	563913 (29201)	518852 (52367) p=NS	4.6 (11.3)	775204 (62077)	832213 (123304) NS	-11.5 (16.0)	0.017 0.05 NS	0.003 NS NS	0.0001 0.044 NS
ESC	159206 (5838)	199055 (14766) p=0.003	-29.2 (9.5)	331434 (20835)	328582 (30892) p=NS	-3.8 (14.1)	585640 (57997)	683389 (106481) p=NS	-20.4 (19.4)	NS NS NS	0.00001 0.043 0.052	0.0001 0.001 NS
SC	244396 (6653)	222134 (17189) p=NS	7.0 (7.4)	232479 (9561)	190270 (27384) p=NS	15.4 (11.8)	189563 (11359)	148825 (33049) p=NS	12.9 (17.2)	0.0174 0.022 NS	0.0061 0.015 NS	0.00001 0.005 NS
EF (%)	60.9 (0.8)	54.0 (1.5) p=0.0001	6.4 (1.6)	41.9 (0.7)	39.2 (1.9) p=NS	2.8 (2.7)	25.8 (1.4)	22.4 (2.4) p=NS	4.1 (3.5)	NS NS NS	0.0001 0.00001 NS	0.00001 0.00001 NS
T-PER (sec)	0.14 (0.00)	0.07 (0.00) p=0.0001	47.2 (3.2)	0.16 (0.01)	0.09 (0.01) p=0.0001	40.3 (5.1)	0.16 (0.01)	0.07 (0.01) p=0.0001	51.2 (5.5)	NS NS NS	NS NS NS	NS NS NS
PER (EDV/sec)	2.87 (0.06)	3.96 (0.14) p=0.0001	-39.3 (5.0)	2.07 (0.08)	2.98 (0.17) p=0.0001	-50.0 (9.1)	1.24 (0.08)	2.04 (0.21) p=0.0001	-55.9 (10.7)	NS 0.0001 0.0001	0.00001 0.00001 0.027	0.0001 0.00001 NS
AV-ER (EDV/sec)	1.81 (0.03)	2.09 (0.08) p=0.0001	-17.0 (4.2)	1.28 (0.04)	1.46 (0.11) p=0.042	-19.5 (9.3)	0.75 (0.04)	0.73 (0.12) p=NS	2.7 (11.4)	NS 0.002 0.004	0.0001 0.00001 NS	0.0001 0.00001 0.005
T-PFR (sec)	0.18 (0.01)	0.12 (0.01) p=0.002	21.2 (6.5)	0.20 (0.02)	0.14 (0.01) p=0.0005	22.3 (6.0)	0.17 (0.01)	0.15 (0.03) p=NS	13.1 (12.2)	NS 0.016 NS	0.056 0.007 NS	NS NS NS
PFR (EDV/sec)	2.41 (0.08)	4.72 (0.20) p=0.0001	-104.7 (9.5)	1.64 (0.12)	3.53 (0.24) p=0.0001	-141.1 (18.2)	1.16 (0.09)	2.23 (0.21) p=0.0001	-124.6 (22.0)	NS 0.016 0.0002	0.00001 0.00001 NS	0.00001 0.0001 NS
AV-RFR (EDV/sec)	1.64 (0.06)	3.27 (0.16) p=0.0001	-110.5 (12.0)	1.04 (0.05)	2.45 (0.24) p=0.0001	-153.4 (25.4)	0.78 (0.07)	1.50 (0.14) p=0.0001	-135.6 (27.6)	NS 0.0001 0.02	0.0001 0.00001 NS	0.0001 0.0001 NS

Values are expressed as Mean (Standard Error). * p values: rest vs exercise. Δ R-E: % change from rest to exercise. Other Abbreviations as per Table I.

Figure 3.1 Patient with coronary artery disease and normal left ventricular systolic function (Group 1)



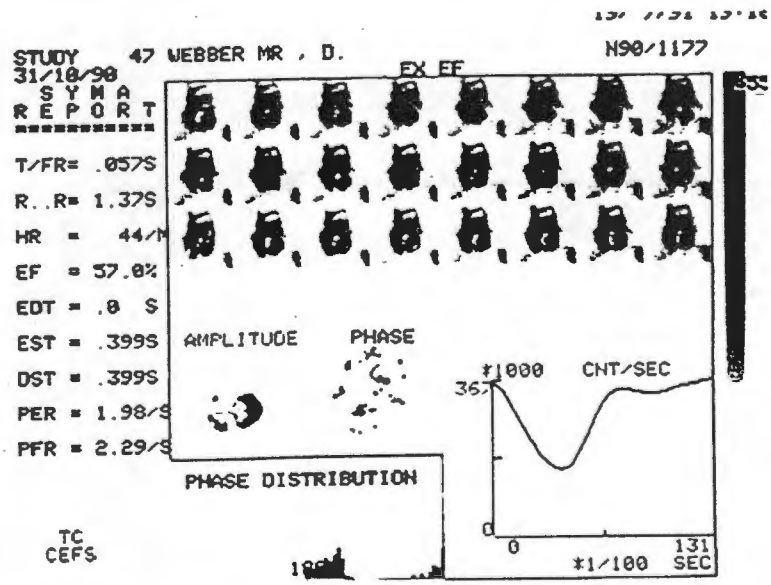
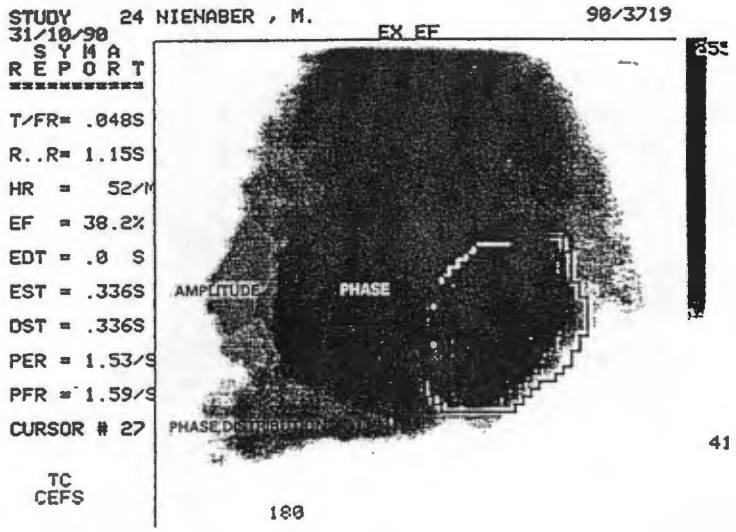


Figure 3.2 Patient with coronary artery disease and moderately impaired left ventricular systolic function (Group 2)



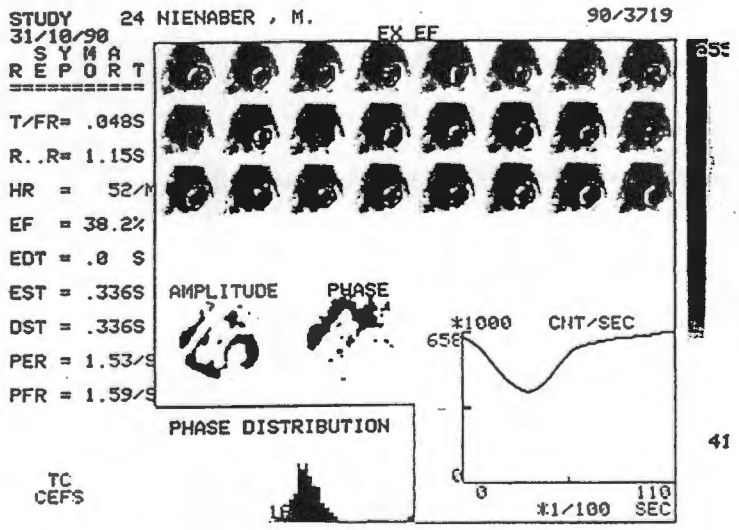
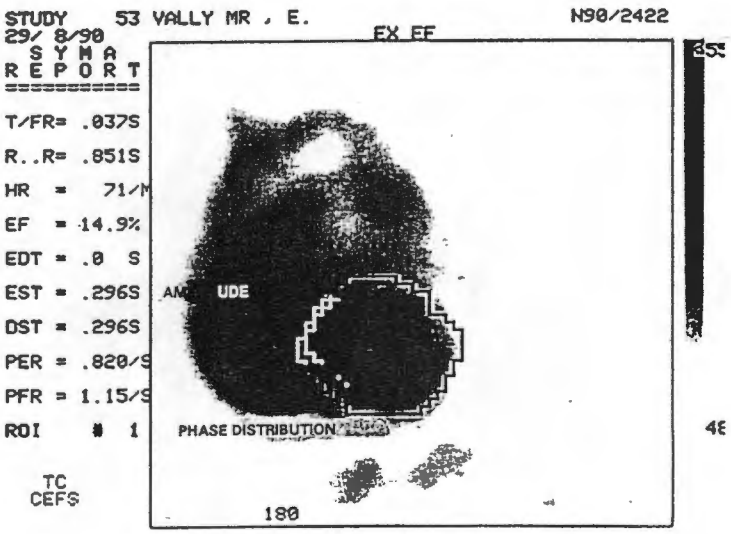
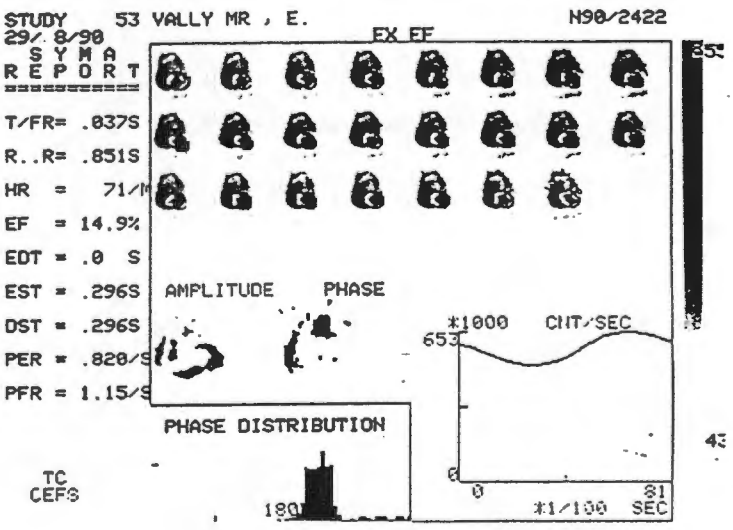
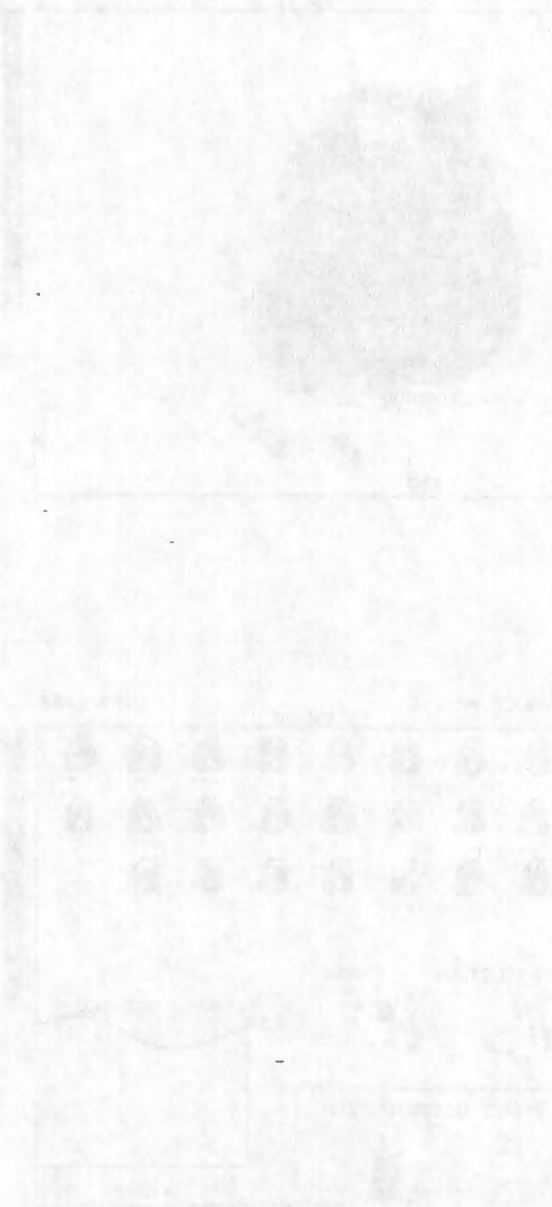


Figure 3.3 Patient with coronary artery disease and severely impaired left ventricular systolic function (Group 3)







3.4 Discussion

The first important finding of this study was that systolic and diastolic function were both impaired at rest as evidenced by significant lower mean values in EF, PER, AV-ER and PFR, AV-RFR respectively in patients on admission to our cardiac rehabilitation program, compared to controls. The second important finding was that there were also significant differences in left ventricular systolic and diastolic function during exercise between the two groups as demonstrated by an attenuation in the increase in PER, AV-ER and PFR in response to exercise in patients compared to controls.

Of interest was the finding that the changes in left ventricular EF between rest and exercise seen in this study were not able to adequately discriminate between normal individuals and patients with coronary artery disease. Some studies have shown that the exercise EF is reduced only in patients with double or triple vessel coronary disease (214,215), while others suggested that a drop in EF during exercise could be indicative of subclinical myocardial ischaemia (44). The lack of increase in EF from rest to exercise in our control group conflict with the results of some researchers (44,211,216) who reported a rise in all normal subjects, but are in agreement with those of other (217,218) who reported unchanged or even a slight decrease in EF during exercise. A postural effect, since all participants were exercised on a supine bicycle ergometer, could explain some of the differences in these results (219), probably as a result of an increased venous return when supine.

PER and AV-ER were more sensitive parameters than EF during exercise to detect systolic abnormalities, being able to differentiate patients from healthy subjects, showing a significantly attenuated increase in response to exercise. In Bacharach et al's series (216), PER increased from rest to exercise in controls, falling in patients with coronary artery disease. This different response to exercise could be explained by the difference in status of the patients included in the studies: Bacharach et al's patients were more likely to be

patients with acute problems while patients joining a cardiac rehabilitation program are more likely to have stable left ventricular function.

Since cardiac output is the product of heart rate and stroke volume and stroke volume is determined by the product of the ejection fraction and end-diastolic volume, the formula Cardiac Output = Heart Rate x End-Diastolic Volume x EF can be used to compare the determinants of cardiac output between patients and controls.

The percentage changes in EF and end-diastolic volume from rest to exercise were similar for both patients and controls indicating that both groups increased their cardiac output during exercise through an increase in heart rate. The greater heart rate in the control group resulted in the higher cardiac output during exercise in normals than in patients with coronary artery disease.

EDC were moderately increased in the control group and unchanged in all patient groups. Two factors may have contributed to the moderate increase in EDC in response to exercise in the control group: 1- The sedentary nature of our control group. Ahmad and Dubiel (220) showed that the Frank Starling mechanism plays a more prominent role in the left ventricular response to exercise in trained healthy subjects. 2- The "masking effect" of the Frank-Starling mechanism produced by exercise tachycardia. The presence of this is confirmed by the fact that fixed atrial pacing during exercise in experimental animals and normal subjects unmasks an increase in end-diastolic dimensions of the left ventricle (211-213). Furthermore, Stein et al. (213) were unable to observe a change in the left ventricular end-diastolic dimension measured with M-mode echocardiogram during exercise, but as the heart rate decreased post-effort the increase in end-diastolic dimension became apparent indicating that the Frank-Starling mechanism of cardiac adaptation may have been masked by increases in heart rate during exercise. In our study, as the heart rate decreased post-effort, we showed an increase in EDC of 25% in the patient group and an increase of 48% in the control group. The difference in conditioning between patients who

were recovering from a recent cardiac event and normal individuals could explain a greater increase in EDC in the latter group.

It is interesting that as many as 38% of patients admitted to the Centre had impaired systolic left ventricular function. The high prevalence of this special population is in keeping with recent studies showing that patients with chronic left ventricular dysfunction can benefit from participation in cardiac rehabilitation programmes (134,136,221). These results should encourage cardiac rehabilitation practitioners to systematically use risk stratification algorithms since patients with left ventricular dysfunction are at moderate to high risk of exercise-related complications, requiring more intense supervision and monitoring (73).

We noted that the more depressed the systolic function, the higher the end-diastolic and end-systolic counts and the lower the stroke counts. As systolic dysfunction progressed and the EF became lower, the cardiac output at rest was maintained mainly by an increase in end-diastolic volume with a small contribution of a higher resting heart rate. The changes from rest to exercise were similar in all groups irrespective of the degree of left ventricular systolic dysfunction, cardiac output being maintained in all groups by an increase in heart rate. However the masking effect of the Frank Starling mechanism produced by tachycardia needs to be considered.

The alterations in diastolic function seen in our patients at rest are probably due to fibrosis as a consequence of previous myocardial infarction, since they are only seen in patients with impaired left ventricular function and not in those with normal EF. The attenuation in the increase of the rate of filling of the left ventricle during exercise seen in patients with normal systolic function could occur as a result of regional asynchronous relaxation due to ischemia. In this regard, improvements in diastolic function have been reported after successful percutaneous transluminal coronary angioplasty suggesting that silent subclinical ischemia is a major determinant of diastolic dysfunction (222). Furthermore, the majority of patients with exercise-induced myocardial ischemia enrolled into our study

were in the group with normal left ventricular function at rest. However, ageing (223) and essential hypertension (224,225) especially in the presence of left ventricular hypertrophy cannot be excluded as contributing factors since they are also known to alter the rate and extent of left ventricular filling: our patients were significantly older than controls and thirty six percent were on treatment for hypertension although not investigated for the presence of left ventricular hypertrophy.

3.5 Conclusions

Patients with coronary artery disease joining a cardiac rehabilitation program had profound alterations in systolic and diastolic function at rest and during exercise. Ejection fraction and peak filling rate were significantly reduced at rest while peak ejection rate, average ejection rate and peak filling rate had an attenuated increase in response to exercise. During exercise, parameters other than the ejection fraction were able to discriminate better between healthy subjects and patients with coronary artery disease.

The analysis of left ventricular function according to the degree of left ventricular dysfunction allowed identification of the compensatory mechanisms used to increase cardiac output in these patients. Patients with left ventricular dysfunction used the Frank Starling mechanism at rest, therein maintaining their cardiac output at rest through an increase in end-diastolic volume, whereas an increase in heart rate played the more important role during exercise.

The high prevalence of left ventricular abnormalities emphasizes the possible need for systematic risk stratification as a tool to guide the monitoring of patients and prevent a possible increase in exercise-related complications as the referral for cardiac rehabilitation of this special population with left ventricular dysfunction continues to increase.

CHAPTER 4

CORRELATION BETWEEN SYSTOLIC AND DIASTOLIC LEFT VENTRICULAR FUNCTION AND EXERCISE CAPACITY IN PATIENTS WITH CORONARY ARTERY DISEASE

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Digenio AG, Noakes TD, Cantor A, Groeneveld H, Daly L, Mavunda D, Esser JD.

Predictors of exercise capacity and adaptability to training in patients with coronary artery disease.

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4.1 Introduction

We have showed in Chapter 3 that patients currently admitted for cardiac rehabilitation have a high prevalence of systolic and/or diastolic LV function abnormalities. The next logical question will be whether these patients can derive physiological benefits from exercise cardiac rehabilitation programmes.

We have discussed in Chapter 1 that the mechanism of exercise intolerance in patients with left ventricular dysfunction is probably multifactorial and may include an increased pulmonary capillary wedge pressure (144), a reduction in cardiac output (143), abnormalities of ventilation and of ventilation-perfusion matching (146), neurohormonal abnormalities (168), a reduction in skeletal muscle blood flow (134) and altered skeletal muscle metabolism (164,1167).

The lack of correlation found between EF and exercise tolerance in patients with left ventricular dysfunction and the importance of the role of peripheral factors as part of the multi-factorial mechanism of exercise intolerance in these patients, has led to the hypothesis that these patients could benefit from exercise training programmes by enhancing their skeletal muscle function regardless of their initial degree of LV dysfunction.

However, in these studies, only left ventricular EF was used as the measurement reflecting changes in central haemodynamics. Possible confounders such as non-cardiac factors were excluded as were measures of LV diastolic dysfunction which could also be a major determinant of the exercise intolerance of these patients. Furthermore only an homogeneous group of patients with an EF below a certain value where included in these studies.

Accordingly there were two principal aims of this chapter of the thesis. First, the study aimed to determine physiologic and other predictors of exercise capacity of patients with

coronary artery disease and various degrees of left ventricular systolic dysfunction at entry to a Phase III, community-based cardiac rehabilitation programme and after 6 months of supervised aerobic training. Second, the investigation attempted to evaluate the effects of this exercise training programme on their effort tolerance. Non-cardiac factors as well as measures of left ventricular diastolic function were included into the analysis and a wider spectrum of patients was studied by classifying them into groups according to their baseline ejection fraction.

4.2 Methods

One hundred and seventy one patients with documented CAD, consecutively referred to the Johannesburg Cardiac Rehabilitation Centre between 1989 and 1991, were enrolled in the study.

On admission to the programme, patients underwent a full medical evaluation which has been discussed in detail in Chapter 2 and which included a multistage, symptom-limited exercise test and resting radionuclide ventriculography. The exercise test was performed on a motorized treadmill according to the Chung protocol (27). Expired air was analysed throughout exercise using a metabolic cart. Peak VO_2, ventilatory threshold (VT), minute volume (VE) and treadmill time to exhaustion (TT) were determined. The VT was defined as the first deviation in linearity of the ventilation plotted against the oxygen consumption. The end-points for fatigue have been described previously in Chapter 2.

Radionuclide ventriculography was performed at rest in all patients, using the equilibrium multi-gated blood pool technique as described in Chapter 2 (44) and EDC, ESC, SC, EF, T-PER, PER, AV-ER, T-PFR, PFR and AV-RFR were derived from time-activity curves as previously shown.

Thereafter, all subjects underwent a 6 month supervised programme of aerobic exercise including risk factor modification. The type, intensity and duration of exercise have already been described in Chapter 2. Patients were carefully monitored by the staff at the rehabilitation centre during all their exercise sessions. Compliance was monitored to ensure that subjects completed at least 60% of the exercise sessions during the 6-month period. Reasons for dropout were obtained telephonically. The complete set of investigations was repeated after 6 months in those 117 subjects who attended more than 60% of the possible sessions.

Statistical analysis

The entire cohort of patients studied was divided into three groups for additional analysis. Four population groups were then evaluated: Group 0 (G0) included all patients irrespective of their left ventricular systolic function at rest, Group 1 (G1) included 106 patients with normal resting left ventricular systolic function (EF≥50%); Group 2 (G2) included 38 patients with moderately depressed resting systolic function (EF≥35 and <50%) and Group 3 (G3) included 27 patients with severely depressed resting systolic function (EF<35%).

The characteristics of patients on admission to the programme were compared within each group between compliers and dropouts.

To determine which factors predicted the effort tolerance of patients on admission to the exercise programme, simple linear regression and stepwise logistic regression analyses were performed in G0. Peak VO_2, VT and TT were used as dependent variables and all measures of left ventricular diastolic and systolic function were used as explanatory variables. Age, gender, medical condition, number of myocardial infarctions, infarct location, medication, degree of ST segment depression and its duration in recovery, ST segment elevation, haemoglobin content, Broca index, forced vital capacity (FVC %) and

the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC %), expressed as percentages of predicted values, were considered as possible confounders. In addition, to determine if variables relating to left ventricular function could predict the changes in submaximal and maximal exercise capacity induced by a 6 month exercise training programme, simple linear and stepwise logistic regression analyses were performed on the data of all patients in GO who complied with the programme for 6 months. The percentage changes between admission and 6 months for Peak VO_2, VT and TT, calculated as the value at 6 months minus the value on admission divided by the value on admission x 100, were used as dependent variables. Percentage attendance was added as an explanatory variable.

To determine if the predictors of exercise tolerance at entry and after exercise training were different in the three patient groups, simple linear regression and stepwise regression analyses were performed for groups 1 through 3 using the same explanatory and dependent variables.

The effect of exercise training on exercise tolerance and haemodynamic variables was evaluated at submaximal and maximal intensities from the data collected during the maximal exercise test, before and after exercise training.

Any subjects who had missing data for certain variables were excluded from the analysis for those variables. Indices of resting systolic and diastolic function and physiological parameters measured during exercise were expressed as least square means after adjusting for confounders and their differences were interpreted using estimated partial regression coefficients. The significance of the model was assessed through analysis of variance and the differences between samples was assessed with individual Fisher's least significance differences test. Significance at the 5% level or lower was reported.

4.3 Results

4.3.1 Characteristics of patients on admission

The baseline characteristics of the 171 patients admitted to the trial, are listed in Table I for all groups. The patients' ages in G0 ranged from 34 to 82 years (mean 56.3 $\pm$ 10 years) with a male/female ratio of 11:1. Sixty six percent of patients had suffered a myocardial infarction, 41% had undergone coronary artery bypass surgery and 24% percutaneous transluminal coronary angioplasty. The infarct was located in the anterior wall in 49% of patients and in the inferior wall in 51%. All patients were classified in the New York Heart Association classes I and II. Twenty seven percent of patients used beta blockers, 29% calcium blockers, 22% nitrates and 28% angiotensin converting enzyme inhibitors. FVC and FEV1/FVC ratio, hemoglobin content and the Broca Index were within the normal population range. Patients in G3 were significantly older than patients in G2 ($p<0.05$), but were of similar age to patients in G1. Although a greater percentage of patients with hypertension were in G1 than in G2 and G3, the difference was not significant. Haemoglobin concentrations on admission to the programme were similar in G1,G2 and G3. G3 and G2 included more patients with MI than G1 ($p<0.001$ and $p<0.001$ respectively); patients in these groups had also experienced a greater number of MI ($p<0.001$ and $p<0.05$ respectively). More patients in G3 than in G2 or G1 had an anterior infarct ($p<001$ respectively), whereas more patients in G1 had an inferior infarct than did patients in Groups 2 or 3 ($p<0.001$ respectively). Medication use was different in the three groups, with G1 using mainly beta blockers and calcium antagonists and G2 patients using calcium antagonists and angiotensin converting enzyme inhibitors, while G3 patients used more nitrates and angiotensin converting enzyme inhibitors. Patients in G2 and G3 had significantly lower FVC% than those in G1 ($p<0.05$ and $p<0.05$ respectively). The FEV1/FVC% ratio was normal in the three groups but significantly higher in G3 than in G2 ($p<0.05$). The Broca index was within the normal range in the three groups.

Table 4.1 Characteristics of all patients on admission.

