Assessments of functional capacity in cardiac rehabilitation

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A thesis submitted for the degree of Doctor of Philosophy

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January 2011

ABSTRACT

Functional capacity is an important predictor of mortality in patients with cardiovascular disease. Exercise walk tests, such as the modified shuttle walking test (MSWT) and the six-minute walking test (6-MWT), are the recommended protocols in the United Kingdom for evaluating functional capacity and the effects of therapeutic interventions on patients enrolled in cardiac rehabilitation (CR) programmes. Due to a lack of research into factors associated with walking test performance in cardiac patients, the main aim of this study is to identify whether routinely taken measures (clinical and non-clinical) and biomechanical parameters can predict test performance. A further aim is to establish reference equations or normative values to predict performance in this population. Finally, this research aims to improve the safety of exercise testing and training in community-based CR settings.

After determining the long-term reliability of the MSWT, this study investigated the claim that only sex, age and anthropometric parameters (stature and weight), and not biomechanical or simple clinical parameters, can predict functional capacity assessed by the MSWT, in patients with less severe cardiac diseases or by the 6-MWT, in heart failure patients. Overweight heart failure patients showed a 13-fold increase, and older patients (>75 years) had a 5-fold increase, in the risk of poor prognosis via 6-MWT assessment. Furthermore, it is shown here that the effect of stature on the magnitude of change in MSWT results is powerful, and can be used to estimate functional capacity improvement in the cardiac population. Finally, poor functional capacity was shown to have no association with risk of cardiovascular events during exercise, and that exercise testing and training can be carried out safely in supervised community-based CR settings. These findings have implications in clinical practice and CR programme improvement, as they can help clinicians to make better-informed decisions about cardiac patients entering CR.

ACKNOWLEDGEMENTS

During the three years of my studies as doctoral student I have been given the opportunity to gain knowledge and to share experiences with many people. It would not have been possible to write this thesis without the help and encouragement of the kind people around me – only some of whom it is possible to mention here.

Firstly, I would like to express my deep and sincere gratitude to my supervisor, Dr Gavin Sandercock, for his unsurpassed knowledge of cardiac rehabilitation, and for his thoughtful guidance and support throughout this project. I am grateful for all the time he has dedicated to my work, and for reviewing several versions of my chapters. This doctoral thesis would not have been possible without his help.

I would also like to acknowledge Dr Paul Bromley, Dr Lee Ingle and Dr Matthew Taylor for their good advice and support for my work. I would also like to thank all the participants who took part in the study, and my fellow group members for their help and support during testing.

I am heartily thankful to my lovely parents who provided me with a love of lifelong learning through their encouragement, support (psychological and financial) and advice throughout all these years of study.

Last, but by no means least, I thank the two doctors in my life: my brother, Dr Georgios Peperas, who as a cardiologist inspired me to want to study in this field, which I find most the fascinating area to work in; and my lovely fiance, Dr Konstantinos Kalatzis, for putting up with my long periods of absence from home and for his wise daily words of encouragement during this endeavour.

This doctoral thesis is dedicated to my wonderful fiance, Dr. Konstantinos Kalatzis, for our wonderful life together.

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6-MWD	Six-minute Walking Distance
6-MWT	Six-minute Walking Test
ACE	Angiotensin-Converting Enzyme
ACSM	American College of Sports Medicine
AEBs	Atrial Ectopic Beats
AF	Atrial Fibrillation
AHA	American Heart Association
BACR	British Association for Cardiac Rehabilitation
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
bpm	Beats per Minute
CABG	Coronary Artery Bypass Graft
CHD	Coronary Heart Disease
CI	Confidence Interval
CR	Cardiac Rehabilitation
CVD	Cardiovascular Disease
ECG	Electrocardiogram
GTN	Glyceryl Trinitrate
HDL	High Density Lipoprotein
HF	Heart Failure
HR	Heart Rate
HRQOL	Health-Related Quality Of Life

LVD	Left Ventricular Dysfunction
LVEDD	Left Ventricular End-Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End-Systolic Diameter
METs	Metabolic Equivalents
MI	Myocardial Infarction
MSWD	Modified Shuttle Walking Distance
MSWT	Modified Shuttle Walking Test
NHS	National Health Service
NO	Nitric Oxide
NRES	National Research Ethics Service
NSF	National Service Framework
NT-pro-BNP	N-Terminal pro-B-type Natriuretic Peptide
NYHA	New York Heart Association
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
RPE	Borg Rating of Perceived Exertion
RVD	Right Ventricular Dysfunction
SD	Standard Deviation
SE	Standard Error
SIGN	Scottish Intercollegiate Guidelines Network
SWT	Shuttle Walking Test
UK	United Kingdom
US	United States
VE	Ventricular Ectopics

VEBs	Ventricular Ectopic Beats
VO2	Oxygen Uptake
VO_{2max}	Maximal Oxygen Consumption
VO_{2R}	Oxygen Uptake Reserve
WHO	World Health Organisation

LIST OF PUBLICATIONS

Articles published or in peer-review

1. Pepera, G. McAllister, J. and Sandercock, G. (2010). Long-term reliability of the incremental shuttle walking test in clinically stable cardiovascular disease patients. *Physiotherapy,* **96**, 222-227. (published; see Appendix C1).

2. Pepera, G.K. Peristeropoulos, A. Taylor, M.J. and Sandercock, G.R.H. Biomechanical predictors of the shuttle walking test performance in patients with cardiovascular disease. *Cardiopulmonary Physical Therapy Journal* (peer-review; see Appendix C2).

3. Pepera, G.K. Bromley, P.D. and Sandercock, G.R.H. Safety of exercise training and exercise testing for cardiac patients, in a supervised, community-based cardiac rehabilitation programme. *European Heart Journal* (manuscript ready for submission in the journal).

4. Pepera, G.K. Ingle, L. and Sandercock, G.R.H. Pacing strategy and changes in step length do not influence six-minute walk test performance in patients with chronic heart failure. *European Journal of Cardiovascular Prevention and Rehabilitation* (manuscript ready for submission in the journal).

Published abstract

1. Pepera, G. Ingle, L. and Sandercock, G. (2010). Simple determinants of six-minute walk test performance in heart failure patients. *Heart Surgery Forum,* **13**, S57.

Presentations

1. Pepera, G. and Sandercock, G. (2008). Reliability of the Modified Shuttle Walk Test in Phase IV Cardiac Rehabilitation clients. 7th Annual Graduate Forum organized by the Department of Biological Sciences of Essex University, Colchester, United Kingdom. (Poster Presentation; see Appendix E1).

2. Pepera, G. and Sandercock, G. (2009). Biomechanical predictors of the modified shuttle walking test performance in patients with cardiovascular disorders. 8th Annual Graduate Forum organized by the Department of Biological Sciences of Essex University, Colchester, United Kingdom. (Oral Presentation; see Appendix D1)

3. Pepera, G. McAllister, J. and Sandercock, G. (2009). Long-term reliability of the Modified Shuttle Walking Test in clinically stable cardiovascular disease patients. BACR (British Association for Cardiac Rehabilitation) Annual Conference, Birmingham, United Kingdom. (Poster Presentation; see Appendix E2).

4. Pepera, G. Sandercock, G. and Ingle, L. (2010). Predictors of six-minute walk test performance in heart failure patients. EuroPrevent organized by the ESC (European Society of Cardiology), Prague, Czech Republic. (Poster Presentation; see Appendix E3).

5. Pepera, G. Ingle, L. and Sandercock, G. (2010). Simple determinants of six-minute walk test performance in heart failure patients. 5th International Meeting of the Onassis Cardiac Surgery Center, Athens, Greece. (Oral Presentation; see Appendix D2)

6. Pepera, G. Peristeropoulos, A. Taylor, M. and Sandercock, G. (2010). Influence of anthropometric and gait parameters on the modified shuttle walking test performance in patients with cardiovascular disorders. BACR (British Association for Cardiac Rehabilitation) Annual Conference, Liverpool, United Kingdom. (Poster Presentation; see Appendix E4).

CHAPTER 1. INTRODUCTION AND OVERVIEW OF THESIS

1.1. Motivation

The literature review for this thesis began in September 2008. It was conducted to evaluate the research related to cardiac rehabilitation (CR). A search was carried out using the following keywords: 'cardiac rehabilitation', 'cardiac diseases', 'coronary heart disease', 'exercise', 'national survey'. The motivation for the thesis came from the results of this search.

Specifically, the motivation came from the results of recent surveys in the United Kingdom (UK), conducted by Brodie *et al.* (2006) and Bethell *et al.* (2007). Despite the well-established benefits of CR for cardiac patients (Oldridge *et al.*, 1988; O'Connor *et al.*, 1989, Jolliffe *et al.,* 2000), these surveys showed that only 28.5% of eligible cardiac patients attend CR programmes (Bethell *et al.*, 2007), while there is a waiting list from three weeks to nine months for patients to join outpatient (phase III, UK classification) CR (Brodie *et al.*, 2006). Two of the main reasons for the poor provision of CR are insufficient financial support for services and the low recognition by cardiologists and patients of the importance of CR (Brodie *et al.*, 2006; Bethell *et al.*, 2007). These results were reflected on and analysed in order to suggest possible solutions to improve and increase CR provision.

The focus of this thesis was the improvement of existing functional walking assessment tests used in CR. Such tests have the potential to replace traditional laboratory-based tests, which are expensive and time consuming and for which patients often need to wait. This, in turn, could reduce long waiting times and the cost of CR services. Laboratory-based tests have the capability to produce direct functional capacity outcomes, but the need for specialist equipment and highly trained staff results in the frequent utilisation and improvement of simpler, field-based protocols.

Such tests include the modified shuttle walking test (MSWT) and the six-minute walk test (6-MWT).

1.2. Aim of the thesis

The overall aim of this thesis was to investigate which factors can predict responses in functional capacity (i.e., the capability to maintain the activities of daily living) during two commonly used walking tests for CR patients: the MSWT and the 6-MWT. The intention was also to develop normative values for functional capacity when using the MSWT for this population; these values are for use in norm-referenced standards for individual patients entering CR.

Such data could help clinicians to stratify patients according to functional capacity more effectively, help them to set better goals and make better-informed decisions about patients enrolled in a CR programme. A secondary aim was to investigate the safety of exercise testing and training in community-based CR settings. In this way, functional capacity evaluation and CR services can be improved, encouraging participation in CR training programmes.

1.3. Structure and main outcomes of the thesis

This thesis is divided into seven chapters. **Chapter 1** is a general introduction, which continues in **Chapter 2** with a review of the relevant literature pertaining to cardiovascular diseases and CR. The literature review summarises existing knowledge on the topic and highlights gaps in the research literature. **Chapter 3** provides an investigation into the long-term reliability of the MSWT. This study was carried out because the literature review showed that only short-term reliability had been assessed. Long-term reliability is important in CR because the MSWT is often administered to patients pre- and post- CR, a gap of four to twelve weeks. To assess the reliability, the test was completed twice, by clinically stable phase IV CR patients, eight weeks

apart. The data showed no systematic bias but a relatively large random variation in test performance over the test period. It is concluded that the test can be used effectively in CR. Tests need to be both reliable, valid and much of the rest of the thesis concerns test validity.

Performance on the 6-MWT is strongly influenced by age and stature of patients, but no comparable data were available for the MSWT. The aim of **Chapter 4** is, therefore, to determine associations between anthropometric and gait parameters with distance walked during the MSWT. This chapter, as a pilot study, provides a preliminary reference equation to estimate MSWT performance in patients participating in maintenance (phase IV, UK classification) CR programme. The results show that only one gait parameter (step length) and two anthropometric measures (stature, leg length) are associated with MSWT performance. Step length is the best predictive measure of MSWT performance, followed by stature. It is concluded here, with regard to clinical practice implications, that tall cardiac patients have an advantage in the MSWT and that practitioners should account for stature when interpreting distance walked.

Exploring the important role of simple anthropometric variables on the estimation of MSWT performance, in combination with the frequent use of the 6-MWT as an outcome measure in heart failure (HF) patients, **Chapter 5** evaluates the degree to which non-clinical variables (age, anthropometric, gait parameters) may have an impact on 6-MWT performance in the HF population. Similar to Chapter 4, the results show that only age and anthropometric variables (stature, body mass, body mass index) are independent predictors of 6-MWT performance, and they must be considered when interpreting performance in this population. It is concluded that age and anthropometric factors can be used in the prognostic stratification of HF patients and the prediction of an individual's expected functional limitation, as assessed in the 6-MWT.

Chapters 4 and **5** eliminate a large number of gait and clinical parameters from the prediction of walk test performance, while suggesting that anthropometric variables may influence test performance in some patients. If decisions on exercise prescription and rehabilitation are taken based on test performance, the influence of such factors may be of importance. To date, normative data, developed using baseline anthropometric features, for functional capacity during treadmill testing, have been established only in American patient populations. **Chapter 6**, which considers only routinely measured variables (age, sex, anthropometric variables and simple clinical variables), tries to determine normative values for MSWT performance and MSWT performance changes in UK cardiac patients receiving phase III CR. The results reveal that age, sex and stature are the best predictive measures for pre-rehabilitation MSWT performance, while stature is the best predictor of magnitude of change in MSWT performance during phase III CR. It is concluded that normative values derived from these determinants can be used to estimate a normal improvement in functional capacity for CR patients. The interpretation of outcome measures obtained from the MSWT can help clinicians to make better-informed decisions about patients at the entrance to or discharge from a CR programme.

There are clear benefits to be gained from functional capacity testing and exercise training in cardiac patients, but there had been no verification regarding the safety of exercise testing or training when applied in a supervised, community-based CR population. **Chapter 7** evaluates the safety of the MSWT and exercise training for cardiac patients in phase IV community-based CR settings. The findings show only minor cardiovascular events provoked during the MSWT or exercise training, and no event-related hospitalisation, syncope episodes or fatality. Poor functional capacity is not shown to be associated with the risk of a cardiac event during exercise. It is concluded here that the MSWT and exercise training can be carried out safely in supervised phase IV CR settings.

The appendices to this thesis are divided into three parts. **Appendix A** contains the results and discussion of subsections 6.3.2. and 6.4.2, respectively ('Validating the prediction equation developed in Chapter 4'). **Appendix B** presents the research ethics committee approval for Chapter 6. **Appendix C** presents the publications related to the work presented in this thesis. **Appendices D and E** provide descriptions of the oral and poster presentations respectively that were produced in the course of this work.

The topic of this thesis is unique, as no previous data concerning the aspects described here were available at the time of this study.

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CHAPTER 2. INTRODUCTION TO CARDIOVASCULAR DISEASES AND CARDIAC REHABILITATION: A REVIEW OF THE LITERATURE

2.1. Introduction: Objectives and definition of cardiac rehabilitation

2.1.1. Epidemiology of cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity throughout the world (Murray and Lopez 1997; Gaziano 2005; Amendezo *et al.,* 2008). A five-year retrospective study of mortality in hospitals (Papadopoulos *et al.,* 2008) showed that coronary heart disease (CHD) (10.3%) and heart failure (HF) (7.9%) were the second and third most common causes of mortality of the 5,836 deaths studied. The number of people aged 65 and over will increase by 53% between 2001 and 2031, based on data selected from hospitals in the United Kingdom (UK) (Majeed and Aylin 2005). The number of people aged under 65 is predicted to change little during this period. The increase in the number of older people is likely lead to an increase in the number of patients with chronic diseases, including CVD. By 2031, it is estimated that in the UK, and probably in most other developed countries, the number of cases of CHD will have increased by 44%, HF will have increased by 54% and atrial fibrillation will have increased by 46% (Majeed and Aylin 2005).

Myocardial infarction (MI) is one of the diseases most frequently encountered by hospital doctors, and bypass graft surgery (CABG) is one of the most frequent surgical interventions. 20% of patients who have had an MI die suddenly; 10% die within 24 hours (West 2003). These patients, who experience an acute cardiac event, underwent a cardiac surgical intervention or suffer from chronic heart disease, need rehabilitation and initiation of secondary prevention therapies (Piepoli *et al.,* 2010).

2.1.2. Introduction to cardiac rehabilitation

The management of cardiac diseases can be usefully discussed in terms of its components. These include the clinical evaluation of the cardiac disorder; including the risk factors, pharmacological treatment, surgical intervention (revascularisation) and secondary prevention. Secondary prevention, which is usually obtained through medication and life style changes, targets the reduction of risk of a new cardiac event in the future (Lockhart *et al.,* 2000).

2.1.2.1. Definition of cardiac rehabilitation

Cardiac rehabilitation (CR) consists of the primary care of patients with cardiac diseases, and secondary prevention. The World Health Organisation (WHO) has defined CR as 'The sum of activities required to influence favourably the underlying cause of the disease, as well as to ensure the patient the best possible physical, mental and social conditions, so that they may, by their own efforts, preserve or resume when lost, as normal a place as possible in the life of the community' (WHO 1993).

A more recent definition by the Scottish Intercollegiate Guidelines Network (SIGN), supported and endorsed as a guideline for the UK by the British Association for Cardiac Rehabilitation (BACR), was: 'Cardiac rehabilitation is the process by which patients with cardiac disease, in partnership with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health' (SIGN 2002).

SIGN's definition seems to be more substantial, and emphasises the importance of physical and psychological balance. So, CR is the sum of physical activities and interventions that are designed to improve the physical, psychological and social functioning of patients with CVD disorders, chronic or post-acute, in addition to stabilising or slowing the progression of the

atherosclerotic process, in order to reduce the associated morbidity and mortality. Patients should be able to preserve by their own efforts a normal place in the community and lead a good quality of mental and social life (Coats *et al.,* 1995; SIGN 2002; Taylor *et al.,* 2004).

Overall uptake of CR by MI, CABG and percutaneous coronary intervention (PCI) patients in the UK has been estimated at only 17%, 44% and 6%, respectively (Evans *et al.,* 2002). Historically, CR in the UK has lagged behind the United States (US), Canada and Northern Europe; areas in which where there are still low levels of participation (Thomas *et al.,* 1996; Grenier *et al.,* 1999; Beswick *et al.,* 2005).