	Group 0 n = 171	Group 1 n = 106	Group 2 n = 38	Group 3 n = 27	P Value
AGE (years)	56.3 (10.0)	56.0 (9.8)	54.5 (8.7)	60.0 (11.8)	<0.05 *
SEX No. (%)					
MALE	156 (91)	97 (91)	33 (87)	26 (96)	NS
FEMALE	15 (9)	9 (8)	5 (13)	1 (4)	NS
HYPERTENSION No. (%)	61 (36)	42 (40)	11 (29)	8 (30)	NS
HAEMOGLOBIN (g/100ml)	15.3 (1.5)	15.3 (1.4)	15.5 (1.5)	15.1 (1.7)	NS
MI No. (%)	113 (66)	58 (55)	31 (82)	24 (89)	<0.001 & <0.001 #
NUMBER MI	0.8 (0.8)	0.7 (0.7)	1.0 (0.8)	1.3 (0.8)	<0.001 & <0.05 #
MI POSITION No. (%)					
ANTERIOR	55 (49)	17 (29)	16 (52)	21 (87)	<0.001 * <0.001 &
INFERIOR	58 (51)	41 (71)	15 (48)	3 (12)	<0.001 * <0.001 #
CABG No. (%)	70 (41)	45 (42)	18 (47)	7 (26)	NS
PTCA No. (%)	41 (24)	28 (26)	9 (24)	4 (15)	NS
MEDICATION No. (%)					
BETA BLOCKERS	46 (27)	36 (34)	9 (24)	1 (4)	<0.01 * <0.001 &
CALCIUM BLOCKERS	50 (29)	27 (25)	14 (37)	9 (33)	NS
NITRATES	37 (22)	18 (17)	6 (16)	13 (48)	<0.001 * <0.001 &
ACE INHIBITORS	48 (28)	20 (19)	11 (29)	17 (63)	<0.001 * <0.001 &
FVC %	88.5 (18.5)	91.4 (18.6)	84.4 (15.3)	83.1 (20.7)	<0.05 & <0.05 #
FEV1/FVC %	98.8 (9.4)	98.5 (10.1)	97.4 (8.2)	102.0 (7.7)	<0.05 *
BROCA INDEX	110.0 (13.9)	110.6 (14.4)	109.2 (13.7)	108.4 (12.2)	NS

MI: myocardial infarction; CABG: coronary artery bypass graft; PTCA: percutaneous transluminal coronary angioplasty; ACE: angiotensin converting enzyme; FVC %: forced vital capacity, percentage of predicted value; FEV1/FVC %: forced expiratory volume in 1 second / FVC, percentage of predicted value.

Values are expressed as Mean (Standard Deviation) unless otherwise stated as number (No.(%)). Group 0: all patients; Group 1: ejection fraction ≥50%; Group 2: ejection fraction ≥35 and <50%; Group 3: ejection fraction <35%; * Group 3 vs Group 2; & Group 3 vs Group 1; # Group 2 vs Group 1.

The physiological parameters measured during the initial exercise test in the same patients are shown in Table 4.2. Patients in G3 had a significantly lower mean rate-pressure product during exercise testing than patients in G1 ($p<0.05$). Peak VO_2, VT and treadmill time were significantly lower in G3 than in the other two groups. There were no significant differences in the three variables between patients in Groups 1 and 2.

Thirty eight patients showed ST segment depression greater than 1mm and 8 patients showed ST segment elevation during the exercise or in the recovery period. Patients with ST segment depression greater than 1mm were evenly distributed among the three groups. A greater number of patients in G3 showed ST segment elevation than in the other groups.

Table 4.2 Exercise test variables of all patients on admission.

	Group 0 n = 171	Group 1 n = 106	Group 2 n = 38	Group 3 n = 27	p value
Peak Oxygen Uptake (ml/kg.min)	24.4 (6.3)	25.2 (6.1)	25.1 (6.5)	20.6 (5.4)	<0.01 * <0.001 &
Ventilatory Threshold (ml/kg.min)	16.5 (3.6)	17.0 (3.7)	16.6 (2.9)	14.3 (3.0)	<0.01 * <0.001 &
Treadmill Time (min)	11.0 (3.5)	11.3 (3.4)	11.4 (3.5)	9.2 (3.4)	<0.05 * <0.01 &
Rate-pressure Product (bpm.mmHg x 10^3)	25.3 (6.4)	26.2 (6.4)	24.3 (6.5)	23.2 (5.7)	<0.05 &
ST Depression	0.4 (0.9)	0.4 (0.9)	0.4 (0.7)	0.5 (0.8)	NS
ST Duration (min)	2.4 (4.7)	2.0 (4.2)	2.6 (5.3)	3.9 (5.3)	NS
ST Elevation	0.1 (0.5)	0.0 (0.2)	0.1 (0.4)	0.6 (1.1)	<0.001 * <0.001 &

All values are expressed as Mean (Standard Deviation)
* Group 3 vs Group 2; & Group 3 vs Group 1; # Group 2 vs Group 1

The resting systolic and diastolic LV function of patients at entry to the programme are listed in Table 4.3. When patients were categorized according to their degree of left ventricular impairment, the more depressed the systolic function, the higher the end diastolic and end systolic counts and the lower the stroke counts. End diastolic and end systolic counts were significantly higher in G3 compared to G2 ($p<0.001$ respectively) and G1 ($p<0.001$ respectively). Stroke counts were significantly lower in G3 and G2 compared with G1 ($p<0.01$ and $p<0.05$ respectively). The time to peak ejection rate and the time to peak filling rate were not different among the three groups. Ejection fraction, peak ejection rate, average ejection rate, peak filling rate, and average rapid filling rate were significantly lower in G3 compared with G2 ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.01$ and $p<0.001$ respectively and G1 ($p<0.001$ respectively) and in G2 compared with G1 ($p<0.001$ respectively).

Table 4.3 Resting left ventricular function of patients on admission.

	Group 0 n = 171	Group 1 n = 106	Group 2 n = 38	Group 3 n = 27	P Value
EDC	499 488 (225 212)	419 520 (178 190)	511 286 (185 391)	793 677 (184 210)	<0.001 # <0.001 & <0.001 *
ESC	269 064 (212 056)	171 931 (130 758)	294 515 (129 095)	614 578 (137 966)	<0.001 # <0.001 & <0.001 *
SC	230 424 (70 522)	238 106 (80 309)	209 104 (78 183)	189 781 (75 005)	NS # <0.01 & <0.05 *
EF %	50.7 (14.6)	59.9 (9.4)	43.1 (8.3)	24.9 (8.4)	<0.001 # <0.001 & <0.001 *
T-PER (sec)	0.15 (0.03)	0.14 (0.03)	0.15 (0.03)	0.15 (0.04)	NS # NS & NS *
PER (EDV/sec)	2.45 (0.81)	2.83 (0.58)	2.18 (0.58)	1.51 0.58	<0.001 # <0.001 & <0.001 *
AV-ER (EDV/sec)	1.53 (0.48)	1.74 (0.41)	1.31 (0.37)	0.84 (0.31)	<0.001 # <0.001 & <0.001 *
T-PFR (sec)	0.18 (0.07)	0.18 (0.07)	0.17 (0.07)	0.20 (0.07)	NS # NS & NS *
PFR (EDV/sec)	2.08 (0.81)	2.28 (0.72)	1.78 (0.68)	1.27 (0.68)	<0.001 # <0.001 & <0.01 *
AV-RFR (EDV/sec)	1.40 (0.53)	1.56 (0.41)	1.21 (0.43)	0.73 (0.42)	<0.001 # <0.001 & <0.001 *

All values are expressed as Mean (Standard Deviation)
Group 2 vs Group 1; & Group 3 vs Group 1; * Group 3 vs Group 2.

EDC: end-diastolic counts; ESC: end-systolic counts; SC: stroke counts; EF: ejection fraction; T-PER: time to peak ejection rate; PER: peak ejection rate; AV-ER: average ejection rate; T-PFR: time to peak filling rate; PFR: peak filling rate; AV-RFR: average rapid filling rate; EDV/sec: end-diastolic volumes per second.

4.3.2 Predictors of exercise tolerance on admission

Statistically significant but minimal associations were found in G0 between measures of resting left ventricular systolic and diastolic function and peak VO_2, VT and TT using simple linear regression analysis (Table 4.4).

Stepwise logistic regression analysis using baseline exercise capacity parameters as dependent variables was performed in all groups. The following predictors were identified in G0 (Table 4.4): Age and the Broca index showed a negative association with all exercise capacity variables whereas FVC% and AV-ER were positively correlated. SC showed a positive association only with VT. Gender was also a significant predictor, as men had significantly better effort tolerance than did women. Age was the strongest predictor of PVO2 and TT, whereas SC were the best predictor of VT. Of all left ventricular systolic function variables, only AV-ER was a significant but weak predictor of exercise capacity. After adjusting for non-cardiac factors, left ventricular diastolic variables no longer showed an association with exercise tolerance.

Table 4.4 Predictors of effort tolerance in 171 patients with coronary artery disease and varying degrees of left ventricular dysfunction.

	PEAK VO_2 (ml/kg.min)				VENTILATORY THRESHOLD (ml/kg.min)				TREADMILL TIME (minutes)			
	LR		SR		LR		SR		LR		SR	
	r^2	p	r^2	p	r^2	p	r^2	p	r^2	p	r^2	p
ESC	0.03	0.02			0.03	0.02						
SC	0.06	0.002			0.11	0.0001	0.13	0.0001	0.06	0.002		
EF	0.04	0.007			0.06	0.002			0.03	0.03		
PER	0.03	0.02			0.05	0.005						
AV-ER	0.05	0.003	0.04	0.001	0.07	0.0006	0.04	0.003	0.03	0.02	0.03	0.00
T-PFR	0.07	0.0007			0.04	0.005			0.06	0.001		
PFR	0.02	0.04			0.04	0.006						
AV-RFR	0.05	0.004			0.06	0.0008			0.04	0.009		
AGE			0.24	0.0001			0.08	0.0001			0.29	0.0001
SEX			0.05	0.0002			0.03	0.005			0.05	0.0006
BROCA			0.10	0.0001			0.08	0.0001			0.07	0.0001
FVC%			0.11	0.0001			0.08	0.0003			0.06	0.0002
MODEL R^2			0.54				0.44				0.50	

AV-ER: average ejection rate; AV-RFR: average rapid filling rate; EF: ejection fraction; ESC: end-systolic counts; FVC%: forced vital capacity, percentage of predicted value; LR: linear regression; Model R^2: model coefficient of determination; PER: peak ejection rate; PFR: peak filling rate; r^2: partial coefficient of determination; SC: stroke counts; SR: stepwise logistic regression; T-PFR: time to peak filling rate;.

4.3.3 Dropouts from the study

Fifty four patients dropped out from the programme before 6 months, 33 from G1, 14 from G2 and 7 from G3. There were no differences in the baseline characteristics of G3 patients between compliers and dropouts. G2 dropouts had a greater number of MI (p=0.0001) and a higher Broca index (p=0.0476) than the compliers in that group. G1 dropouts had less ST segment depression (p=0.0001), higher VT (p=0.0310) and greater end-diastolic (p=0.0042) and stroke counts (p=0.0012) than G1 compliers. There was also a greater proportion of patients who had a coronary bypass operation (p=0.034) among G1 dropouts.

There were also no differences in the reported reasons for dropout between the 3 groups. These were related mainly to work problems and the inconvenient location of the rehabilitation centre for certain patients.

Two G1 dropout patients showed progression of disease and one died from a non-cardiac disorder. One non-complier in G2 also died from a non-cardiovascular cause. Sudden death occurred in two G3 dropout patients, one before and the other 2 months after starting the exercise programme. No complications occurred in compliers in the 3 groups during exercise training. All G3 patients who completed the programme were alive 12 months after their initial cardiac event.

4.3.4 Physiological adaptations induced by exercise training

The effects of training on the 117 patients who completed the 6 month exercise training programme are shown in Table 4.5. Highly significant increases in peak VO_2, VT, treadmill time and peak minute volume were noted after 6 months of training in all groups. A significant increase in peak heart rate and a significant decrease in submaximal systolic blood pressure were seen after training in all groups except G2. All seven patients in G3

with exercise-induced ST segment depression showed an improvement in peak VO_2 (mean peak VO_2 % change was 16.8). One of six patients in G2 and three of seventeen patients in G1 with an electrocardiographic ischaemic response did not show an improvement in peak oxygen uptake (mean peak VO_2 changes were 13.8 and 12.5, respectively).

Table 4.5 Effects of exercise training on exercise tolerance, haemodynamics and ventilation.

	Group 0 n = 117		Group 1 n =73		Group 2 n 24		Group 3 n =20	
	Adm	6 ms	Adm	6 ms	Adm	6 ms	Adm	6 ms
Peak VO_2 (ml/kg.min)	24.6 (6.0)	28.3 (7.1) p<0.001	25.2 (6.1)	28.7 (7.1) p<0.001	25.1 (6.5)	30.5 (6.3) p<0.001	20.6 (5.4)	24.1 (6.9) p<0.001
VT (ml/kg.min)	16.5 (3.3)	18.4 (4.2) p<0.05	17.0 (3.7)	18.9 (4.4) p<0.001	16.6 (2.9)	18.8 (3.4) p<0.01	14.3 (3.0)	16.4 (3.8) p<0.001
Treadmill Time (min)	11.1 (3.5)	13.5 (3.9) p<0.001	11.3 (3.4)	13.6 (3.9) p<0.001	11.4 (3.5)	14.7 (3.4) p<0.001	9.2 (3.4)	11.5 (4.0) p<0.001
Resting HR (bpm)	76.0 (14.1)	73.6 (12.0) p<0.05	73.9 (13.0)	71.4 (10.5) NS	76.1 (18.7)	75.9 (15.6) NS	83.0 (9.8)	78.8 (10.9) NS
Peak HR (bpm)	142.3 (18.5)	147.6 (17.2) p<0.001	142.5 (17.3)	146.9 (16.2) p<0.01	143.5 (22.1)	150.3 (22.7) NS	140.8 (19.4)	146.9 (13.5) p<0.05
Peak RPP (bpm.mmHg X 10^3)	25.7 (5.7)	25.3 (5.7) NS	26.6 (5.5)	26.1 (5.2) NS	24.1 (5.9)	25.2 (6.8) NS	24.3 (5.9)	22.3 (5.2) NS
Peak VE (L/min)	80.2 (22.5)	89.7 (23.2) p<0.001	80.3 (23.4)	89.7 (24.7) p<0.001	85.0 (23.7)	95.3 (24.1) p<0.05	74.2 (16.4)	82.8 (13.6) p<0.01
Submaximal VO_2 (ml/kg.min)	17.2 (2.3)	17.5 (2.7) NS	17.4 (2.2)	17.6 (2.7) NS	16.8 (2.6)	17.6 (2.3) NS	16.8 (2.1)	17.3 (3.0) NS
Submaximal HR (bpm)	115.0 (19.1)	111.8 (19.0) NS	113.2 (16.4)	109.5 (18.9) p<0.05	113.6 (23.1)	109.7 (19.6) NS	122.9 (21.7)	122.2 (16.1) NS
Submaximal BP (mmHg)	166.5 (31.8)	151.1 (24.3) p<0.001	171.3 (31.3)	152.8 (25.1) p<0.001	151.8 (27.9)	148.5 (23.2) NS	167.0 (34.3)	148.0 (23.3) p<0.01
Submaximal VE (L/min)	47.5 (14.6)	45.0 (12.0) NS	47.2 (15.4)	44.9 (13.0) NS	42.9 (8.7)	41.3 (7.1) NS	53.9 (15.8)	49.9 (11.8) NS

All values are expressed as Mean (Standard Deviation).
Adm: admission; BP: blood pressure; HR: heart rate; ms: months; RPP: rate-pressure product; VE: ventilation; VO_2: oxygen uptake; VT: ventilatory threshold.

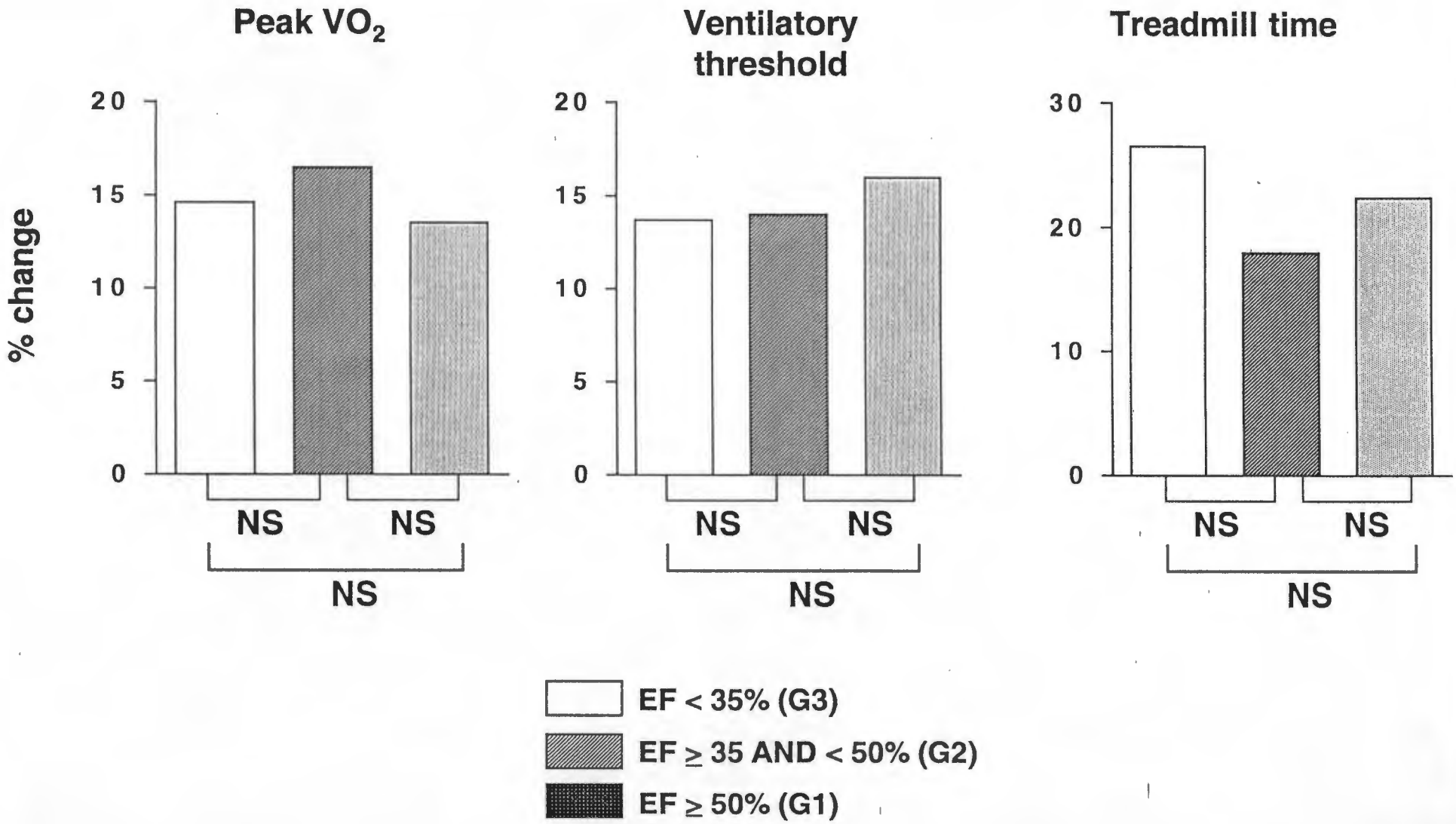
4.3.5 Predictors of changes in exercise tolerance after exercise training

There was no association in G0 between baseline left ventricular function variables and the percentage change in peak VO_2, VT and TT as a result of 6 months of aerobic training.

The magnitude of the improvement in peak VO_2, VT and treadmill time was the same in all patient groups regardless of their resting ejection fractions (Figure 4.1). The percentage increase in treadmill time was significantly greater than the increase in VT and peak VO_2 in G1 ($p<0.001$ and $p<0.001$ respectively) and in G3 ($p<0.05$ and $p<0.01$ respectively).

Figure 4.1

EFFECTS OF EXERCISE TRAINING IN PATIENTS WITH NORMAL AND IMPAIRED SYSTOLIC FUNCTION



4.4 Discussion

The first important finding of this study was that, after adjustment for possible confounders, resting ejection fraction did not correlate with either peak oxygen consumption, ventilatory threshold or treadmill time to exhaustion in the overall population of patients with coronary artery disease. These results are consistent with those of most studies, which show that ejection fraction is unrelated to exercise tolerance in patients with chronic left ventricular dysfunction (226-228). Furthermore, when adjusted for possible confounders, left ventricular diastolic function was also unrelated to maximal exercise capacity.

There is little information about the relationship between diastolic function and exercise tolerance in patients with preserved left ventricular systolic function. It has been suggested that left ventricular diastolic dysfunction in patients with heart failure, prevents a normal increase in stroke volume despite large increases in left atrial and pulmonary capillary pressures (184). However, these data suggest that left ventricular diastolic function does not influence exercise capacity in a mixed population of patients with coronary artery disease with various degrees of left ventricular dysfunction.

The second relevant finding was that non-cardiac factors, including age, gender, the Broca index and forced vital capacity, explained nearly 50% of the variation in exercise tolerance variables in the total group of patients.

The third important finding was that significant physiological adaptations to training were seen in all groups. A surprising finding was that most of these adaptations were identified most clearly during maximal exercise. Although there was a trend towards an improvement in all physiological parameters during submaximal exercise in all patient groups, only the ventilatory threshold increased significantly.

Of importance is the fact that patients with severely depressed left ventricular function and myocardial ischaemia also showed an improvement in peak oxygen uptake. This contrasts with the finding of Arvan and colleagues (190) who found that patients with an ejection fraction greater than 40% showed an improvement in peak oxygen uptake after training whether they had a baseline ischaemic exercise test or not, whereas patients with an ejection fraction less than 40% and associated exercise-induced ischaemia did not show any such improvement. In this study, however, the association of left ventricular dysfunction and an ischaemic exercise test was not a predictor of a poor response in these patients to training.

Furthermore, all patient groups showed a similar degree of adaptation to training as shown by equivalent increases in peak oxygen uptake, ventilatory threshold and exercise time to exhaustion regardless of their degree of resting left ventricular systolic or diastolic dysfunction. Thus, the extent of the improvement in exercise capacity experienced by these patients after the 6-month exercise programme, was not predicted by baseline measurements of left ventricular systolic or diastolic function in any of the groups. Spontaneous recovery of left ventricular function during the training period was excluded as a potential factor, as patients were accepted on the programme only 3 months after their cardiac event.

Although other studies have already shown that patients with chronic cardiac failure can benefit from a cardiac rehabilitation programme (133,134,136), this study appears to be the first to compare the magnitude of the improvement in maximal exercise capacity among groups of patients with different degrees of impairment in left ventricular systolic or diastolic function. An obvious limitation to these findings is the lack of a control group without exercise training for all levels of left ventricular impairment.

As would be expected, patients with severely depressed left ventricular systolic function also showed a significantly lower exercise tolerance as measured by a lower oxygen uptake, a lower exercise time to exhaustion, and an earlier ventilatory threshold than did

patients with moderately depressed or normal left ventricular systolic function. These patients also showed greater abnormalities in left ventricular volumes and diastolic properties than patients in the other groups.

The patient population in this study included a mixed group with coronary artery disease, including those receiving revascularization therapy and those with recent ischaemic myocardial events. This may appear to be a possible limitation, as the data could potentially be confounded by a mixed population with various degrees of ischaemia and ventricular dysfunction. However, all of the variables previously mentioned, including medical condition, and indices of myocardial ischaemia and ventricular dysfunction, have been included in a stepwise logistic regression analysis, which did not indicate that these variables could have predicted in any way the response to exercise training in these patients. The fact that the data in this study could be generalised to a wide population of patients with coronary artery disease, those who have had myocardial infarctions, or those undergoing revascularization, with various degrees of myocardial ischaemia and/or left ventricular dysfunction (either systolic or diastolic) strengthens the argument and is what differentiates this study from previous reports.

4.5 Conclusions

After adjusting for confounding factors, resting left ventricular systolic and diastolic function did not predict the exercise capacity of patients with coronary artery disease on admission to an exercise programme or the degree of improvement in these measures after 6 months of exercise training. Non cardiac factors including age, gender, Broca index and forced vital capacity explained 50% of the variation in peak oxygen uptake.

Patients with severe chronic heart failure showed improvements in exercise capacity similar to those in patients with normal and moderately impaired systolic function. Even

patients with left ventricular dysfunction and associated myocardial ischaemia were able to increase their maximal exercise capacity as a result of exercise training.

CHAPTER 5

PHYSIOLOGICAL EFFECTS OF EXERCISE TRAINING IN PATIENTS WITH SEVERE LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Published:

Digenio AG, Cantor A, Noakes TD, Cloete L, Mavunda D, Esser JD.
Is severe left ventricular dysfunction a contraindication to exercise cardiac rehabilitation programmes ?
S Afr Med J 1996; 86: 1106-1109.

5.1 Introduction

Patients with chronic congestive heart failure were previously not admitted for cardiac rehabilitation because of the hypothesis that they were at a much greater risk of sudden death during exercise and that exertion could adversely affect the natural history of the disease, precipitating or accelerating further decompensation of the left ventricle.

In Chapter 3 we showed that left ventricular dysfunction is very prevalent among patients enrolling into a cardiac rehabilitation programme. In Chapter 4 we demonstrated that there is no correlation between the degree of LV dysfunction at entry to a cardiac rehabilitation programme and exercise capacity and that patients with severely depressed LV dysfunction could achieve similar adaptations to training during maximal exercise, than those derived by patients with moderately depressed or normal LV function.

The hypothesis that patients with severe left ventricular dysfunction could safely derive full adaptations at both submaximal and maximal exercise levels remains to be evaluated. The measurement of EF not only at rest but also in response to acute exercise, will provide a valuable tool to quantify the effects of exercise training on the LV function of these patients.

The aim of the present chapter of this thesis was to determine whether a 6 month exercise training programme could improve the exercise capacity and cardiovascular efficiency of high risk patients with severe left ventricular impairment, and whether it could be performed safely without any adverse effects on their left ventricular function.

Since cardiac rehabilitation is just in its infancy in South Africa, the demonstration that exercise training could induce benefits in patients with chronic congestive heart failure without deteriorating their LV function could have important implications for the practice of cardiac rehabilitation in the country.

5.2 Methods

Twenty eight patients recovering from an acute MI and with a left ventricular EF of 30% or less at rest were included in this study. They all had compensated, stable, non-oedematous, chronic heart failure. Their ages ranged from 44 to 71 years with a mean of 63.5 $\pm$ 7.5 years. The MI was located on the inferior wall in 5 patients and anteriorly in the remaining 23; four of these patients had also suffered a previous inferior wall infarction. Seven patients had clinical evidence of congestive heart failure, and 3 suffered pulmonary oedema during the acute phase of their illness. Functionally, 15 patients were classified in the NYHA Class I, 10 in Class II and 3 in Class III. All patients were on angiotensin converting enzyme inhibitors, 76% on nitrates and 52% on calcium channel blockers. It is unknown whether the use of calcium channel blockers could have contributed to the depression in left ventricular function in some patients. Only one patient had a change of medication during the training period. This patient was on antiarrhythmic therapy, which was modified during the rehabilitation programme.