Richardson *et al.* (2000) studied cardiac patients who took part in CR over a 10-year period (from 1986 to 1996). In 1986, the programme started with 53 patients; by 1996 this had increased to 309. They noted that the majority of patients involved in CR were elderly men (>65 years), who were in a high-risk category, with the potential to obtain the greatest benefit from a CR programme. Other investigators have observed that all types of people with cardiac disorders participate in CR programmes (McGee and Horgan 1992; Pell and Morrison 1998; Taylor *et al.,* 2001), while patients with MI, males and the middle aged, seem more willing to follow a CR programme than other groups (Thompson *et al.,* 1997). Above all, men who participate in CR outnumber women, but the predominant age range cannot be predicted.

2.2. Risk factors for coronary heart disease

Cardiovascular risk factors are traditionally divided into two categories: modifiable and non-modifiable risk factors. The main modifiable cardiovascular risk factors are dyslipedemia (particularly high levels of low-density lipoprotein [LDL] and low levels of high-density lipoprotein [HDL]), hypertension, diabetes (glucose intolerance), obesity (mainly central obesity), smoking, excess alcohol, physical inactivity, inflammatory markers,

hyperhomocystinaemia and psychological factors. The non-modifiable risk factors are: age, sex and hereditary factors (Poulter 2003). In the following sections, non-modifiable and modifiable cardiovascular risk factors will be discussed separately.

2.2.1. Non-modifiable risk factors

Non-modifiable risk factors cannot be changed; it remains important, however, to be aware of an individual's overall CHD risk in order to focus on the elimination of modifiable risk factors. The non-modifiable risk factors including age, sex and hereditary factors are discussed below.

2.2.1.1. Age

Coronary heart disease is a progressive, degenerative progress that affects the coronary arteries. There is a slow but progressive accumulation of atherosclerotic plaque in coronary arteries, which starts in childhood and develops throughout life. The probability of an acute coronary event relates to the total burden of coronary plaque (Schisterman and Whitcomb 2004). Coronary heart disease often occurs under the age of 60. By this age, 1/15 men and 1/17 women will have a CHD (Castelli 1984).

2.2.1.2. Sex

The literature identifies sex differences in the prevalence of cardiac diseases. For many years, it was thought that men were more affected by cardiac disorders than women. The lifetime risk of coronary events seems to be 1/2 for men and 1/3 for women by the age of 40, while at the age of 70 it seems to be 1/3 for men and 1/4 for women (Lloyd-Jones *et al.,* 1999). This sex ratio decreases with age and varies between populations. Among middle-aged people, the sex ratio in CHD mortality is higher in the white than in the black population. At the age of 45, white men have a six times higher risk of CHD compared with white women, while black men have double

the risk of a CHD compared with black women. At age 95, men and women have an equal risk ratio across both racial types (Ho *et al.,* 2005).

The main cause for the difference in prevalence between the sexes is biological factors, and many relates to differences in the reproductive system and hormones. Particularly, endogenous oestrogens have a protective role in the development of CVD in women (van der Schouw *et al.,* 1996; Hu *et al.,* 1999).

A study of 1,684 participants (Tremollieres *et al.,* 1999) showed that the relative risk of CVD in postmenopausal women increased by 13% in comparison with perimenopausal women. This agrees with the findings of Azizi and Ainy (2003), which showed that CHD risk factors, such as cholesterol levels, glucose levels and BP, changed after menopause. The metabolic syndrome, which also includes cardiac disorders, is related to depressive symptoms and the stressful life events that women may encounter in middle age (Raikkonen *et al.,* 2007). This seems to relate to the menopause and the hormonal changes that woman undergo at this time (Smoller *et al.,* 2007). According to Matthews *et al.* (2001), cardiovascular risk for women increases around this time, especially during menopause, because of changes in BP and fasting glucose levels, which both affect lipid metabolism.

Oestrogen is believed to have cardioprotective effect in women; however in past trials (1960s and 1970s), men showed no beneficial therapeutic effect from being given high doses of oestrogen (The Coronary Drug Project Research Group 1973). Lawlor *et al.* (2001) found differences in the incidence of CHD between the sexes in different geographic areas and they stated that CHD does not relate exclusively to sex differences such as the hormone oestrogen (Henttonen *et al.,* 2007; Smoller *et al.,* 2007). They suggested that the higher risk that men may have in comparison with women relates to the different lifestyles adopted by the sexes. The

higher incidence of CHD in men is related to dietary habits; for example, in the way that they prepare food. Some other studies have focused on the relationship between different methods of socialisation and reaction to heart diseases. Women seem to be more socially supported than men, which appears to be cardioprotective (Berkman and Syme 1979).

Rosengren *et al.* (2001) studied patients on the Swedish National Acute Myocardial Infarction Register, which included over 350,000 cases of nonfatal and fatal acute MI. Younger women who were hospitalised had higher short-term and long-term mortality in comparison with men of the same age. There was no difference in the mortality rates of men and women with MI, who were non-hospitalised (aged between 50 and 70 years old). They also demonstrated that women over the age of 70 years old had a better survival rate within 28 days and 1 year after the MI, while women under 50 had higher mortality within 28 days and 1 year after the MI, compared with men. These findings are in contrast with other studies that have demonstrated that there are significant differences between men and women's mortality after an MI (Udvarhelyi *et al.,* 1992; Brett and Madans 1995; Kober *et al.,* 1996). The differences in the results may be associated with the fact that some of the post-MI patients were also suffering from other diseases such as diabetes, hypertension and HF, which may have affected the results.

A combination of factors is responsible for the sex differences observed in CHD epidemiology. Females' endogenous oestrogens and healthier lifestyles seem to play a cardioprotective role in CHD. This might have changed, as women have begun to indulge in habits that used to be regarded as a male 'privilege'. Thus, there is a need for a new epidemiological study, to update lifestyles and habits, so that it will be possible to confirm, or not, the previously assumed sex differences in CHD mortality.

2.2.1.3. Hereditary factors

Coronary heart disease runs in families. Family history is an independent risk factor for atherosclerotic disease in men and women (Juonala *et al.,* 2006). A positive family history of CHD is associated with early markers of subclinical atherosclerosis. This is explained by the fact that people with a positive family history are more vulnerable to metabolic risk factors, such as high LDL, low HDL, high triglycerides and high-glucose levels (Juonala *et al.,* 2006). The absolute cardiovascular risk increases in middle age to 50% for men and 70% for women, when at least one parent had a cardiovascular disorder before the age of 55 (in the father) or 65 (in the mother) (Lloyd-Jones *et al.,* 2004; Murabito *et al.,* 2005).

Some forms of CVD are more common in specific racial and ethnic groups. For instance, black adults, in contrast with white, may be at higher risk of CHD because of dietary habits and anthropometric differences, but they have higher HDL and lower triglyceride levels. These cardioprotective phenotypes are an advantage and may be due to genetic influences (Whittle *et al.,* 2002). An epidemiological study carried out from 1990 to 2000 demonstrated that black people and Asian Indian people have the highest mortality rates due to CHD; they have been identified as particularly high risk populations (Palaniappan *et al.,* 2004).

2.2.2. Modifiable risk factors

The main modifiable cardiovascular risk factors – dyslipedemia, hypertension, diabetes, obesity, smoking, excess alcohol, physical inactivity, inflammatory markers, hyperhomocystinaemia, psychological factors- are discussed below. There are quantitative studies in this area, and each of these factors is analyzed.

2.2.2.1. Dyslipidaemia

Studies have attempted to explain how hyperlipidaemia is linked to MI. It was initially thought that the cholesterol obtained from the diet records is associated with the blood cholesterol levels to create atherosclerosis. Atherosclerosis, as mentioned above, occurs with CHD (Connor 1999). The pathophysiologic association between dyslipidaemia and atherosclerosis is described further in the section below (see 2.4.1.2.1. Atherosclerosis). This process begins with the oxidation of LDL, and leads to reduction in nitric oxide (NO) availability, which involves vascular injury, inflammation and vessel remodelling. This endothelial dysfunction plays a key role in atherosclerotic plaque destabilisation and rapture, promoting the development of acute vascular syndromes (Vogel 1999; Bae 2001).

Panagiotakos *et al*. (2004a, 2004b) demonstrated, in a sample of 2,282 Greek people, that the Mediterranean lifestyle, and especially the diet, affects the management of hyperlipidaemia and assists the reduction of LDL-cholesterol levels. The Mediterranean diet in the general population appears to improve the survival of patients with CHD (Panagiotakos *et al.,* 2004a, 2004b; Trichopoulou *et al.,* 2005).

Lavie and Milani (1999) demonstrated that a majority of CHD patients has hypertriglyceridaemia, and low levels of HDL cholesterol. CR and exercise training usually affects the HDL more than the LDL cholesterol. Exercise has more of an effect in terms of reducing triglycerides than it does in terms of LDL reduction. On the other hand, HDL is usually increased after a long-term exercise programme. Reductions in triglyceride levels and increases in HDL cholesterol concentrations can slow the progression of atherosclerotic CHD (Lavie and Milani 2000).

2.2.2.2. Hypertension

Hypertension is defined as a systolic blood pressure (SBP) of 160 mmHg, and a diastolic blood pressure (DBP) of 95 mmHg (Wolf-Maier *et al.,* 2004). Elevated BP is a risk factor for death from CHD. Among the risk factors, hypertension is significantly associated with CHD, playing an important role in its pathogenesis. The WHO reported that hypertension causes 7.1 million deaths annually (Whitworth 2003). A 25-year follow-up study, which took place among six populations (in the US, Europe, Japan and the Mediterranean), showed that the relative risk of death due to CHD was 1.17 per 10 mmHg increase in SBP, and 1.13 per 5 mmHg increase in DBP (Van den Hoogen *et al.,* 2000). Data from randomised control studies showed that reductions in SBP of 10 mmHg, and DBP of 5mmHg, decrease the risk of CHD by 20–25% (Collins *et al.,* 1990; Collins and Peto 1994; Pahor *et al.,* 2000; Lawes *et al.,* 2002; Law *et al.,* 2003; Turnbull 2003).

There are several mechanisms by which hypertension leads to the development of acute CHD syndrome. Hypertension is associated with endothelial dysfunction and thus with the development of atherosclerosis (Ferroni *et al.,* 2006; Landmesser and Drexler 2007). Abnormal endothelial function is defined as an alteration in the functioning of the endothelial cells, resulting in a reduction in NO synthesis and an increase in oxidative stress (Landmesser and Drexler 2007). The increase in oxidant stress results in several modifications to the vascular wall. In particular, oxidant stress results in an increase in lipid oxidation and platelet activation; it plays a significant role in the promotion of a prothrombotic state in the vascular system (Mariano *et al.,* 2003; Ferroni *et al.,* 2006). When this occurs, there is a formation of atheromatous plaque and thus vascular luminal narrowing, reducing blood flow and triggering ischaemia (Andrews *et al.,* 2001; Perticone *et al.,* 2001; Ferroni *et al.,* 2006).

Nitric oxide prevents oxidation of LDL cholesterol. Oxidation of LDL has been defined as a key factor in accelerating the atherosclerotic process (Steinberg and Witztum 2002; Stocker and Keaney 2004; Rubbo and O'Donnell 2005; Huang *et al.,* 2008); the increased levels of oxidised LDL relate to plaque rapture and instability (Piek *et al.,* 2000; Meuwissen *et al.,* 2006). When this occurs, plasma and macrophage accumulate in coronary rapture plaques, and cause progression of plaque inflammation, plaque instability and acute coronary syndromes (Ehara *et al.,* 2002; Huang *et al.,* 2008). Thus, it seems clear that oxidised LDL levels relate significantly and directly to the severity of acute coronary syndromes (Ehara *et al.,* 2001; Ehara *et al.,* 2002; Huang *et al.,* 2008). The atherosclerosis process is described in detail in the section below (see 2.4.1.2.1. Atherosclerosis).

2.2.2.3. Diabetes mellitus

The American Heart Association (AHA) has established that diabetes is a major cardiovascular risk for both women and men (Grundy *et al.,* 1999). Diabetes mellitus (or type 2 diabetes) is associated with insulin secretion insulin resistance, resulting dyslipidemia (Pyorala *et al.,* 1987; Juutilainen *et al.,* 2005). Dyslipidemia is one of the most important mechanism by which diabetes promotes atherosclerotic lesion formation (Dokken 2008). Individuals with type 2 diabetes have a two- to four-fold increase in risk of CHD compared with non-diabetic people (Ferdinand 2006); over 50% of patients with diabetes mellitus die of CHD (Pyorala *et al.,* 1987; Juutilainen *et al.,* 2005).

An 18-year follow-up study showed that patients with type 2 diabetes, who had not had a previous CHD event, had an increased risk of acute coronary syndrome over non-diabetic people with prior evidence of CHD, especially in women (Juutilainen *et al.,* 2005). The results of this study demonstrate the need for primary prevention of CHD in patients with diabetes mellitus.

2.2.2.4. Smoking

Smoking acts synergistically with other risk factors to increase the risk of CHD. Both women and men in middle age who are current smokers have a two- to three-fold increased mortality risk (Ekberg-Aronsson *et al.,* 2007). Smoking has an unfavourable effect on endothelial function. Specifically, smoking causes arterial wall thickening, increases inflammation, thrombosis, oxidation of LDL cholesterol, oxidative stress and hence contribute to the development of atherosclerosis (Poredos *et al.,* 1999; Ambrose and Barua 2004; Thomas *et al.,* 2008). Active female smokers reach menopause on average two years earlier than non-smokers; ex-smokers reach it one year earlier. This fact results in an earlier loss of the protective effect of oestrogen (Hu *et al.,* 1999; Kinney *et al.,* 2006). The acute effects of smoking are increased BP and heart rate (HR), vasospasm of the coronary arteries and reduction in the oxygen carrying capacity of the blood (Primatesta *et al.,* 2001; Barutcu *et al.,* 2005) creating an increased demand for oxygen but reduced ability to an increase supply.

Cigarette smoking is associated with acute and chronic cardiovascular events for both active and passive (environmental) smokers (Ambrose and Barua 2004). Passive smoking is also related to endothelial dysfunction and the development of atherosclerosis, at higher rates compared with non-smokers and at a lower rate compared with active smokers, in healthy young adults (Woo *et al.,* 2000; Holay *et al.,* 2004). There is also a relationship between the number of cigarettes smoked daily and the risk of CVD. The risk increases with an increase in the number of cigarettes smoked each day and the total number of years as a smoker (Prescott *et al.,* 2002; Godtfredsen 2003). Specifically, smoking very little per day (3–5 gr) can be a significant risk factor for developing MI and other cardiovascular disorders, which increases mortality. For people who have been diagnosed with CHD, smoking cessation reduces the risk of a further MI,

sudden cardiac death and mortality by 50%. Women seem to be more affected than men (Prescott *et al.,* 2002).

An analysis of the Framingham Heart study focused on the relationship between smoking and the reaction in the cardiovascular system regarding age; it demonstrated that smokers' life spans are shorter than the population average both in terms of CVD mortality and from other causes of death (Mamun *et al.,* 2004). Women who had never smoked lived about 6.22 more years, and men 4.93 more years, free of CVD. The incidence of CVD in people who smoke is continuously higher before the age of 70 for males and females. 6/10 non-smoking males and 7/10 non-smoking females could reach the age of 70 with no sign of heart disease; while 4/10 male and 6/10 female smokers would be expected to reach the same age having contracted cardiovascular disorders (Mamun *et al.,* 2004).

2.2.2.5. Physical inactivity

Physical inactivity is an independent risk factor for CVD, diabetes mellitus and hypertension (Yung *et al.,* 2009); it seems to have a similar risk ratio to other risk factors, such as smoking, dyslipidaemia and hypertension (Nanchahal *et al.,* 2005). On the other hand, physical activity in leisure is cardioprotective, reducing the risk of death from CHD (Barengo *et al.,* 2004; Khaw *et al.,* 2006). Physical activity improves endothelial function, improving dilation of the coronary arteries. It also decreases total cholesterol, triglycerides, body fat and BP, while it increases 'protective' HDL and insulin sensitivity (Couillard *et al.,* 2001; Panagiotakos *et al.,* 2003; Yang *et al.,* 2008). However, there is an association between the intensity of physical activity and mortality. The effects of physical activity can be graded, and greater cardiovascular protection is achieved by higher levels of activity (of vigorous intensity) (Lee and Paffenbarger 2000; Yu *et al.,* 2003).

2.2.2.6. Overweight and obesity

The impact of obesity in terms of cardiovascular risk has been clearly demonstrated in the 'Framingham Heart Study', the 'Nurses Health Study' in women, the 'Buffalo Health Study' and the 'Cancer Prevention Study II' (Hubert *et al.,* 1983; Manson *et al.,* 1990; Keil *et al.,* 1993; Dorn *et al.,* 1997). Obesity interacts with other cardiovascular risk factors and independently increases the risk of CHD and mortality.

Obesity is defined as a body mass index (BMI) equal to or above 30 $kg \cdot m^{-2}$, while 'overweight' is defined as a BMI of equal to or above 25 $kg \cdot m^{-2}$ (WHO 2000). The WHO uses BMI cut-off points for each different population type, taking into account their health risks. There is evidence that risk of chronic disease in some populations, like Asians, can increase progressively beyond a BMI of 21 (WHO 2004). Abdominal obesity also increases cardiovascular risk in men and women (Yarnell *et al.,* 2001; Lakka *et al.,* 2002; Onat *et al.,* 2004; Canoy 2008). Abdominal obesity is defined as a waist circumference measurement of over 102 cm in men and 88 cm in women (National Institutes of Health 1998).

BMI, waist circumference, waist-to-hip ratio (WHR), abdominal fat and measures of intra-abdominal fat are all associated with common carotid artery plaques (Rubba *et al.,* 2001; Takami *et al.,* 2001; De Michele *et al.,* 2002). Among normal and moderately overweight people, BMI and WHR were related to diastolic hypertension (White *et al.,* 1986). Guagnano *et al.* (1997) demonstrated that among a sample of averagely obese women (mean BMI of 36 $kg \cdot m^{-2}$), WHR is related to diastolic and systolic hypertension, while BMI was not correlated to diastolic or systolic hypertension. The Atherosclerosis Risk in Communities study documented that there is a linear increase in CHD risk as BMI increases, although WHR seems to be a better predictor for a cardiac event, especially in women (Folsom *et al.,* 1998). A more recent study confirmed that a BMI of up to 35 $kg \cdot m^{-2}$ is associated with an increased BP (SBP and DBP), higher triglyceride

concentrations and increased blood glucose concentrations in non-diabetic people (Whitelaw *et al.,* 2001).

De Michele *et al*. (2002) concluded that BMI and WHR were significant predictors of carotid wall thickness in a sample of 310 women; they also noticed that obese woman (BMI $\geq$30 $kg \cdot m^{-2}$) had higher SBP and DBP, triglycerides, fasting glucose and insulin, and lower HDL concentrations, compared with lean women. According to this study, obesity is defined either by BMI or WHR, or by abdominal fat; it is combined with a number of cardiovascular factors and they increase the risk of a new or secondary cardiac event.

Lavie and Milani (1997) reported that 40% of people with cardiovascular disorders are overweight. A number of studies have focused on the relationship between obesity and the development of atherosclerosis, which is the main condition that leads to CVD. Atherosclerosis can begin at a young age, as deposits of cholesterol on the large, muscular arteries (Berenson *et al.,* 1992; Mahoney *et al.,* 1996; McGill *et al.,* 2000). Control of the risk factors would be a good method of primary prevention. McGill *et al.* (2000) analysed the levels of atherosclerosis in arteries and tissues, in 3,000 young persons (age of 15 to 34) who had died from non-CVD factors. Higher BMI is associated with fatty streaks and raised atherosclerotic lesions in both coronary arteries in young men but not in women.

Based on McGill's (2000) study, Grundy (2002) concluded there may be two reasons for the lack of a significant correlation between obesity and atherosclerosis in women. The first reason is that perimenopausal women have a delay in the development of atherosclerotic plaques on the arteries; the second is that men tend to have an abdominal fat accumulation, and hence a higher atherosclerotic risk than women. It is clear that most studies are based on indirect measures for

obesity, like BMI; however abdominal fat distribution is becoming recognised as a more important risk factor for CHD than BMI.

2.2.2.7. Inflammatory markers

Inflammation is a significant feature of atherosclerotic lesions. Elevated plasma levels, C-reactive protein (CRP) and fibrinogen are markers of inflammation in subclinical and clinical atherosclerosis, and they have been established like cardiovascular risk factors (Liuzzo *et al.,* 1994; Hirschfield and Pepys 2003; Kamath and Lip 2003; Naghavi *et al.,* 2003a, 2003b; Khreiss *et al.,* 2004). The concentrations of C-reactive protein in blood plasma are associated with coronary events in patients with stable and unstable angina. CRP concentrations correlate with other cardiovascular risk factors, such as age, BMI, smoking, lipids, cardiac medical history, coronary stenosis and lower left ventricular ejection fraction (LVEF). 33% of cardiovascular events occur in patients with a high CRP concentration (>3.6 $mg \cdot l^{-1}$). High rates of CRP concentration in the plasma double the risk of a coronary event (Haverkate *et al.,* 1997). The exact mechanism these inflammatory markers play in the arteriosclerosis process is still not fully known.

2.2.2.8. Hyperhomocystinaemia

Homocysteine is an amino acid that forms when the essential amino acid is metabolised to cysteine. A meta-analysis of 30 studies found that for every 2.5 $mmol \cdot l^{-1}$ increase in plasma total homocysteine levels, the risk of MI increases by about 10% (Homocysteine Studies Collaboration 2002).

Hyperhomocystinaemia is associated with atherosclerotic vascular disease and other conditions, such as venous thrombosis (Ford *et al.,* 2002b; Den Heijer *et al.,* 2005). The increased risk of

CVD associated with elevated homocysteine levels may be a result of endothelial function, the promotion of LDL protein oxidation, its reduction of NO synthesis and its stimulation of increased platelet adhesion (Fallon *et al.,* 2001; Faraci 2003; Lentz 2005; Griffiths *et al.,* 2006).

Hyperhomocystinaemia can also be caused by nutritional deficiencies (folate, vitamin B12), alcoholism, hypothyroidism, and genetic or renal defects (Lentz 2005). There may be benefits of lowering fasting homocysteine levels, to <10 $mmol \cdot l^{-1}$; the treatment of hyperhomocystinaemia includes dietary additions of folate and vitamins B_{12} and B_6. In case that dietary source is ineffective, supplements of vitamins, including at least 400 mg of folic acid, 2 mg of vitamin B_6 and 6 mg of B_{12}, are recommended (Booth and Wang 2000).

2.2.2.9. Excess alcohol

Moderate alcohol consumption (equal to or less than 2 glasses of wine, 2 pints of beer per day) has a cardioprotective effect. A standard drink of wine contains 4 ounces (113 g) and beer 12 ounces (340 g) of alcohol (Karatzi *et al.,* 2004; Elkind *et al.,* 2006; Suzuki *et al.,* 2009). The mechanism of this effect may be explained by alcohol's favourable effect on HDL, serum lipids, thrombotic tendency, insulin resistance, vasodilatation and thus on endothelial function (Hines and Rimm 2001; Elkind *et al.,* 2006; Suzuki *et al.,* 2009).

Higher alcohol intake (≥3 drinks per day) is associated with hypertension, increased triglyceride levels (especially with the consumption of beer and spirits), arrhythmias, dilated cardiomyopathy and higher levels of CHD mortality (Shaper and Wannamethee 2000; Foerster *et al.,* 2009).

2.2.2.10. Psychological factors

Psychological distress is a significant risk factor for CHD, and it is one of the major predictors of recovery after major CHD events (Rozanski *et al*. 2005; Lavie and Milani 2006). The Interheart

study, which included people from 52 countries, found that psychosocial factors were a strong, independent risk factor for MI; indeed, they accounted for almost a third of the population's risk factor (Rosengren *et al.,* 2004; Yusuf *et al.,* 2004).

Most research has focused on the high prevalence of depression in patients with CHD, and on depression as a CHD risk factor. Anxiety and hostility are associated with an increased prevalence of CHD events (Lavie and Milani 2004, 2006; Rozanski *et al.,* 2005). These psychological risk factors are related to dyslipidemia, hypertension, obesity, inflammatory biomarkers, coronary calcium and atherosclerosis (Whiteman *et al.,* 2000; Rutledge *et al.,* 2001). Coronary heart disease is also related to a certain personality type, defined as type A (Rosenman *et al.,* 1964; Friedman 1989). Type A is used to describe persons who are depressed, highly competitive, urgent, aggressive, ambitious, obsessed with finishing everything on time and those who easily express hostility and anger. More recently, hostility has been linked with metabolic syndrome and an increased risk of mortality, especially in younger patients (Boyle *et al.,* 2005; Todaro *et al.,* 2005).

The mechanism by which psychological and behavioural risk factors may cause premature CHD is unclear, but according to Lavie and Milani (2006) these are likely to be multifactorial. Psychological factors may increase platelet activation, level of catecholamines and coronary vasoconstriction, resulting in CHD (Lavie and Milani 2006). Also, anxiety may increase sympathetic activity, reduce vagal tone and increase the risk of malignant ventricular arrhythmias, all of which may lead to sudden cardiac death (Lavie and Milani 2004, 2006).

Some of these risk factors are identifiable because they can be used to identify high-risk individuals for developing CHD. Studies have attempted to determine associations between the risk factors; the difficulty in such studies seems to be identifying which factors are 'cause' and

which are ‘effect’ (i.e., obesity, diabetes). In this case cardiovascular risk clustering may be a useful and reliable tool to evaluate cardiovascular abnormalities. The next section will discuss the most widely used risk calculations to estimate the risk of developing CHD or suffering an acute coronary event.

2.3. Cardiac risk stratification

Risk stratification is often used as an important tool for evaluating an individual’s risk of developing CHD. Such stratification may be beneficial in primary or secondary prevention of CHD. There are several different algorithms available to evaluate risk of CHD. Some of the most important assessment systems are: the Framingham Risk Score (FRS), the Prospective Cardiovascular Münster (PROCAM) algorithm, the European Society of Cardiology [ESC] score (SCORE), the Cardiovascular Risk Management (GRACE) model, the Coronary Artery Calcification (CAC) score and the QRISK2.

The Framingham Heart Study began in 1948 to examine the epidemiology of CVD in the US, by analysing men and women from 35 to 62 years old (Dawber *et al.,* 1951). The Framingham study became the worldwide gold standard for cardiovascular epidemiology (Dawber *et al.,* 1963; Jaquish 2007), and this risk prediction algorithm is frequently referred to in the literature. The Framingham Risk Score is frequently used in developed countries (for example, in the US). The Framingham Risk Score uses a scoring system including assessing the following CVD risk factors: hypertension, smoking, total cholesterol and HDL cholesterol. The total score is assessed using Framingham scoring tables, which provide an individual’s 10-year risk for developing CVD. There are separate score tables and charts for women and men (National Cholesterol Education Program Expert Panel on Detection 2002; McPherson *et al.,* 2006). A projected 10-year risk-level below 10% is indicated as low risk, while a score above 20% is considered a high

risk; a score between 10 and 20% is considered a moderate risk (National Cholesterol Education Program Expert Panel on Detection 2002) (see table 2.1).

The Framingham Risk Score is higher than those of PROCAM and ESC algorithms. The FRS overestimated the risk of CHD in European countries (UK, Italy) with a lower incidence of coronary events (Menotti *et al.,* 2000; Brindle *et al.,* 2003). The Framingham study is (chronologically) older than the other two, and at the beginning of the data collection, CHD had a high incidence, which declined over the following years (Assmann *et al.,* 2002).

Table 2.1. Framingham risk levels and desirable lipid results (Guidelines and Protocols Advisory Committee 2008)

Classification	Risk level	LDL ($mmol \cdot l^{-1}$)	ApoB ($g \cdot l^{-1}$)	TC/HDL RATIO
High	≥ 20%	< 2.5	< 0.85	< 4.0
Moderate	10 % - 19 %	< 3.5	< 1.05	< 5.0
Low	< 10%	< 5.0	< 1.25	< 6.0

Definition of abbreviations: Apo B = apolipoprotein B; CHD = coronary heart disease; LDL = low-density lipoprotein; TC/HDL = total cholesterol/high-density lipoprotein ratio

The PROCAM study in Europe provides another algorithm for individual stratification in relation to developing CHD. The PROCAM score is based on data from a German study and it estimates the risk of suffering an MI or acute coronary event. The algorithm is mostly based on men, aged 35 to 65 years. The variables that the PROCAM study used were age, LDL and HDL cholesterol levels, triglycerides, smoking, diabetes mellitus, MI in family history and SBP (Assmann *et al.,* 2002). The PROCAM predicted event rate is about 25% lower than the Framingham score and 80% higher than the ESC event rate (Agabiti-Rosei *et al.*, 2008).

The ESC algorithm, SCORE (Systematic Coronary Risk Evaluation), was based on an analysis of European data from 12 countries. The SCORE is based on factors, such as sex, age, total cholesterol, SBP and smoking status. This algorithm is used for risk stratification in the primary

prevention of total CVD. The SCORE project aimed to estimate the total number of cardiovascular events rather than the risk of CHD (Conroy *et al.,* 2003). However, SCORE event rates were lower than the Framingham and PROCAM event rates (Agabiti-Rosei *et al.*, 2008). In each of the three risk algorithms (FRS, PROCAM, SCORE), some prognostic variables, such as cardiac and ECG markers, were not included.

These prognostic variables were included in a more recent research. The global registry of acute coronary events (GRACE) was used to estimate the risk of death for patients with acute coronary syndrome. The study took place in 94 hospitals across 14 countries (in Europe, North and South America, Australia, and New Zealand). The GRACE risk prediction tool includes nine variables: age, presence of HF, peripheral vascular disease, SBP, HF class, initial serum creatinine concentration, positive initial cardiac markers, cardiac arrest on admission and ST-segment changes (Fox *et al.,* 2006). This model takes into account many variables; however it is applicable only for patients who had experienced an acute coronary syndrome (i.e., MI). This algorithm is used for risk stratification in the secondary prevention of CVD.

The new Cardiovascular Risk Management (CARISSMA) system covers more, important prognostic variables, such as functional capacity, body weight and number of cigarettes consumed per day. CARISSMA provides more detailed cardiac risk stratification and details of treatment that could be provided in primary prevention, especially at moderate risk levels for CHD (Gohlke *et al.,* 2007).

The Coronary Artery Clacification (CAC) score has been used in the prediction of atherosclerotic CVD events in symptomatic or asymptomatic individuals. The calcium score is assessed by computed tomography and is related to the extent of atherosclerosis in combination with age and sex (Kondos *et al.,* 2003; Arad *et al.,* 2005; Nasir *et al.,* 2006). The more extensive

the coronary calcification, the more likely it is that a coronary event may occur (Wexler *et al.,* 1996). A zero CAC score relates to a very low risk of a coronary event. People with a zero CAC score may not have developed any coronary plaque; however, they may have early stages of plaque accumulation (fatty streaking) that is undetectable (Raggi *et al.,* 2001; Nasir *et al.,* 2006). The CAC score is combined with the FRS score. The CAC score can modify the predicted FRS score, especially at a moderate-risk level (when FRS is predicted to be in the range of 10 to 19% over 10 years). The CAC score does not significantly change the predicted risk for people with an FRS of lower than 10% or higher than 20% (Greenland *et al.,* 2004).

The QRISK2 risk score has been recently developed at the University of Nottingham for use in the UK. This calculator includes risk factors such as age, sex, smoking status, total and HDL cholesterol, BMI, family history of CVD and SBP (Hippisley-Cox *et al.,* 2007). This risk calculator is used to predict the 10 year risk of developing CVD. It has been validated on large UK databases, including more than a million patients (Hippisley-Cox *et al.,* 2008; Collins and Altman 2010). This calculator takes into consideration more risk factors than established FRS. It has been demonstrated that QRISK2 risk calculator is more accurate to predict the development of CVD in UK population than FRS (Collins and Altman 2010).

Cardiovascular risk prediction models are constantly changing, being adapted to accommodate new risk factors. Different cardiovascular risk prediction models have been developed to provide country-specific risk prediction. The diverse risk stratification models share a common primary goal; to identify high-risk individuals and manage primary and secondary prevention of CHD. The following section will analyze the most common forms of CVD, to ensure a better understanding of the role of CR as secondary prevention.

2.4. Cardiovascular Diseases

2.4.1. Coronary heart disease

2.4.1.1. Definition of coronary heart disease

Coronary heart disease (CHD) is the consequence of the atherosclerotic plaque that forms in the larger arteries. Cholesterol is a constituent of atherosclerotic plaque. Coronary heart disease accounts for nearly 50% of all CVD deaths (Nasir *et al.,* 2006).

2.4.1.2. Nature and causes of coronary heart disease

Complex interactions between diet, lifestyle and lipoprotein metabolism determine the progress of atherogenesis; the development of atherosclerotic plaques inside the vessels. This process results in atherosclerosis (McGill *et al.,* 2000).

2.4.1.2.1. Atherosclerosis

The atherosclerotic process starts in childhood with the development of atherosclerotic lesions, defined as a fatty streak in the intima of the large, muscular arteries (Holman *et al.,* 1958). Fatty streaks begin to appear first in the aorta and then in coronary arteries 5 to 10 years later (Strong and McGill 1962; McGill 1968). Fatty streaks and raised lesions in both the aorta and the coronary arteries contain atherogenic lipoproteins and macrophage foam (Hata *et al.,* 1974; Guyton and Klemp 1994; Chilton 2004).

The mechanism by which the fatty streak transforms to atherosclerotic lesions (plaques) is consistent with the cellular and molecular mechanisms derived when the oxidised LDL, macrophages and scavenger receptors involved. LDL has oxidant properties, and HDL has antioxidant properties (Graham *et al.,* 1997). Macrophages appear in all tissues including the

arterial lumen. Each macrophage is a versatile receptor, and some of the arterial macrophages react with oxidised LDL. Factors including LDL concentration, LDL oxidation, macrophage lipid accumulation, fewer antioxidants and genetic factors, lead to the development of a fibromuscular cap and then to fibrous plaque in the lumen of the arteries (Gelissen *et al.,* 1996; Giry *et al.,* 1996; Wang *et al.,* 1996). Inflammatory cytokines attract more macrophages and these stimulate muscle cells to accumulate lipid, so a chronic inflammatory process is continued. Over the years, these fibrous plaques enlarge and provoke haemorrhages, ulceration or rupture, and thrombosis. The clinical disease depends on which artery has been affected (McGill *et al.,* 2000).

Such pathophysiology explains how the fatty streak transforms to pathologic lesions and then to fibrous plaques, which play a critical role in the development of acute coronary syndromes (Chilton 2004). Plaques vary in their characteristics, but all types of plaque can result in a serious coronary syndrome (Naghavi *et al.,* 2003a, 2003b). When the lumen of the coronary arteries decrease by more than 50%, blood supply to the myocardium becomes limited. The advanced atherosclerotic lesions and the development of atherosclerotic disease are associated with a number of clinical risk factors such as age, sex, genetic factors, high LDL-cholesterol concentrations, low HDL-cholesterol concentrations, hypertension, smoking, diabetes, obesity and psychological factors (McGill *et al.,* 2000). Atherosclerosis is the pathology underlying most of the manifestations of CHD; these are discussed in turn below.

2.4.2. Manifestations of coronary heart disease

2.4.2.1. Angina

2.4.2.1.1. Definition and causes of angina pectoris

The ESC (1997) defines angina pectoris as the clinical diagnosis that is usually caused by CHD; it is described mainly in relation to chest pain or discomfort. According to the American Heart Association (AHA) and the American College of Cardiology (ACC) guidelines for the management of patients with chronic stable angina, angina results from ischaemia, due to imbalance between oxygen demand and supply to the heart muscle (Gibbons *et al.,* 1999). The underlying cause of angina is coronary atherosclerosis, but in some cases can result of cardiomyopathies or aortic stenoses (Collins and Fox 1990).