Within 75 to 90 days after the MI, all patients underwent a treadmill symptom-limited exercise test using the Chung protocol (27), before being accepted onto the exercise cardiac rehabilitation programme. Respiratory gas analysis using a metabolic cart was carried out and peak oxygen uptake was determined. Continuous heart rate and electrocardiogram were recorded and the blood pressure was monitored at every minute of the exercise test and in the recovery phase. The exercise end-points were previously described in Chapter 2.

Radionuclide ventriculography, using the equilibrium multi-gated blood pool technique (44) was performed at rest in all patients and during exercise in the supine position in 18 patients. Global EF at rest and during exercise was determined in these patients. All tests were repeated 6 months after the beginning of the exercise programme. A follow-up resting EF could not be obtained in one patient because of lack of consent.

The exercise training programme was medically supervised and of 6 months duration. The intensity of exercise was set between 65 and 85% of each patient's maximal heart rate achieved during treadmill testing. Patients were required to exercise at their prescribed intensity 3 times a week continuously for 30-45 minutes. Aerobic exercise consisted of walking or jogging, or stationary cycling if weight-bearing exercise was contraindicated. The exercise session was preceded by a warm-up and followed by a cool-down period. The exercise intensity for each patient was progressed slowly over a number of weeks until the required intensity of exercise was achieved.

Five patients showed 1.5-2.5 mm ST depression without chest pain during the exercise test; in these patients the training intensity was set 15-20 beats/minute below the heart rate that produced ST segment changes.

The patients' compliance with the programme was monitored on a daily basis in terms of attendance at exercise sessions. Patients with a compliance below 60% of all prescribed sessions were excluded from the study.

Haemodynamic, left ventricular function and effort tolerance parameters were compared before and after training using the Student's t test for paired samples.

5.3 Results

Twenty two patients completed the exercise training programme with an attendance greater than 60% of the possible sessions. Two patients in NYHA Class III died suddenly, one before starting exercising and the other 2 months after starting the exercise programme. This death occurred whilst the patient was at home. Four patients dropped out for non-medical reasons.

The mean resting EF at the beginning of the study was 25.4 $\pm$ 5% (range 11 to 30%), increasing to 28.5 $\pm$ 7.9% (range 12 to 50%) after 6 months of exercise training ($p<0.05$) (Fig 5.1). The mean exercise EF was 27.3 $\pm$ 7.7% (range 10 to 40%) at the beginning of the study and 29.9 $\pm$ 9.5% (range 11 to 45%) at the end of training ($p=0.11$) (Fig 5.1). The individual exercise EF increased in 12 patients, decreased in 4 and did not change in 2. The resting heart rate decreased significantly from the beginning to the end of the training period (78.1$\pm$7.1 vs 70.9$\pm$6.9 bpm, $p<0.001$).

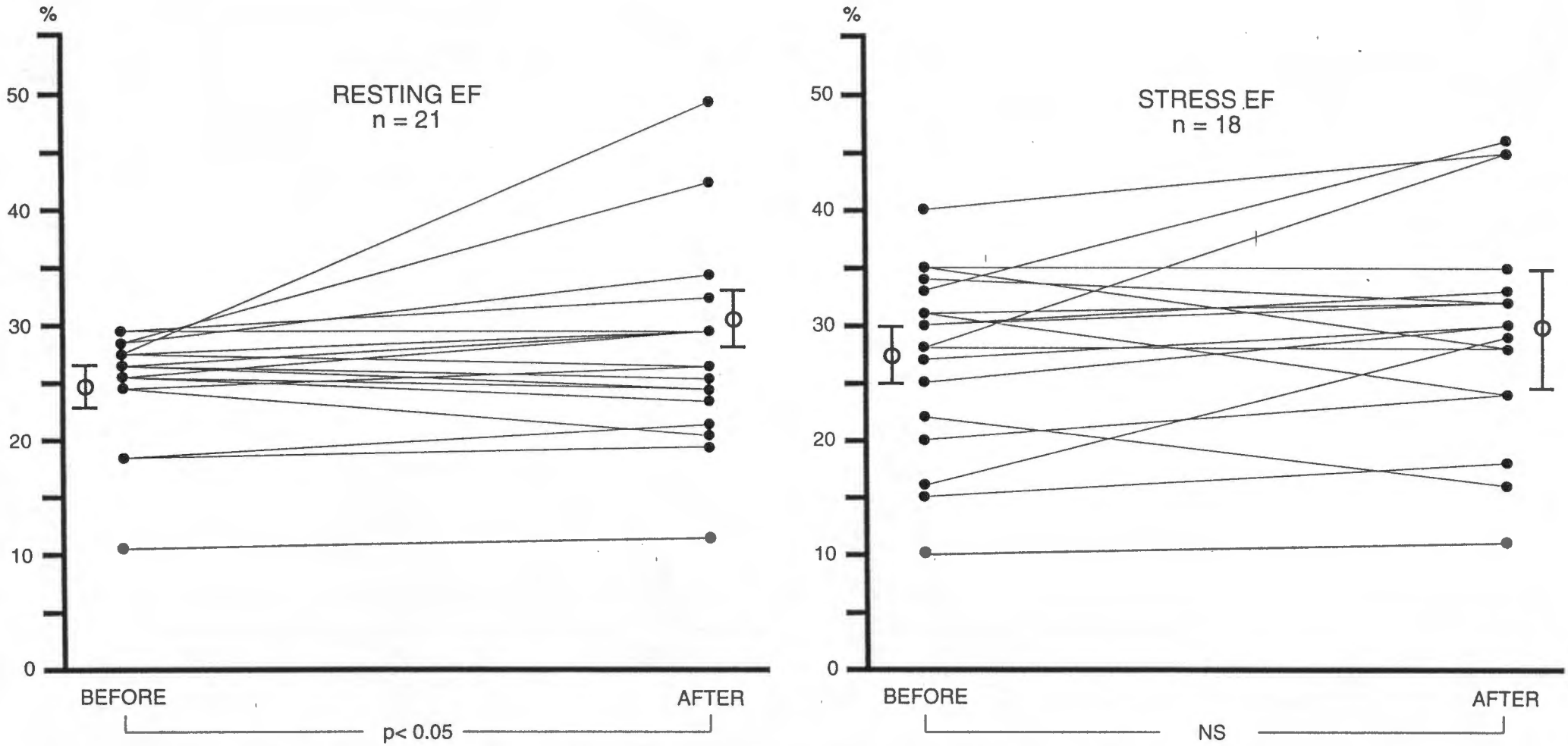


Figure 5.1 Comparison of left ventricular ejection fraction at rest and during exercise before and after 6 months of exercise training

Mean ± 2 SEM ● Individual values

The peak oxygen consumption improved significantly from 19.4 ± 3 (range 13.3 to 23.9 ml/kg.min) to 21.8 ± 4.8 ml/kg.min (range 11.4 to 28.7 ml/kg.min) after exercise training ($p<0.05$) (Figure 2). The exercise time to exhaustion on the treadmill increased significantly from 527 ± 171 (range 250 to 880) to 700 ± 186 seconds (range 330 to 1020) after 6 months of exercise training ($p<0.001$) (Figure 5.2). The exercise time on the treadmill increased by 32.8% after exercise training whereas peak oxygen uptake improved by only 12.4%. Heart rate increased significantly at peak exercise from 138.2 ± 6.2 to 146.3 ± 7.4 bpm ($p<0.01$) and decreased during submaximal work from 129 ± 8.5 to 122 ± 9.0 bpm ($p<0.05$) as a result of exercise training. There were no changes in systolic or diastolic blood pressure at maximal or submaximal levels due to training. The maximal double product was significantly increased after training ($p<0.05$) (Figure 5.2), while the double product at the same submaximal work load was significantly reduced (214 ± 52 vs 194 ± 44 bpm.mmHg x 100, $p<0.05$).

No correlation was found between the EF at rest or during exercise and peak oxygen consumption.

Three of the 5 patients who showed ST segment changes on admission had a normal ST segment response during the second exercise test after exercise training.

Training complications such as congestive heart failure, complex ventricular arrhythmias, accelerated angina pectoris, syncope, or new ischaemic changes were not observed. All patients who completed the exercise course were alive after a mean follow-up of 26 months (range 8-32 months). One was hospitalized for recurrent ventricular arrhythmias within the first two months of exercise training, and underwent major abdominal surgery without any complications, 24 months after the end of the training programme. Four others were hospitalized for chest pain during the follow-up period after training; myocardial ischaemia was diagnosed in three.

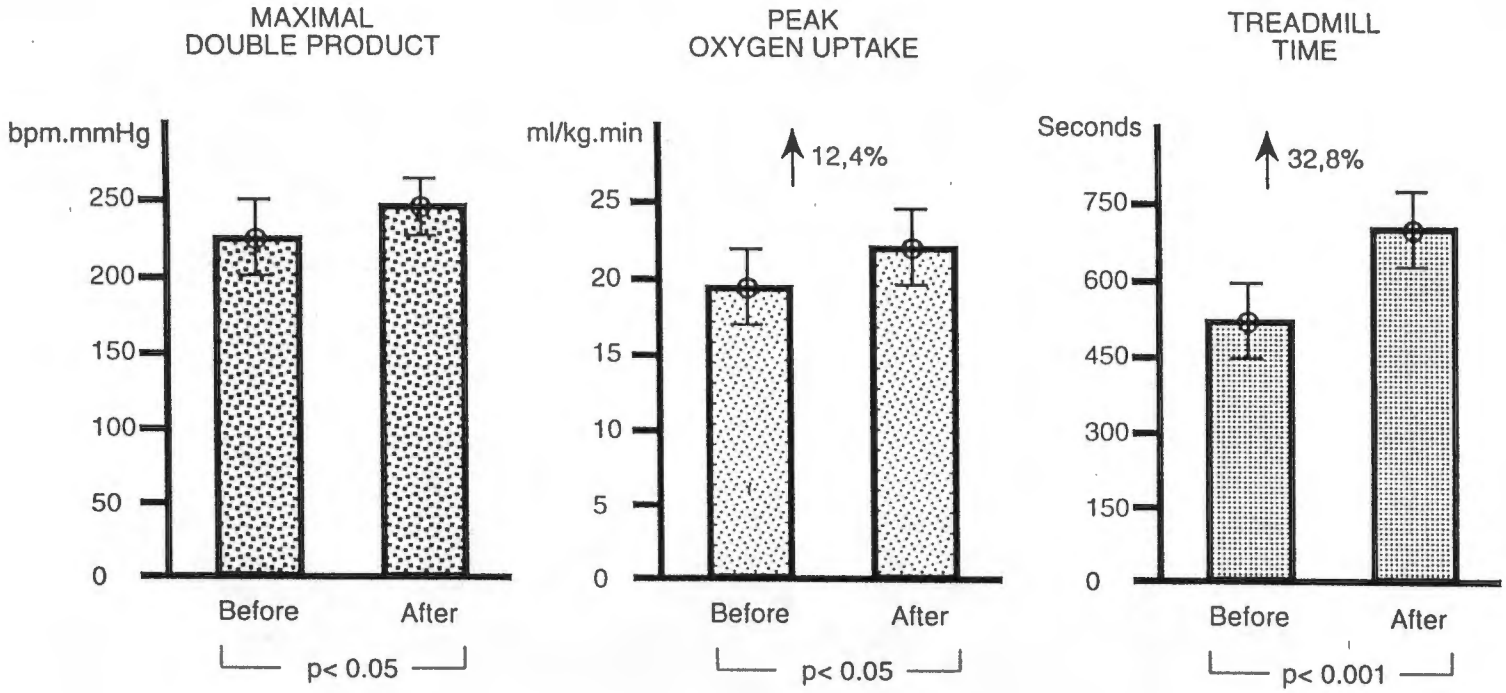
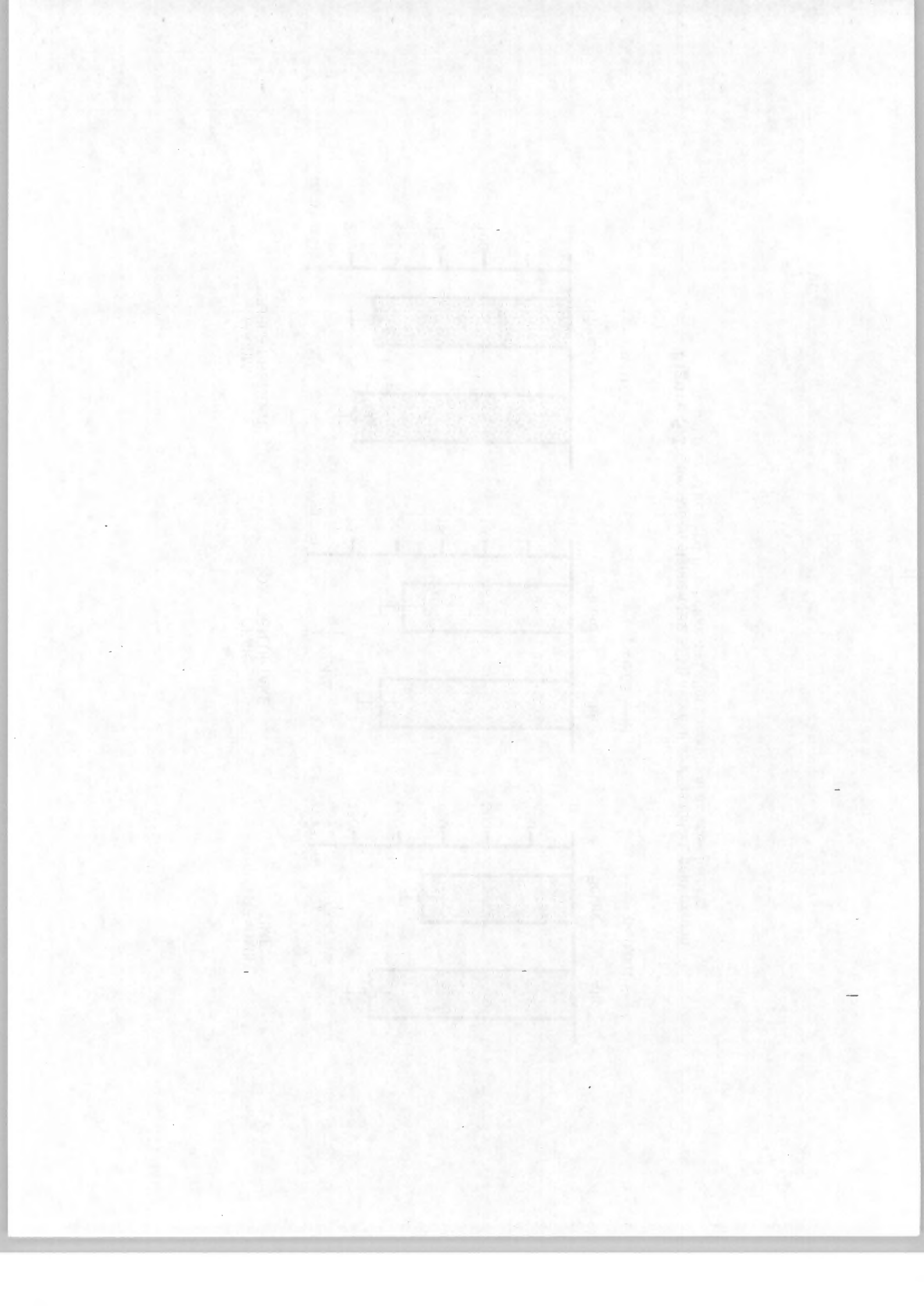


Figure 5.2 Comparison of mean (± 2 SEM) maximal double product, peak oxygen uptake and treadmill time before and after 6 months of exercise training



5.4 Discussion

Our observations demonstrate the feasibility of exercise training for patients with severe left ventricular dysfunction. After 6 months of exercise training our patients improved their exercise performance by increasing peak oxygen consumption, exercise time to exhaustion and the double-product at maximal effort. Furthermore cardiovascular demands during submaximal exercise were also significantly reduced. This is in agreement with other authors who have also shown that patients with severely depressed left ventricular systolic function can derive benefits from exercise training (98,132-134,138).

As in Chapter 4 we found lack of correlation between EF at rest or during exercise and maximal exercise capacity. This is in keeping with the findings in the above studies and suggests that peripheral adaptations have ocurred.

An increase in vagal tone could confer some protection regarding fatal ventricular arrhythmias (122). The reduction in resting heart rate seen in our patients could be some evidence of a training-induced increase in vagal activity.

After 6 months of training no deterioration in left ventricular function was observed in our study, even in patients with the lowest EFs and with ST segment depression on admission. This is in agreement with the above studies (98,132-134,138) which showed a lack of change in left ventricular systolic function in patients without myocardial ischaemia but conflicts with the finding that patients with left ventricular dysfunction and ongoing myocardial ischaemia may show deterioration in left ventricular function after exercise training (190). The limitations of electrocardiographic ST segment analysis alone in predicting myocardial ischaemia are appreciated. In our study, the sensitivity of the method was enhanced by also including an analysis of the ST segment time course in the post-effort period. Only patients with ST segment depression both during and post-effort were considered as having a possible ischaemic response.

There was a remarkable increase in EF after 6 months in two patients, perhaps indicating the presence of myocardium which was either "stunned" or "hibernating" at the time of the initial test (229). The former is more likely since none of these patients showed any electrocardiographic evidence of myocardial ischaemia during exercise testing. When those patients were excluded from the analysis, the difference between the mean EF before (25.6 $\pm$ 4.7%) and after training (26.6 $\pm$ 5.3%) was not statistically significant. It is unlikely that the improvement in ejection fraction seen in the above two patients could be attributed to the exercise programme since improvements in left ventricular function have only been noted with more intensive exercise training of greater frequency, intensity and duration (115,199). The EF of 2 subjects during exercise was lower after training but their values were still within the confidence interval for normal exercise EF from our laboratory.

Two patients enrolled into the study died, one before starting the programme and the other 2 months after starting the training. The latter patient attended very few sessions during those 2 months and he failed to reach the prescribed training heart rate. His low peak VO2 on admission (12.5 ml/kg.min) and his low exercise time to exhaustion (5.5 minutes) suggest that he was very sick prior to exercise training and that training was unlikely to have caused the deterioration in his condition.

Whether physiological adaptations to exercise training will result in a better prognosis in this high risk group of patients is unknown. Patients with an EF below 40% had a 26% 1 year mortality if they showed signs of heart failure during their stay in hospital compared with 12% if they did not show such clinical signs (119). All our patients were still alive between 8 and 32 months after their cardiac event although 10 showed signs of congestive heart failure while in hospital. However, myocardial ischaemia was diagnosed in three patients in the follow-up period after exercise training, suggesting progression of disease.

All our patients were on angiotensin converting enzyme inhibitors and it is impossible to determine the extent to which these drugs contributed to the improvements seen in submaximal and maximal exercise capacity. A recent study which evaluated the effect of

physical training in patients with impaired left ventricular function showed only a small improvement when medical treatment was added, demonstrating the strong influence of endurance exercise (230).

5.5 Conclusions

Patients with severe left ventricular dysfunction in NYHA classes 1 and 2 were able to participate in and derive physiological benefits from a supervised exercise rehabilitation programme, without any deleterious effect on their left ventricular function. As a consequence of their participation in the programme, they achieved a significant improvement in peak oxygen uptake, treadmill time and maximal double product whilst they were able to reduce significantly the double product at a fixed submaximal load. We could speculate that patients with a severe impairment in LV function might benefit the most from a cardiac rehabilitation programme, since small increases in effort tolerance could represent a meaningful improvement in their quality of life.

This suggests that whilst rest retains an essential role in the management of an acute episode of heart failure, once the patient has been fully stabilized, physical training could be used as part of their integral treatment together with medication or after revascularization procedures, even in patients with stable, compensated chronic heart failure.

This would appear to be the first evaluation of the possible benefits and risks of exercise training in patients with severe left ventricular dysfunction enrolled in a community-based cardiac rehabilitation programme in South Africa.

CHAPTER 6

EFFECTS OF EXERCISE-INDUCED MYOCARDIAL ISCHAEMIA ON LEFT VENTRICULAR FUNCTION AND ADAPTABILITY TO EXERCISE TRAINING, IN PATIENTS WITH CORONARY ARTERY DISEASE

In Press:

Digenio AG, Noakes TD, Joughin H, Daly L.
Effect of myocardial ischaemia on the left ventricular function and adaptability to exercise training of patients with coronary artery disease.
Med. Sci. Sports Exerc. July 1999.

6.1 Introduction

Patients with residual myocardial ischaemia post-myocardial infarction or revascularization procedures are more frequently accepted for exercise rehabilitation in modern programs.

The diagnosis of myocardial ischaemia (191) is usually made by the demonstration of transient ST segment depression, horizontal or downward sloping, of 0.1 mV or more for 80 milliseconds in the electrocardiogram during an exercise test but could be greatly enhanced with myocardial perfusion imaging techniques (193,194). A common observation is that a high percentage of positive treadmill tests for ischaemia are not associated with reported chest pain (231,232).

Exercise training may have special significance in this type of patient since previous research studies have shown that the physiological adaptations elicited by training are translated into a greater amount of work done before angina or ST segment depression occurs (110,233,234), leading to an improved quality of life.

In Chapter 3 we evaluated the compensatory mechanisms used by patients with left ventricular dysfunction to increase their cardiac output during exercise and in Chapter 5 we evaluated the adaptability to training of patients with chronic left ventricular dysfunction. We know that myocardial ischaemia can have a deleterious impact on the left ventricular function of cardiac patients but we know little about the effect of exercise training on that relationship.

The aim of this section of the thesis was therefore to evaluate the effects of exercise-induced myocardial ischaemia -whether silent and/or symptomatic- on the left ventricular function and the adaptability to training of patients with coronary artery disease enrolled into an exercise cardiac rehabilitation programme.

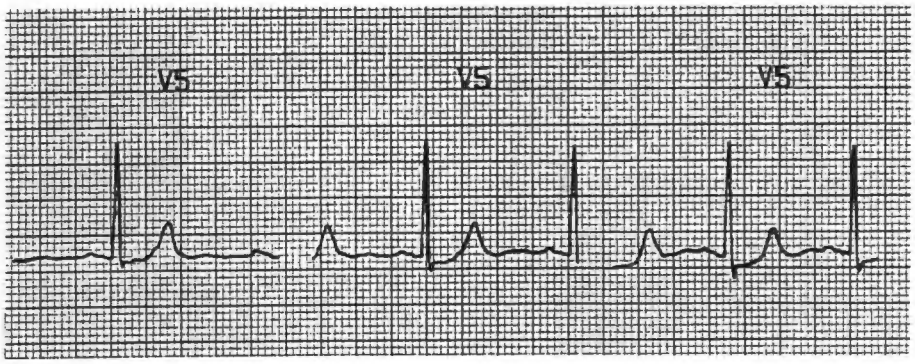
6.2 Methods

Seventy two consecutive patients with documented coronary artery disease were selected for the study after undergoing a symptom-limited exercise test on admission to our cardiac rehabilitation centre. Fifty patients without signs and/or symptoms of myocardial ischaemia during exercise testing were used as a control group for exercise training (CG-ET). Patients showing planar or downsloping ST segment depression ≥1mm during exercise testing underwent radionuclide imaging studies using Technetium 99m methoxy isobutyl isonitrile (Tc-MIBI). Patients not showing at least one transient defect were excluded from the study. Twenty two patients showed a transient defect during radionuclide perfusion imaging and formed our experimental group (EG). Of those, 10 patients had symptomatic ischaemia during exercise testing and 12 did not develop symptoms. Figure 6.1 shows the ECG tracings during and post-effort of a patient with silent ischaemia. Figure 6.2 shows the Tc-MIBI scintigram at rest and post-effort in the same patient.

EXERCISE ECG TEST USING THE CHUNG PROTOCOL IN A PATIENT WITH SILENT ISCHAEMIA

Figure 6.1

Stress

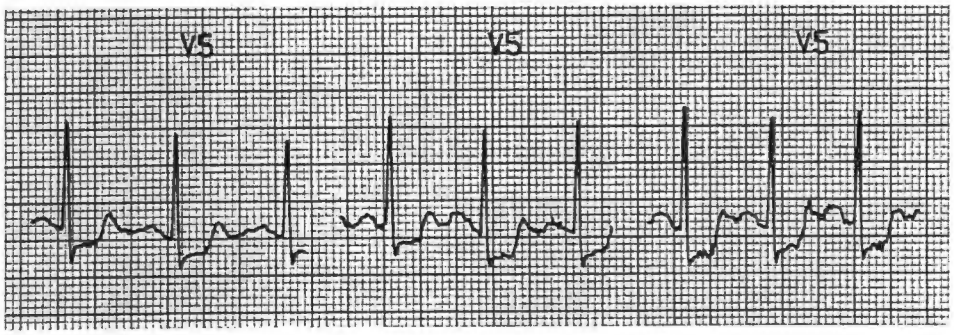


2'
Stage I

5'
Stage II

8'
Stage III

Stress

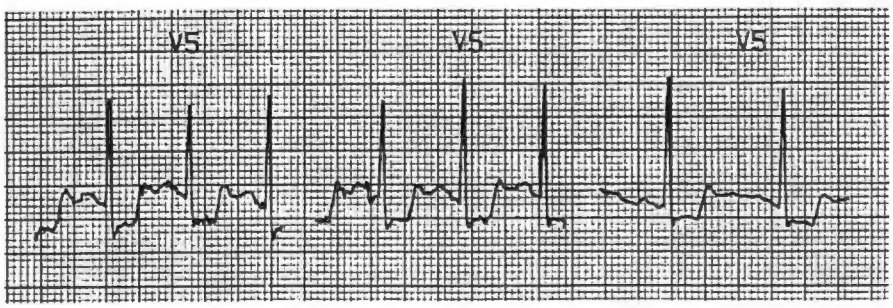


11'
Stage IV

14'
Stage V

15'30"
Peak

Post-effort



0'

30"

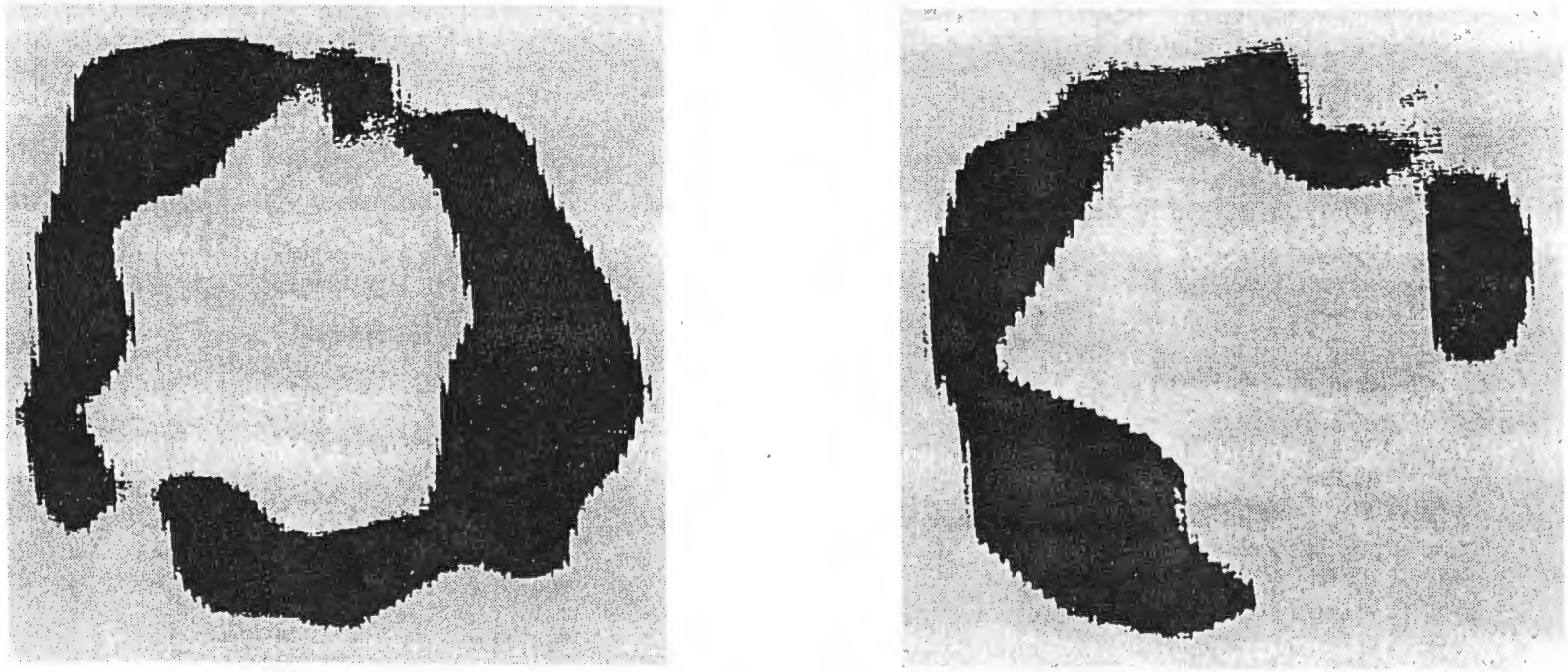
1'

Figure 6.2

NUCLEAR IMAGING TEST USING TC-MIBI IN THE SAME PATIENT

REST

POST-EFFORT



POSTERO-LATERAL DECREASED PERFUSION
WAS SEEN POST-EFFORT

Radionuclide ventriculography testing was subsequently performed in both groups EG and CG-ET at rest and also during exercise in EG. In addition, the control group used in previous Chapter composed of 31 volunteers (42 to 64 years, mean 52 $\pm$ 8.1 years), without any history, signs or symptoms of cardiac disease and with normal results for an exercise test, were selected as a control group for the measures of resting and exercise left ventricular function (CG-LV).

Both groups, CG-ET (n=50) and EG (n=22) underwent a 6 month exercise training programme. Exercise testing and radionuclide ventriculography tests were repeated at the end of the training period, the former in all patients and the latter in 12 patients with myocardial ischaemia.

The stress ECG test consisted of a treadmill symptom-limited exercise test using the Chung protocol (27). Respiratory gas analysis using a metabolic cart was carried out and peak oxygen uptake was determined. Continuous heart rate and electrocardiogram were recorded and the blood pressure was monitored every 3 minutes of the exercise test and in the recovery phase. The test was considered positive for ischaemia if 1mm horizontal or down-sloping ST depression was observed 80 milliseconds after the J point.

Myocardial perfusion studies were performed at rest and during exercise in all patients in EG according to the protocol of the Department of Nuclear Medicine of the Johannesburg Hospital, University of the Witwatersrand.

Radionuclide ventriculography was performed at rest in all patients, using the equilibrium multi-gated blood pool technique as described in Chapter 2 (44) and EDC, ESC, SC, EF, T-PER, PER, AV-ER, T-PFR, PFR and AV-RFR were derived from time-activity curves as previously shown. Changes from rest to exercise were evaluated by the use of the percentage change from rest to exercise, calculated as the value during exercise minus the value at rest divided by the value at rest x 100.

The exercise training programme was of 6 months duration and the intensity of exercise was set at the ventilatory threshold identified in the initial exercise test which typically occurred between 70 and 85% of each patient's maximal heart rate. Patients developing ST segment depression during exercise testing had their intensity set 10 to 15 beats per minute below the ischaemic threshold. The exercise training programme was described in detail in Chapter 2.

The patients' adherence to the programme was monitored on a daily basis in terms of attendance at exercise sessions and the intensity of their training programmes and the data was captured on a computer.

Statistical analysis

The data for the EG on admission to the programme and the CG-LV were compared with respect to their systolic and diastolic left ventricular function at rest and during exercise, including the percentage change from rest to exercise.

The data for EG and CG were compared regarding their adaptation to 6 months of exercise training.

In the EG, patients with silent ischaemia were compared to those with symptomatic ischaemia with respect to their left ventricular function and adaptation to exercise training. Group comparisons were made by ANOVA or chi-square analysis where appropriate. If F was significant, differences between groups were determined using Fisher's LSD tests. Significance at the 5% level or lower was reported. All data are presented as mean $\pm$ standard error.

6.3 Results

There were no differences in subjects in CG-ET and EG groups on admission to the programme with respect to age, medical condition, medication and mean left ventricular ejection fraction (Table 6.1).

Table 6.1 Characteristics of patients with coronary artery disease on admission.

	CAD CONTROL (CG) n=50	MYOCARDIAL ISCHAEMIA (EG) n=22
Mean AGE ± SD (years)	58.2 ± 6.9	59.3 ± 7.1
MI • Anterior • Inferior • Lateral	 35 (70%) 16 (46%) 19 (54%)	 12 (54.5%) 5 (42%) 7 (58%)
CABG	26 (52%)	9 (40.9%)
PTCA	8 (16%)	4 (18.2%)
MEDICATION • Beta Blockers • Calcium Blockers • Nitrates • ACE inhibitors • Diuretics	 16 (32%) 13 (26%) 5 (10%) 7 (14%) 5 (10%)	 12 (54.5%) 9 (40.9%) 4 (18.2%) 4 (18.2%) 6 (27.3%)
Mean EF ± SD (%)	51.9 ± 9.3	55.1 ± 11.5

Values are expressed as number (%) unless specified.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; EF: ejection fraction; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; SD: standard deviation.

The ischaemic response on admission assessed by electrocardiographic and nuclear imaging criteria is shown in Table 6.2 for all EG patients and for the subgroups with silent or symptomatic ischaemia. The average number of transient defects was 1.41 per patient. Patients with silent ischaemia had a maximum of two transient defects, whereas one patient with symptomatic ischaemia had three ($p<0.001$).

Table 6.2 Differences in the ischaemic response on admission to the trial in 22 patients with coronary artery disease.

	MYOCARDIAL ISCHAEMIA n=22	SILENT ISCHAEMIA n=12	SYMPTOMATIC ISCHAEMIA n=10
ST DEPRESSION (mm) #	1.95 ± 0.21	2.1 ± 0.31	1.7 ± 0.2
ST RECOVERY TIME (min) #	9.2 ± 0.9	10.3 ± 1.2	7.9 ± 1.3
NUMBER OF TDs • ONE • TWO • THREE	 14 (64%) 7 (32%) 1 (5%)	 8 (67%) 4 (33%) ---	 6 (60%) 3 (30%) 1 (10%) *
AVERAGE NUMBER OF TDs PER PATIENT	1.41	1.33	1.50
CORONARY ARTERY TERRITORY • RC • CX • LAD	 15 TD (48%) 6 TD (19%) 10 TD (32%)	 8 TD (50%) 3 TD (19%) 5 TD (31%)	 7 TD (47%) 3 TD (20%) 5 TD (33%)

Values are expressed as mean ± standard error. Other values are expressed as number (percentage).
TDs: transient defects defined as areas of decreased perfusion when comparing stress to resting scans; RC: right coronary artery; CX: circumflex; LAD: left anterior descending.
* Patients with symptomatic ischaemia had more significant transient defects than patients with silent ischaemia, $p<0.001$.

The mean attendance at sessions was slightly better for the EG group than the CG group (EG: 80.6 ± 14.9 % vs CG: 71.9 ± 14.9 %, p=0.051). Although there was a trend towards a lower exercise intensity in the EG, there were no significant differences in training heart rate, percentage of the maximal heart rate, training oxygen uptake, percentage of peak oxygen uptake and kilocalories per session between EG and CG-ET (Table 6.3).

Table 6.3 Similarities in the training stimulus in patients with coronary artery disease with or without myocardial ischaemia.

	CAD CONTROL (CG-ET) n=50	MYOCARDIAL ISCHAEMIA n=22	p
PERCENTAGE ATTENDANCE	71.9 ± 2.1	80.6 ± 3.2	0.051
TRAINING HR (beats per minute)	106.5 ± 2.2	99.5 ± 4.2	NS
% MAXIMAL HR	78.6 ± 1.0	77.4 ± 1.2	NS
TRAINING VO_2 (ml/kg/min)	17.6 ± 2.6	17.2 ± 3.8	NS
% PEAK VO_2	71.0 ± 1.4	69.3 ± 2.2	NS
KCAL PER SESSION	268.6 ± 11.2	261.8 ± 17.3	NS

Values are expressed as mean ± standard error.
HR: heart rate; KCAL: kilocalories; VO_2: oxygen uptake.

Significant differences in left ventricular haemodynamics and systolic and diastolic function were seen between patients with myocardial ischaemia and CG-LV (Table 6.4).

At rest.

There were no differences in heart rate between the groups. SC were significantly decreased in patients with CAD, when compared to controls (p=0.007), while there were no differences in EDC and ESC between the two groups. EF, PER and AV-ER were significantly lower in patients than controls (p=0.03, p=0.035 and p=0.005 respectively). AV-RFR was also significantly reduced in patients compared to controls (p=0.01), while there were no differences in PFR between the two groups.

During exercise.

Heart rate was significantly increased during exercise in patients and controls (CG-LV) but the percentage increase was significantly higher in the control group (99% vs 67%, p=0.0001). EDC and ESC were significantly increased during exercise in both groups, without changes in SC. Although the magnitude of the change from rest to exercise appeared greater in patients than in controls, this was not statistical significant. EF was significantly reduced in patients during exercise (p=0.0001) while it did not change in CG-LV. The percentage change from rest to exercise was not significantly different between the groups. T-PER and T-PFR were equally shortened in both groups. PER, AV-ER, PFR and AV-RFR were significantly increased during exercise in both groups, the magnitude of the change being greater in controls than in patients (p=0.0001, p=0.01, p=0.0001 and p=0.01 respectively).

Table 6.4 Differences in resting and exercise left ventricular function between patients with coronary artery disease and myocardial ischaemia (EG) and healthy individuals without known cardiac disease (CG-LV).

	MYOCARDIAL ISCHAEMIA			HEALTHY CONTROL (CG-LV)			p VALUE
VARIABLES	Rest n=22	Exercise n=22 *	Δ R-E n=22	Rest n=31	Exercise n=31 *	Δ R-E n=31	Rest Exercise Δ R-E
HEART RATE (bpm)	62.3 (2.8)	101.7 (3.7) p=0.0002	-66.8 (6.2)	62.4 (2.4)	121.9 (2.5) p=0.0001	-98.7 (5.5)	NS 0.0001 0.0001
EDC	436401 (27532)	557909 (48292) p=0.007	-34.1 (13.3)	454895 (32856)	541477 (52420) p=0.034	-20.4 (9.5)	NS NS NS
ESC	207737 (23541)	298799 (32480) p=0.001	-57.4 (14.0)	180400 (31312)	244226 (26493) p=0.001	-40.9 (11.8)	NS NS NS
SC	228663 (11199)	259096 (49409) p=NS	-16.1 (13.6)	274494 (10379)	297251 (30211) p=NS	-10.0 (10.2)	0.007 0.02 NS
EF %	55.1 (2.4)	47.5 (2.5) p=0.0001	7.6 (1.2)	61.1 (2.4)	58.4 (1.6) p=NS	3.8 (3.4)	0.03 0.0001 NS
T-PER (sec)	0.13 (0.01)	0.07 (0.01) p=0.0001	42.1 (7.4)	0.15 (0.00)	0.07 (0.00) p=0.0001	50.1 (4.5)	NS NS NS
PER (EDV/sec)	2.53 (0.12)	3.27 (0.18) p=0.0001	-32.0 (7.0)	2.86 (0.13)	5.00 (0.21) p=0.0001	-77.4 (7.2)	0.035 0.00001 0.0001
AV-ER (EDV/sec)	1.58 (0.07)	1.88 (0.12) p=0.03	-19.5 (6.6)	1.86 (0.08)	2.53 (0.11) p=0.0001	-37.8 (7.3)	0.005 0.00001 0.01
T-PFR (sec)	0.18 (0.01)	0.11 (0.01) p=0.004	35.7 (6.4)	0.16 (0.01)	0.10 (0.01)	37.2 (8.8)	NS NS NS
PFR (EDV/sec)	2.19 (0.13)	4.21 (0.33) p=0.002	-98.6 (16.2)	2.39 (0.13)	6.27 (0.28) p=0.0001	-167.3 (14.6)	NS 0.0001 0.0001
AV-RFR (EDV/sec)	1.47 (0.09)	2.89 (0.22) p=0.0004	-106.1 (18.4)	1.81 (0.09)	4.46 (0.27) p=0.0001	-157.7 (18.8)	0.01 0.002 0.01

Values are expressed as mean (standard error). * p values: rest vs exercise.

Δ R-E: % change from rest to exercise; AV-ER: average ejection rate; AV-RFR: average rapid filling rate; CAD: coronary artery disease; EDC: end-diastolic counts; EDV/sec: end-diastolic volumes per second; EF: ejection raction; ESC: end-systolic counts; PER: peak ejection rate; PFR: eak filling rate; SC: stroke counts; T-PER: time to peak ejection rate; T-PFR: time to peak filling rate.

The effects of exercise training are shown in Table 6.5.

Peak oxygen uptake, peak ventilation and ventilatory threshold were significantly increased in both EG and CG-ET groups (EG: $p<0.02$, $p<0.006$ and $p<0.003$; CG: $p<0.001$, $p<0.002$ and $p<0.001$; respectively), while treadmill time to exhaustion and maximal heart rate were increased only in the CG ($p<0.001$ and $p<0.02$ respectively). Heart rate, blood pressure and the rate-pressure product measured at a submaximal level (6 minutes on the treadmill) were significantly reduced only in the CG ($p<0.001$, $p<0.002$ and $p<0.001$ respectively). Resting heart rate was not significantly reduced in any of the two groups as a result of training.

The subcategories of the EG, silent and symptomatic ischaemia failed to elicit any significant physiological adaptations to exercise training. The only differences found were that the treadmill time to exhaustion increased significantly more in the silent than in the symptomatic group ($p<0.02$) and that the respiratory quotient increased significantly more in patients with symptomatic rather than silent ischaemia ($p<0.004$).

Table 6.5 Haemodynamic, ventilatory and metabolic changes in all patients after 6 months of exercise training.

	CAD CONTROL (CG) n = 50			MYOCARDIAL ISCHAEMIA (EG) n = 22			SILENT ISCHAEMIA n=12			SYMPTOMATIC ISCHAEMIA n = 10		
	Admission	6 months	p	Admission	6 months	p	Admission	6 months	p	Admission	6 months	p
REST												
• HR (bpm)	73.4 (2.1)	70.6 (1.6)	NS	65.2 (3.9)	60.8 (2.6)	NS	62.1 (3.7)	59.2 (4.0)	NS	68.9 (4.3)	62.7 (3.4)	NS
SUBMAXIMAL EXERCISE												
• HR (bpm)	110.7 (2.5)	104.5 (2.0)	<0.001	100.8 (4.3)	98.2 (3.5)	NS	98.6 (4.5)	99.0 (5.2)	NS	103.5 (9.2)	97.2 (5.1)	NS
• SBP (mmHg)	168.8 (4.2)	154.3 (3.5)	<0.002	148 (3.6)	142.8 (4.5)	NS	153.7 (4.5)	150.2 (5.8)	NS	141.1 (5.9)	134 (6.4)	NS
• HR x SBP x 10^3 (bpm x mmHg)	18.9 (0.7)	16.3 (0.5)	<0.001	15 (0.8)	14.1 (0.7)	NS	15.2 (0.8)	14.9 (1.0)	NS	14.9 (1.6)	13.1 (1.1)	NS
• VO_2 (ml/kg.min)	18.2 (0.3)	18.3 (0.5)	NS	16.8 (0.5)	17.5 (0.5)	NS	17.1 (0.8)	18.4 (0.7)	NS	16.3 (0.7)	16.4 (0.6)	NS
• VE (L/min)	46.8 (1.5)	43.1 (1.5)	NS	38.1 (2.0)	39.9 (1.5)	NS	37.8 (2.6)	40.9 (2.0)	NS	38.4 (3.3)	38.7 (2.5)	NS
• VT (ml/kg.min)	16.9 (0.3)	18.4 (0.4)	<0.001	16.8 (0.6)	18.7 (0.5)	<0.003	17.6 (1.0)	19.3 (0.8)	NS	15.9 (0.7)	17.9 (0.6)	NS
MAXIMAL EXERCISE												
• HR (bpm)	138.1 (2.9)	142.2 (2.8)	<0.02	131.7 (5.4)	133.5 (4.7)	NS	134.5 (6.1)	138.5 (7.4)	NS	128.3 (10.0)	127.6 (5.5)	NS
• SBP (mmHg)	184.7 (4.3)	178.8 (4.7)	NS	159.1 (4.3)	162.8 (5.6)	NS	162.9 (4.0)	173.7 (5.9)	NS	154.5 (8.5)	148.7 (9.0)	NS
• HR x SBP x 10^3 (bpm x mmHg)	25.8 (0.9)	25.7 (0.9)	NS	21.3 (1.1)	21.7 (1.3)	NS	21.9 (1.1)	24.2 (1.7)	NS	20.5 (2.1)	18.8 (1.6)	NS
• VO_2 (ml/kg.min)	25.1 (0.6)	27.4 (0.7)	<0.001	25.2 (1.0)	26.9 (1.1)	<0.02	26.6 (1.5)	29.4 (1.5)	NS	23.6 (1.5)	24.0 (1.2)	NS
• VE (L/min)	82.8 (3.0)	89 (3.2)	<0.002	81.8 (3.7)	91.3 (3.5)	<0.006	79.8 (4.5)	93.0 (4.1)	NS	84.1 (6.6)	89.2 (6.4)	NS
• RQ	1.08 (0.01)	1.07 (0.00)	NS	1.06 (0.01)	1.10 (0.01)	<0.02	1.07 (0.02)	1.08 (0.02)	NS	1.04 (0.02)	1.12 (0.01)	NS
• TT (minutes)	10.7 (0.3)	12.7 (0.3)	<0.001	11.8 (0.4)	12.4 (0.4)	<0.001	11.9 (0.6)	12.9 (0.7)	NS	11.6 (0.8)	11.9 (0.7)	NS

Values are expressed as mean (standard error)HR: heart rate; RQ: respiratory quotient; SBP: systolic blood pressure; TT: treadmill time to exhaustion; VE: minute volume; VO_2: oxygen uptake; VT: ventilatory threshold.

There were no differences in the heart rate at the onset of ST segment depression or the treadmill time to ST segment depression before and after exercise training in the EG group and in the subgroups with or without myocardial ischaemia (Table 6.6). However, patients with symptomatic ischaemia had a significantly lower heart rate at the onset of ST segment depression than patients with silent ischaemia after training ($p<0.02$).

Table 6.6 Heart rate and treadmill time at ST segment depression in patients with myocardial ischaemia and in the subgroups with or without symptoms, before and after exercise training.

	MYOCARDIAL ISCHAEMIA n=22		SILENT ISCHAEMIA n=12		SYMPTOMATIC ISCHAEMIA n=10	
	Admission	6 months	Admission	6 months	Admission	6 months
HR-ST (bpm)	119.8 ± 4.7	119.7 ± 4.7	122.3 ± 5.9	124.6 ± 6.7 *	116.8 ± 8.1	113.8 ± 6.8 *
TIME-ST (min)	9.3 ± 0.5	9.9 ± 0.6	10.3 ± 0.7	10.3 ± 0.6	8.1 ± 0.4	9.3 ± 1.1

HR-ST: heart rate at the beginning of ST segment depression; TIME-ST: treadmill time to ST segment depression.
Values are expressed as mean ± standard error.
There were no significant differences as a result of training in any of the groups.
* Silent vs symptomatic: $p<0.02$

The left ventricular function of the subgroup of 12 patients in the EG who underwent repeated radionuclide ventriculography testing after exercise training is shown in Table 6.7. On admission to the programme, EDC and ESC did not increase during exercise, to the same extent, in these patients as in the whole group, but all other parameters were very similar. There were no significant differences before and after training in resting and exercise LV function and in the change from rest to exercise. However there was a trend towards a decrease in EDC and SC after training.

Table 6.7 Left ventricular function of coronary artery disease patients with myocardial ischaemia before and after 6 months of exercise training.

	ADMISSION n=12			6 MONTHS n=12			p VALUE
VARIABLES	REST	EXERCISE *	Δ R-E	REST	EXERCISE *	Δ R-E	Rest Exercise Δ R-E
HEART RATE (bpm)	60.5 (3.8)	95.2 (3.7) p=0.00002	-61.7 (8.8)	61.9 (2.4)	95.6 (3.8) p=0.0001	-55.3 (5.5)	NS NS NS
EDC	435723 (34420)	476853 (51334) p=NS	-13.4 (12.2)	467990 (39583)	374190 (58856) p=NS	17.3 (14.0)	NS NS NS
ESC	213671 (35230)	258978 (35019) p=NS	-35.3 (17.6)	229431 (36186)	244811 (52736) p=NS	-7.4 (19.5)	NS NS NS
SC	222052 (14105)	217876 (28890) p=NS	3.2 (9.7)	238559 (16647)	166878 (26168) p=0.026	27.9 (10.9)	NS NS NS
EF %	52.8 (3.5)	45.9 (3.5) p=0.01	7.0 (2.0)	52.7 (3.2)	43.6 (3.3) p=0.003	9.1 (2.3)	NS NS NS
T-PER (sec)	0.14 (0.00)	0.07 (0.00) p=0.00001	52.7 (4.5)	0.13 (0.00)	0.08 (0.01) p=0.01	34.5 (9.4)	NS NS NS
PER (EDV/sec)	2.45 (0.17)	3.06 (0.19) p=0.01	-30.8 (12.2)	2.43 (0.17)	3.13 (0.35) p=NS	-33.5 (14.8)	NS NS NS
AV-ER (EDV/sec)	1.44 (0.08)	1.70 (0.13) p=NS	-20.7 (10.3)	1.50 (0.10)	1.62 (0.14) p=NS	-6.9 (9.7)	NS NS NS
T-PFR (sec)	0.17 (0.01)	0.11 (0.01) p=0.007	31.8 (7.5)	0.18 (0.01)	0.13 (0.01) p=NS	27.6 (10.7)	NS NS NS
PFR (EDV/sec)	2.11 (0.19)	3.85 (0.43) p=0.003	-90.9 (24.4)	2.05 (0.14)	3.73 (0.36) p=0.001	-87.0 (19.7)	NS NS NS
AV-RFR (EDV/sec)	1.44 (0.15)	2.73 (0.31) p=0.002	-99.0 (25.8)	1.35 (0.10)	2.50 (0.19) p=0.0001	-88.2 (8.5)	NS NS NS

Values are expressed as mean (standard error). * p value: rest vs exercise.
Abbreviations as per Table IV.

6.4 Discussion

We investigated the effects of exercise-induced myocardial ischemia on the left ventricular function and adaptability to training of patients with coronary artery disease.

The first important finding was that at rest, our group with myocardial ischemia showed significant abnormalities in systolic and diastolic left ventricular function when compared with normal controls and that these abnormalities were no different from that of other patients with coronary artery disease as described in Chapter 3.

The effects of myocardial ischaemia on left ventricular function during exercise were our second important finding. There was a significant increase in end-diastolic counts leading to an acute ventricular dilatation and a tendency towards an increase in stroke counts during exercise. It is interesting to note that these results were similar to those seen in volunteers without coronary artery disease who also had a significant increase in EDC, although of a lesser magnitude, but were significantly different from those of patients with coronary artery disease without myocardial ischaemia in whom EDC did not increase during exercise and SC tended to fall.

Our results are in agreement with the study of Rerych et al (211) who evaluated the effect of ischaemia on left ventricular function by comparing the left ventricular performance of patients with single (n=10) and multi-vessel (n=20) coronary artery disease with that of normal individuals (n=30) using first transit angiocardiography at rest and during exercise in the erect position. Their results showed that the degree of cardiac dilatation during exercise was directly proportional to the severity of the ischaemia and emphasized the importance of an increase in preload as a basis for preservation of left ventricular function during exercise in this type of patients.

Both groups of patients with coronary artery disease, with and without myocardial ischaemia, showed a significant increase in maximal exercise capacity and ventilatory

threshold as a result of exercise training. However patients with myocardial ischaemia failed to show the expected reduction in heart rate, blood pressure and rate-pressure product during submaximal exercise and a reduction in heart rate or treadmill time at the onset of ST segment depression; changes which were present in the CAD groups of patients without myocardial ischemia. These are probably the most desirable training adaptations expected in this group of patients since this would have been translated into fewer symptoms and greater cardiovascular efficiency during their daily activities. This is in disagreement with some studies which have shown a significant submaximal training effect in patients with and without myocardial ischaemia (195,235-238). Such adaptations have been shown to be due to an increased arterio-venous extraction of oxygen rather than to changes in cardiac performance (94,112,195,239).

A possible explanation for this discrepancy in training effect in the presence of myocardial ischaemia in our patients could have been an inadequate training stimulus. In this regard, in the experimental group the intensity of exercise was set below the ischaemic threshold in order to increase the safety and therefore reduce the likelihood of exercise-related cardiovascular complications. However, training heart rate, percentage of the maximal heart rate, training oxygen uptake, percentage of peak oxygen uptake and kilocalories per session, although slightly lower in patients with ischaemia compared to those in the control group without ischaemia, were not significantly different between the groups, leading to the conclusion that the training stimulus was similar for patients with or without myocardial ischaemia.

Ades et al. (237) in a recent study evaluating the effects of exercise training of 3 and 12 months duration in older coronary patients, concluded that it appears that a stimulus of sufficient intensity is required for patients to reach a training threshold at which submaximal changes are likely to occur. The authors trained their older population at a higher relative intensity (75-90% of maximal heart rate from preconditioning treadmill testing) than is commonly utilised in cardiac rehabilitation programmes, based on their previous observation that older coronary patients rarely exercise to a true physiological

maximum at baseline (240). Although our patients exercised at an intensity which falls in the lower end of the range proposed by Ades et al., this threshold hypothesis is an unlikely explanation for our findings since both groups, with and without myocardial ischaemia, were of a similar age and trained at the same relative intensity.

The maximal rate-pressure product was unchanged after training in both groups with or without myocardial ischaemia and the exercise recommendations were of the conventional type for both groups of patients. Improvements in coronary blood supply have only been suggested in exercise programmes of much higher intensity, duration and frequency (241) which showed a significant increase in the maximal rate-pressure product considered by many as an indirect indicator of changes in myocardial blood flow, and a reduction in the magnitude of ST segment depression.