2.4.2.1.2. Functional classification of angina

The Canadian Cardiovascular Society (CCS) defined a four-level angina functional classification for patients, according to the symptoms experienced. Class I refers to patients without symptoms during ordinary physical activity in whom angina may occur during laborious, prolonged work or exercise. Class II angina is detectable when walking, climbing stairs, or during fast uphill walking. This classification refers to angina experienced after a meal, in cold and windy weather, or under stressful conditions; it also encompasses angina that occurs while walking more than two blocks and climbing more than a stairway under normal conditions and at a normal pace. Angina Class III relates to walking one to two blocks, or climbing a stairway at a normal pace. Class IV refers to angina that is present at rest (Campeau 1976) (see table 2.2).

Table 2.2. Canadian Cardiovascular Society Angina Classification (Campeau 1976)

Class	Activity that occurs angina	Limitations in ordinary physical activity
Class I	Exhausted and prolonged exertion	None
Class II	Climbing > 2 blocks	Slight limitation
Class III	Climbing < 2blocks	Marked limitations
Class IV	At rest	Inability to carry on any physical activity without discomfort (severe)

2.4.2.1.3. Types of angina

2.4.2.1.3.1. Stable Angina

Diagnosis of stable angina is usually based on a patient's history and pattern of symptoms. Stable angina is described as chest discomfort, which can be referred to the jaw, shoulder, back or arm. Chest pain is usually observed on exertion and lessens when the patient rests (Snow *et al.,* 2004; Jawad and Arora 2008).

Patients with chronic angina need evaluation for CHD. A resting electrocardiogram (ECG) does not usually help, as it does not identify abnormalities (unless it takes place during angina event). Patients with suspected angina can undertake a stress test during which the heart's electrical activity is recorded by ECG during exercise on a treadmill or bike. Coronary angiography is usually required to confirm CHD and identify its extension and severity (Snow *et al.,* 2004; Jawad and Arora 2008).

2.4.2.1.3.2. Unstable angina

Unstable angina is defined as one of the following: angina with symptoms at rest; angina with symptoms at exertion, meeting the CCS criteria for class III, or even IV, variant angina, post MI angina or MI without Q-waves in the ECG (Braunwald *et al.,* 1994). The ESC Joint Study Group

refers to refractory angina and describes it as a chronic condition (>3 months duration), which is caused by myocardial ischaemia and cannot been treated by medical care or surgical intervention (CABG, PCI) (Mannheimer *et al.,* 2002).

2.4.2.1.3.3. Prinzmetal (variant) angina

Prinzmetal *et al.* (1959) first described another form of angina – Prinzmetal or variant angina. Prinzmetal's angina is characterised by episodes of chest pain that occur at rest or when asleep, and it is caused by coronary vasospasm. It is associated with atherosclerosis of the vessels and the vasospasm usually occurs close to the blockage. It is associated with ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, acute MI and sudden cardiac death (Keller and Lemberg 2004).

2.4.2.1.4. Mortality and prognosis of angina

The prognosis of angina is quite difficult as it relates to many parameters, such as the severity of the angina (see notes on the CCS classification system, above), duration of symptoms, type of angina, previous MI, symptoms after revascularisation, severity of left ventricular damage, number of vessels involved, parts of arteries affected, diabetes and ST-segment changes on the resting ECG (Daly *et al.,* 2006; Jones *et al.,* 2006). These parameters can be used as criteria to estimate prognosis, including the probability of death or MI one year after the presentation of stable angina (Daly *et al.,* 2006).

The incidence of total morbidity and mortality rates in angina patients ranges from 2.8 to 6.6 in 100 patients per year; the incidence of cardiovascular death ranges from 1.4 to 6.5 in 100 patients per annum; and the (nonfatal) MI rate ranges from 0.3 to 5.5 in 100 patients per year (Jones *et al.,* 2006).

2.4.2.1.5. Management of angina (medical treatment)

The first approach to an angina event is to give anti-anginal drugs, which include three main categories: nitrates, β-blockers and calcium antagonists. Nitrates help by increasing the blood supply in the veins and the most usual form administered is glyceryl trinitrate (Jones and West 1995). Nitrates usually relieve pain and can increase exercise tolerance. If nitrates are used frequently for more than 24 hours, the patient can become tolerant to the drug. So, a high dose of nitrates once a day (i.e., 16 mg molsidomine) is recommended (Messin *et al.,* 2005).

Beta-blockers decrease BP and HR (Jones and West 1995). Patients with angina should be given high doses of β-blockers to reduce resting HR to 55–60 beats per minute (bpm). Third-generation β-blockers generate vasolidation, increase coronary blood flow and improve microvascular angina pectoris or silent ischaemia in patients with artery stenosis (Galderisi and D'Errico 2008).

Calcium antagonists relax the arteries, including the coronary arteries. There are two groups of calcium antagonists: those which increase the HR, and those that decrease it. The antagonists that decrease the HR cannot be combined with β-blockers (Dunselman *et al.,* 1997; Knight and Fox 1998; Emanuelsson *et al.,* 1999).

Aspirin produces good results in the acute phase of unstable angina and is associated with a reduced incidence of MI (Theroux *et al.,* 1988; The RISC Group 1990). Aspirin combined with heparin also reduces the risk of CHD events and refractory angina incidents (The RISC Group 1990; FRISC study group 1996). Harding *et al.* (2002) concludes that an early clinical assessment and stratification of the patients according to their risk levels is essential to ensure that the appropriate medical intervention can be used with good therapeutic results.

2.4.2.1.6. Management and follow-up of unstable angina

Unstable angina may lead either to nonfatal MI, or to death, or to a lessening of the symptoms. Patients with unstable angina should be admitted as an emergency to a coronary care unit. ECG monitoring is important, while anti-anginal drugs, aspirin and heparin should be administrated as soon as possible. Patients who do not get relief from their symptoms, and patients at high risk, should have revascularisation therapy with CABG or a PCI intervention (Reeder 2000; Aronow 2003).

2.4.2.1.7. The role of cardiac rehabilitation for patients with angina

The effects of CR and especially of exercise training in patients with angina pectoris have been studied for years. Exercise training is useful for patients with angina pectoris who are not involved in revascularisation intervention (Clausen and Trap-Jensen 1976). Exercise can improve the endothelial function; reduce HR exertion and the severity of angina pectoris (Hambrecht *et al.,* 2000b).

2.4.2.2. Myocardial infarction

2.4.2.2.1. Definition of myocardial infarction

Myocardial infarction is the irreversible necrosis of heart muscle and occurs secondary to prolonged ischaemia. It is usually caused by an imbalance between myocardial oxygen demand and supply. This is usually the result of the atheromatous plaque rupture and thrombus formation in a coronary artery, which obstructs blood flow to a portion of the myocardium (Garas and Zafari 2010).

2.4.2.2.2. Presentation of myocardial infarction

Chest pain is the most frequently experienced primary feature for diagnosis of MI in women and men (Milner *et al.,* 1999; Albarran *et al.,* 2007). Usually, patients with MI present with chest pain and other typical symptoms, such as fatigue, weakness, sweating and nausea (Milner *et al.,* 1999; Omran and Al-Hassan 2006; Albarran *et al.,* 2007). Women are more likely to present with dyspnea, palpitations, nausea, diaphoresis, fatigue, mid-back pain, arm or shoulder pain, neck pain and syncope (Milner *et al.,* 1999, 2002; Patel *et al.,* 2004; Omran and Al-Hassan 2006; Albarran *et al.,* 2007). However, there are more similarities than differences in the way that male and female patients present with MI.

2.4.2.2.3. Diagnosis of myocardial infarction

Symptoms may be a strong indicator of MI, but the diagnosis can only be confirmed by specific clinical measurements. The most common medical examinations are echocardiography and enzyme measurements (troponin, creatine kinase [CK], creatine kinase MB [CK-MB]). ECG changes, such as depression or elevation in the ST-segment, and an elevation in the development of pathologic Q waves indicate ischaemia (Alpert *et al.,* 2000; Galvani *et al.,* 2002).

Measurements of troponin, CK and CK-MB are used as diagnostic tools and prognostic criteria in MI (Alpert *et al.,* 2000; Galvani *et al.,* 2002; Roger *et al.,* 2006). Karras and Kane (2001) suggested that the cardiac troponins are the more useful and sensitive tool in the diagnosis of MI. It is preferable to CK and CK-MB because the latter start to rise a few hours from onset. Patients who present typical symptoms, such as chest pain, are advised to wait a few hours after the onset of symptoms, before cardiac marker testing. CK-MB is a reliable and sensitive measure which usually rises six or more hours after chest pain begins. Abnormal levels of cardiac troponins at

any time following the onset of chest pain are predictive of an adverse cardiac event (Karras and Kane 2001).

Previously, myoglobin appeared promising as a marker of early cardiac ischaemia, but it now appears to be only marginally more sensitive than CK-MB soon after symptom onset. Myoglobin is less sensitive than CK-MB at >8 hours after chest pain starts (Karras and Kane 2001). Within 6-8 hours of the initial symptoms, cardiac markers are highly sensitive and effective in the diagnosis of MI. The accuracy of the diagnosis is also related to the time that the patient had to go to the emergency department. In this time, the biochemical markers of myocardial necrosis may have normalised (Alpert *et al.,* 2000; Galvani *et al.,* 2002).

Troponin is a sensitive diagnostic marker for MI, but it is insensitive as an indicatory of the extent of the MI. In contrast, CK-MB can determine with accuracy the extent of the MI (Costa *et al.*, 2008). Troponin could not be looked at on its own, because only half of the patients that had elevated troponin levels met the criteria for having undergone an MI (Lim *et al.*, 2005). Above all, it seems that an isolated cardiac serum marker cannot be used as an ideal marker of MI, which explains why so many examinations are made when an MI is suspected.

2.4.2.2.4. The role of cardiac rehabilitation after myocardial infarction

Cardiac rehabilitation is designed to reduce coronary artery risk factors, promote a healthy lifestyle and decrease rates of morbidity and mortality following MI (Goto *et al.,* 2002, 2003a). Data from meta-analyses of more than 4,000 post-MI patients showed that exercise-based CR, compared with usual medical care, is associated with reductions in cardiovascular mortality and fatal reinfarction (20-25%) throughout at least 2 years after MI (Oldridge *et al.*, 1988; O'Connor *et al.*, 1989).

In particular, patients with MI who attended CR showed significant improvements in physiological and psychological parameters. Exercise training improves functional capacity, muscle strength and maximal oxygen uptake (VO_{2max}) (Izawa *et al.,* 2004). Adams *et al.* (1999) and Izawa *et al*. (2004) used aerobic and resistance training, at an intensity of 60–80% (11–13 on the Borg scale) over an 8-week programme; they found important physiological benefits (17% muscle strength increase) without any cardiac or orthopaedic injury. Moreover, regular exercise training can improve endothelium vasodilatation, lessen epicardial coronary stenosis and, as a result of these improved factors, can reduce myocardial ischaemia (Hambrecht *et al.,* 2000b, 2003) and improve symptom-free periods (Hambrecht *et al.,* 2004).

Cardiac rehabilitation has shown significant improvements in the psychological area as well, such as decreased depression, more effective stress management and an improvement in health-related quality of life (HRQOL) (Sledge *et al.,* 2000; Izawa *et al.,* 2004). Resistance and aerobic exercise can improve physiological and psychological outcomes in patients with MI; however, long-term follow-up studies with larger samples are essential for CR to be established as beneficial and safe for use in recovery from MI. Further discussions of issues related to CR in post-MI patients will be found in the next chapters.

Except CHD, other serious cardiovascular conditions are heart failure (HF), valvular heart disease and arrhythmias (Fleisher *et al.,* 2007) and they will be analyzed below.

2.4.3. Other forms of cardiovascular disease

2.4.3.1. Heart failure

Heart failure (HF) is one of the most prevalent forms of heart disease in the elderly, affecting >10% of people over 80 (Schocken 2000; Lee *et al.,* 2003). HF is a progressive disease, in which

an imbalance occurs between cardiac output and the body's requirements. The most common symptoms in HF patients are muscle weakness, fatigue, exercise intolerance, cachexia and dyspnoea as a result of reduced oxygen delivery to the working skeletal muscle (Troosters *et al.,* 2004). Heart failure cannot actually be cured, but can be treated to relieve the symptoms, improve the quality of life and prolong patient's life (Alhaddad 1999; Dunderdale *et al.,* 2005; Davies *et al.,* 2010)

2.4.3.1.1. The role of cardiac rehabilitation for patients with heart failure

In light of the main symptoms HF patients experience, exercise interventions have concentrated on improving the skeletal muscle function, and especially muscle strength and tolerance (Dickstein *et al.,* 2008). Systematic reviews show that improvements in muscle strength and exercise tolerance by exercise training reduce morbidity (hospitalization) and mortality in HF patients, compared with usual care (Smart and Marwick 2004; Dickstein *et al.,* 2008; Smart and Steele 2010). A meta-analysis of 9 studies, involving 801 HF patients, showed that exercise training is significantly associated with lower mortality and admission to hospital (hazard ratio 0.65, 95% confidence interval [CI] 0.46 to 0.92, $p < 0.005$) compared to non-exercisers. The mean follow-up was approximately from 5 months to 6 years (Piepoli *et al.,* 2004). Debate still surrounds the type and intensity of exercise should be recommended to HF patients.

There is some evidence that both aerobic and resistance exercises can reduce the levels of catecholamine concentration (Tyni-Lenne *et al.,* 2001) and improve neurohormonal modulation (renin angiotensin system). Neurohormonal modulation has an impact on quality of life (Maria Sarullo *et al.,* 2006) and improves exercise tolerance and functional capacity (Belardinelli *et al.,* 1995; Sturm *et al.,* 1999; Jonsdottir *et al.,* 2006). These studies concentrated on peripheral

adaptations due to exercise, but there was insufficient reporting on the improvement that exercise may bring about on the central cardiovascular function.

Sturm *et al.* (1999) demonstrated that moderate aerobic exercise (at 50% of VO_{2max}) increases peak oxygen uptake and functional capacity, in patients with severe HF. The authors (Sturm *et al.,* 1999) reported that at this level of exercise patients could work individually, without supervision by a CR professional. Belardinelli *et al.* (1995) found that low intensity exercise (at 40% of VO_{2max}) can also help patients with stable HF. Low intensity exercise improved mitochondrial energy metabolism by improving the oxidative capacity of the trained muscles. In this way, functional muscular performance can be improved, as well.

Silva *et al.* (2002) examined patients with the signs and symptoms of HF; they studied the result of exercise on this group in comparison with a control group. The exercise programme that they used was performed at intervals: 3 days a week, 30–60 minutes per day, for 3 months, at an intensity of 60–80% of peak HR. It included walking and stretching exercises using the upper and lower limbs. In contrast with other investigators, Silva *et al*. (2002) used a high intensity exercise programme, but the patients who took part were examined by a cardiologist to be sure that they did not have any of the exclusion criteria, such as arrhythmia, angina, MI in the last 3 months, hypertrophic myocardiopathy, cardiopathy that required surgery, or hypertension. The results of this control study showed that exercise programmes increase distance walking, decrease resting HR and reduce the double product at peak exercise levels (HR × SBP). Double product is the indirect index of myocardial oxygen demand (Williams *et al.,* 2007). You Fang and Marwick (2003) refer to long-term programmes (3–6 months) that can maximise the benefits that would be obtained via exercise for patients with HF.

To summarise, the characteristics of a CR programme for patients with HF, in order for it to be safe and for patients to obtain the maximum benefit, could aim for the following constituent parts:

- Frequency: 3 days per week
- Intensity: moderate
- Type of exercise: interval, aerobic and resistance exercise
- Duration: 30–60 minutes, over a longer term (3–6 months)

2.4.3.2. Valvular heart disease

2.4.3.3.1. Nature and causes of valvular heart disease

Disorders of the heart valves (mitral, aortic, tricuspid or pulmonary valves) and their structural abnormalities are referred to as valvular heart disease. Valvular heart disease can affect blood flow in two ways: (i) due to valve stenosis, blood flow is obstructed; (ii) valve does not close properly, occurring blood regurgitation. Several conditions can cause valvular heart disease, the most common of which are congenital factors (i.e., inherited connective tissue disorders), rheumatic fever, CHD, cardiomyopathy and degenerative changes in the valves. The most common symptoms of valvular heart disease are dyspnea on exertion or rest, fatigue, palpitations and ankle oedema (Rapaport 1975; Soler-Soler and Galve 2000; Boudoulas 2002).

Many cases of valvular disorders, valve repair or replacement, are treated with surgery (Rapaport 1975). Recovery from heart valve surgery is a gradual process, which usually involves firstly healing of the surgical wound and then gradual increase in muscle strength and endurance by participating in outpatient exercise-based CR programmes (Gohlke-Barwolf *et al.,* 1992; Jairath *et al.,* 1995).

2.4.3.3.2. The role of cardiac rehabilitation for patients with valvular heart disease

Cardiac rehabilitation is effective following the onset of most cardiovascular system diseases, but there is a paucity of research focused on the effects of exercise following the surgical repair of valvular heart disease. Meurin *et al*. (2005) demonstrated that patients who had undertaken CR programmes soon after their operations (within 1–3 weeks after the mitral operation), for about three weeks, showed improvement in VO_{2max} and lactate threshold, while their LVEF and diastolic diameter also increased significantly. Although there was no healthy control group to validate the results, no worsening of post-surgical mitral regurgitation was observed during the CR programme. There were no ischaemic or hemorrhagic strokes, peripheral thromboembolic events, severe HF or arrhythmias.

There are limitations to the studies that have focused on the assessment of exercise results after valvular surgery. Their non-randomised design means it is difficult to separate natural recovery from effects or CR. Despite this weakness, most studies demonstrate that exercise can maintain and improve patient outcome following surgery as well as having a positive effect on cardiac risk factors (Sire 1987; Toyomasu *et al.,* 1990; Gohlke-Barwolf *et al.,* 1992; Jairath *et al.,* 1995).