Although there were no statistical significant differences between the groups, medication usage seemed greater in the group of patients with myocardial ischaemia with respect to beta-blockers, calcium channel blockers and nitrates (Table 6.1). Suggestive evidence of more beta-blocker usage by the group with myocardial ischaemia is provided by a significantly lower heart rate and blood pressure at rest and at submaximal and maximal exercise levels (Table 6.5). Our results showed that the ability of this group of patients to increase their maximal oxygen consumption was not blunted by the use of these drugs. However reductions in myocardial oxygen consumption induced by pharmacologic therapy (242) could have attenuated the expected beneficial haemodynamic effects of exercise training at submaximal levels.

When patients with myocardial ischaemia were separated into silent and symptomatic subcategories, neither showed any training effects. This is probably due to the small numbers, but the trend was toward more favourable adaptations to maximal exercise in the group with silent myocardial ischaemia. Patients with symptomatic ischaemia had a lower heart rate at the onset of ST depression after training than patients with silent ischaemia, suggesting more progression of disease in this group of patients. Weisz et al (243) who

performed a second treadmill test after one year in patients with CAD found that treadmill parameters seemed to remain similar to those measured in the first test except for a longer exercise duration and a lower heart rate at the time of 1 mm ST depression. Our results could be consistent with the hypothesis that symptomatic ischaemia is of greater severity than silent ischaemia, although this interpretation is not shared by all (231,244).

The twelve patients with myocardial ischaemia, in whom we were able to assess left ventricular function before and after training, showed no major changes in left ventricular function as a result of training. However, we noted a significant fall in stroke counts during exercise and a lack of increase in PER after training, changes which could be interpreted as early indicators of progression of disease. In any case, these results should be taken with caution because of the small number of subjects.

If we accept that the general trend is towards deterioration, our results would conflict with those of Jiang et al. (245), who recently found that higher levels of physical fitness were associated with less transient myocardial ischaemia assessed in the laboratory (wall motion abnormalities at rest and during mental and exercise stress using radionuclide ventriculography and treadmill exercise testing), and during daily life (Holter monitoring) in 47 patients with CAD with a recent positive exercise test. The results of Schuler et al. (246) who adding a low fat diet to exercise training were able to demonstrate a 54% reduction in exercise-induced Thallium-201 scintigraphy relative to a matched control raise questions about what goals we should set for patients with coronary artery disease and myocardial ischaemia joining a cardiac rehabilitation programme. In this type of patients, aggressive coronary risk factor management leading to possible regression of disease could become more effective than exercise training, a strategy which was unable to produce improvements in cardiovascular efficiency or coronary blood supply in our study. This study antedated effective cholesterol-lowering trials and as consequence very few patients were on cholesterol lowering medications. It is possible that in the absence of significant cholesterol-lowering, exercise is of marginal benefit in improving or delaying progression of disease.

6.5 Conclusions

Patients with coronary artery disease and myocardial ischaemia preserved their cardiac output during exercise through an increase in heart rate and by utilising the Frank Starling mechanism leading to acute ventricular dilatation.

These patients showed improvements in maximal work capacity but failed to elicit physiologic adaptations at a submaximal workload or to increase the threshold for ischaemia after exercise training. Furthermore, the minor changes seen in left ventricular function after training may suggest progression of disease despite participation in an adequate exercise training programme.

It is possible that the main emphasis in the management of this type of patient in a cardiac rehabilitation setting should be placed more on coronary risk factor modification to slow progression of disease than on an improvement in cardiovascular efficiency. It is possible that aggressive cholesterol lowering, which was not practised at the time of the study, could have altered the natural progression of the disease and improve some of the functional outcomes evaluated in this study in patients with myocardial ischaemia.

CHAPTER 7

VENTILATORY RESPONSES TO EXERCISE BEFORE AND AFTER EXERCISE TRAINING IN PATIENTS WITH VARIOUS DEGREES OF LEFT VENTRICULAR DYSFUNCTION

In Press:

Digenio AG, Noakes TD, Joughin H, Daly L.
Ventilatory responses to exercise in patients with asymptomatic left ventricular dysfunction.
Med. Sci. Sports Exerc. July 1999.

7.1 Introduction

Dyspnea is frequently a factor limiting the exercise tolerance of patients with chronic heart failure (148,247-249). It has been shown that for the same workload, patients with heart failure have a greater ventilatory response than healthy controls (250-234). This increased ventilation can be identified by examining the relationship between minute ventilation (VE) and minute carbon dioxide production (VCO_2). Although VE is linearly related to VCO_2 in both controls and patients with heart failure, the slope of this relation has been found to be greatly increased in the latter group (146,148,247,252,253).

This relationship has been analysed for patients with chronic heart failure defined as in NYHA Classes II and III and ejection fractions (EF) below 50%, but has not been evaluated over a wide range of left ventricular impairment and in asymptomatic patients. It has been suggested that exercise training could favourably reduce the slope of this relationship in patients with chronic heart failure (250).

It was the purpose of this chapter of the thesis to assess the ventilatory responses to effort in patients with coronary artery disease and various degrees of asymptomatic left ventricular dysfunction and to determine whether a 6 month exercise training programme could correct any measured ventilatory abnormality.

7.2 Methods

Of the original cohort of 171 patients enrolled into the study in Chapter 4, only 102 patients were enrolled into the present study, 63 patients in G1, 21 in G2 and 18 in G3. Fifteen patients were excluded because of the presence of lung disease on medical history, physical examination and/or lung function testing on admission to the program and 54 because they failed to attend at least 60% of the possible sessions.

The medical evaluation, the patients' physical and physiological characteristics and the exercise training programme have been described in detail in Chapter 4. All patients were classified in the New York Heart Association classes I and II. Medication use was different between groups, with G1 using mainly beta blockers and calcium antagonists and G2 patients using calcium antagonists and angiotensin converting enzyme inhibitors, while G3 patients used more nitrates, angiotensin converting enzyme inhibitors and diuretics. None of the patients was on digitalis preparations. None of the patients had clinical evidence of congestive heart failure. Twenty four patients showed ST segment depression greater than 1mm and 7 patients showed ST segment elevation during exercise testing or in the recovery period. Patients with ST segment depression were evenly distributed among the three groups whereas G3 had a greater percentage of patients with ST segment elevation than the other groups ($p<0.01$ respectively).

Peak VO_2 and treadmill time were used to evaluate the maximal exercise capacity of patients and ventilation was assessed in all groups by VE, VCO_2 and by the VE/VCO_2 ratio and the slope of that relationship. All parameters were determined at rest, as the average of the last two minutes' values, at 6 and 9 minutes of effort on the treadmill, and at maximal effort. The relationship between VE and VCO_2 was evaluated, its slope correlated to peak VO_2 and the VE/VCO_2 ratio correlated to treadmill time. As in Davey's study (230), we determined the point of maximal ventilatory efficiency, defined as the point at which patients required the least minute ventilation per unit of carbon dioxide excretion during the exercise test.

Statistical analysis

Comparisons between groups were made by analysis of variance. When significant differences were indicated in the analysis of variance, individual comparisons were made with Fisher's LSD tests. The relations between VE and VCO_2 , the VE/ VCO_2 slope and peak VO_2 and the VE/ VCO_2 ratio and treadmill time were studied using a simple

regression analysis in each EF category before and after training, and using a multiple regression analysis including the EF category and the exercise training effect in the model. Data points were obtained during maximal treadmill testing for the former correlation and from the values at peak exercise for the latter two. Slopes were determined with a least square fitting procedure. All values were expressed as mean $\pm$ standard error. A p value of less than or equal to 0.05 was accepted as statistically significant.

7.3 Results

There were no differences in peak VO_2 and treadmill time to exhaustion between G2 and G1 on admission to the programme. However both parameters were significantly reduced in G3 compared to G2 and G1, as demonstrated by a lower mean peak VO_2 ($p=0.001$ and $p=0.007$ respectively) and a lower mean treadmill time ($p=0.001$ and $p=0.01$ respectively). In spite of these differences on admission, the tolerance to effort increased significantly in all groups as a result of training (Table 7.1).

Table 7.1 Peak VO2 and treadmill time before and after training according to ejection fraction category.

	GROUP 3 EF<35% n=18		GROUP 2 EF≥35 - <50% n=21		GROUP 1 EF≥50% n=63		p value Differences between groups		
	Adm	6 ms	Adm	6 ms	Adm	6 ms	3 vs 2 Adm 6 ms	3 vs 1 Adm 6 ms	2 vs 1 Adm 6 ms
Peak VO_2 (ml/kg/min)	20.2 (0.9)	22.4 (1.1) p=0.008	24.6 (0.9)	29.0 (1.3) p=0.0001	24.2 (0.7)	27.6 (0.8) p=0.0001	0.001 0.001	0.007 0.001	NS NS
Range	*13.3-28.9*		*14.5-30.7*		*13.3- 38.7*				
TT (minutes)	8.4 (0.6)	10.5 (0.7) p=0.002	11.6 (0.6)	13.8 (0.5) p=0.001	10.5 (0.4)	12.8 (0.4) p=0.0001	0.001 0.001	0.012 0.007	NS NS
Range	*4-12.3*		*6.3-16.3*		*4.3-18*				

Except for the range on admission, all values are expressed as Mean (Standard Error).
Adm: admission; EF: ejection fraction; 6 ms: 6 months; TT: treadmill time
The change from admission to 6 months was the same for all ejection fraction categories.

The ventilatory response to exercise before and after training is shown in Table 7.2 for all groups. There were no differences in minute ventilation and carbon dioxide excretion at rest, before or after training, and within groups. As exercise progressed, G3 patients showed a significantly lower VCO_2 and a significantly higher VE/VCO_2 , both before and after training than those in G2 and G1. At 9 minutes of exercise, VCO_2 was significantly lower in G3 than in G2 on admission ($p=0.011$) and after 6 months ($p=0.029$), and also than in G1 on admission ($p=0.028$). At peak exercise, VCO_2 was significantly lower in G3 than G2 and G1, both before ($p=0.012$ and $p=0.015$ respectively) and after training ($p=0.001$ and $p=0.004$ respectively). The VE/VCO_2 ratio was significantly higher in G3 patients than in G2 and G1 patients, at 6 and 9 minutes of exercise and at peak exercise, both before (6 minutes: $p=0.005$ and $p=0.002$; 9 minutes: $p=0.046$ and $p=0.026$; peak: $p=0.024$ and $p=0.002$) and after training (6 minutes: $p=0.001$ and $p=0.0003$; 9 minutes: $p=0.011$ and $p=0.005$; peak: $p=0.001$ and $p=0.001$).

Training produced a significant increase in VE and VCO_2 at 9 minutes ($p=0.014$ and $p=0.016$) and at peak effort ($p=0.0001$ and $p=0.0001$) in G1 patients and at peak effort only ($p=0.002$ and $p=0.0001$) in G2 patients. As a result of training patients in G3 also increased their peak ventilation ($p=0.006$) but without an increase in peak VCO_2.

Table 7.2 Differences in resting, submaximal and maximal ventilatory responses to exercise before and after training according to ejection fraction category.

	GROUP 3 EF < 35% N=18		GROUP 2 EF ≥35 - <50% n=21		GROUP 1 EF ≥ 50% n=63		p value Differences betwen groups		
	Adm	6 ms	Adm	6 ms	Adm	6 ms	3 vs 2 adm 6 ms	3 vs 1 adm 6 ms	2 vs 1 adm 6 ms
VE rest	12.8 (0.5)	13.5 (0.5) p=NS	11.4 (0.6)	12.4 (0.6) p=NS	12.2 (0.4)	12.7 (0.4) p=NS	NS NS	NS NS	NS NS
VCO_2 rest	0.22 (0.01)	0.23 (0.01) p=NS	0.22 (0.01)	0.23 (0.01) p=NS	0.22 (0.01)	0.23 (0.01) p=NS	NS NS	NS NS	NS NS
VE/VCO_2 rest	59.8 (2.3)	59.8 (2.6) p=NS	54.2 (2.5)	55.0 (2.0) p=NS	55.1 (1.3)	55.6 (1.2) p=NS	NS NS	NS NS	NS NS
VE - 6	43.5 (5.4)	48.6 (3.9) p=NS	40.4 (2.7)	40.7 (1.4) p=NS	41.9 (2.1)	42.5 (1.7) p=NS	NS NS	NS NS	NS NS
VCO_2 - 6	1.03 (0.13)	1.13 (0.09) p=NS	1.12 (0.08)	1.12 (0.04) p=NS	1.13 (0.05)	1.13 (0.04) p=NS	NS NS	NS NS	NS NS
VE/VCO_2 - 6	42.6 (2.3)	43.7 (2.0) p=NS	36.7 (1.1)	36.5 (0.8) p=NS	37.0 (0.7)	37.9 (0.7) p=NS	0.005 0.001	0.002 0.0003	NS NS
VE - 9	31.5 (8.2)	46.1 (7.7) p=NS	48.6 (5.9)	58.0 (2.2) p=NS	42.7 (3.8)	51.6 (3.0) p=0.014	NS NS	NS NS	NS NS
VCO_2 - 9	0.76 (0.20)	1.10 (0.18) p=NS	1.34 (0.16)	1.60 (0.06) p=NS	1.18 (0.10)	1.40 (0.08) p=0.016	0.011 0.029	0.028 NS	NS NS
VE/VCO_2 - 9	41.2 (2.0)	42.1 (1.8) p=NS	36.3 (1.2)	36.8 (1.2) p=NS	36.4 (0.9)	36.9 (0.8) p=NS	0.046 0.011	0.026 0.005	NS NS
Peak VE	70.6 (3.7)	79.6 (3.6) p=0.006	80.4 (4.4)	93.1 (5.2) p=0.002	75.7 (2.7)	87.0 (3.0) p=0.0001	NS NS	NS NS	NS NS
Peak VCO_2	1.56 (0.09)	1.69 (0.09) p=NS	2.00 (0.12)	2.35 (0.14) p=0.0001	1.92 (0.07)	2.16 (0.08) p=0.0001	0.012 0.001	0.015 0.004	NS NS
Peak VE/VCO_2	46.2 (2.3)	48.3 (2.3) p=NS	40.8 (1.3)	40.4 (1.5) p=NS	40.1 (0.9)	40.8 (0.8) p=NS	0.024 0.001	0.002 0.0001	NS NS

Values are expressed as Mean (Standard Error). Adm: admission; EF: ejection fraction; 6 ms: 6 months; VCO_2: carbon dioxide production; VCO_2 - 6 and 9: carbon dioxide production at 6 and 9 minutes on the treadmill; VE: ventilation per minute; VE - 6 and 9: ventilation at 6 and 9 minutes on the treadmill.

The relation between minute ventilation and the rate of carbon dioxide production was linear in all patients by visual inspection and linear regression with correlation coefficients exceeding 0.90 in all groups (Figure 7.1 and Table 7.3). By multiple regression the model correlation coefficient was 0.96 ($p=0.0001$). Groups 1 and 2 had similar slopes but their slopes were significantly smaller than for Group 3 ($p=0.0001$ respectively). The slope of the relation between minute ventilation and the rate of carbon dioxide production showed a very modest and negative correlation with peak oxygen uptake (model $r = -0.47$, $p=0.0001$) (Figure 7.2 and Table 7.3). The slope was significantly higher for group 3 than for groups 1 and 2 ($p<0.01$ respectively). The ratio of the relation of minute ventilation and rate of carbon dioxide production showed a non linear correlation with treadmill time (model $r = -0.70$, $p=0.0001$) (Figure 7.3 and Table 7.3). There were no significant differences in the slopes as a result of training in any group.

Table 7.3 Relation between minute ventilation and carbon dioxide production, relation between its slope and peak oxygen uptake and relation between its ratio and treadmill time, before and after training according to ejection fraction category.

	Group 3 EF < 35%		Group 2 EF ≥ 35 and < 50%		Group 1 EF ≥ 50%	
	Adm.	6 months	Adm.	6 months	Adm.	6 months
Relation: minute volume – carbon dioxide production $y = \beta_o + \beta_1 \times VCO_2$						
Intercept	5.57	5.25	4.34	4.18	4.98	5.15
Slope *	37.94	37.66	34.48	34.1	34.12	33.35
r	0.95	0.95	0.96	0.97	0.96	0.96
p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Model r = 0.96 – p=0.0001						
Relation: slope VE/VCO_2 – peak oxygen uptake $y = \beta_o + \beta_1 \times$ Peak VO_2						
Intercept	60.2	63.4	49.0	39.7	45.4	44.9
Slope #	-0.92	-0.90	-0.51	-0.12	-0.39	-0.30
r	-0.36	-0.46	-0.43	-0.13	-0.32	-0.33
p	NS	0.053	0.052	NS	0.011	0.007
Model r = -0.47 – p=0.0001						
Relation: VE/VCO_2 ratio – treadmill time $y = \beta_o + \beta_1 \times TT + \beta_2 \times TT^2$						
Intercept	56.25	55.91	51.25	52.42	52.64	52.46
$Slope_1$	-3.74	-3.00	-3.33	-3.70	-3.80	-3.34
r	-0.49	-0.47	-0.49	-0.51	-0.54	-0.52
p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
$Slope_2$	0.22	0.15	0.17	0.20	0.20	0.17
r	0.40	0.37	0.38	0.36	0.41	0.40
p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Model r = -0.70 – p=0.0001						

Adm: admission; Peak VO_2: peak oxygen uptake; TT: treadmill time; VE: minute ventilation; VCO_2: carbon dioxide production.

* Groups 1 and 2 had similar slopes but significantly smaller than Group 3 ($p<0.0001$ respectively).

The slope in Group 3 was significantly higher than in Groups 1 and 2 ($p<0.01$ respectively).

There were no significant differences in the slopes as a result of exercise training.

Figure 7.1 **Example of the relation between minute volume and rate of carbon dioxide production on admission to the programme in 3 patients with normal, moderately depressed and severely depressed left ventricular function**

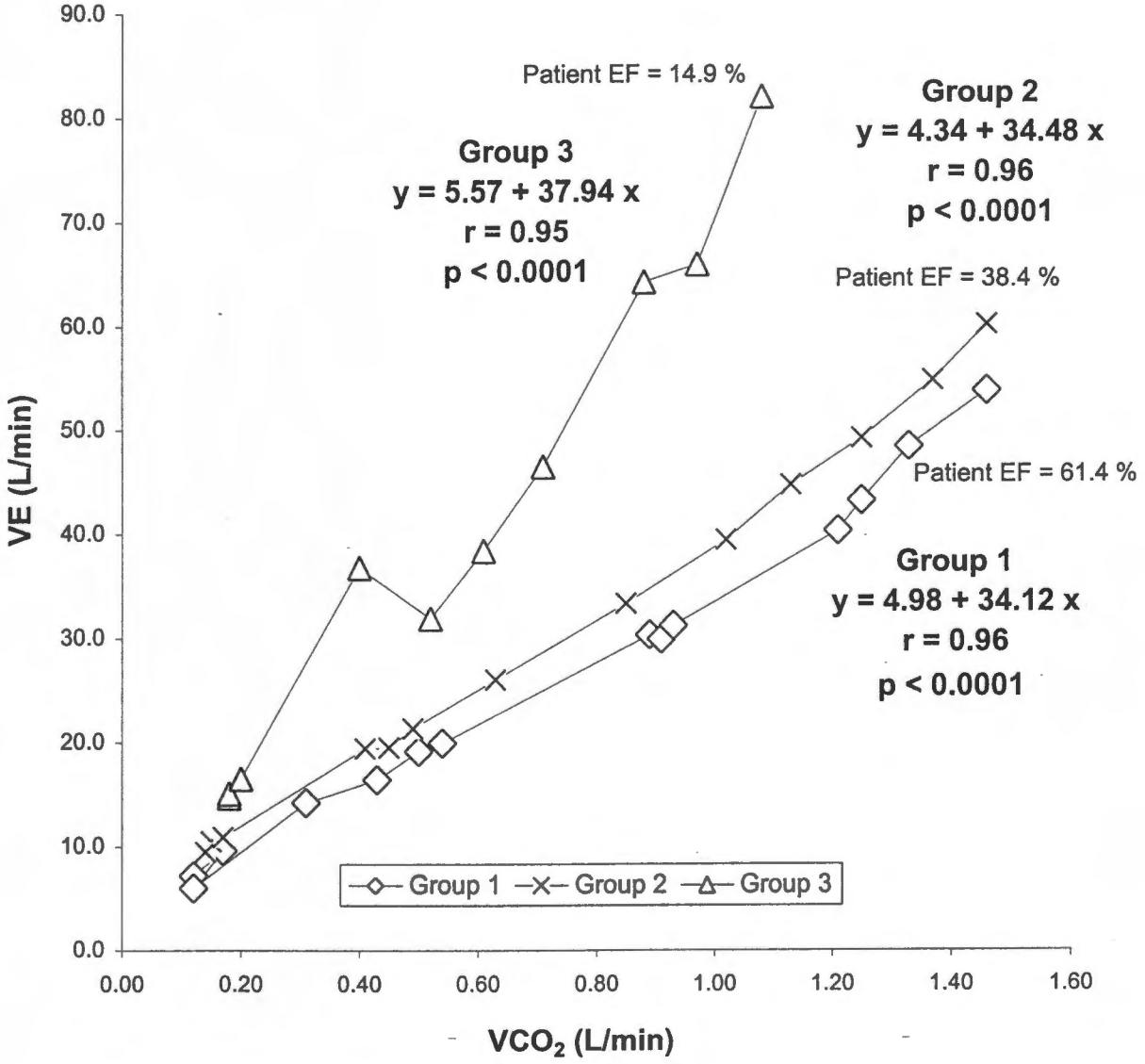


Figure 7.2 **Relation between the slope of the relation of minute ventilation and rate of carbon dioxide production and peak oxygen uptake on admission to the programme**

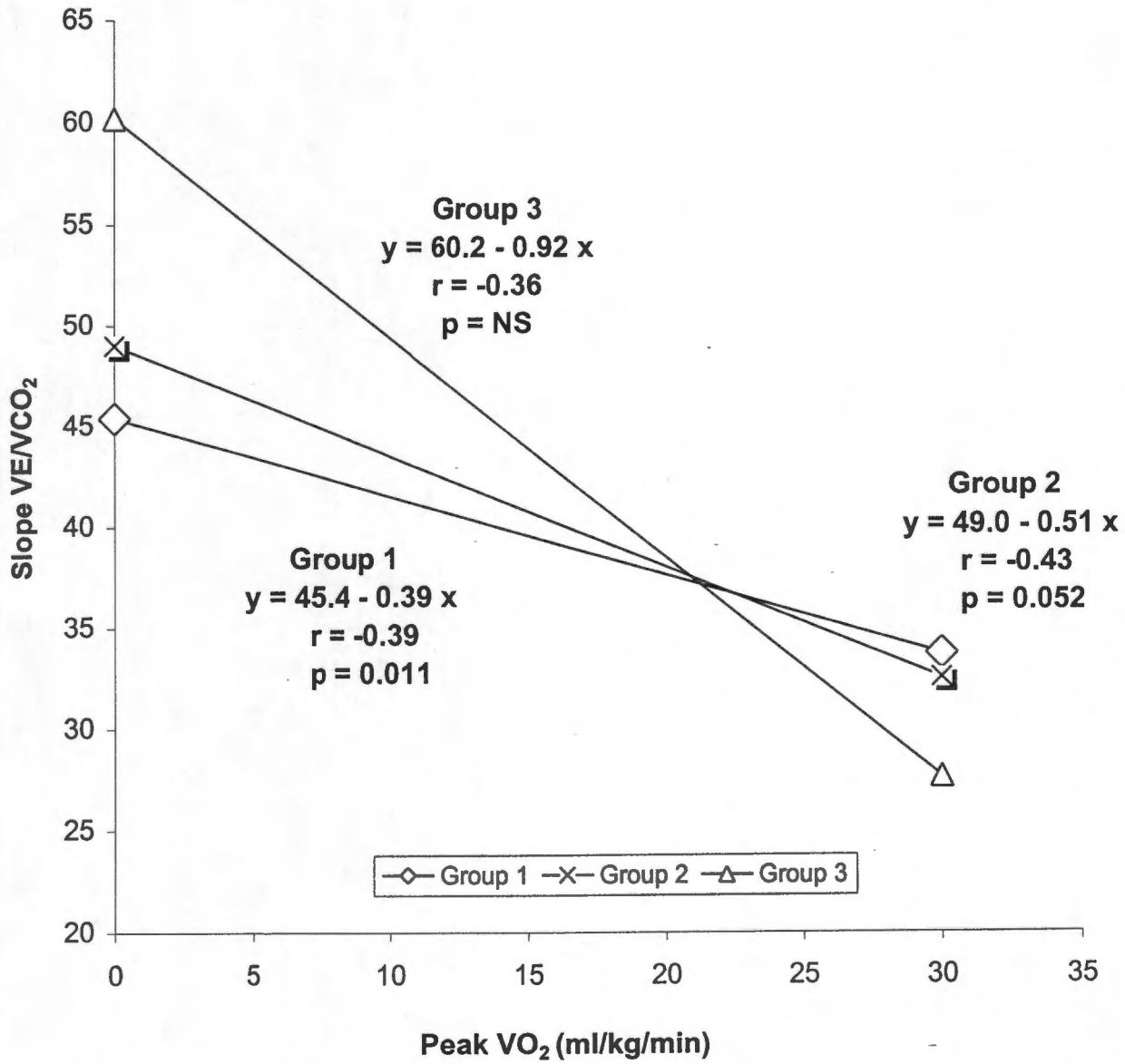
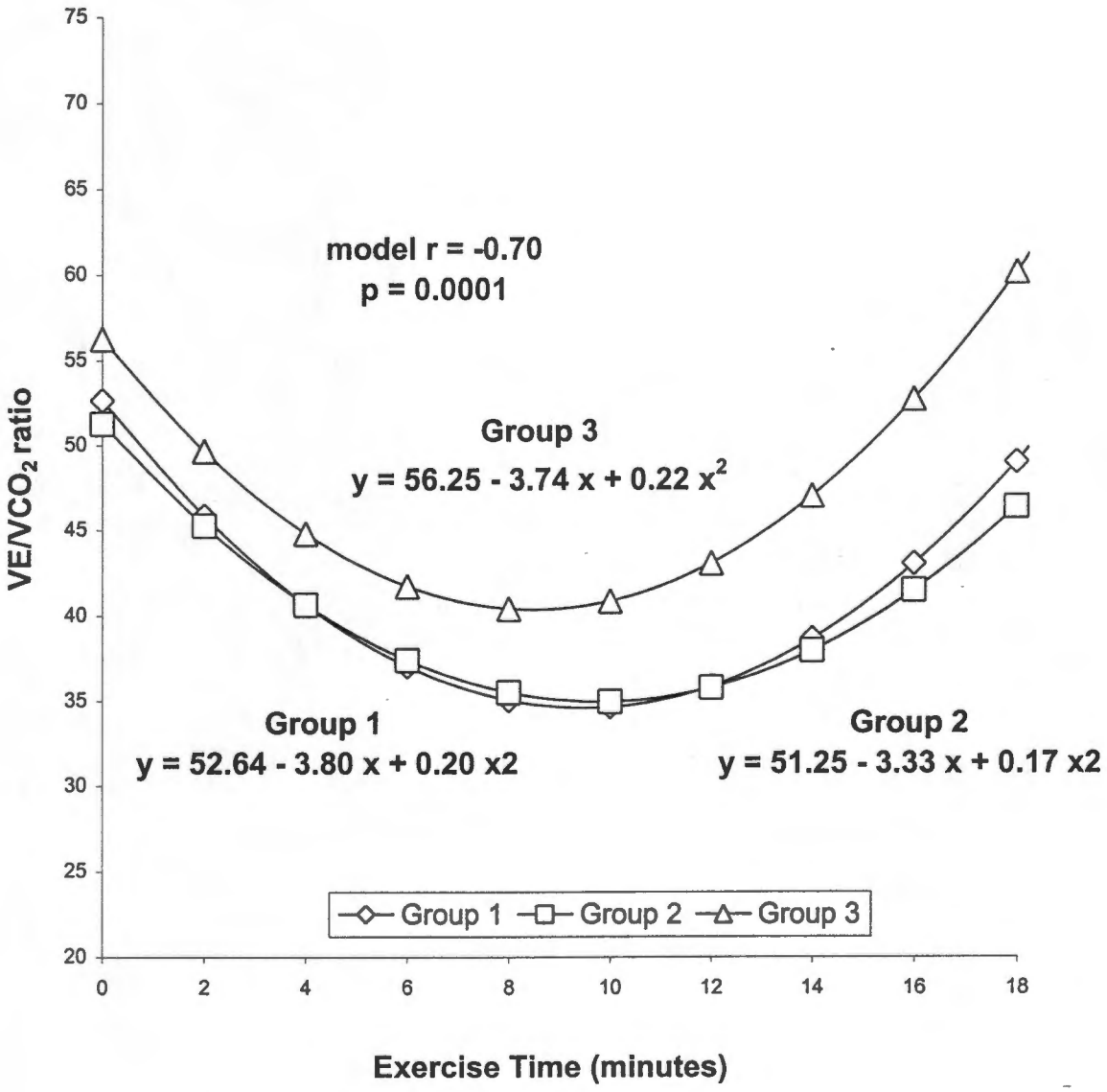


Figure 7.3 Relation between the VE/VCO_2 ratio and exercise time during the exercise test on admission to the programme



The treadmill time and the ratio VE/ VCO_2 at the point of maximal ventilatory efficiency were determined and compared between groups before and after training (Table 7.4). The treadmill time was significantly delayed in groups 2 and 1 compared to group 3, both before ($p=0.038$ and $p=0.009$ respectively) and after training ($p=0.025$ and $p=0.012$ respectively), but although there was a trend towards a delay in reaching maximum ventilatory efficiency after training, the differences were not significant for any group. The ratio VE/VCO_2 was significantly higher in Group 3 than in Groups 2 and 1, both before ($p=0.016$ and $p=0.009$ respectively) and after training ($p=0.001$ respectively).