2.4.3.3. Arrhythmias

It is useful here to make some reference to HR abnormalities, which are defined as arrhythmias. There are many different types of cardiac arrhythmia caused by abnormalities of the electrical conductance system of the myocardium. The most common types are atrial fibrillation, paroxysmal atrial tachycardia, bradycardia, ventricular arrhythmias, supraventricular tachycardia; and ventricular fibrillation, which is a cause of cardiac arrest and sudden cardiac death. Ventricular arrhythmias can be detected in individuals with or without a cardiac disorder. They can be detected as an incident during a physical examination with ECG monitoring.

Asymptomatic ventricular arrhythmias commonly occur in stable post-MI patients, and in patients with cardiomyopathy or HF (Zipes *et al.,* 2006; Epstein *et al.,* 2008; Jaeger 2010).

The most common heart diseases have been discussed in this section along with brief examples of the role that exercise training may play in their treatment. This discussion was essential in order to understand the role of CR. The following sections will analyze the role of exercise training in revascularization procedures and will introduce the existing clinical guidelines on CR.

2.5. Revascularisation procedures and the role of cardiac rehabilitation

Intensive lifestyle modification can help prevent or reverse CHD in some cases (Ornish *et al.,* 1990). However, patients with advanced CHD or previous adverse cardiovascular events (i.e., MI) may benefit more from revascularization procedures, compared with usual medical care and lifestyle changes alone (O'Keefe *et al.,* 2009). Percutaneous coronary intervention with intracoronary stent implantation and CABG are the usual therapeutic procedures for patients with significant CHD (Hambrecht *et al.,* 2004).

Tsai *et al.* (2006) found that patients involved in exercise training for 8 weeks after PCI, independent of the device used (balloon or stent), had better cardiac autonomic function, increased parasympathetic modulation and, as a result, a lower HR, in comparison with a non-exercising control group. The Exercise Training Intervention after Coronary Angioplasty (ETICA) trial recruited a sample of 130 patients, post-PCI, to an exercise training or control group. Exercise-trained people participated in a six month programme comprising three weekly sessions of 30 minutes cycling at 60% of VO_{2max}, followed by 15 minutes of stretching. VO_{2max} increased by 26% for patients who exercised; their functional capacity and quality of life were also improved. During the follow-up period, (33±7 months), exercise-trained patients had fewer cardiovascular events than the control group, including fewer repeat angioplasties, CABG

procedures and lower hospital readmission rates (Belardinelli *et al.,* 2001). Aerobic exercise training in elective cardiac surgery patients can improve respiratory efficiency and left ventricular systolic function; it can provide a level of protection against a new coronary event (Vasiliauskas *et al.,* 2007). A follow-up control study with a larger sample is now essential in this area.

2.6. Current clinical guidelines and cardiac rehabilitation phases

Cardiac rehabilitation is a key component in the management of cardiovascular disorders, especially in developed countries such as the UK and US. Over the past twenty years, participation in CR programmes has become more commonplace (Paquet *et al.,* 2005), and CR is now included in some national healthcare guidelines.

2.6.1. United Kingdom guidelines for cardiac rehabilitation

Guidelines for the provision of CR in the UK are available from:

a. BACR guidelines (Coats *et al.,* 1995; BACR 2007);

b. SIGN guidelines (2002), endorsed by the BACR;

c. National Service Framework (NSF) guidelines (2000) for CHD;

d. National Institute for Health and Clinical Excellence (NICE) (2008).

The NSF (2000) states that major lifestyle risk factors for CHD are lack of exercise, smoking and an unhealthy diet. People who are physically inactive have a two-fold greater risk of CHD than those who exercise regularly (Department of Health 2000). Lifestyle changes (in terms of exercise, weight management, smoking cessation) constitute the basic component of CR programmes (BACR 2007). Other core components of CR are: education, risk factor

management, psychological recovery, cardiac drug therapy and self-management strategies for long-term use (BACR 2007).

Cardiac rehabilitation services should be delivered by a highly trained healthcare team, including a consultant cardiologist, a cardiac nurse, an exercise professional, a dietician, a physiotherapist, an occupational therapist and a psychologist (Department of Health 2000; BACR 2006). In most (96%) of the CR services established in the UK, more than five healthcare professionals are included in the rehabilitation team (Brodie *et al.,* 2006).

2.6.1.1. Cardiac rehabilitation phases in the United Kingdom

According to SIGN (2002), and the BACR (1995), CR is divided into four phases in the UK. Each phase includes some specific criteria suitable to the patient's stage of recovery, to help the patient improve their physiological and psychological parameters. Phase I is carried out in the hospital. It contains a summary of medical evaluations, advice and education for the patient, to help them overcome the disease, make a fuller recovery and understand their illness (SIGN 2006).

Phase II takes place when the patient leaves the hospital, before they are involved in a methodological rehabilitation programme. During this phase, patients can elect to have a home visit and on-call support from CR professionals who are able to check their progress, or to attend a supervised cardiac programme suitable for each patient's circumstances (SIGN 2002). At this stage, the patient usually receives a manual on home-based exercise rehabilitation after a heart attack (SIGN 2002). This phase typically lasts 2-6 weeks, depending on whether the patient is fit enough to enter phase III CR (BACR 2006).

Phase III comprises a supervised group rehabilitation programme, which typically has an eight-week duration. It includes exercise programmes, advice on how patients can reduce the risk factors associated with CHD (such as smoking cessation, healthy diet, weight management) in order to lead a healthier lifestyle, and psychological support to help the patient return quickly to a healthy social life (SIGN 2002; BACR 2006).

Phase IV is the final CR stage. It consists of a long-term maintenance programme, building on the principles established in phase III. The aim is to encourage patients to maintain over their lifespan the benefits and lifestyle changes gained during phase III. This phase can be hospital, community or home-based, supervised or independent (BACR 2006).

Despite efforts to promote the existing guidelines, there is evidence that only a few CR centres (21%) in the UK follow exactly the recommendations by national guidelines (Brodie *et al.,* 2006). This will be discussed further below. The research in this thesis will use the UK guidelines, but US guidelines remain relevant due to the large amount of research completed in North America.

2.6.2. American guidelines for cardiac rehabilitation

The most common US guidelines for the provision of CR are those of:

a. the American Heart Association (AHA) (2006);

b. the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) (2004).

The AHA recommends the following guidelines for patients with coronary and other atherosclerotic vascular diseases: (1) physicians should assess the patient's cardiac risk with a physical activity history and/or an exercise test; (2) patients should be encouraged to do 30 to 60

minutes of moderate intensity aerobic activity, such as brisk walking, on most, preferably all, days of the week, supplemented by daily lifestyle changes. Medically supervised programmes should be given to high-risk patients (i.e., after recent acute coronary syndrome, revascularisation or HF); (4) the goal of rehabilitation should be to follow exercise programmes for 30 minutes, 7 days/week, with a minimum frequency of 5 days/week (Smith *et al.,* 2006). The AACVPR recommends the use of exercise testing, pre- and post-rehabilitation. The outcomes can provide important information on a patient's functional capacity (American Association of Cardiovascular and Pulmonary Rehabilitation 2004).

2.6.2.1. Cardiac rehabilitation phases in the United States

According to the AHA guidelines (1994), the CR service is divided into three phases. Phase I is an inpatient process. The patient is given encouragement and advice about the disease and the recovery process. Phase II is a discharge process. After 2–6 weeks of recovery at home, patients can participate in a supervised exercise programme, which lasts 3–6 months. Phase III is a long-term maintenance exercise programme. Guidance states that, in this phase, ECG monitoring may not be necessary. Chapter 7 (see '*Safety of exercise training and exercise testing for cardiac patients, in a supervised, community-based cardiac rehabilitation programme'*) will address this issue in the present thesis.

Cardiac rehabilitation and service provision varies across countries due to differences in culture, demographic characteristics and socioeconomic status (Davidson *et al.,* 2010). However, all national and international CR committees encourage attendance at CR programmes and they have set their guidelines around a common set of goals.

2.7. Goals of cardiac rehabilitation

The goals of CR as a secondary prevention tool are:

(a) to reduce the disability of the patient, particularly in older people after an MI;

(b) to improve functional capacity;

(c) to prevent secondary cardiovascular events, hospitalisation and death from cardiac causes;

(d) to identify coronary risk factors in order to reduce morbidity and mortality due to cardiac diseases.

The primary goal of CR is to improve the physiological and psychological parameters of the patient so that they can return to a normal life (Balady *et al.,* 1994). These goals are achievable through a programme of prescribed exercise and interventions designed to modify coronary risk factors with the use of optimised drug therapy and appropriate lifestyle changes (Hambrecht *et al.,* 2000a, 2000b; Ades 2001; Pasquali *et al.,* 2001; Balady *et al.,* 2007; Lavie *et al.,* 2009). In order to achieve these goals, clinical guidelines for CR were designed across various populations.

2.8. The role of exercise training in cardiac rehabilitation

Cardiac rehabilitation is secondary prevention, which should include patient assessment, risk factor reduction, as well as nutritional recommendations, psychological support, exercise training appropriate to the patient's cardiovascular disorder and the cardioprotective drugs prescribed (Leon *et al.,* 2005). Regular exercise is associated with a 50% lower risk of CVD mortality in adults with CHD risk factors (Ardern *et al.,* 2005). The exercise pattern, which is associated with the reduction of mortality, includes an exercise programme undertaken 4 to 5 times per week, for 30 minutes per session (i.e., 130 to 138 minutes per week). The results of this study were significant, although its status is unclear as it was not a follow-up study; as a result of this, it is

unclear if the changes in the cardiovascular system could be maintained over the year (Ardern *et al.,* 2005). In its primary role, physical activity can prevent the onset of pathology, and in its secondary role, it can prevent the onset of a new cardiac event. The following section will demonstrate the important role of exercise in the secondary prevention of CVD.

2.8.1. Physiological effects of exercise training

The benefits of exercise training, as part of CR, are multifactorial and there are several studies in this area. A full review is, however, beyond the scope of this section and the present study will review some findings of the area. Exercise training that contains aerobic activities, such as walking, climbing stairs or cycling, can improve the functional capacity of the participants (Leon *et al.,* 2005). Low functional capacity is an independent CVD risk factor associated with increased rates of cardiovascular morbidity and mortality (Myers *et al.,* 2002; Kavanagh *et al.,* 2003; Mark and Lauer 2003). Exercise increases the VO_{2max} level from 11% to 66% after 3 to 6 months in cardiac patients, with the greatest improvements seen among those patients with the lowest initial VO_{2max} levels (Belardinelli *et al.,* 1995, 1999; Sturm *et al.,* 1999).

Exercise improves myocardial function by increasing VO_{2max} (and hence myocardial oxygen delivery), increasing the size of the myocardial cells and increasing their contractility. Experimental protocols in animals have shown that exercise training can increase the width and length of myocardial cells by 20 to 22% and estimated volume by 46%. All these adaptations can be reversed after a 2–4 week detraining period (Kemi *et al.,* 2004, 2005). Moreover, contractility can be improved with exercise after an acute coronary event (i.e., MI). Changes in the expression of troponin I isoforms have been identified with exercise. Specifically, there is an increase in the a-myosin heavy chain expression, which is associated with increased ATPase activity and myocardial contractility. The increase of sarcoplasmatic reticulum Ca–ATPase leads to an

increase in Ca^{2+} release from the sarcoplasmic reticulum, contributing to smooth muscle contractile activation (Wisloff *et al.,* 2001, 2002). Such animal investigations are of great scientific interest; however, further studies in humans are required to confirm the results.

In humans, it has been demonstrated that exercise promotes hemodynamic adaptation and changes in regional blood flow. It increases functional capacity by decreasing the HR and SBP (Balady and Weiner 1992; Balady *et al.,* 1994). Autonomic imbalance, increase in autonomic parasympathetic, and/or decrease in cardiac sympathetic activity, are associated with lower HR in those who undertake endurance training (Sandercock *et al.,* 2005).

Exercise has also a favorable effect on the brain natriuretic peptide (BNP) and the N-terminal pro-B-type natriuretic peptide (NT-pro-BNP). BNP is a peptide hormone produced by the cardiac ventricles as an inactive hormone BNP, which are split into the active hormone BNP and the inactive NT-pro-BNP. BNP has several effects, including vasodilatation, sodium output and increased urinary volume. BNP also decreases the function of the sympathetic nervous system and the rennin-angiotensin system (Hall 2004). Both BNP and NT-pro-BNP increase left ventricular wall stress and, as a result, can be used as prognostic tools of mortality and morbidity in patients with HF and CHD (Kragelund *et al.,* 2005), especially in elderly people (Ueda *et al.,* 2003). Exercise reduces NT-pro-BNP plasma levels, which react to left ventricular wall stress (Giallauria *et al.,* 2006a, 2006b); this leads to an improvement in arterial endothelial function (Walther *et al.,* 2004).

Exercise improves endothelial function in healthy people, but the most significant improvement can be noticed in patients with endothelial dysfunction (Hambrecht *et al.,* 2000b; Moyna and Thompson 2004). Exercise leads to an increase in acetylcholine concentration, in the arteries, and, as a result, vasodilatation and peak flow velocity can be significantly enhanced. Regular

exercise, independent of cholesterol levels, does not improve the endothelial function in young, healthy adults, but it can have a beneficial effect in young people with endothelial dysfunction, such as those with hypertension (Hambrecht *et al.,* 2000b; Moyna and Thompson 2004). The mechanism of this increased vasodilatation could include the fact that exercise increases the release of NO and prostacyclin. Exercise also increases vascular expression, modulates the flow of paracrine substances, and decreases the sympathetic vasoconstrictive tone (Niebauer and Cooke 1996; Cheng *et al.,* 1999; Maiorana *et al.,* 2003).

Exercise training affects the management of certain metabolic CHD risk factors, including obesity, diabetes, hypertension and hypercholesterolemia (Lavie and Milani 1996, 1997; Morrin *et al.,* 2000; Bader *et al.,* 2001). In combination with a low-fat diet and a weight reduction programme, if required, exercise reacts on lipid profiles, insulin resistance and abdominal obesity. Physical activity can increase the HDL cholesterol concentration by 5 to 16%. Evidence that exercise affects LDL and total cholesterol levels is more mixed (Bittner and Oberman 1993). Controlled trials of CHD patients on a regime of exercise plus a low-fat diet show significant reductions in total cholesterol, LDL and triglyceride levels, accompanied by increases in HDL levels (Schuler *et al.,* 1992a, 1992b; Allison *et al.,* 1999; Taylor *et al.,* 2004).

Exercise training may reduce also inflammation, which plays a significant role in the progress of atherosclerosis and the progress of cardiovascular pathogenesis. The National Health and Nutrition Examination Survey (NHANES) III, sampled 13,748 adults and demonstrated that the intensity of the exercise is inversely related to C-reactive proteins, plasma fibrinogens and the white blood cell count (Ford 2002a). In the same way, the Attica study showed that light to moderate exercise can cause a reaction in the inflammation markers, although a lot of studies suggest only vigorous activity has a beneficial effect on cardiovascular risk (Pitsavos *et al.,* 2003). High-intensity exercise can increase oxidative stress, whereas long-term moderate

intensity exercise enhances the endothelial vasodilatation function (Goto *et al.*, 2003b). These findings are important, when considering the intensity of exercise required, and provide strong evidence for the value of vigorous exercise activity in relation to the cardiovascular system.

In patients with CHD, exercise increases the ischaemic threshold (double product at which 1 mm ST depression was first recorded), which means that cardiovascular events tend to occur at higher work levels (Jensen *et al.,* 1980; Todd and Ballantyne 1990). The mechanism that might change the ischaemic threshold needs to be determined. Todd *et al.* (1992) demonstrated that intense exercise for ten minutes daily over six months had similar effectiveness (i.e., in the reduction of HR, ST threshold, double product ST threshold) to medical treatment with β-blockers in patients with stable angina. Additionally, however, physical training increased exercise tolerance by twice the amount that β-blockers did. There are insufficient reports that document the increase in the ischaemic threshold, probably due to the inherent difficulties in performing such studies. In these studies, exercise testing or training should reach the ischaemic threshold, which might not be pleasant or safe for patients.

The evidence presented above suggests that the physiological adaptations to aerobic conditioning can benefit the primary and secondary prevention of CHD. Many of these adaptations can only be identified via maximal treadmill test assessment, which however requires expensive equipment and specialized staff. Exercise can promote not only physiological but also psychological adaptations. The overall objective of CR is to take advantage of these dual effects and to restore and maintain both physiological and psychological status (Coats *et al.,* 1995; SIGN 2002; Taylor *et al.,* 2004).

2.8.2. Psychological effects of exercise training

Exercise training has a positive effect in improving psychological factors, such as anxiety, depression, mood and general quality of life (Lavie and Milani 2004, 2005, 2006). Kennedy *et al.* (2003) investigated the psychological effects of CR in women aged between 33 and 82 years old. The women participated for 7 weeks in a supervised aerobic CR programme, and for 7 weeks in an unsupervised home exercise programme that ran alongside lifestyle modifications. After 14 weeks of CR, the participants were assessed using a modified treadmill test, BP measurements, a blood lipid test and a Cardiac Quality of Life Index questionnaire. Quality of life and psychosocial symptoms (worry and depressive symptoms) were also improved after 14 weeks of CR. The results of the study are in line with other investigations (Verrill *et al.,* 2001; Lavie and Milani 2004, 2006) but the lack of a control group, and the fact that it was a lengthy period of unsupervised training, threaten the validity of the results. Patients' education about the severity of their illness can make them more responsible for the underlying processes of the disease and help them to manage their own recovery. This fact, in addition to the effectiveness of their socialisation with other patients at various stages of recovery, improves the social and mental recovery process (Lavie and Milani 2005, 2006).

Lavie and Milani (2004) demonstrated that CR and exercise training programmes reduce levels of anxiety by more than half. In patients with high anxiety, exercise marks improvements in functional capacity, lipids (HDL, total cholesterol/HDL ratio, and triglycerides/HDL ratio), behavioural characteristics and in obesity indices (weight, percentage of fat and body mass index), including improvements in quality of life (Lavie and Milani 2004, 2006).

Exercise CR programmes improves emotional well-being and maximizes caloric expenditure, contributing in the treatment of obesity (Bader *et al.*, 2001; Lavie and Milani 2004, 2006; Sierra-Johnson *et al.*, 2005). Nearly 80% of patients who enter a CR programme are overweight or

obese (Bader *et al.*, 2001; Sierra-Johnson *et al.*, 2005). The follow section will introduce the role of exercise in weight reduction for overweight or obese people.

2.8.3. Exercise and obesity in cardiac patients

Obesity is an independent CVD risk factor (primary and secondary) and exercise, when combined with calorific restriction, is efficient in terms of weight reduction (Lavie and Milani 1997; Ades *et al.,* 2010). Weight reduction in overweight and obese patients can reduce other cardiac risk factors and also act as an important tool in the secondary prevention of CHD. Coronary heart disease patients who enter CR not only show great improvement in BMI (reduction of more than 2%) but also show improvement in almost all the lipid fractions (an LDL/HDL reduction of 6%), BP, insulin resistance, clotting abnormalities, behavioural characteristics (anxiety, depression) and general quality of life issues by the end of CR programme (Lavie and Milani 1997; Ades *et al.,* 2010).

For obese cardiac patients, exercise is beneficial in terms of weight control or reduction, physiological parameters and psychological status. Thus, CR exercise, as a comprehensive secondary prevention program, should include weight loss programmes for obese or overweight patients (Ades *et al.,* 2010). The beneficial effect of regular exercise training in obesity is not limited to weight reduction (Kokkinos *et al.,* 2001, 2006, 2007). There is little information regarding the exact amount of exercise training required for obese people, but it is clear that endurance exercise and dietary caloric restriction can both help in the management of obesity.

2.8.4. Exercise and hypertension

For cardiac patients who participate in CR programmes, exercise can reduce SBP by 3.2 mmHg and DBP by 1.2 mmHg (Taylor *et al.,* 2004). Exercise can have safe and positive effects for all

hypertensive patients. For hypertensive patients, systematic exercise for three months reduces BP, with SBP and DBP reductions of approximately 11 mmHg and 8 mmHg, respectively. There is also some evidence to suggest that exercise training may lead to regression of pathological left ventricular hypertrophy in hypertensive patients (Kokkinos and Papademetriou 2000; Kokkinos *et al.,* 2001, 2006, 2007). As a result of these factors, exercise can significantly improve the quality of life (Jolliffe *et al.*, 2000; Kokkinos and Papademetriou 2000; Kokkinos *et al.,* 2001, 2006, 2007).

Regular aerobic endurance exercise can decelerate and restore in some ways the age-associated reduction in central, arterial compliance. This means that middle-aged and older people, who exercise regularly, can have a lower incidence of CVD (Tanaka *et al.*, 2000). Moreover, a moderate intensity (30% of the maximum voluntary contraction force) of isometric training, carried out for a short duration, can also change the function of the autonomic neurological system, which leads to a reduction of resting HR and BP in older people with hypertension (Taylor *et al.,* 2003). However, the small sample (n=9, control group: n=8) of this study (Taylor *et al.,* 2003) threatens the validity of the results. The effectiveness of isometric exercise on hypertension requires further study.

Moderate physical activity reduces the risk of CHD in a number of populations as follows: by 12% for controlled hypertensive patients, by 5% for uncontrolled hypertensive patients and 9% for hypertensive patients (who are not taking any medication) (Chrysohoou *et al.,* 2003). Exercise training in combination with (a Mediterranean) diet reduces CHD risk as follows: by 25% in hypertensive controlled patients, by 11% in untreated patients and 17% in uncontrolled patients (Pitsavos *et al.,* 2002).

Exercise training programmes can modify CHD risk factors (hypertension, obesity) and reduce the impact of established CHD. However, there is always a risk of developing a cardiac event during exercise in this population. In the following section, the main issues regarding safety of CR will be presented.

2.9. Safety of exercise for cardiac patients

Although CR and particularly exercise can reduce cardiac mortality and morbidity, cardiovascular events can also occur during an exercise stress test or an exercise training programme. According to recent studies the event risk during exercise in CR centres is low, 1.4 per 10,000 tests and 20.2 per million patient exercise hours (Pavy *et al.,* 2006); however cardiac events cannot be predicted (Vongvanich *et al.,* 1996; Pavy *et al.,* 2006). Existing data are largely limited to low or moderate CVD patients. The benefit-risk ratio of exercise-based CR has not yet been well established, while the existing data are limited to low or moderate CVD patients. More studies are needed to determine event rates during exercise. Further discussion on this topic will follow in Chapter 7 (see '*Safety of exercise training and exercise testing for cardiac patients, in a supervised, community-based cardiac rehabilitation programme'*).

Despite the unpredictability of cardiovascular events, clinical guidelines encourage CVD patients to participate in exercise-based CR programmes due to the benefits derived from such participation (SIGN 2002; Leon *et al.,* 2005). To eliminate potential cardiac events during exercise, clinical risk stratification based on the assessment of cardiovascular function and functional status should, therefore, be used in deciding which patients should admit to exercise CR programmes and in regulating CR exercise intensity, respectively (SIGN 2002).

2.10. Evaluation of functional capacity in cardiac patients

Cardiac patients' functional capacity is the best predictor of overall mortality when measured against all the other cardiovascular risk factors (Myers *et al.,* 2002). Functional capacity can be expressed in metabolic equivalents (METs) (Peeters and Mets 1996). A functional capacity of >10 METs indicates good prognosis, in contrast with a functional capacity of <5 METs, independent of cardiac disorder; each 1 MET increase in functional capacity results in a 10% reduction in mortality, during an average of 6 years of follow-up (Franklin *et al.,* 2003). It is, therefore, clinically useful to be able to measure such an important prognostic factor in a reliable and valid way. In routinely clinical practice, reliable and valid prognostic stratification patients can help in lifestyle modifications and therapeutic decisions making. What follows is a brief review of this topic but the reader is directed to Chapters 3, 4, 5 and 6 where more detail is given.

There are many tests which can be used to detect the level of functional capacity and changes in functional capacity after a CR treatment. Most of the tests that are used to evaluate the effects of CR exercise programmes concentrate on either the measurement of VO_{2max} or HR (HR recovery, time of HR recovery after the exercise), or the distance covered during the test (Guyatt *et al.,* 1985a; Singh *et al.,* 1994; Cole *et al.,* 1999, 2000; Nishime *et al.,* 2000; Shetler *et al.,* 2001; Messinger-Rapport *et al.,* 2003; Tiukinhoy *et al.,* 2003). Laboratory-based treadmill and cycle ergometer protocols are the gold standard in clinical assessment in determining cardiorespiratory function due to their ability to provide a direct and easy measurement of maximal aerobic capacity (VO_{2max}) via gas analysis (Myers *et al.,* 2000; American College of Sports Medicine 2001). Despite the capability of laboratory-based tests to produce such direct and detailed outcome measures, the process is costly and time consuming. Moreover most of CVD patients do not meet criteria for a true maximal test performance (VO_{2max}) during treadmill testing (Lewis

et al., 2001). SIGN (2002) and the AACVPR guidelines (Sanderson *et al.,* 2004) recommend the use of simple sub-maximal walking tests to assess cardiac patients for exercise prescription.

The six-minute walking test (6-MWT) and the shuttle walking test (SWT) are used frequently in CR services because they require little equipment and basic staff training (Guyatt *et al.,* 1985a; Singh *et al.,* 1992). The 6-MWT has high prognostic value in patients with mild to moderate HF. Patients with a 6-MWT score lower than 300 m have a higher mortality rate than those with a 6-MWT score greater than 300 m (Rostagno *et al.,* 2003). The results of this study (Rostagno *et al.,* 2003) were confirmed by a more recent study (Arslan *et al.,* 2007). Despite the limitations of the latest study, such as its small sample size and short duration, the 6-MWT has been established as a reliable and independent predictor of cardiac death. Moreover, other studies have shown that the 6-MWT can give the same results as a sub-maximal treadmill exercise test, with close to 85% of the age predicted HR target (Elved *et al.,* 2006), or close to 80% of VO_{2max} (Kervio *et al.,* 2004). Several studies have focused on how closely distance walked on SWT is related to traditional measurements, like VO_{2max}. Distance walked in SWT appears strongly related to VO_{2max} produced during the traditional treadmill protocol (Singh *et al.,* 1994; Fowler *et al.,* 2005).

The 6-MWT and the SWT are frequently used in CR, there is a knowledge gap surrounding potential factors (clinical and non-clinical) which affect test performance; while there are no established normative values of functional capacity for these walking tests. This research gap creates the opportunity to investigate this area further.

Exercise testing facilitates exercise prescription and makes it safe for CVD patients. Exercise may not be beneficial for all patients, due to a number of absolute contraindications to CR participation. The CR participation is not indicated, when the risks of exercise training are

greater than the benefits (Thompson 2005). It would be of interest to explore whether or not the prognosis for those CVD patients who cannot be tested is worse than for those who are able to perform (even low levels) of exercise testing.

2.11. Patients for cardiac rehabilitation

2.11.1. Indications to exercise

Cardiac rehabilitation is indicated for all patients with a diagnosis of acute MI and for those with CHD risk factors such as hypertension, hypercholesterolemia and diseases related to the circulatory system. It is also appropriate for patients who have undergone cardiac surgical procedures, such as a CABG, PCI and valvular heart surgery (Balady *et al.,* 2000; Hambrecht *et al.,* 2000a; Ades 2001; Pasquali *et al.,* 2001; Leon *et al.,* 2005; Meurin *et al.,* 2005). Patients with chronic stable angina, stable HF, those who have undergone cardiac transplantation, peripheral arterial disease with claudication, or other forms of CVD could also participate in CR programmes (Balady *et al.,* 2000; Hambrecht *et al.,* 2000a; Ades 2001; Pasquali *et al.,* 2001).

2.11.2. Contra-indications to exercise

Exercise is proscribed or restricted in cardiac patients with the following pathology or symptoms: (1) during the first week after an MI and in those with unstable angina; (2) patients with increasing angina or reduced effort tolerance should not be enrolled in exercise programmes until their status is clarified and appropriate treatment is initiated; (3) patients having ventricular tachycardia should not exercise until the rhythm is controlled (resting HR> 100 bpm); (4) after CABG surgery, patients can exercise after one to two weeks if no events are found, the incision is closed and they can exercise without any serious discomfort; (5) patients with postoperative thrombophlebitis should be effectively anticoagulated for at least two weeks before exercise training is initiated; (6) patients with symptomatic congestive HF or active pericarditis or active

myocarditis or uncontrolled diabetes should avoid exercise (Gonzalez *et al.*, 2004; Thompson 2005).

When exercise is indicated, there are a number of ways of delivering CR across a local health economy. Models of CR services in the UK are discussed below.

2.12. Models of cardiac rehabilitation

Cardiac rehabilitation can take place in hospital or in the community, where patients can be supervised by specialised staff (Brodie *et al.,* 2006). Home-based programmes have also been developed in the UK. The NSF for CHD guidance refers to numerous home-based services which can be supervised by nurses or general practitioners (Higgins *et al.,* 2001; Robertson and Kayhko 2001) or supported by telephone (Lewin *et al.,* 1992). Patients attending a home-based programme could also be supported by electronic media that include education and instruction for safe exercise (Southard *et al.,* 2003); in some cases, support can be provided through telemetrically monitored cycle ergometers (Brodie *et al.,* 2006). Patients at high risk after a cardiac event usually join hospital-based programmes (Brodie *et al.,* 2006).

According to the Birmingham Rehabilitation Uptake Maximisation Study (Jolly *et al.,* 2007), of 525 patients, there was no difference in clinical outcomes between patients with low and moderate risk levels after a cardiac event who participated in home-based CR programmes, and those who participated in centre-based CR programmes. The cost of home-based CR was higher than centre-based CR, but participation levels in the former were greater than in the latter.

A recent meta-analysis of 12 studies, involving 1,938 participants, showed that home-based CR has the same effectiveness in terms of quality of life as centre-based CR, in low-risk post-MI, post-revascularisation, angina or HF patients (Dalal *et al.,* 2010). The researchers recommended

that patients should have the opportunity to choose whether to participate in home-based CR, receiving a manual-based programme, or in centre-based CR.

Similarly, hospital versus community-based phase III CR seems to be the same valuable and effective service for patients. No significant difference in functional capacity improvement was observed between hospital-based and community-based CR group (Blake *et al.,* 2009; Robinson *et al.,* 2009). Maintaining patients' attendance is more difficult in the community settings (Blake *et al.,* 2009). The reasons for the lower exercise adherence in community-based CR, compared to participation in hospital-based CR, have not yet well addressed (Blake *et al.,* 2009). Much effort has been invested into improving home-based and community-based programmes; more research is still required to demonstrate their safety. Further research is also needed on the long-term benefits of home-based and centre-based CR on CVD mortality. Home-based CR has not yet shown that it can reduce mortality like centre-based CR does (Jolly *et al.,* 2006). These further studies could guarantee the continuity of community-based and home-based CR as an alternative tool in the secondary prevention of cardiac disorders. One of the reasons for creating home- and community-based services is to reduce some of the barriers to CR reported by non-attendees.

2.13. Barriers to cardiac rehabilitation

The physiological and psychological benefits of participation in CR programmes are established (Oldridge *et al.*, 1988; O'Connor *et al.,* 1989; Jolliffe *et al.,* 2000). Despite these benefits, there is evidence that there are still many barriers that may lead patients to interrupt or permanently withdraw from rehabilitation, or not to follow a programme in the first place (Brodie *et al.,* 2006). Less than 1/3 of patients finally participate in CR, in European countries (EUROASPIRE II Study Group 2001; Vanhees *et al.,* 2002). Some of the most reported barriers to participation in CR programmes are: poor motivation, ethnic minority status, geographical barriers (distance).

There are also between-sex disparities, age-related differences, and a consensus that the importance of CR has not yet been recognised by the public (Ades 2001; Allen *et al.,* 2004; Leon *et al.,* 2005).

Yohannes *et al.* (2007) found that 22% of patients (from n=189) interrupted a CR programme: most were female, younger in age, with high anxiety and lower illness perception. A study across 30 CR centres found that older people were less likely to be invited by staff to follow CR programmes than younger ones. Age and factors connected with older age, such as lower exercise tolerance, medical aliments and poor access to transport, may prevent older people using CR programmes (Clark *et al.,* 2002). On such occasions, the CR supervisors may play a key role. They should determine access for these patients to healthcare by clinical need, not age. Above all, the most significant barrier to CR participation is the failure of doctors to motivate patients to participate in these programmes; doctors also fail to point out to patients the progress they have made over the course of a programme they have undertaken.

Other studies have investigated that there are a number of physical or medical conditions which leads the patients to interrupt or withdraw permanently from an exercise programme. Nishi *et al.* (2007) demonstrated that, in HF patients, the main disorders that associated with interruption or withdrawal from the programme were: pacemakers, a large left ventricular end-diastolic diameter ≥ 65mm, low exercise tolerance or greater ventilatory drive. Webb-Peploe *et al.* (2000) agree that these disorders were the most common, in addition to ischaemic cardiomyopathy. Vanhees *et al.* (2004) showed that a ventricular tachycardia event was one of the main factors that led patients to stop attending a CR exercise programme. The fact that these cohort studies were not controlled, the sample was not representative of the whole population, and the exercise selected was neither well supervised nor specific to each patient, undermines the generalisability

of the results. The results would be more valid if the exercise programme was matched to the patients according to their psychosocial and physiological characteristics.

2.14. Conclusion

A number of high-quality studies demonstrate the benefits of CR in terms of increased survival, reduced morbidity and improved quality of life in CVD patients. Evidence is more limited for improvement in many risk factors, such as functional capacity, due to CR. Medications can modify almost all CVD risk factors, but only exercise can improve functional capacity and thus quality of life. Outcomes of CR, such as improvements in functional capacity, should be evaluated via reliable and valid exercise testing procedures. The standard Bruce treadmill test remains the most valid assessment in common use, but has numerous, methodological, temporal, financial and practical limitations. This thesis will look at the validity, reliability and usefulness of the most common functional walking tests (SWT and 6-MWT), and it will identify the predictors for functional outcome in these walking tests. The following chapters will, also, try to address research gaps relating to the safety of CVD patients in CR settings. The research in this thesis aims to improve the CR evaluation process, in terms of exploring the determinants of functional performance measures, which represents an important factor for the success of the CR service.

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CHAPTER 3. LONG-TERM RELIABILITY OF THE MODIFIED SHUTTLE WALKING TEST IN CLINICALLY STABLE CARDIOVASCULAR DISEASE PATIENTS

3.0. Abstract

The shuttle walking test (SWT) is a valuable tool for assessing and monitoring changes in patients' functional capacity during cardiac rehabilitation. Much evidence suggests that the SWT is a valid, reliable, sensitive and useful tool for detecting cardiorespiratory capacity. However, as most of the scientific sources refer to short-term tests, the purpose of this study was to examine over longer term the reliability of a modified SWT (MSWT) in clinically stable cardiac patients.

A convenience sample of 30 phase IV (UK classification) cardiac rehabilitation patients (50% males, 50% females, age: 67.1±8.1 years) participated in this study. A test–retest design was used and the patients were assessed twice using the MSWT, with a minimum of eight weeks between test administrations. Using the 15-level MSWT, the patients were required to walk up and down a 10 m course at increasing speeds, indicated by an audible signal. Heart rate and Borg rating of perceived exertion (RPE) score were recorded at the end of each level. Intraclass correlation coefficient (ICC) and limits of agreement (LoA) were used to assess reliability.