Table 7.4 Treadmill time and ratio of minute ventilation and carbon dioxide production at the point of maximal ventilatory efficiency, before and after training, according to ejection fraction category.

	GROUP 3 EF < 35% n=18		GROUP 2 EF ≥35 - <50% n=21		GROUP 1 EF ≥ 50% n=63		p value DIFFERENCES BETWEN GROUPS		
	Adm	6 ms	Adm	6 ms	Adm	6 ms	3 vs 2 adm 6 ms	3 vs 1 adm 6 ms	2 vs 1 adm 6 ms
TREADMILL TIME	8.22 (2.24)	9.28 (2.93) p=NS	9.86 (1.85)	11.05 (2.13) p=NS	9.94 (2.47)	10.92 (2.55) p=NS	0.038 0.025	0.009 0.012	NS NS
VE/VCO_2	41.0 (2.0)	41.9 (1.6) p=NS	35.9 (1.1)	35.1 (1.0) p=NS	36.4 (0.8)	36.5 (0.7) p=NS	0.016 0.001	0.009 0.001	NS NS

Values are expressed as Mean (Standard Error).
Adm: admission; 6 ms: 6 months.

7.4 Discussion

We reported in Chapter 4 that exercise training was able to increase maximal exercise capacity in patients with severely depressed left ventricular dysfunction and that the magnitude of the improvement in this group of patients was similar to that of moderate or no left ventricular impairment (221). Using the same cohort of patients, but excluding 15 patients because of pulmonary disease, we were able to replicate the above physiological adaptations to training.

The analysis of the ventilatory responses to exercise on admission to the program allowed us to separate patients with severely depressed left ventricular impairment from those with a moderate impairment or normal function. VE and VCO_2 were significantly correlated ($r=0.96$, $p<0.0001$) in all groups, showing that ventilation is linked to carbon dioxide production in order to maintain eucapnia. However, patients with an EF<35% showed a higher VE/VCO_2 ratio during submaximal and maximal exercise and a higher VE/VCO_2 slope ($p=0.0001$) than the other two groups. These results confirm the findings of other authors (147,148,247,250,251,254) that the ventilatory response to exercise is significantly increased in patients with severely depressed left ventricular function. However this is the first study, to our knowledge, that shows these changes in asymptomatic patients in NYHA functional classes I and II without clinical signs or symptoms of congestive heart failure, since all other studies have included patients in classes II and III, with overt compensated heart failure who were on treatment with diuretics and digoxin (134,250,252,253,255,256).

This excessive ventilation was only seen below a certain threshold of left ventricular impairment which in our series was EF<35% and of peak oxygen uptake since patients in G3 also had the lower maximal oxygen consumption. Patients with moderate left ventricular impairment (EF≥35% and <50%) had a ventilatory response and values of peak oxygen uptake similar to those of patients with normal left ventricular function. A good correlation between peak oxygen uptake and the slope of VE/VCO_2 would therefore be

expected as previously shown by Fink et al. (147), r= -0.59, p<0.01, Buller et al. (254), r= -0.86, p<0.001 and Davies et al. (253), r= -0.53, p<0.002. We found a significant but weak negative correlation, however, between the slope of VE/VCO_2 and peak VO_2 in our study (model r=-0.47, p=0.0001). This is possibly due to higher peak VO_2 in our patients (range 13.3 to 28.9 ml/kg/min) since Davies (253) clearly showed that the association becomes stronger when chronic left ventricular dysfunction exceeds a critical level of severity as assessed by a peak VO_2 falling below 20 ml/kg/min.

The ratio VE/VCO_2 showed a negative non-linear correlation with treadmill time. The curve correlating these two variables represents ventilatory efficiency by giving the minute ventilation at any workload once it has been standardized for carbon dioxide production (250). In our study, patients with moderately impaired or normal LV function had lower VE/VCO_2 ratio and longer treadmill time at the point of maximal ventilatory efficiency than those with severe left ventricular impairment indicating a greater ventilatory efficiency.

The precise mechanisms for the increased ventilation during exercise and lower ventilatory efficiency in patients with chronic heart failure remain unclear. Early oxygen independent metabolism, an abnormal respiratory pattern, an increased pulmonary capillary wedge pressure and an increase in dead space ventilation have all been implicated as possible pathophysiologic factors. An increase in pulmonary capillary wedge pressures during exercise in patients with valvular disease can cause a reduction in pulmonary compliance and stimulation of juxtacapillary receptors leading to an exaggerated ventilatory response (257) . However Sullivan et al. (146) and Fink et al. (147) failed to show any relationship between the increase in the VE/VCO_2 ratio during exercise and elevated pulmonary wedge pressures in patients with chronic heart failure.

No correlation was found either between plasma lactate levels and the VE/VCO_2 ratio during exercise (146) in patients with chronic heart failure in spite of those patients

showing an earlier increase in blood lactate concentration when compared to healthy controls.

Several studies have suggested that this excessive ventilation in patients with heart failure is due to an increase in the ventilation of the dead space (146,249,251,252,254). Sullivan et al. (146) who demonstrated a strong correlation between the VE/VCO_2 ratio and the dead space per breath, concluded that the increase was likely due to an increase in physiological dead space rather than in the anatomical dead space which should have increased in a similar fashion between patients and controls during exercise. Buller et al. (254) showed that an increased anatomical dead space only contributes about 1/3 to the increase hyperventilation and that the other 2/3 are explained by an increased physiological dead space. Similarly Wasserman et al. (251) proposed that an increase in physiological dead space is a more important mechanism than the altered respiratory pattern of higher respiratory rate and lower tidal volume seen in these patients.

An inverse relationship between cardiac output and the VE/VCO_2 ratio and the ventilation of dead space (146) suggests that an inadequate cardiac output leading to lack of perfusion of certain ventilated areas of the lungs could accentuate ventilation perfusion mismatching in patients with severe left ventricular dysfunction producing an increase in their ventilatory response to exercise.

Thus, a combination of the above can probably explain the abnormal ventilatory responses in patients with severely depressed left ventricular dysfunction seen in our study. An increase in physiologic dead space due to a ventilation perfusion mismatch probably was the main mechanism in patients with low peak oxygen uptake values. An altered respiratory pattern with a lower tidal volume due to mild restrictive pulmonary abnormalities as demonstrated by a significantly lower FEV_1 and a normal FEV_1 ratio in this patient group could partially explain the ventilatory abnormalities in some patients.

Our results differ from those of Davey et al. (250) in that exercise training failed to reduce the slope of the relation of minute ventilation and carbon dioxide production in patients with severely or moderately depressed left ventricular function. Training also failed to reduce the VE/VCO_2 ratio at the point of maximum ventilatory efficiency and/or to increase the exercise duration required to reach this point. The same investigators suggested that the changes associated with exercise training in patients with heart failure, such as an increase in the blood supply to the working muscles and an improvement in muscle aerobic metabolism could revert some of the changes associated with the condition decreasing the production of carbon dioxide and delaying acidosis leading to a reduction in submaximal minute ventilation. If exercise training did not alter this relationship then we could speculate that either it does not increase muscle blood flow or, more likely, the increased ventilatory response seen in patients with heart failure is unrelated to a reduction in muscle blood flow. It is possible that for these changes to occur patients have to be more severely compromised since Davey's patients were in NYHA classes II and III and had a mean peak VO_2 of 14.1 $\pm$ 2.8 ml/kg/min, while our patients were all NYHA classes I and II and their mean peak VO_2 was higher (20.2 $\pm$ 3.8 ml/kg/min).

7.5 Conclusions

A higher ventilatory response to exercise and lower ventilatory efficiency can differenciate patients with severe left ventricular dysfunction from those with moderately impaired or normal left ventricular function.

Exercise training increased maximum oxygen uptake and maximum ventilation in all patients irrespective of their degree of left ventricular impairment, but was ineffective in reducing the higher ventilatory responses to effort of patients with ejection fractions below 35%.

CHAPTER 8

THE EFFECT OF ADHERENCE TO EXERCISE TRAINING OF 6 AND 18 MONTHS DURATION ON THE EXERCISE CAPACITY AND LEFT VENTRICULAR FUNCTION OF PATIENTS WITH CORONARY ARTERY DISEASE

8.1 Introduction

There are conflicting reports about the effects of exercise training on LV function in persons with CAD undergoing cardiac rehabilitation. A number of conventional exercise training programmes (98,99,103,1134,195-198) have not shown changes in resting LV function with exercise training whereas reports from high-intensity, high-frequency and high-duration programmes (115,199,200) demonstrated improvements in LV systolic function. Age-related deterioration in left ventricular function could be another contributory factor to the lack of improvement in cardiac function seen by some authors in training studies (201-204).

A careful recording of the patient's adherence with the training programme was often lacking in some of the above studies. Furthermore, little attention was given to changes in diastolic function as a result of exercise training. It has also been suggested that measurement of LV function during exercise may be a more sensitive means for detecting beneficial effects of a treatment programme than resting measures (58).

Most conventional exercise rehabilitation programmes recommend that their cardiac patients exercise 3 times a week for 30 to 45 minutes at an intensity between 70 to 85% of maximal heart rate, which corresponds to between 50 and 70% of VO_2 max, for a period of 3 to 6 months. Exercise is prescribed in a similar way at the Johannesburg Cardiac Rehabilitation Centre with the difference that we recommend a minimum duration of 6 months and preferably a duration of 18 months.

Chapter 5 showed that exercise training improved exercise capacity in patients with LV dysfunction and Chapter 6 showed that training improved exercise capacity but not LV function in patients with myocardial ischaemia.

The aim of this chapter of the thesis is to assess the effects of adherence to exercise training of 6 and 18 month duration on the exercise capacity and left ventricular function of patients with coronary artery disease.

8.2 Methods

Patients with documented coronary artery disease consecutively referred to the Johannesburg Cardiac Rehabilitation Centre between 1990 and 1993 were considered for the trial. All patients are encouraged to attend our programme for 18 months. Only patients who stayed in the programme for at least 6 months were enrolled into the study. One hundred and eighteen patients entered the 6 month exercise training programme (ET6) and 40 of those completed the 18 month programme (ET18). Patients who suffered an MI or a CABG were enrolled 3 months after the event to ensure that the spontaneous recovery in LV function which occurs as part of the healing process, did not confound the interpretation of training-induced adaptations. Patients who underwent a percutaneous transluminal coronary angioplasty were enrolled 4 weeks after the revascularization procedure.

In addition, a group of 31 volunteers matched for age, without any history, signs or symptoms of cardiac disease and with normal results for an exercise test, was selected as a control group for the evaluation of LV function variables at rest and during exercise.

The characteristics of patients and controls have been discussed previously in Chapter 3.

On admission all patients underwent a symptom-limited treadmill exercise test using the Chung protocol (27), before being accepted onto the exercise cardiac rehabilitation programme. Respiratory gas analysis using a metabolic cart was carried out and peak oxygen uptake was determined.

Radionuclide ventriculography, using the equilibrium multi-gated blood pool technique (44) was performed at rest in all patients and controls and, during exercise, in the supine position in all but 26 ET6 patients using the protocol previously discussed. As in previous studies, EDC, ESC, SC, EF, T-PER, PER, AV-ER, T-PFR, PFR and AV-RFR were derived from time-activity curves. The use of counts and particularly of their percentage change from rest to exercise as an expression of volume change, has previously been validated.

All tests were repeated 6 and 18 months after the beginning of the exercise programme.

The exercise training programme was medically supervised and of 6 and 18 months duration. The intensity of exercise was set at the heart rate achieved at the ventilatory threshold measured during the initial treadmill testing. Patients were required to exercise at their prescribed intensity 3 times a week continuously for 30-45 minutes. Aerobic exercise consisted of walking or jogging or stationary cycling if weight-bearing exercise was contraindicated. The exercise session was preceded by a warm-up and followed by a cool-down period. Each patient was progressed slowly over a number of weeks up to his ultimately required intensity of exercise.

Each patient's compliance with the programme was monitored on a daily basis and recorded on a computer. The following variables were recorded: training heart rate expressed in absolute values and as a percentage of the maximal heart rate, training oxygen uptake expressed in absolute values and as a percentage of peak VO_2, attendance expressed as a percentage of the possible sessions, and caloric expenditure per session expressed in kilocalories (kcal). Kilocalories per session were calculated as the product of the intensity of the exercise session in METs multiplied by body weight in kg and by the duration of the exercise session expressed as minutes/60.

Statistical Analysis

For the purposes of this study percentage attendance was used as a measure of compliance and patients were classified into compliance categories. The cohort ET6 was divided into 4 compliance categories: 16 patients, <40% attendance ($C1_6$); 23 patients, ≥40-<60% ($C2_6$); 33 patients, ≥60-<80% ($C3_6$); and 46 patients, ≥80% ($C4_6$). The cohort ET18 was divided into 3 compliance categories by averaging the attendance between admission and 6 months and between 6 and 18 months: 11 patients, <60% ($C1_{18}$); 14 patients, ≥60-<80% ($C2_{18}$); and 15 patients ≥80% ($C3_{18}$).

Normal subjects were compared to patients in all compliance categories, on admission to the programme, with respect to their systolic and diastolic left ventricular function at rest and during exercise.

The effect of exercise training on physiological and left ventricular function variables was evaluated separately in the two cohorts of patients ET6 and ET18, by analysis of variance using the Wilks' Multivariate Lambda criterion, according to compliance category. When significant differences were indicated in the analysis of variance, pairwise comparisons were made with t tests. All data are expressed as mean $\pm$ standard error. A p value of less than or equal to 0.05 was accepted as statistically significant.

Because of the great variability in individual responses when dealing with LV parameters, we calculated the interval mean $\pm$ 2 standard deviations for all left ventricular variables in the control group, at rest and during exercise and determined the number of patients below, in, or above this interval for all variables, in all compliance categories, before and after training.

8.3 Results

There were no differences in medical condition and medication use between patients in the different compliance categories for both cohort of patients.

8.3.1 Compliance with the exercise programme

The compliance data for the ET6 cohort is shown in Table 8.1 and for the ET18 cohort in Table 8.2.

In ET6, the only differences were that patients in $C3_6$ and $C4_6$ exercised at a higher percentage of the maximal heart rate than did patients in $C1_6$ and $C2_6$.

In ET18, patients exercised at a higher intensity but attended less during the second period between 6 and 18 months than during admission and 6 months. Between 6 and 18 months patients exercised at a higher training heart rate ($p=0.001$), at a higher percentage of the maximal heart rate ($p=0.039$), at a higher oxygen uptake ($p=0.001$), had a higher caloric expenditure per session ($p=0.004$) and a lower percentage attendance ($p=0.001$). A higher oxygen uptake during exercise sessions as well as a lower attendance were consistent in all compliance categories during the same period.

Table 8.1 Compliance data for the cohort-6 of patients with coronary artery disease per compliance category.

	ET-6 0 - 6 ms n=118	**$C1_6$** <40 % n=16	**$C2_6$** ≥40 - <60 % n=23	**$C3_6$** ≥60 - <80 % n=33	**$C4_6$** ≥80 % n=46	p
THR (bpm)	112.1 (15.2)	109.0 (16.5)	113.7 (15.1)	111.7 (13.4)	112.7 (16.4)	NS
% MHR	78.3 (6.1)	75.8 (6.8)	76.2 (6.5)	79.5 (5.6)	79.3 (5.7)	0.047 #
TVO_2 (ml/kg/min)	18.2 (4.7)	17.7 (3.4)	17.7 (5.0)	18.8 (4.3)	18.3 (5.3)	NS
% PEAK VO_2	71.3 (7.8)	71.1 (7.6)	70.7 (6.7)	72.6 (7.9)	70.7 (8.5)	NS
% ATTENDANCE	67.8 (24.3)	24.4 (12.3)	49.9 (5.5)	68.4 (6.1)	91.3 (6.7)	0.0001 *
KCAL/SESSION	267.5 (93.9)	261.8 (107.4)	269.3 (107.8)	272.1 (86.3)	265.4 (89.8)	NS

Values are expressed as Mean (Standard Deviation)
1 vs 2, p=NS; 1 vs 3, p=0.052; 1 vs 4, p=0.047; 2 vs 3, p=0.048; 2 vs 4, p=0.044; 3 vs 4, p=NS.
* p=0.0001 for all.

C: compliance; KCAL: kilocalories; ms: months; %MHR: percentage of maximal heart rate; % PEAK VO_2: percentage peak oxygen uptake; THR: training heart rate; TVO_2: training oxygen uptake.

Table 8.2 Compliance data for the cohort-18 of patients with coronary artery disease per compliance category.

	ET - 18 n=40		**$C1_{18}$** <60 % n=11		**$C2_{18}$** ≥60 - <80 % n=14		**$C3_{18}$** ≥80 % n=15	
	0 - 6 ms	6-18 ms	0 - 6 ms	6-18 ms	0 - 6 ms	6-18 ms	0 - 6 ms	6-18 ms
THR (bpm)	110.4 (12.4)	117.9 (15.7) p=0.001	111.5 (5.8)	118.1 (15.4) p=NS	111.6 (11.0)	119.4 (14.4) p=0.034	108.3 (17.0)	116.5 (17.9) p=NS
% MHR	78.9 (5.7)	81.1 (4.2) p=0.039	76.6 (5.9)	80.9 (3.7) p=0.042	81.9 (3.1)	81.7 (4.0) p=NS	77.8 (6.5)	80.8 (4.9) p=NS
TVO_2 (ml/kg/min)	18.4 (4.9)	22.6 (6.7) p=0.001	18.2 (4.4)	21.9 (4.6) p=0.003	18.0 (4.4)	21.1 (6.6) p=0.015	19.0 (5.9)	24.5 (7.9) p=0.008
% PEAK VO_2	72.4 (8.5)	75.6 (8.2) p=NS	73.0 (9.7)	78.6 (5.3) p=NS	73.5 (7.1)	72.1 (9.2) p=NS	70.8 (9.1)	76.7 (8.2) p=NS
% ATTENDANCE	76.6 (16.6)	70.3 (16.3) p=0.001	58.6 (9.5)	45.6 (14.8) p=0.053	74.2 (9.8)	58.9 (12.2) p=0.007	93.5 (8.2)	84.6 (10.3) p=0.031
AVERAGE % ATTENDANCE 0 - 18 MONTHS	71.0 (16.5)		52.1 (7.5)		66.6 (6.6)		89.1 (5.4)	
KCAL/SESSION	281.8 (94.8)	314.1 (98.3) p=0.004	269.0 (97.9)	319.0 (119.9) p=NS	282.0 (93.6)	317.1 (94.8) p=NS	290.0 (99.1)	307.7 (90.8) p=NS

Values are expressed as Mean (Standard Deviation)
C: compliance; KCAL: kilocalories; ms: months; %MHR: percentage of maximal heart rate; % PEAK VO_2: percentage peak oxygen uptake; THR: training heart rate; TVO_2: training oxygen uptake.

8.3.2 Physiological adaptations after exercise training

8.3.2.1 In patients attending for 6 months (ET6 cohort) (Table 8.3)

After 6 months of exercise training, significant increases in peak VO_2 ($C1_6$: p=0.015, $C2_6$, $C3_6$ and $C4_6$: p=0.0001) and peak ventilation ($C1_6$: p=0.004, $C2_6$: p=0.001, $C3_6$: and $C4_6$: p=0.0001) were seen in all compliance categories. $C2_6$, $C3_6$ and $C4_6$ patients had an additional significant increase in ventilatory threshold (p=0.008, p=0.009 and p=0.0001 respectively). Furthermore $C2_6$ and $C3_6$ patients had significant increases in treadmill time (p=0.001 and p=0.003 respectively) and peak heart rate (p=0.04 and p=0.035). $C2_6$ and $C4_6$ patients showed a significant decrease in blood pressure (p=0.013 and p=0.023) and rate-pressure product (p=0.017 and p=0.0003) at a submaximal level. $C4_6$ patients in addition showed a significant reduction in resting and submaximal heart rate (p=0.004 and p=0.006 respectively) and a significant increase in submaximal VO_2 (p=0.006). $C2_6$ patients showed a significant reduction in the Broca index (p=0.025)) while $C3_6$ patients showed a significant increase in ST segment depression (p=0.014) and its duration in the post-effort period (p=0.004).

8.3.2.2 In patients attending for 18 months (ET18 cohort) (Table 8.4)

The 3 compliance groups showed significant increases in peak VO_2 and peak ventilation after 6 months of exercise training which were maintained but not further increased by 18 months of training. Significant increases in ventilatory threshold were also observed in $C2_{18}$ and $C3_{18}$ (p=0.003 and p=0.004 respectively) by 6 months, being also maintained by 18 months (p=0.036 and p=0.043 respectively). Paradoxically only $C1_{18}$ showed significant reductions in heart rate (p=0.04), blood pressure (0.006) and rate-pressure product (p=0.009) at submaximal effort, probably because the initial test values were abnormally high.

Table 8.3 Effects of 6months of exercise training on physiological parameters of the cohort-6 of patients with coronary artery disease according to compliance category.

	$C1_6$ <40 % Attend. n=16		$C2_6$ ≥40 - <60 % Attend. n=23		$C3_6$ ≥60 - <80 % Attend. n=33		$C4_6$ >80 % Attend. n=46	
VARIABLES	Adm.	6 months	Adm.	6 months	Adm.	6 months	Adm.	6 months
Broca %	106.9 (3.3)	107.4 (3.3)	113.9 (2.9)	111.8 * (3.0)	105.6 1.6	104.6 2.0	106.2 1.7	106.4 1.8
Treadmill Time (min)	11.5 (0.7)	12.2 (0.6)	11.3 (0.8)	13.6 # (0.7)	11.5 0.5	13.2 # 0.5	11.5 0.6	12.3 0.5
Resting HR (bpm)	71.7 (3.0)	70.4 (3.3)	72.6 (2.7)	69.8 (2.6)	72.2 2.8	73.0 2.4	75.0 2.4	70.8# 2.2
Peak HR (bpm)	144.1 (5.2)	149.4 (4.7)	148.6 (3.9)	154.4 * (3.1)	139.2 3.1	145.7 * 3.7	142.2 3.1	145.6 2.9
VT (ml/kg.min)	16.8 (0.8)	16.7 (0.8)	16.5 (0.7)	18.6 # (0.8)	17.4 0.6	19.0 # 0.6	16.4 0.5	19.1 # 0.5
Peak VO2 (ml/kg.min)	24.8 (1.3)	26.9 * (1.7)	24.4 (1.3)	28.7 # (1.4)	25.8 1.0	29.7 # 1.1	26.1 0.9	29.7 # 1.1
Peak VE (L/min)	84.3 (5.0)	93.3 # (5.2)	83.2 (6.0)	98.4 # (5.9)	81.6 3.9	96.1 # 4.8	84.7 3.1	96.9 # 3.5
Peak RPP (bpm.mmHg x 10^3)	28.2 (1.5)	26.2 (1.5)	25.7 (1.3)	24.6 (0.9)	24.7 1.1	25.8 1.1	24.4 0.9	24.6 0.8
ST depression (mm)	0.50 (0.30)	0.44 (0.22)	0.61 (0.20)	0.50 (0.20)	0.27 0.10	0.61 * 0.16	0.51 0.11	0.58 0.13
ST duration (min)	1.25 (0.82)	2.62 (1.39)	2.00 (0.77)	2.61 (1.07)	1.06 0.45	3.61 # 0.94	2.63 0.74	2.76 0.64
Peak RQ	1.06 (0.02)	1.09 (0.02)	1.07 (0.02)	1.07 (0.01)	1.06 0.01	1.08 0.01	1.05 0.01	1.07 0.01
Submaximal HR (bpm)	110.7 (4.1)	111.1 (4.1)	116.3 (4.2)	110.7 (2.8)	107.6 3.3	106.2 3.2	113.5 3.4	108.3 # 3.1
Submaximal BP (mmHg)	169.4 (5.1)	154.7 * (6.1)	159.6 (6.9)	142.2 * (4.7)	160.7 6.2	154.4 5.1	156.8 4.4	147.8 * 3.7
Submaximal VE (L/min)	43.0 (2.8)	46.3 (2.8)	45.5 (2.2)	42.9 (1.6)	42.2 1.7	42.4 1.5	47.2 1.9	47.4 1.5
Submaximal VO2 (ml/kg/min	16.4 (0.8)	17.6 (0.7)	16.9 (0.3)	17.5 (0.7)	17.6 0.5	18.5 0.6	17.7 0.3	19.1 # 0.4
Submaximal RPP (bpm.mmHgx10^3)	18.8 (1.0)	17.2 (1.0)	18.7 (1.1)	15.8 * (0.8)	17.7 1.1	16.7 0.9	18.0 0.9	16.0 # 0.6

Values are expressed as Mean (Standard Error)

* $p<0.05$; # $p<0.01$ (admission vs 6 months)

Adm.: admission; Attend.: attendance; BP: blood pressure; C: compliance; HR: heart rate; RPP: rate-pressure product; RQ: respiratory quotient; SE: standard error; VE: ventilation; VO_2: oxygen uptake; VT: ventilatory threshold.