In the assessment of test–retest reliability, there were no significant differences between the two assessments in respect of the distance walked (MSWD), maximal walking speed, maximum heart rate and RPE scale (p>0.05). However, there were significant correlations between the MSWD (Pearson's r=0.80, p<0.001) and maximal walking speed in the two trials (Pearson's r=0.76, p<0.001). There was a small increase in the MSWD, from trial 1 to trial 2, from 502 (±161) m to 509 (±146) m – a difference of 7 m. The maximum heart rate decreased from 128 (±18) beats per minute in the trial 1 to 127 (±18) beats per minute in the trial 2. The mean RPE (range 6–20) reduced from 14.5 (±1.4) to 13.9 (±1.5) from the first to the second assessment.

Test–retest reliability in terms of the ICC was high for the MSWD, maximal walking speed, maximum heart rate and time taken to recover, while it was moderate for heart rate recovery and low for the maximum RPE value. The high ICC for MSWD (R=0.80) indicated good reliability, while the LoA indicated a small systematic test–retest bias of -7 m. The LoA for MSWD were large, ranging from -203 m to 189 m.

The results confirmed that long test–retest durations appeared to have no learning effect in the MSWT, negating the need for a practice walk. The long-term random variation in the MSWT was larger than in previous studies. This was most probably due to greater physiological and psychological variation in the patients when tested over an eight-week period, when compared with that seen in day-to-day testing. Factors influencing the long-term reliability of the MSWT required further elucidation.

3.1. Introduction

The benefits of cardiac rehabilitation (CR) programmes in improving health and quality of life of patients with cardiac disorders are well established (Goto *et al.,* 2003a; Izawa *et al.,* 2004) and were described in Chapter 2 of the present work (see '*Introduction to cardiovascular diseases and cardiac rehabilitation: a review in the literature*'). Low functional capacity was identified as the strongest predictor of overall mortality above all other cardiovascular risk factors in cardiac patients (Myers *et al.,* 2000). One aim of CR should be to increase functional capacity, but in order to verify such changes reliable functional capacity tests, which can be carried out CR practitioners such as nurses and physiotherapists, are needed.

As mentioned in Chapter 2, in the UK a phase IV CR programme is provided for patients with cardiac disorders, such as those with post-myocardial infarction (MI), post-revascularisation, post-transplant, post-valve replacement, stable angina, heart failure (HF) or peripheral arterial

disease. Patients who join phase IV CR programmes should be clinically stable and should be free of specified cardiac symptoms and signs (see table 3.1). According to the British Association for Cardiac Rehabilitation (BACR) guidelines (Bell *et al.,* 1995; BACR 2006), phase IV is a long-term follow-up training programme, where the goal is the maintenance of physical activity and lifestyle changes in cardiac patients.

Various cardiorespiratory assessment tests and functional measurements have been developed in order for patients who participate in the programme to receive feedback on their cardiovascular capacity and functional capacity levels.

Table 3.1. Contraindications to exercise (BACR 2006)

Unstable angina • new event of angina within the past 4 weeks • angina occurring at rest • angina occurring more easily on less effort • angina that does not respond so easily to nitrates medicines
Uncontrolled blood pressure, where SBP >180 mmHg and/or DBP >100 mmHg
BP decreases more than 20 mmHg during the exercise training
Resting tachycardia, where HR>100bpm
Uncontrolled atrial or ventricular arrhythmias
Unstable diabetes
Unstable heart failure
A fever or systematic illness

Definition of abbreviations: *MSWD=modified shuttle walk distance; bpm=beats per minute*

3.1.1. Evaluation of functional capacity in cardiac patients

Graded exercise tests aim to provoke a physiological response to continuously increasing exercise intensities (Mora *et al.,* 2003; Jouven *et al.,* 2005). The cardiorespiratory system is challenged as the intensity increases, and the body's ability to cope with these demands can be investigated to provide an insight into functional capacity.

Several cardiorespiratory assessment tests and functional measurements have been developed to determine prognosis, prescribe exercise and assess the efficacy of CR. It is standard practice to evaluate, through exercise testing, the improvement of HR response to exercise, HR recovery and the total time taken to attain HR recovery (Cole *et al.,* 1999, 2000; Nishime *et al.,* 2000; Messinger-Rapport *et al.,* 2003; Tiukinhoy *et al.,* 2003). Heart rate recovery is a predictor of mortality in asymptomatic (Cole *et al.,* 1999, 2000; Messinger-Rapport *et al.,* 2003) and symptomatic patients with cardiovascular disease (CVD) (Nishime *et al.,* 2000; Shetler *et al.,* 2001; Elved *et al.,* 2006).

A multivariate analysis of 2,994 asymptomatic women without evidence of CVD showed that women with a low functional capacity of <7.5 METs and poor HR recovery of >55 beats per minute (bpm) (measured at two minutes after testing) had a 3.5 fold increased risk of cardiac mortality during a mean follow-up of 20 years (Mora *et al.,* 2003). The authors (Mora *et al.,* 2003) concluded that exercise testing (Bruce treadmill test) has prognostic ability when functional capacity-related outcome measures, such as low functional capacity, poor HR recovery were analysed. Similar, Jouven *et al.* (2005) analyzed 5,713 asymptomatic men without diagnosis of CVD and showed that poor HR recovery of >40 bpm or <25 bpm (measured at two minutes after bike exercise testing) is associated with a 2.1 fold increased risk of sudden death and 1.3 fold increased risk of death from any cause, at a mean follow-up of 23 years. The authors (Jouven *et al.,* 2005) observed, also, an increased risk of sudden cardiac death (relative risk 3.92), when the resting HR was >75 bpm. These examples of the diversity and functionality of outcome measures obtained from incremental exercise testing illustrate their importance in clinical assessment.

Walk tests are the most commonly utilized tool for assessing the functional capacity of cardiac patients, the effectiveness of a CR programme and prognosis of CVD. Treadmill tests are a well-established means of assessing functional capacity in patients with cardiac disorders. The most widely used treadmill test is the Bruce Protocol (American College of Sports Medicine 2001), with a

recent study in America reporting that 82% of treadmill tests used either the typical Bruce test or a modified Bruce test (Myers *et al.,* 2000).

3.1.1.1. The Bruce treadmill test

The Bruce treadmill test was developed specifically for the diagnosis of coronary heart disease (CHD) (Bruce *et al.,* 1963). The Bruce Protocol is an incremental treadmill exercise test where the incline and speed increase every three minutes, while the patient has to work until exhaustion. A modified Bruce treadmill test was developed with a more gradual initial workload, for patients with lower functional capacity (see table 3.2) (Foster *et al.,* 1984).

Table 3.2. The modified Bruce treadmill test protocol (Bruce 1971; Bruce *et al.,* 1973)

Stage	Grade (%)	Speed (mph)	Duration (min)
0	0	1.7	3
0.5	5	1.7	3
1	10	1.7	3
2	12	2.5	3
3	14	3.4	3
4	16	4.2	3
5	18	5.0	3
6	20	5.5	3
7	22	6.0	3

Definition of abbreviations: mph=miles per hour

Unfortunately, such formal tests are not always easy for clinicians to conduct, either because the equipment is not available to them or the tests are too expensive for both patients and clinicians. For these reasons, clinicians sometimes assess the functional capacity of patients using simpler and cheaper equipment, such as functional walking tests.

3.1.1.2. Functional walking tests

There are several walking function tests in cardiorespiratory assessment, which are based on one of the following factors: time, distance or walking speed. The most commonly used time-based walking function tests in cardiorespiratory assessment are of the following durations: 2, 5, 6, 9 and 12 minutes. The distance covered over a given time (2 to 12 minutes) is considered as the score for the time-based tests. The most common distance-based walking function tests are carried out over the following distances: 100 m, half a mile, and 2 km. The time taken to cover a given distance (100 to 2 km) is considered as the score for the distance-based tests (Solway *et al.,* 2001). The most common velocity-based walking function tests in cardiorespiratory assessment are: the self-paced six-minute walking test (6-MWT) and the controlled-paced incremental shuttle walking test (SWT). The distance covered, commonly, constitutes as the score for the velocity-based tests (Solway *et al.,* 2001).

The two most popular and recently developed walking tests for cardiorespiratory assessment are reviewed below: the 6-MWT and the incremental SWT.

3.1.1.2.1. The six-minute walking test

The 6-MWT (Guyatt *et al.* 1985) is a functional capacity test commonly used in both clinical assessment and research settings. It is a simple, safe, reliable, valid and inexpensive measure and is used to evaluate the functional capacity of cardiorespiratory disorders. The 6-MWT is self-paced, allows intermittent rest periods and is usually used to assess patients with severe cardiorespiratory problems. The 6-MWT is described in further detail in Chapter 5 of the present work (see '*Predictors of six-minute walking test performance in heart failure patients*').

3.1.1.2.2. The shuttle walking test

3.1.1.2.2.1. Shuttle walking test: development

More recently, the 12-level SWT was originally developed (Singh *et al.,* 1992) for patients with respiratory diseases. This test has also been used as an assessment tool for patients with CVD, and by creating the modified (15-level) version (MSWT) (Bradley *et al.,* 1999, 2000). This test is used to evaluate the improvement of functional capacity after a CR programme in patients with HF, and for those who have had cardiovascular surgery or pacemaker insertion (Payne and Skehan 1996; Tobin and Thow 1999; Francis 2000; Morales *et al.,* 2000).

The test is easy to perform and inexpensive as it requires only simple equipment, such as an audio player, the test CD, a HR monitor, two cones and a 10 m walkway. The SWT is a safe test, in that it increases incrementally the speed of walking (Jolly *et al.,* 2008), causing less physiological stress for the patient than the 'gold standard' treadmill test (Singh *et al.,* 1994; Zwierska *et al.,* 2004; Fowler *et al.,* 2005). During the SWT, participants have to walk back and forth between two cones, at an incrementally increased speed, which is controlled by an audio signal. The test is stopped when the subject is not able to reach the cone in the required time and/or when the subject wishes to withdraw from the test.

3.1.1.2.2.2. Shuttle walking test: use in prognosis

Morales *et al.* (2000) reported that the SWT, but not the 6-MWT, could be used as a predictor of cardiovascular events within one year of patients with HF. In their study, in which 46 patients with HF, it was found at 17 month average follow-up that 33% of patients had undergone a major cardiac event, such as cardiac death, urgent transplantation, or hospital admission for medical or mechanical support. They showed that those patients who walked <450 m in the test could be categorised as being at high risk of suffering a cardiac event in the short term (one

year). The authors concluded that the SWT can be used as a predictor of cardiovascular events. Lewis *et al.* (2001) compared the SWT with the gold standard measurement (the treadmill test) in a group of patients with severe HF (n=25) and concluded that a distance of >450 m covered during the SWT related to a VO_{2max}>14 $ml \cdot min^{-1} \cdot kg^{-1}$; this indicates that patients with values below this level have a high risk of short-term mortality. This study (Lewis *et al.,* 2001) is described in more detail below.

3.1.1.2.2.3. Shuttle walking test: validity and reliability

Clinical tests should be valid and reliable. Reliability refers to the reproducibility of the measurement and defines the degree to which two or more repeated measurements could provide similar results (de Vet *et al.,* 2006). Validity refers the degree to which a test or test's outcome addresses its intended purpose (Messick 1998). The SWT has been shown, by the following studies, that is a valid measure of cardiorespiratory capacity (compared with the gold standard measurement) and reliable according to its high test–retest reproducibility.

Singh *et al.* (1994) were the first to evaluate the validity of the SWT, by comparing it with the gold standard treadmill test. They found a strong correlation between exercise performance and VO_{2max} in patients with airflow limitations (n=29). In their first experiment, they found a strong relationship between the distance walked in the SWT and the VO_{2max} measured during a treadmill test (r=0.88). They created a predictive equation (with 95% confidence intervals) for VO_{2max} (see equation 3.1).

Equation 3.1. Singh *et al.* (1994)

$VO_{2max} = 4.19 \times (1.12–7.17) + 0.025 \times (0.018–0.031) \times SWD$

where: VO_2max is maximal oxygen uptake ($ml \cdot min^{-1} \cdot kg^{-1}$); SWD is distance walked in shuttle walking test (m)

The high correlation between the exercise performance (distance walked) and VO_{2max} was verified in a second experiment assessing the physiological responses to the SWT (r=0.81). They concluded the SWT showed a high correlation to the conventional measurement of functional capacity, which is the maximal oxygen consumption, while the SWT can be used as a predictor of the VO_{2max}. They concluded the SWT was a valid, simple, incrementally maximal exercise test that can be used safely in the evaluation of cardiorespiratory capacity. Despite producing comparable final walking speeds, maximum HR was higher in the treadmill test than in the SWT. As mentioned in Chapter 2, increased HR is related with an increase in double product, which is an indirect index of myocardial oxygen demand (Williams *et al.*, 2007). This might suggest the treadmill test provokes greater physiological stress on the cardiovascular system than the walking test. Regarding that these tests applied in patients with established CVD and cardiovascular events tend to occur when oxygen demand exceeds supply, SWT appears to be safer than treadmill test for CVD patients.

Lewis *et al.* (2001) combined the SWT and the treadmill exercise test for patients (n=25) being assessed for cardiac transplantation. The results of patients undergoing three SWTs and two treadmill tests, during which VO_{2max} was recorded, showed that the distance walked during the SWT was highly correlated with the VO_{2max} reached during the test. These authors also developed a predictive equation for estimating VO_{2max} (equation 3.2).

Equation 3.3. Lewis *et al.* (2001)

$VO_2max = 6.4 + (0.022 \times SWD)$

where: VO_2max is maximal oxygen uptake ($ml \cdot min^{-1} \cdot kg^{-1}$); SWD is distance walked in the shuttle walling test (m).

The authors (Lewis *et al.,* 2001) concluded that the SWT is a reliable tool, which can be used to evaluate the functional capacity of patients with severe HF and also to predict VO_{2max} in this group. Unfortunately, according to the authors, only a few of the patients reached the anaerobic

threshold (blood lactate concentration) during the treadmill test, while some terminated the test because of angina symptoms. As normal anaerobic threshold usually occurs at more than 40% of the predicted VO_{2max} (Pepera *et al.*, 2008; Chin *et al.,* 2010), the VO_{2max} and peak VO_2 measurements were not the same in each patient of the Lewis *et al.* (2001) study. Most of the patients did not reach maximal parameters (VO_{2max}) during the treadmill test. Thus, the peak VO_2 achieved did not reflect the true maximal functional capacity during the treadmill test.

Fowler *et al.* (2005) investigated the validity and reliability of the incremental SWT patients (n=39) six to eight weeks after coronary artery bypass graft (CABG) surgery. Patients completed three SWTs and a treadmill test one week later. Eleven of the patients were assessed once more, using the SWT after attending a six-week hospital-based CR programme. There were strong correlations and no significant differences between the distances recorded in the three SWTs. The treadmill test, however, produced higher maximum HRs and breathlessness scores than the SWT. This again suggests the treadmill test causes greater physiological stress than the SWT. The SWT was able, also, to detect changes in cardiorespiratory capacity after the CR programme. The authors concluded that the SWT is a valid, reliable and sensitive tool for investigating changes in exercise tolerance for patients who have had a CABG surgery. They also found a learning effect between the first and second SWT (mean difference 40 m), but not between the second and third. As a result, they noticed that a pre-practice of the test was not necessary but that it would be useful for clinical reasons in order for the results to be established on a stable baseline. These results were taken over a short period (1 week). Given that MSWT is used to assess changes in functional capacity during a six to twelve-week CR programme, a follow-up study using results taken over a longer period would be more clinically useful.

In addition to comparing walking tests with treadmill protocols, it is also of interest to compare different types of walking tests. Zwierska *et al.* (2004) compared two different SWTs – an

incremental SWT and a constant-pace SWT (walking speed 4 $km \cdot h^{-1}$) – with a constant workload treadmill test (walking speed 3.2 $km \cdot h^{-1}$ at 12% gradient) for evaluating the functional capacity of patients with intermittent claudication (n=55). They found that the claudication distance (where the pain was first determined) and the maximum walking distance (the distance patients covered until they could no longer tolerate claudication pain) achieved during the two SWTs were similar. These distances were almost twice those achieved during the treadmill test. Test–retest reliability for maximal walking distance was better than that for claudication distance in each of the three tests. Test–retest reliability was higher for all measures during the incremental SWT than in the constant-pace SWT or treadmill test. Higher maximum HR and blood pressure were observed during the treadmill test in comparison to the shuttle walking tests. This might be explained by the fact that most patients said they preferred the incremental SWT to the treadmill test, for instance, because they were frightened of falling on the treadmill, or because they found the treadmill more difficult and too fast. The constant-pace SWT also failed to detect the real maximum walking distance in patients with mild claudication symptoms (because some of the patients were walking for more than 10 minutes without any claudication pain). The incremental shuttle walking test was shown to be a good tool for assessing the effects of lower to high severity peripheral arterial diseases. The authors concluded that the SWT has the same reliability as the treadmill test but that the former has the advantage of being easier, cheaper and less stressful for the patients.

Jolly *et al.* (2008) found a significant increase in the distance walked between the practice test and the second SWT in a group of 353 cardiac patients. There were no significant differences for maximum HR and rating of perceived exertion score (RPE) between the two trials. The authors concluded that the increase in distance covered during the second trial might be due to familiarisation. These results were shown across quite a large sample of patients, but,

unfortunately, no third test was conducted to test the hypothesis that a learning effect was present.

There is evidence to suggest that the SWT is a reliable, valid and sensitive tool for measuring cardiorespiratory capacity. In the UK, the SWT is currently the recommended protocol (Scottish Intercollegiate Guidelines Network [SIGN] 2002; BACR 2006) to assess functional capacity in patients with HF, post-MI patients and patients who have undergone cardiovascular surgery or pacemaker insertion (Payne and Skehan 1996; Tobin and Thow 1999; Francis 2000; Lewis *et al.,* 2001; Woolf-May and Ferrett 2008). The results of the test can be also used for prescribing exercises in CR programmes.

3.1.1.2.2.3.1. Shuttle walking test and duration of reliability

Only the short-term test–retest reliability of the SWT has been reported (Fowler *et al.,* 2005; Campo *et al.,* 2006). This has a potential impact upon relevant outcome measures, such as distance walked. A short-term test–retest may have an impact on the performance outcome. A shorter interval between tests would mean the pacing and protocol would be more prominent in the subject's memory, allowing them to have a possible advantage over a subject who has had a longer interval between tests.