Table 8.4 Physiological parameters of the cohort-18 of patients with coronary artery disease on admission and after 6 and 18 months of exercise training according to compliance category.

	$C1_{18}$ <60 % Attendance n=11			$C2_{18}$ ≥60 - <80 % Attendance n=14			$C3_{18}$ ≥80 % Attendance n=15		
VARIABLES	Adm.	6 ms	18 ms	Adm.	6 ms	18 ms	Adm.	6 ms	18 ms
Broca %	107.3 (2.4)	104.2 (3.1)	104.1 (3.1)	107.3 (4.5)	107.6 (4.8)	107.5 (4.6)	102.0 (2.9)	101.9 (2.8)	100.8 (3.1)
Treadmill Time (min)	10.7 (1.0)	13.0 * (0.6)	12.6 (0.5)	10.8 (0.8)	12.9 # (0.9)	12.0 (0.6)	12.1 (1.1)	13.2 (1.0)	12.0 (0.7)
Resting HR (bpm)	71.4 (4.0)	69.2 (3.3)	70.7 (3.8)	78.3 (4.7)	79.2 (3.5)	75.8 (3.2)	71.3 (3.1)	67.4 (2.9)	67.7 (2.1)
Peak HR (bpm)	146.6 (3.7)	145.4 (6.2)	143.4 (5.3)	136.0 (3.9)	146.0 * (4.8)	147.6 * (4.6)	139.4 (4.9)	144.0 (4.6)	150.1 (4.3)
VT (ml/kg.min)	17.4 (0.8)	18.9 (1.1)	17.6 (0.7)	16.1 (0.6)	19.1 # (1.1)	17.7 * (0.9)	16.9 (0.8)	20.1 # (0.9)	19.6 * (1.1)
Peak VO2 (ml/kg.min)	24.6 (1.3)	28.2 # (1.5)	27.5 # (1.6)	24.7 (1.6)	29.0 # (2.0)	28.7 # (2.0)	27.4 (1.7)	31.8 # (1.9)	32.0 # (2.1)
Peak VE (L/min)	80.8 (6.8)	90.2 * (8.1)	89.3 * (6.6)	79.6 (4.3)	97.2 # (6.9)	99.0 (7.8)	86.2 (5.9)	100.8 # (5.8)	111.2 # (9.3)
Peak RPP (bpm.mmHg x 10^3)	27.6 (1.5)	24.3 (1.7)	24.6 (1.3)	23.4 (1.6)	24.3 (1.4)	25.2 (1.5)	24.2 (1.8)	24.7 (1.8)	24.8 (1.3)
ST depression (mm)	0.27 (0.14)	0.32 (0.17)	0.27 (0.19)	0.14 (0.14)	0.36 (0.17)	0.25 (0.14)	0.37 (0.20)	0.07 (0.07)	0.07 (0.07)
ST duration (min)	2.18 (1.13)	2.91 (1.51)	1.00 (0.75)	0.21 (0.21)	2.86 (1.45)	3.07 (1.64)	2.00 (1.45)	0.00 (0.00)	0.00 (0.00)
Peak RQ	1.03 (0.02)	1.06 (0.02	1.06 (0.03)	1.06 (0.03)	1.08 (0.01)	1.07 (0.03)	1.07 (0.02)	1.06 (0.03)	1.07 (0.03)
Submaximal HR (bpm)	115.9 (6.2)	105.0 * (4.5)	106.4 (4.7)	106.1 (4.5)	108.3 (4.6)	110.9 (4.3)	109.3 (5.1)	100.8 (4.2)	107.8 (4.3)
Submaximal BP (mmHg)	173.4 (7.7)	146.0 # (4.5)	149.9 (10.8)	148.7 (6.8)	148.3 (7.6)	149.9 (7.1)	158.4 (11.1)	149.3 (7.9)	145.4 (6.6)
Submaximal VE (L/min)	47.5 (4.1)	43.6 (2.5)	40.7 (2.4)	47.7 (3.1)	43.1 (2.6)	41.2 (2.3)	43.3 (2.4)	50.2 (2.5)	52.7 (2.8)
Submaximal VO2 (ml/kg/min	18.2 (0.3)	18.2 (0.8)	17.8 (0.8)	18.2 (0.6)	18.2 (1.0)	17.5 (1.1)	17.1 (0.5)	20.4 (0.6)	20.4 (1.0)
Submaximal RPP (bpm.mmHgx10^3)	20.3 (1.7)	15.4 # (0.9)	17.3 (2.0)	16.0 (1.2)	16.3 (1.4)	16.8 (1.3)	17.8 (1.8)	15.0 (1.0)	15.6 (0.8)

Values are expressed as Mean (Standard Error).
* $p<0.05$; # $p<0.01$ (admission vs 6 months and admission vs 18 months).
No significant changes were seen when comparing 6 months vs 18 months for all groups.
Adm.: admission; ms: months. Other abbreviations as per Table III.

8.3.3 Left ventricular function after exercise training

8.3.3.1 In patients attending for 6 months (ET6 cohort) (Table 8.5)

Apart from a significant reduction in resting heart rate in $C2_6$ ($p=0.035$) and in EDC in $C4_6$ ($p=0.035$) there were no changes in resting left ventricular function after 6 months of exercise training.

During exercise, cardiac output was increased before and after training in all compliance categories through a significant increase in heart rate ($p=0.0001$ respectively). However in $C4_6$, the magnitude of the increase was greater after, than before training ($p=0.036$). EDC and SC tended to be further reduced during exercise after training, the magnitude of the change being significant only in $C3_6$ ($p=0.037$) for the former and in $C1_6$ ($p=0.027$) and $C3_6$ ($p=0.028$) for the latter. EF fell during exercise in all groups, both before and after training. However, the magnitude of the change from rest to exercise showed a trend towards a lower decrease in $C3_6$ and $C4_6$, a similar decrease in $C2_6$ and a further decrease in $C1_6$ after exercise training. T-PER and T-PFR were reduced to a similar extent before and after training. In $C2_6$, $C3_6$ and $C4_6$, PER increased significantly during exercise and to the same extent before and after training. In $C1_6$, PER did not show a significant increase during exercise after training. AV-ER tended to increase further during exercise after training in $C2_6$, $C3_6$ and $C4_6$, while it was significantly reduced after training in $C1_6$ ($p=0.027$). PFR and AV-RFR increased significantly during exercise before and after training in all compliance categories. The magnitude of the change was significantly greater after training for both parameters in $C4_6$ ($p=0.037$ and $p=0.046$ respectively) and for PFR in $C2_6$ ($p=0.04$).

8.3.3.2 In patients attending for 18 months (ET18 cohort) (Table 8.6)

After 18 months of exercise training and at rest, HR was significantly reduced in $C3_{18}$ (p=0.039) and PFR and AV-RFR significantly reduced in $C2_{18}$ (p=0.032 and p=0.042 respectively).

ET18 patients had a very similar response in left ventricular function from rest to exercise, before and after 6 and 18 months of training. $C1_{18}$ and $C3_{18}$ patients showed no changes. $C2_{18}$ patients showed a significant reduction in the percentage change from rest to exercise in EDC and SC by 6 months (p=0.02 and p=0.028 respectively), a reduction which was maintained by 18 months for SC (p=0.019). In the same group, in PFR and AV-RFR the exercise-induced increase was greater after training particularly after 18 months (p=0.033 and p=0.012 respectively).

Table 8.5 Effects of 6 months of exercise training on the left ventricular function of the cohort-6 of patients with coronary artery disease at rest and during exercise according to compliance category.

	$C1_6$ (<40 % Attendance) R (n=16) EX (n=9) Δ R-EX (n=9)		$C2_6$ (≥40 - <60 % Attendance) R (n=16) EX (n=9) Δ R-EX (n=9)		$C3_6$ (≥60 - <80 % Attendance) R (n=16) EX (n=9) Δ R-EX (n=9)		$C4_6$ (>80 % Attendance) R (n=16) EX (n=9) Δ R-EX (n=9)	
	Admission	6 months	Admission	6 months	Admission	6 months	Admission	6 months
HEART RATE (bpm)	61.1 (2.8) 104.7 (3.5) # -76.1 (7.8)	60.4 (2.1) 100.0 (5.1) # -69.5 (8.7)	68.7 (3.2) 113.7 (4.3) # -69.0 (7.6)	62.4 (1.7) ! 110.2 (2.4) # -78.5 (5.2)	67.0 (2.3) 106.3 (2.7) # -61.4 (5.8)	63.4 (2.5) 103.7 (2.8) # -65.6 (6.2)	65.9 (2.2) 98.6 (2.5) # -57.0 (4.9)	61.8 (1.8) 103.0 (2.7) # -70.1 (5.6) !
EDC x 10^3	490 (68) 516 (153) 2.9 (17.8)	499 (53) 358 (120) 37.3 (17.4)	511 (37) 525 (49) -8.4 (8.8)	492 (33) 456 (65) 6.8 (11.8)	440 (19) 504 (49) -13.1 (9.5)	437 (18) 367 (40) * !! 18.3 (8.1) !	533 (32) 499 (56) 2.5 (9.0)	484 (27) ! 430 (40) 5.8 (9.0)
ESC x 10^3	262 (68) 364 (145) -20.2 (23.8)	245 (50) 282 (112) 4.6 (24.0)	265 (32) 286 (310) -24.1 (12.7)	248 (30) 269 (47) -15.4 (15.5)	210 (19) 284 (36) * -30.7 (10.5)	214 (20) 206 (26) !! -1.0 (12.8)	302 (32) 315(48) -13.3 (10.6)	271 (26) 270 (32) -12.3 (11.2)
SC x 10^3	228 (11) 152 (33) 25.0 (15.1)	254 (24) 76 (16) # 68.0 (8.0) !	246 (16) 239 (33) 3.6 (11.6)	244 (13) 187 (24) * 24.3 (9.6)	230 (9) 220 (24) 0.7 (10.8)	223 (11) 161 (21) # 27.0 (8.3) !	231 (8) 184 (21) * 17.0 (9.9)	212 (9) 160 (17) # 20.9 (8.9)
EF %	55.1 (4.8) 43.6 (6.6) 16.7 (6.7)	55.6 (4.7) 37.4 (5.5) * ! 26.3 (8.5)	50.8 (2.6) 46.8 (3.3) * 9.3 (5.0)	52.6 (2.7) 47.4 (3.1) * 9.7 (4.5)	54.4 (2.3) 48.6 (2.6) * 7.4 (3.1)	53.6 (2.7) 48.2 (2.8) 4.8 (4.5)	47.7 (2.1) 43.1 (2.7) # 10.7 (3.7)	47.4 (2.1) 44.8 (2.6) * 5.6 (3.9)
T-PER (sec)	0.14 (0.03) 0.07 (0.01) # 50.8 (4.4)	0.15 (0.01) 0.08 (0.01) # 43.9 (10.7)	0.15 (0.01) 0.07 (0.00) # 49.2 (6.0)	0.15 (0.01) 0.06 (0.00) # 55.0 (2.6)	0.15 (0.01) 0.07 (0.00) # 48.5 (3.6)	0.14 (0.01) 0.07 (0.00) # 44.0 (5.3)	0.15 (0.01) 0.08 (0.01) # 41.3 (5.5)	0.15 (0.01) 0.07 (0.00) # 48.2 (4.1)
PER (EDV/sec)	2.50 (0.24) 3.46 (0.50) # -48.9 (12.4)	2.53 (0.24) 3.25 (0.62) -44.4 (20.3)	2.38 (0.15) 3.63 (0.26) # -51.1 (10.6)	2.38 (0.12) 3.77 (0.25) # -60.4 (6.5)	2.65 (0.13) 3.60 (0.19) # -43.6 (7.0)	2.54 (0.14) 3.54 (0.23) # -46.2 (7.8)	2.30 (0.11) 3.19 (0.21) # -40.6 (6.6)	2.21 (0.11) 3.41 (0.21) # -56.2 (7.7)
AV-ER (EDV/sec)	1.63 (0.15) 1.80 (0.30) -20.5 (13.9)	1.65 (0.15) 1.24 (0.28) 20.0 (14.1) !	1.53 (0.09) 1.78 (0.17) -14.9 (13.1)	1.52 (0.09) 1.89 (0.14) # -24.8 (6.9)	1.62 (0.08) 1.88 (0.14) # -19.5 (7.0)	1.57 (0.10) 1.83 (0.13) * -31.4 (11.0)	1.42 (0.07) 1.57 (0.12) -9.1 (6.5)	1.40 (0.06) 1.61 (0.12) -15.2 (7.4)
T-PFR (sec)	0.19 (0.01) 0.13 (0.01) * 24.3 (7.1)	0.17 (0.01) 0.12 (0.02) # 35.4 (8.2) !	0.16 (0.01) 0.13 (0.02) 3.8 (20.8)	0.16 (0.01) 0.09 (0.00) # 39.2 (4.2)	0.20 0.01 0.12 (0.01) # 35.8 (4.8)	0.18 (0.01) 0.12 (0.00) # 25.6 (8.1)	0.18 (0.01) 0.14 (0.01) * 15.4 (8.4)	0.19 (0.01) 0.13 (0.01) # 27.6 (6.4)
PFR (EDV/sec)	2.06 (0.19) 4.29 (0.54) # -144.5 (28.4)	2.10 (0.19) 4.80 (0.99) * -151.4 (43.0)	2.16 (0.98) 4.44 (0.42) # -116.1 (20.3)	2.05 (0.14) 4.78 (0.34) # -153.8 (20.4) !	2.20 (0.15) 4.23 (0.29) # -116.8 (16.6)	1.96 (0.12) 4.30 (0.26) # -143.9 (16.9)	1.87 (0.10) 3.64 (0.24) # -110.0 (13.0)	1.74 (0.09) 4.05 (0.27) # -146.0 (14.1) !
AV-RFR (EDV/sec)	1.40 (0.51) 3.01 (0.43) # -149.7 (27.1)	1.45 (0.14) 3.35 (0.66) # -153.1 (40.0)	1.52 (0.14) 3.05 (0.36) # -111.7 (27.3)	1.40 (0.08) 3.34 (0.25) # -149.1 (17.2)	1.42 (0.09) 2.95 (0.23) # -139.8 (21.4)	1.35 (0.08) 3.05 (0.22) # -160.2 (23.4)	1.24 (0.07) 2.50 (0.18) # -113.7 (16.3)	1.31 (0.09) 3.06 (0.25) # ! -160.8 (17.2) !

Values are expressed as Mean (Standard Error). * $p<0.05$; # $p<0.01$ (rest vs exercise); ! $p<0.05$; !! $p<0.01$ (admission vs 6 months). AV-ER: average ejection rate; AV-RFR: average rapid filling rate; Δ R-E: delta rest-exercise; EDC: end-diastolic counts; EDV/sec: end-diastolic volumes per second; EF: ejection fraction; ESC: end-systolic counts; EX: exercise; PER: peak ejection rate; PFR: peak filling rate; R: rest; SC: stroke counts; T-PER: time to peak ejection rate; T-PFR: time to peak filling rate.

Table 8.6 Effects of 6 and 18 months of exercise training on the left ventricular function of the cohort-18 of patients with coronary artery disease at rest and during exercise according to compliance category.

	$C1_{18}$ (<60 % Attendance) R (n=11) EX (n=9) Δ R-EX (n=9)			**$C2_{18}$ (≥60 - <80 % Attendance)** R (n=14) EX (n=9) Δ R-EX (n=9)			**$C3_{18}$ (≥80 % Attendance)** R (n=15) EX (n=9) Δ R-EX (n=9)		
	Admission	6 months	18 months	Admission	6 months	18 months	Admission	6 months	18 months
HEART RATE (bpm)	65.2 (3.0) 107.3 (3.9) # -67.1 (8.0)	59.5 (1.5) 102.1 (3.2) # -72.3 (6.4)	61.2 (1.8) 100.9 (3.0) # -67.3 (9.2)	73.6 (4.1) 106.5 (4.0) # -50.2 (9.7)	69.8 (2.8) 109.8 (4.2) # -59.4 (6.8)	66.3 (3.1) 99.6 (2.0) # -53.6 (6.1)	64.0 (3.3) 100.7 (4.4) # -60.0 (6.8)	61.1 (3.3) 102.3 (3.5) # -74.0 (11.1)	56.9 (2.1) ^ 96.5 (4.7) # -72.8 (11.3)
EDC x 10^3	432 (38) 490 (44) -20.3 (14.5)	397 (28) 346 (63) 12.1 (14.6)	414 (39) 416 (80) 0.7 (16.3)	526 (46) 656 (65) -30.2 (13.1)	496 (46) 450 (61) !! 7.7 (12.4) !	516 (49) 491 (65) ^ 0.6 (10.2)	538 (71) 535 (117) 7.7 (12.0)	500 (48) 425 (67) 14.3 (9.7)	530 (45) 448 (65) 16.1 (10.2)
ESC x 10^3	187 (35) 238 (33) -44.5 (18.7)	183 (34) 172 (29) -16.8 (25.0)	186 (34) 268 (55) -53.2 (25.6)	276 (43) 372 (58) * -39.2 (14.5)	269 (46) 268 (44) -9.0 (16.2)	274 (46) 314 (54) -22.0 (12.5)	326 (77) 358 (105) 0.3 (12.1)	288 (52) 263 (61) 6.4 (12.1)	306 (51) 312 (65) -0.1 (14.3)
SC x 10^3	245 (15) 251 (42) -3.4 (17.2)	214 (19) 174 (40) 22.6 (12.6)	228 (21) 148 (37) * 36.8 (14.4)	249 (15) 284 (39) -21.0 (18.0)	227 (12) 182 (28) !! 17.4 (13.4) !	243 (23) 177 (27) ^ 16.8 (13.1) ^	211 (11) 18 (30) 13.6 (15.0)	211 (22) 162 (25) 18.8 (9.7)	224 (15) 136 (21) # 37.8 (9.5)
EF %	58.9 (3.6) 52.5 (4.4) * 11.9 (4.4)	56.0 (4.7) 52.0 (3.7) 2.1 (7.5)	56.6 (4.1) 45.9 (3.4) * 17.0 (5.5)	50.1 (3.7) 47.0 (5.0) 7.2 (6.8)	49.8 (4.4) 46.2 (4.2) 5.2 (6.7)	51.1 (4.5) 43.3 (4.9) * 15.5 (6.0)	46.0 (4.6) 42.9 (4.7) 6.3 (5.4)	46.4 (4.9) 46.5 (4.6) -3.7 (5.7)	47.0 (4.7) 43.3 (4.7) 7.8 (5.4)
T-PER (sec)	0.16 (0.01) 0.06 (0.00) # 56.0 (5.8)	0.14 (0.01) 0.07 (0.00) # 51.3 (3.0)	0.15 (0.01) 0.07 (0.01) # 50.0 (7.7)	0.16 (0.01) 0.08 (0.01) # 46.6 (6.4)	0.14 (0.01) 0.07 (0.01) # 48.1 (4.4)	0.14 (0.01) ^ 0.08 (0.01) # 36.2 (7.0)	0.14 (0.02) 0.09 (0.01) # 29.0 (10.8)	0.16 (0.01) 0.07 (0.01) # 53.2 (5.3) !	0.15 (0.01) 0.09 (0.01) # 44.7 (7.9)
PER (EDV/sec)	2.86 (0.25) 3.84 (0.41) # -35.1 (9.1)	2.56 (0.18) 3.89 (0.29) # -55.7 (11.4)	2.73 (0.22) 3.43 (0.31) -30.2 (11.9) $	2.50 (0.20) 3.32 (0.29) # -37.4 (10.0)	2.48 (0.28) 3.53 (0.38) # -49.2 (13.7)	2.56 (0.26) 3.29 (0.41) * -30.4 (10.6)	2.27 (0.27) 3.12 (0.45) # -36.6 (10.2)	2.18 (0.27) 3.35 (0.40) # -57.7 (9.8)	2.06 (0.20) 3.23 (0.33) # -58.2 (12.8)
AV-ER (EDV/sec)	1.76 (0.14) 2.01 (0.27) -9.4 (11.7)	1.62 (0.14) 2.1 (0.19) * -36.2 (14.3)	1.70 (0.12) 1.57 (0.22) ^ 8.6 (13.3)	1.52 (0.12) 1.79 (0.21) -17.2 (11.4)	1.60 (0.18) 1.72 (0.17) -15.3 (10.8)	1.54 (0.16) 1.56 (0.20) -5.6 (10.8)	1.40 (0.15) 1.64 (0.22) -16.9 (11.3)	1.36 (0.15) 1.74 (0.22) * -31.4 (11.2)	1.38 (0.16) 1.48 (0.24) -1.8 (10.4) $
T-PFR (sec)	0.17 (0.01) 0.13 (0.02) 3.1 (34.9)	0.20 (0.01) 0.11 (0.01) # 43.0 (6.4)	0.22 (0.04) 0.12 (0.01) * 37.0 (10.6)	0.17 (0.01) 0.13 (0.05) * 20.7 (8.9)	0.23 (0.03) ! 0.07 (0.01) # 44.8 (7.1) !	0.22 (0.01) ^ 0.12 (0.01) # 40.9 (7.5)	0.19 (0.02) 0.13 (0.01) * 22.7 (9.3)	0.21 (0.02) 0.12 (0.01) # 33.2 (9.0)	0.19 (0.02) 0.13 (0.01) * 26.9 (11.8)
PFR (EDV/sec)	2.21 (0.19) 4.43 (0.54) # -107.7 (24.0)	1.86 (0.19) 4.58 (0.51) # -162.6 (30.6)	2.14 (0.21) 4.29 (0.41) # -113.1 (22.3)	2.35 (0.34) 3.95 (0.54) # -83.0 (20.8)	1.99 (0.23) 4.47 (0.48) # -139.5 (18.1)	1.78 (0.20) ^ 4.13 (0.40) # -147.0 (20.4) ^	1.69 (0.19) 3.51 (0.35) # -124.2 (19.8)	1.69 (0.20) 4.04 (0.42) # -149.4 (21.3)	1.63 (0.16) 3.89 (0.53) # -136.0 (20.8)
AV-RFR (EDV/sec)	1.42 (0.12) 2.92 (0.41) # -114.6 (28.8)	1.26 (0.12) 3.22 (0.34) # -189.3 (48.3)	1.40 (0.16) 3.24 (0.31) # -160.4 (30.6)	1.57 (0.24) 2.50 (0.36) * -73.5 (20.6)	1.22 (0.15) 3.49 (0.50) # ! -202.5 (33.7) !!	1.18 (0.15) ^ 2.97 (0.35) # -180.9 (34.2) ^	1.18 (0.15) 2.44 (0.27) # -130.5 (26.5)	1.20 (0.16) 3.01 (0.38) # ! -172.8 (25.3)	1.09 (0.11) 3.11 (0.43) # -191.1 (38.4)

Values are expressed as Mean (Standard Error). * $p<0.05$; # $p<0.01$ (rest vs exercise); ! $p<0.05$; !! $p<0.01$ (admission vs 6 months); $ $p<0.05$ (6 months vs 18 months); ^ $p<0.05$ (admission vs 18 months). Δ R-E: % change from rest to exercise; Other abbreviations as per Table IV.

8.3.4 Individual responses to exercise training

The wide variation in individual responses as a result of exercise training in cardiac patients suggests that means should be interpreted with caution.

However, in all compliance categories and for both cohorts, there were very few changes in individual left ventricular function responses to exercise training when expressed as a function of the responses of the control group (Chapter 3). Furthermore, there were no differences in individual responses between compliance categories before or after training.

8.3.5 Differences in physiological and left ventricular function variables between compliance categories

There were no substantial significant differences between compliance categories for both physiological and resting and exercise left ventricular function variables, on admission or after 6 and 18 months of exercise training. In ET6, the Broca index was significantly higher in $C2_6$ than in the other compliance categories ($p<0.05$), and heart rate rose more in $C2_6$ and $C3_6$ at 6 months than in $C4_6$ ($p=0.0009$ and $p=0.049$ respectively) during the exercise radionuclide ventriculography test. In ET18, the only significant differences between compliance categories were seen for resting heart rate that was higher in $C2_{18}$ than in $C1_{18}$ and $C3_{18}$ at 6 months ($p=0.044$ and $p=0.011$ respectively), submaximal ventilation that was higher in $C3_{18}$ than in $C1_{18}$ and $C2_{18}$ at 18 months ($p=0.003$ and $p=0.002$ respectively), heart rate during exercise radionuclide ventriculography that was higher in $C2_{18}$ than in $C1_{18}$ and $C3_{18}$ at 6 months ($p=0.018$ and $p=0.029$ respectively) and than $C3_{18}$ at 18 months ($p=0.008$), and resting SC that were lower in $C3_{18}$ than in $C2_{18}$ on admission ($p=0.049$).

8.3.6 Prevalence of systolic dysfunction in patients with different levels of compliance to the training programme (Table 8.7)

There were no significant differences in the number of patients with severely depressed (EF<35%), moderately depressed (EF ≥35 - <50%) and normal (EF ≥50) systolic left ventricular function between compliance categories for both cohorts of patients.

8.3.7 Differences in left ventricular function between patients and controls

On admission to the programme, all compliance groups for both cohorts, ET6 and ET18, showed similar significant differences in systolic and diastolic left ventricular function to the control group. These differences were similar to those previously reported for the whole ET6 cohort in Chapter 3.

Table 8.7 Prevalence of systolic dysfunction in the 2 cohorts per compliance category.

	COHORT ET 6			
	EJECTION FRACTION			
COMPLIANCE	<35 %	≥35 - <50%	≥50%	TOTAL
<40%	3 18.7 16.7	2 12.5 7.4	11 68.7 15.1	16
≥40 - <60%	2 8.7 11.1	6 26.1 22.2	15 65.2 20.5	23
≥60 - <80%	4 12.1 22.2	5 15.1 18.5	24 72.7 32.9	33
≥80%	9 19.6 50.0	14 30.4 51.8	23 50.00 31.5	46
TOTAL	18	27	73	118

Likelihood Ratio Chi-Square= 0.367

	COHORT ET 18			
	EJECTION FRACTION			
COMPLIANCE	<35 %	≥35 - <50%	≥50%	TOTAL
<60%	1 9.1 12.5	0 0 0	10 90.9 40.0	11
≥60 - <80%	3 21.4 37.5	3 21.4 42.9	8 57.1 32.0	14
≥80%	4 26.7 50.0	4 26.7 57.1	7 46.7 28.0	15
TOTAL	8	7	25	40

Likelihood Ratio Chi-Square= 0.103

Values are expressed in the following order: frequency (top); row percent (middle) and column percent (bottom)

8.4 Discussion

The design of our study, by comparing individuals with different attendance to the exercise programme, allowed patients to decide for themselves whether they wanted to attend exercise sessions or not. The conclusions derived from such design are obviously not as powerful as those derived from a controlled randomised study, which could be considered unethical, today, in the light of our knowledge about the benefits derived from exercise rehabilitation programmes.

Our approach in terms of compliance categorization led to a small number of individuals in each group but it is this same stratification by compliance category that constitutes the greatest strength of the study allowing us to establish a threshold level above which patients can obtain maximal favourable physiological adaptations.

Prevalence of myocardial infarction, medication use, presence of residual myocardial ischaemia, peak oxygen uptake and left ventricular function were no different between patients in the different compliance categories upon enrollment into the cardiac rehabilitation programme. These similar baseline characteristics between compliance categories support the hypothesis that the results seeing in this study are a consequence of the differences in attendance rather than the result of self-selection of healthier subjects to the better adherence group.

The first important finding of this study was that exercise training of 6 months duration resulted in the most favourable physiologic adaptations during both maximal and submaximal exercise. Exercise training of 18 months duration only served the purpose of maintaining the changes in maximal exercise tolerance obtained at 6 months, as well as the favourable changes in ventilatory threshold, but was unable to sustain the beneficial submaximal changes in haemodynamics that were seen at 6 months. A lower attendance during the period 6-18 months than in the period admission-6months, as well as progression of the disease leading to a more unfavourable myocardial oxygen supply and

demand balance, could explain the lack of maximal adaptations to training after 18 months.

The second important finding of the study was that maximal adaptations to training including an improvement in maximal exercise capacity, an improvement in cardiovacular efficiency demonstrated by beneficial changes during submaximal exercise and a resting bradycardia, required an attendance equal or greater than 80% for a period of 6 months.

Third, it is also in the group with the highest compliance that favourable changes in LV function were observed. The 18 month cohort failed to elicit any further changes in LV function irrespective of the compliance with the programme. Patients who attended 80% or more sessions during the 6 month period showed a significantly greater increase in PFR and AV-RFR during exercise and a trend towards a lesser reduction in SC, a lesser fall in EF and a greater increase in PER during exercise than the other groups. On the other hand, patients with the lowest compliance (<40%) had the greatest decrease in SC and greater reduction in EF and AV-ER during exercise. Furthermore, even patients attending between 60 and 80% of the possible exercise sessions did not show any deterioration in EF or AV-ER, and ESC were more reduced after training, in spite of these patients having had an increase in ST segment depression and its duration post-effort.

Since EDC failed to increase, an increase in heart rate from rest to exercise was the main mechanism by which patients in this study were able to maintain an adequate cardiac output during exercise, both before and after training. The increase in heart rate during exercise was significantly greater after training only in patients with the highest compliance. Such response could be due to a higher sympathetic activity or an increased sensitivity to catecholamines as a result of training and could be indicative of some improvement in contractile function even in the absence of a larger increase in SC at similar changes in EDC and of a reduction in ESC.

The definite improvement in diastolic function and the trend towards better systolic LV function during exercise in patients who attended ≥80% of the sessions is probably a consequence of a reduction in myocardial oxygen demands since heart rate, blood pressure and rate-pressure product at submaximal effort were significantly reduced in these patients after 6 months of exercise training. Since alterations in diastolic function occur early after occlusion of the coronary vasculature and improvements in diastolic function are also seen early after successful percutaneous transluminal coronary angioplasty (222), a faster and more meaningful improvement in diastolic rather systolic function could be expected in the presence of a more favourable balance between myocardial oxygen demand and supply after training. It is possible that meaningful changes in systolic function may require more intense training as has been suggested by some (115,199,201).

Patients in the highest compliance categories (≥80% and between ≥60 and <80% of the possible sessions) also trained at a significantly higher percentage of maximal heart rate than patients in the lower compliance categories. However only the group who attended 80% or more of the possible sessions exhibited the greatest benefits. It is interesting to note that the energy expended per session expressed in kilocalories was the same for both groups indicating that these two groups only differed in the volume of exercise accumulated over time. Hence, volume appears to be more important than exercise intensity in these adaptations suggesting that there is a threshold in exercise volume above which exercise could induce maximal physiological changes and beneficial central adaptations in these patients.

Our results in patients who complied with 80% or more of the possible sessions are somewhat different from most studies where the intensity of exercise training was set between 70 and 85% of the patient's maximal heart rate that showed little change in LV function after exercise training in patients with CAD (98,99,103,134,195-198).

Ehsani and colleagues (115) showed that prolonged and intense exercise training is capable of improving the left ventricular systolic function of coronary artery disease

patients. In their study VO_2 max increased by 37% from 23 to 31.5 ($p<0.001$) as a result of training and submaximal HR, SBP and RPP at the same workload were significantly lower. Five of the 10 patients who had effort angina became entirely asymptomatic. The magnitude of ST segment depression was significantly less (0.16 ± 0.02 before and 0.09 ± 0.03 after, $p<0.005$). EF at rest was unchanged, but was increased at the work rate equivalent to the peak work rate before training (51 ± 3 vs 57 ± 3 % after training, $p<0.005$) and during maximal supine exercise (58 ± 3 vs 52 ± 3 % before training, $p<0.001$). LV exercise reserve (change in EF from rest to exercise) was -1.0 ± 1% before and 4.0 ± 1% after training ($p<0.005$). They also concluded that the primary mechanism for improvement in LV function in the majority of the patients was an improvement in contractility due to a reduction in myocardial ischaemia. Since patients adapted to this training regime have previously attained a higher concentration of plasma norepinephrine which per se raises myocardial oxygen demands, the improvement in LV contractile function in their patients was not likely due to a lower myocardial oxygen requirement, but rather to an improvement in oxygenation of some of the underperfused regions of the myocardium.

The fall in EF during exercise in our patients was caused by a decrease in SV with a minimal change in EDV. In spite of EF falling in all patient groups both before and after training, a trend towards less reduction in SC and EF was observed the higher the compliance. Our results are similar to those of Hindeman and Wallace (258), who compared the haemodynamic response to exercise conditioning of 14 subjects with coronary artery disease and normal subjects by performing first pass radionuclide studies in the erect position before and after 6 months of training. They reported that perhaps one of their most important findings was that ejection fraction which fell in all subjects during exercise before training, failed to decrease in most subjects after training. A more attenuated response in our patients could be explained by the fact that our patients exercised in the supine position and Hindeman's upright.

The Fick equation defines the relationship between cardiac output and the arteriovenous oxygen difference to VO_2 during exercise: VO_2 = Cardiac Output x arteriovenous O_2 difference. Since Cardiac Output = Stroke Volume x Heart Rate and Stroke Volume = EF x End-Diastolic Volume, the relationship can be expressed as: VO_2 = EF x End-Diastolic Volume x Heart Rate x arteriovenous O_2 difference. At a submaximal level, the significant increase in VO_2 seen in our patients in the presence of an unchanged stroke volume suggests a compensatory increase in the arteriovenous oxygen difference to balance the decrease in heart rate. At a maximal level, in the absence of an increase in end-diastolic volume and EF, our results suggest that the increase seen in peak VO_2 after 6 and 18 months of exercise training is principally the result of an improved heart rate response to exercise and widening of the arteriovenous oxygen difference. This is in keeping with most studies which have shown skeletal muscle changes -improved capillary supply and increased oxidative enzymes- after training in patients with coronary artery disease (98,134,259) and normal subjects (260-263).

Furthermore, the LV response to training in our patients could also be explained by the age-related impairment of LVEF response to exercise which is characterized by a smaller rise in EF and a lack of decrease in ESV at peak exercise in the elderly compared with young subjects. This age-related deterioration in LV systolic function could be improved by relatively prolonged vigorous exercise training in older men (264,265), but not by programmes of moderate intensity.

8.5 Conclusions

Compliance in terms of attendance had a significant influence on the changes in physiological and left ventricular function variables induced by exercise training of 6 months duration. Patients who attended 80% or more of the possible sessions showed in addition to a significant increase in maximal exercise capacity, a resting bradycadia and a significant reduction in heart rate and blood pressure during submaximal exercise. These

favourable adaptations were matched by a significant improvement in diastolic function during exercise and a trend towards an improvement also in systolic function. Attendance for 18 months showed no other physiological advantages than maintaining maximal exercise capacity.

CHAPTER 9

CONCLUSIONS

9.1 Final Discussion

We succeeded in addressing several methodological issues raised by previous studies and discovered novel findings about the relationship between left ventricular function and exercise tolerance in patients with coronary artery disease undergoing exercise training in a community-based cardiac rehabilitation programme in Johannesburg, South Africa.

We studied a wide spectrum of patients with documented coronary artery disease 12 weeks post-myocardial infarction and post-coronary artery bypass surgery and 4 weeks post-coronary angioplasty referred to a cardiac rehabilitation programme. Previous studies evaluated mainly patients post-myocardial infarction while admitted to the hospital or shortly after their cardiac event. These patients are not necessarily representative of patients attending outpatient cardiac rehabilitation programmes. Furthermore those studies do not take into account the spontaneous improvement in left ventricular function during the healing process.

It is possible that the subjects enrolled into this study were not fully representative of the general population of patients with coronary artery disease because of prescreening by referring physicians in favour of motivated subjects or subjects thought to be poor candidates for surgical revascularization procedures. In addition there was self-selection of those subjects who continued in their exercise programmes for the duration of the study or who chose to comply more fully with the programme. Despite these potential selection factors, our study population included individuals with a broad range of clinical characteristics at baseline. Because of the heterogeneous nature of our study population, the possibility existed that physiologically significant effects of training occurring only within certain subgroups might be obscured by an analysis of data from the entire group.

We used a control group representative of a population of normal healthy subjects for the measurements of left ventricular function while previous studies used institutionalized

patients without demonstrable coronary artery disease who were expected to have normal function, as their control group .

We used a method of assessment of left ventricular function that allowed us to quantify with precision systolic as well as diastolic function, at rest and during exercise expanding the results obtained in previous studies that evaluated only systolic left ventricular function at rest.

We evaluated a complete spectrum of left ventricular dysfunction by dividing patients into 3 categories according to their level of impairment in LV systolic function. Most investigators have used an arbitrary cut-off point in ejection fraction as the criteria for classification of their population.

Adherence to the training regime was taken into account when reporting results after exercise training. We used two different criteria: (a) For most studies, compliance with attendance was monitored to ensure that participants completed at least 60% of the exercise sessions during the period studied. (b) When we evaluated the effects of exercise training on left ventricular function, we divided patients into 4 categories according to their compliance with the exercise training program. This allowed us to use patients with poor attendance as a control group.

Patients were enrolled into the study consecutively depending on their availability and consent for radionuclide ventriculography studies. We studied two major cohorts of patients: Cohort 1 included 171 patients who had the radionuclide ventriculography test done on admission and at rest only, and Cohort 2 included 118 patients who had the tests done on admission and after 6 months, at rest and during exercise.

We confirmed our suspicions that patients enrolling into a contemporary community-based cardiac rehabilitation programme are of increasing medical complexity because of associated left ventricular dysfunction and/or myocardial ischaemia:

- In Chapter 3 we compared the left ventricular function of patients in cohort 2 to that of a control group and found that patients had profound alterations in diastolic and/or systolic left ventricular function both at rest and during exercise. In Chapters 3 and 4 we demonstrated that both cohorts were very consistent in the number of patients with moderate (EF≥35 and <50%: cohort 1– 22 % vs cohort 2 - 23%) and severe (EF<35%: cohort 1- 16% vs cohort 2 - 15%) left ventricular dysfunction.
- We also found that several patients had residual myocardial ischaemia as assessed by electrocardiographic criteria: in Cohort 1 there were 38 patients with ST segment depression (22%) (Chapter 4) and in Cohort 2 there were only 9 (8%) (Chapter 3). In Chapter 6, we also identified 22 patients with myocardial ischaemia using a combined electrocardiographic and radionuclear myocardial perfusion imaging criteria (Cohort 3). Risk stratification guidelines stratify patients according to the presence of left ventricular dysfunction and myocardial ischaemia, into low risk (no ischaemia, normal LV function), moderate risk (moderate ischaemia and LV dysfunction) and high risk (severe myocardial ischaemia and LV dysfunction). If our cardiac rehabilitation programme can be considered representative of other cardiac rehabilitation programmes around the world, we could conclude that a higher percentage of moderate to high risk patients are being accepted today into this type of programmes. Since we know that the incidence of exercise-related cardiovascular complications increases with the risk of the population studied, we have to assume that the risk of these complications could easily increase if cardiac rehabilitation practitioners do not adhere to risk stratification guidelines to guide the monitoring of their patients.

Patients with severely depressed left ventricular function had a significantly lower exercise tolerance (Chapter 4) than patients with moderately impaired or normal LV function on admission to the programme, as evidenced by lower peak oxygen uptake, lower ventilatory threshold and lower treadmill time. However, the degree of adaptation to training was the same for all patients regardless of their degree of resting systolic or diastolic left ventricular dysfunction as demonstrated by equivalent increases in peak oxygen uptake, ventilatory threshold and treadmill time to exhaustion in all groups (Chapter 4). The

reporting of improvements in exercise tolerance in patients with chronic heart failure is not new. Earlier studies showed that improvements in maximal exercise capacity could be seen in patients with modest impairment in left ventricular function (Letac et al. (98): EF<45% and Lee et al. (132): EF<40%) and in patients with more severely depressed LV function (Cohn et al. (133): mean EF=27% and Sullivan et al. (134): mean EF=24%; Coats et al. (136): mean EF=19%).

However we are the first to report that the degree of improvement in exercise capacity is the same for patients with severely depressed (EF<35%), moderately depressed (EF<50 and ≥35%) and normal left ventricular function (EF≥50%).

Our findings that the exercise tolerance of patients on admission or its improvement after training could not be predicted in any group by baseline measurements of resting systolic or diastolic left ventricular function (Chapter 4) is then not surprising. Our results are consistent with those of other studies that have also reported a lack of correlation between ejection fraction and exercise tolerance in patients with chronic left ventricular dysfunction (226-228).

However, in most studies the correlation was restricted mainly to patients with severe heart failure and not made across a wide spectrum of patients with various degrees of left ventricular dysfunction. Perhaps of more novel interest is our finding about the lack of correlation between diastolic function and exercise capacity since little has been published about the relationship between these two variables. Since alterations in the diastolic properties of the myocardium may limit or prevent the increase in stroke volume during exercise (184), it would have been expected that patients with diastolic dysfunction had lower exercise capacity. But traditional non-cardiac factors such as age, gender, the Broca Index and forced vital capacity included in a multiple regression model explained nearly 50% of the variance in exercise capacity.

It was previously thought that training patients with severe left ventricular dysfunction was unsafe because of possible training-induced deleterious effects on their already compromised left ventricle. In addition, it is well known that these patients are at higher risk of sudden death during exercise. These were some of the reasons for excluding patients with chronic heart failure from cardiac rehabilitation programmes. Cardiac rehabilitation is not well developed in South Africa and it was the responsibility of its largest cardiac rehabilitation programme to prove that patients with LV dysfunction could exercise safely in programmes of this type and derive physiological benefits.

Accordingly, in Chapter 5 we were able to show significant increases in maximal exercise capacity and a reduction in the rate-pressure product at a submaximal workload as a result of training in 22 patients with EF≤30%. These results are similar to those reported for patients in the EF<35% category in Chapter 4. The main difference between the two studies is that in this study, we measured the ejection fraction at rest and during exercise before and after exercise training and we were able to demonstrate that exercise training did not induce any deleterious effect in the left ventricular function of these patients. Although it remains unknown whether these favourable physiological adaptations could improve the prognosis of these patients, they were still alive after a mean follow-up of 26 months (8 to 32 months). These results are quite hopeful if we consider that 10 of our patients have had congestive heart failure while in the hospital and a 26% 1 year mortality has been reported for patients with a history of signs and/or symptoms of heart failure (119). We could speculate that the reduction in resting heart rate seen in our patients after training, a manifestation of an increase in vagal tone, could have increased their resistance for fatal ventricular arrhythmias as it has been seen in animal models (122).

It is interesting to note that only patients with severely depressed EF (<35%) on admission to the programme, had an abnormally increased ventilatory response to exercise, that is, a higher VE/VCO_2 ratio at submaximal and maximal levels and a higher VE/VCO_2 slope (Chapter 7). Patients with moderate left ventricular impairment had a similar ventilatory response to those with normal LV function. However this is the first study to show these

changes in asymptomatic patients in NYHA functional classes I and II who did not have clinical signs and symptoms of congestive heart failure, since the other studies included patients mainly in classes II and III, with overt heart failure and who were on treatment with diuretics and digoxin (134,147,250,252,254-256). The higher the severity of heart failure, as assessed by the peak oxygen uptake, the higher the ventilatory response to exercise. Since patients whose peak VO_2 fell below 20 ml/kg/min seemed to have the higher ventilatory response, we could hypothesize that an inadequate cardiac output in these patients lead to lack of perfusion of certain ventilated areas of the lungs (253) producing a ventilation perfusion mismatch and an increase in dead space ventilation. Again these were the patients with the lowest ventilatory efficiency. Although exercise training increased maximum oxygen uptake and maximum ventilation in all patients irrespective of their left ventricular function, it was ineffective in reducing the higher ventilatory response to effort at any level of VCO_2 in the group of patients with more severe LV impairment (Chapter 7). There was good correlation between a low ejection fraction, peak oxygen uptake and the slope of the relation between minute ventilation and carbon dioxide production indicating as it has been suggested by others (252) that the latter could provide a more objective way of evaluating the degree of severity of heart failure since it is not dependent of the patient's motivation while doing the test.

It was important to analyse the relationship between ischaemia and left ventricular function since it has previously been reported that patients with chronic heart failure and myocardial ischaemia may show a deterioration in their left ventricular function without any associated physiological benefits as a result of exercise training (190). This hypothesis was tested in different ways using different population groups. In Chapter 4 we demonstrated that all 7 patients with myocardial ischemia from the group with severely depressed LV function (EF<35%) showed an improvement in maximal exercise tolerance as evidenced by a mean increase of 16% in peak VO_2. Only 1 of 6 patients with myocardial ischaemia in the group with moderate LV impairment did not improve his maximal oxygen uptake but the remaining 5 patients improved their mean peak oxygen uptake by 13.8% after training. In Chapter 5 we reported no deterioration in left ventricular

function even in patients with associated myocardial ischaemia and 3 of the 5 patients who showed ST segment depression on admission normalized their ST segment response after training. Making a diagnosis of myocardial ischaemia based only on electrocardiographic criteria has important limitations, so in order to increase the sensitivity of the method throughout the study we required the ST segment changes to be present both during and after exercise for the response to be considered ischaemic.

Since we are accepting more patients with myocardial ischaemia for cardiac rehabilitation, we decided also to evaluate the adaptability to exercise training of these patients and the effect of ischaemia on left ventricular function. For years we observed that a high percentage of these patients did not experience chest pain during their exercise test in spite of clear electrocardiographic changes. In this regard some reports have indicated that the presence of pain could indicate the presence of myocardium that is more at jeopardy.

To overcome the electrocardiographic diagnostic limitations we utilised a well accepted imaging technique using Tc-SestaMibi which had the advantage of not being washed out in the immediate post-effort period allowing for the patient to be evaluated at another facility, in this case the Department of Nuclear Medicine of the Johannesburg Hospital which was two kilometres away from our Center.

It is well accepted that a drop in ejection fraction during exercise, measured by radionuclide ventriculography, represents an imbalance between myocardial oxygen supply and demand and can be considered a strong indicator of exercise-induced myocardial ischaemia. Little is known however, about how exercise training can affect the association between ischaemia and left ventricular dysfunction.

We studied the mechanisms by which ischaemia affects ventricular function at rest and during exercise in patients with normal left ventricular function (Chapter 6) speculating that they could be extrapolated to patients with LV dysfunction. We already discussed that patients with coronary artery disease at entry to our programme had significant alterations

in the contractile and filling properties of the left ventricle when compared with normal controls (Chapter 3). We found that the heart with ischaemia differed from the heart with left ventricular dysfunction in its method of maintaining the cardiac output during exercise. The mechanism by which patients with left ventricular dysfunction maintained their cardiac output differed from healthy controls mainly at rest while in patients with myocardial ischaemia the differences between patients and healthy controls became more marked during exercise. Patients with systolic LV impairment maintained their cardiac output at rest at the expense of a chronic increase in end-diastolic volume and a higher heart rate than healthy subjects (Chapter 3). As reported by others (211), patients with myocardial ischaemia developed an acute ventricular dilatation during exercise with higher increases in EDC than the control group (Chapter 6). The increase in EDC post-effort in both groups, patients with left ventricular dysfunction and control group, suggests that as heart rate decreases patients and controls are both able to dilate their ventricles to maintain cardiac output in the post-effort period (Chapter 3).

As a result of training, patients with myocardial ischaemia increased their peak oxygen uptake and ventilatory threshold but failed to improve their cardiovascular efficiency by reducing their heart rate and blood pressure at submaximal workloads. Exercise training also, did not change the relationship between ischaemia and left ventricular function. The twelve patients with myocardial ischaemia, in whom we were able to assess left ventricular function before and after exercise training, showed no major changes in their left ventricular function when re-evaluated 6 months later, but showed some signs that could be interpreted as early indicators of progression of disease (Chapter 6).

As expected, the physiological benefits induced by exercise training varied with the number of sessions attended and the duration of the stay on the programme. Patients attending 80% or more of the possible sessions for a period of 6 months, showed the most optimal adaptations to exercise training demonstrating the greatest improvement in exercise capacity not only at maximal but also at a submaximal level. In addition they showed a resting bradycardia (Chapter 8). Our results are quite unique in that the same

patients also showed an increase in the heart rate response to exercise and an improvement in diastolic function by increasing peak filling rate and average rapid filling rate during exercise significantly more than patients who attended fewer sessions (Chapter 8). The possibility of spontaneous left ventricular function recovery was excluded by enrolling patients post-myocardial infarction or coronary bypass surgery 12 weeks after their event, so we can conclude that the changes in left ventricular function seen in our patients must have been produced by exercise training. Central adaptations have only been reported previously in programmes of higher intensity, higher frequency (5 times per week) and longer duration (12 months) (200). We found a threshold for favourable changes in diastolic function with an attendance around 90% of a possible 72 sessions, at an intensity around 78-80% of the patient's maximal heart rate which is the middle of the conventional range of 70 to 85% of maximal heart rate. It is very possible that an improvement in systolic function may require a higher volume of exercise. We postulate that a reduction in myocardial oxygen demands as seen in our patients after 6 months of training is the most likely mechanism for the improved diastolic function. This may have also contributed to the trend towards an improvement in systolic function seen in the same patients: a lesser reduction in SC, a lesser fall in EF and a greater increase in PER during exercise than the other groups.

The patients who exercised for 18 months did so at the expense of a lower quality of attendance: 93.5 % during the first 6 months vs 84.6 % between 6 and 18 months and failed to demonstrate a reduction in heart rate and blood pressure at the same submaximal workload. This coupled to some signs suggestive of progression of disease probably explain the lack of improvement in left ventricular function in these patients.

9.2 Final Conclusions

The most important conclusions of this study are:

1) That patients with left ventricular dysfunction constitute a significant proportion of patients admitted to contemporary cardiac rehabilitation programmes.

2) That there is no correlation between measures of both systolic or diastolic LV function at entry to a cardiac rehabilitation programme, and exercise capacity, before or after training and that the physiological effects induced by exercise training are of a similar magnitude irrespective of the degree of impairment in these patients' LV function.

3) That patients with asymptomatic left ventricular dysfunction and an ejection fraction of 30% or less can derive physiological benefits from exercise training, at both submaximal and maximal levels, without deleterious effects on their left ventricular function. That in spite of the above beneficial effects, exercise training was ineffective in reducing the excessive ventilatory response seen in this group of patients.

4) That exercise training is able to improve the maximal exercise capacity of patients with residual myocardial ischaemia enrolling into cardiac rehabilitation programmes but is unable to elicit physiological adaptations during submaximal exercise or to increase the threshold for ischaemia. These results suggest that aggressive coronary risk factor modification, particularly lipid lowering, should complement exercise training in the rehabilitation of this group of patients in order to slow the progression of the disease.

5) That the mechanisms used to maintain cardiac output at rest or to increase it during exercise are different between patients with left ventricular dysfunction and patients with myocardial ischaemia. Patients with left ventricular dysfunction use the Frank Starling mechanism at rest, maintaining their cardiac output through an increase in end-diastolic volume, whereas an increase in heart rate plays the more important role

during exercise. Patients with myocardial ischaemia do not differ from healthy controls in the way they maintain cardiac output at rest but they increase their cardiac output during exercise also through an increase in heart rate but most importantly by utilising the Frank Starling mechanism leading to acute ventricular dilatation.

6) That adherence has a significant effect on the type and on the magnitude of adaptations derived from exercise training: Patients who participated in 80% or more of the possible exercise sessions for 6 months derived most physiological benefits from exercise training programmes being able to increase their maximal exercise capacity, improve their cardiovascular efficiency, reduce their resting heart rate and even improve their LV diastolic function during exercise.

7) That attendance for 18 months does not offer physiological advantages other than maintaining the maximal exercise capacity achieved by 6 months. However it may play an important role in promoting longer lasting lifestyle changes.

9.3 Recommendations as a result of the findings of this study

- Recommendations are made for patients to be accepted onto cardiac rehabilitation exercise programmes irrespective of their degree of LV dysfunction. These patients can derive physiological benefits from this type of program and maybe increase their threshold for ventricular fibrillation without adverse effects on their LV function.

- These recommendations can be extended to patients with myocardial ischaemia with the understanding that fewer physiological benefits are to be expected as a result of their participation in these programmes and that efforts should concentrate on education, improvements in psychological wellbeing and coronary risk factor modification aimed at slowing the progression of the underlying disease process. Aggressive lipid management with diet and cholesterol lowering drugs may be more important than exercise alone in reversing the disease process in patients with demonstrable exercise-induced myocardial ischaemia.

- Even patients with both left ventricular dysfunction and associated myocardial ischaemia could benefit from participation in cardiac rehabilitation programmes.

- There is little doubt that patients being accepted to modern programmes are of increasing cardiac complexity and because of the above at a higher risk of exercise-related complications. Practitioners must therefore adhere to risk stratification recommendations to guide the degree of monitoring of their patients during exercise sessions.

- Cardiac rehabilitation practitioners should monitor and enhance the compliance of their patients during participation in exercise training programmes in order to maximise the beneficial results obtainable from this treatment modality. It is possible that through better adherence patients could achieved improvements in LV function in programmes of conventional intensity without the need to embark into high intensity

regimes which are impractical and probably not adequate for moderate to high risk patients.

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