There are questions to be raised about the potential learning effect due to the tests being so close together, alongside whether a sufficient rest period was provided. Often in clinical studies, repeated exercise tests are carried out on the same day or within a few days of each other. Short time periods between tests are common in all SWT studies, assessing the repeatability of outcome measures from repeated exercise tests.

There are no available data regarding the long-term reliability of SWT. Reasons for this are unclear. It may be that in an attempt to control external influencing factors, such as an increase in functional capacity, repeated tests are carried out in close succession to ensure that the repeatability of outcome measures is being recorded and not an increase in functional capacity or the effect of an intervention. The difficulty of protocols assessing SWTs via short-term retest periods is that it is not representative of pre- and post-rehabilitation assessment. In normal care, an exercise stress test would occur to evaluate patients' functional capacity, in order to enable effective exercise prescription. The patient would then enter an eight to ten week CR programme; on successful completion of the programme, the patient would be re-assessed with the same exercise test for improvements in functional capacity as an indication of the effectiveness of the programme and an increase in the patient's functional capacity.

It would clearly be useful to investigate the SWT's reliability over longer periods in clinically stable cardiac patients, in order to judge whether potential learning effects could be minimised. According to Fowler *et al.* (2005), due to the learning effect over short-term test–retest durations, the benefits of CR intervention may not be recognised. On the other hand, it seems less likely that the participants will remember their performance measures over a long time. It seems likely that this learning effect would be removed if tests were conducted with a longer interval (before the retest), so that participants would be unable to recall the exact protocol and pacing of the test. The need for a practice test may thus be shown to be unnecessary. To achieve this goal, longer periods of time would need to be left between tests in studies undertaken to gain greater insight into the repeatability of SWTs in a situation that is replicable in normal CR care.

3.1.2. Methods to assess reliability

The most common and frequently referenced methods in the literature for assessing the reliability of equipment or measurements are reliability and agreement parameters (Bland and Altman 1986, 1990; de Vet *et al.,* 2006).

3.1.2.1. Reliability parameters

The reliability of a measurement is an important process, in order that primary outcome measures can be used for clinical reasons (Lachin 2004). It reflects the ability of instruments to discriminate among subjects in a sample population, despite measurement errors (de Vet *et al.,* 2006). The intraclass correlation coefficient (ICC) is commonly used as metric of reliability. The ICC gives a direct coefficient of the agreement between repeated measurements and it ranges between 0 (representing an unreliable measurement) and 1 (indicating perfect reliability). Various forms of ICCs exist (Shrout and Fleiss 1979). Some studies support their use (Lee *et al.,* 1989, 1992), while others (Bland and Altman 1986, 1990) have found this technique inappropriate for assessing the reliability of a measurement.

3.1.2.2. Agreement parameters

Bland and Altman (1986, 1990) recommended the use of agreement parameters, which are based on graphical techniques and calculations (the mean and standard deviation of differences between measurements). Agreement parameters estimate the measurement error in repeated measurements and assess how close the results of test-retest measurements are (Bland and Altman 1986, 1990; de Vet *et al.,* 2006). It was also found that the agreement measurements relate to the measurement error, in contrast with reliability (ICC), which is based more on the heterogeneity of the study sample (Bland and Altman 1986, 1990; de Vet *et al.,* 2006). The parameter used depends on the aim of the study. If it focuses on the measurement of changes in

health status, agreement parameters are preferred (de Vet *et al.,* 2006). It has been suggested that both reliability and agreement parameters are important when assessing the reproducibility of a measurement, because neither test alone can provide sufficient information (Rankin and Stokes 1998; Weir 2005).

3.1.3. Aim and hypothesis

There is a lack of reliability studies in relation to specific cardiac patient groups, as well as an obvious gap in research concerning long-term retest periods. The present study will focus on the long-term retest reliability of the MSWT in clinically stable cardiac patients.

The hypothesis of this study was that the MSWT is a reliable tool for use in the long-term assessment of cardiovascular function in clinically stable CVD patients.

3.2. Methods

3.2.1. Study Population

Thirty CVD patients (15 males and 15 females; age range: 55-80 years) volunteered to participate in this study. All patients were defined as clinically stable according to the BACR (2006) criteria. The majority of these patients had undergone a heart operation, CABG or percutaneous coronary intervention (PCI). There were also patients with stable angina, patients who had affected by an MI or patients who had undergone both an MI and a surgical procedure on the heart. Other diseases (which were the reason the patients joined the CR programme) included HF, arrhythmias, hypertension and chronic obstructive pulmonary disease (asthma, chronic bronchitis). There were also a low proportion of patients with diabetes, while the half of the group had a history of high cholesterol, and attempted to control it with medical support (statins). There were low rates of other risk factors, such as alcohol and smoking, and 70% of

patients had someone in their family with cardiac diseases or disorders; 33% had a family member (parent, sister or brother) who had died from a heart attack event. Also, according to the pharmacological history, 53% of patients were using β-blockers but none changed their medication from test to retest. Table 3.3 represents the descriptive characteristics and baseline measurements of the patients. The means of body mass index (BMI) were similar to both of the two sexes.

All patients were attending a community-based phase IV CR programme at the University of Essex. They were mainly cardiac patients, who had finished phase III CR at the local General Hospital, or who had been referred to phase IV CR by their general practitioner. This phase IV CR programme offers the opportunity of life-long supervised exercise. The programme comprises a twice-weekly, 60 minute, circuit-based exercise session, in accordance with the BACR guidelines (Bell *et al.,* 1995; BACR 2006); it is designed to maintain the functional capacity gains achieved in phase III CR. All patients had been enrolled on the programme for a minimum of ten weeks. All patients met the inclusion criteria for the community-based phase IV CR programme, which excluded patients with severe locomotor limitations. During the study, the patients continued taking their normal prescribed medications.

Patients were verbally recruited by instructors prior to two consecutive exercise classes. Each volunteer gave written informed consent, after receiving an information sheet outlining an explanation of the procedure. The study took place between January 2008 and March 2009. All procedures were approved by The University Ethics Committee and conformed to the declaration of Helsinki (World Medical Association Inc 2009) guidelines for research with human participants.

Table 3.3. Descriptive characteristics and baseline measurements of cardiac rehabilitation patients

Clinical characteristics and baseline measurements	**Values**
Number of patients	30
Age (years) (mean ± SD)	67.1 ± 8.1
Sex	
Males	15 (50%)
Females	15 (50%)
Body mass index ($kg \cdot m^{-2}$) (mean ± SD)	*Trial 1:* 27.4 ± 3.7 *Trial 2:* 27.4 ± 3.8
Waist Circumference (cm) (mean ± SD)	*Trial 1:* 96.2 ± 11.6 *Trial 2:* 95.4 ± 11.3
Medical History/Reason for joining CR	
MI	n=5 (17%)
Stable Angina	n=9 (30%)
Surgical procedure (CABG, PCI)	n=18 (60%)
MI and surgical procedure	n=3 (10%)
MI and non-surgical procedure	n=2 (7%)
Heart Failure	n=3 (10%)
Hypertension	n=5 (17%)
Arrhythmias	n=2 (7%)
Other	n=2 (7%)
Diabetic (diabetes mellitus)	n=2 (7%)
High Cholesterol	n=14 (47%)
Excess Alcohol	n=8 (27%)
Current smokers	n=2 (7%)
Family History	
Heart attack death	n=10 (33%)
Heart Failure	n=5 (17%)
CABG	n=2 (7%)
Angina	n=4 (13%)
No Family History	n=10 (30%)
Medication	
β-blockers	n=16 (53%)
Statin	n=14 (47%)
Aspirin	n=13 (43%)
Nitrates	n=6 (20%)
Other	n=10 (33%)

*Definition of abbreviations: MI=myocardial infarction; CABG=coronary artery bypass graft; PCI=*percutaneous *coronary intervention*

3.2.2. Study design

To determine the long-term reliability of the MSWT, patients were assessed twice, with a minimum of eight weeks between assessments. During this period, patients continued to attend phase IV CR programmes.

Before the initial MSWT, each participant had a primary health assessment (pre-exercise health questionnaire) and interview (medical, pharmacological and family history). During this time, anthropometric measurements such as stature, mass and waist circumference were recorded (see table 3.3). Stature was recorded using a stadiometer (Seca 240 stature measuring rod, Germany) and body mass was recorded with a weight scale (Seca 888 Class III Floor Scale, Germany) without shoes. From these measurements, BMI was calculated as follows: body mass (kg)/stature^2 (m^2). Additionally, waist circumference was measured with a tape at the level of the natural waist, at the narrowest point between the ribs and the iliac crest (Lohman *et al.*, 1988). The health assessment and anthropometric measurements were replicated prior to the second MSWT.

Patients were fitted with a HR monitor (Polar Electro Sports Tester S810I, Heart Rate Monitor, Kempele, Finland) and instructed to lie supine on a bed with their head supported by a pillow. They lay still for 10 minutes without talking or moving. After this period of relaxation, the patients were asked to stand up, and then to sit on the edge, where the HR, according to Polar instructions, was recorded. Blood pressure was also measured at this time, using an automated arm blood pressure machine (Omron Digital Automatic Blood Pressure Monitor MX3 Plus, Omron Health Care Co., Ltd, Kyoto, Japan). Next, patients were advised to sit up slowly and they received oral instructions for completing the MSWT.

3.2.3. Modified shuttle walking test procedure

The modified 15-level SWT was used for this experiment. This test is analogous to the original incremental test (Singh *et al.,* 1992) but has 15 levels instead of 12. The modified version is useful for monitoring patient groups who may be able to complete the original 12-level protocol. Patients were required to walk on a gymnasium floor, which was marked by two cones, set 0.5 m from either end of a 10 m course (see figure 3.1). Throughout the first level, the operator was walking alongside the participant to maintain the correct pace.

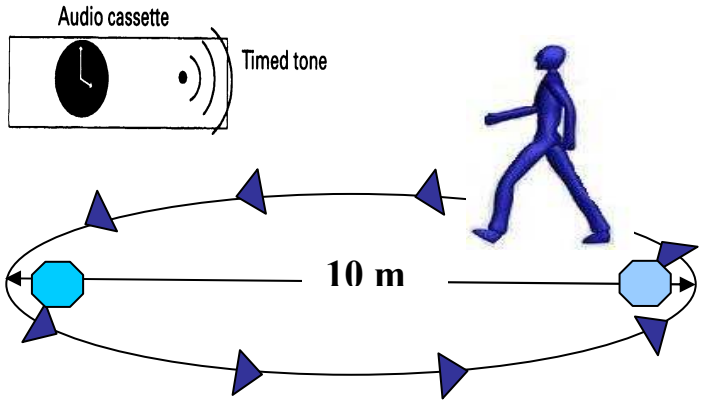

Figure 3.1. The shuttle walking test diagram

The speed at which the patient was required to walk was indicated by an audio signal from a CD player. The start of the test was indicated by a triple bleep, while a single bleep indicated that the subject had to be next to the cone, rounding the cone, change direction and continue back to reach the second cone. The test started with a speed of 0.5 $m \cdot s^{-1}$, and the subject had to complete three shuttles per minute. At the end of each level one more shuttle was added, and the walking speed was increased by 0.13 $m \cdot s^{-1} \cdot min^{-1}$. A change in speed was indicted by a second audible signal. Instructors also reminded patients to walk faster after each minute. Patients were allowed to run at any time during the test. The MSWT has 15 levels; the number of shuttles, the walking speed and the distance covered in each level are presented in table 3.4.

Table 3.4. The modified shuttle walking test protocol

Levels	**Speed ($m \cdot sec^{-1}$)**	**Speed ($km \cdot h^{-1}$)**	**Speed ($miles \cdot h^{-1}$)**	**No of shuttles**	**Distance covered (m)**	**METs** (ACSM 2005, Woolf-May & Ferrett 2008)
1	0.50	1.80	1.12	3	30	3.2
2	0.67	2.41	1.50	4	70	3.4
3	0.84	3.03	1.88	5	120	3.6
4	1.00	3.63	2.26	6	180	3.9
5	1.18	4.25	2.64	7	250	4.2
6	1.35	4.86	3.02	8	330	4.6
7	1.52	5.47	3.40	9	420	5.0
8	1.69	6.08	3.78	10	520	5.5
9	1.86	6.69	4.16	11	630	6.0
10	2.03	7.31	4.54	12	750	6.6
11	2.20	7.92	4.92	13	880	7.1
12	2.37	8.53	5.30	14	1020	7.7
13	2.54	9.14	5.68	15	1170	8.4
14	2.71	9.75	6.06	16	1330	9.1
15	2.88	10.36	6.44	17	1500	9.9

Test termination criteria were as follows: (a) by the participant, when s/he was unable to continue the test because of breathlessness, other symptoms or because they were unwilling to continue (voluntary withdrawal), (b) by the operator, when the participant failed to reach the marker (by 0.5 m) on time, (c) the achievement of 85% of the predicted maximum HR: 210-(0.65×age), or a RPE ≥ 15 (Borg 1998) and (d) completion of all levels.

Heart rate was monitored during the test and was recorded at the end of each level, using short-range telemetry (Polar Electro Sports Tester S810 I), while the RPE scale (6-20) was used to determine the perceived exercise intensity at the end of each level (see table 3.5) (Borg 1982). During the procedure, a lap marker was indicated in the monitor HR watch by pressing the button of the Polar at the end of its level until the end of the test.

Table 3.5. The Borg scale for Rating Perceived Exertion (RPE) (Borg 1982)

20-Grade Scale	
6	No exertion at all
7 8	Very, very light
9 10	Very light
11 12	Fairly light
13 14	Somewhat hard
15 16	Hard
17 18	Very hard
19 20	Very, very hard

At the end of the test, the maximum HR was recorded, and the patient was asked to sit on a chair for this. Blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) was measured as soon as possible after test termination while the participant remained seated. The patient was advised to relax and breathe in a normal way. After one minute of resting, HR and blood pressure were measured again. Patients remained in the sitting position until their HR was within ± 10 bpm of the pre-exercise HR. The time to this point from the end of the test was also recorded.

3.2.3.1. Heart rate measurements

Heart rate was recorded at the beginning of the test (resting HR), at the end of each level of the test, at the end of the test, and 1 minute after the end of the test. The HR recovery was calculated

from the difference between the maximum exercise HR and the one that was recorded one minute after the end of the test. Total HR recovery time was also recorded as time to resting HR ± 10 bpm (Cole *et al.,* 1999; Jouven *et al.,* 2005).

3.2.3.2. Heart rate data transfer

Heart rate data from the Polar monitor were transferred and filtered using a desktop computer and the Polar Precision Performance 3.0 training software, version 3.01.005.

All measurements were repeated eight weeks after the first assessment.

3.2.4. Statistical analysis

Statistical analysis was carried out using SPSS version 16.0 (SPSS inc., Chicago, IL, US), whereas calculations were performed in Microsoft Office Excel 2003 (Microsoft Corporation**,** Washington, US). Data were presented as mean and standard deviation, unless otherwise stated. The variables that were used in this protocol were: modified shuttle walking distance (MSWD) (m), maximum HR, RPE, HR recovery in 1 minute, and total HR recovery time.

3.2.4.1. Reliability analysis

Different statistical measurements were used to evaluate the reliability and agreement of the two assessments. First, the change in mean scores between the test and retest was calculated for all the above variables. Differences between the two MSWTs were evaluated by using the paired-samples t-test for waist circumference, BMI, SBP and HR recovery, with the significance level set at $p<0.05$. Relationships for each of the variables between the two trials were tested using Pearson's product moment coefficient and regression linear plots (Singh *et al.,* 1994).

Intraclass correlation coefficient (ICC) Level 3.1 (Atkinson and Nevill 1998) and the limits of agreement (LoA) test (Bland and Altman 1986) were used to assess the test–retest reliability of total walking distance and maximum walking speed. ICC values greater than 0.7 were taken to indicate good reliability (Pallant 2007).

Agreement between the two assessments was estimated by using the repeatability coefficient (twice the standard deviation of the differences) (Bland and Altman 1986). The measure of agreement was evaluated using a graphical method, in line with Bland and Altman's (1986) recommendations. Specifically, the difference in MSWD between the first and the second assessment was plotted against the mean of the sum MSWD for each subject. Next, the mean and standard deviation of the differences in MSWD were calculated. The standard deviation of this difference was multiplied by 2 and added to the mean difference to create the 95% limits of agreement (LoA), which were drawn as lines on the graphs. The 95% confidence interval of the difference in MSWD was estimated by using the one sample t-test.

3.3. Results

3.3.1. Changes in physiological measurements due to phase IV cardiac rehabilitation

Table 3.6 provides values for the physiological measurements taken eight weeks apart during phase IV CR using the MSWT as an assessment tool. None of the patients completed the 15-level protocol MSWT (1500 m). MSWD ranged from the minimum 120 m to the maximum 880 m. A paired-samples t-test was conducted to evaluate the changes in the physiological variables between the two MSWTs. There was a statistically significant difference ($p<0.05$) in recovery times, the SBP measurements (both pre-exercise and post-exercise) and waist circumference measurements, but not in any other physiological variables (MSWD, maximum HR, RPE score, HR recovery, DBP). Of particular note is the fact that there was a significant reduction in

recovery time from trial 1 (6.12±4.17 min) to trial 2 (4.88±4.31 min): t=1.71, $p<0.05$ (two-tailed). The mean decrease in recovery time was 1.24 min, whereas the magnitude of the differences in the means was small: d=0.29 (Cohen 1988). A non-significant small increase between the two assessments was found for MSWD (difference 7m) and maximal walking speed (difference 0.05 $m \cdot sec^{-1}$). Small non-significant decreases were also noticed, across the two MSWTs, in the RPE score (difference 0.6), maximum HR (difference 1 bpm) and HR recovery (difference 2 bpm). Moreover, the resting HR remained unchanged.

Other physiological variables, such as blood pressure (SBP, DBP), which were measured pre- and post-exercise, showed a marked decrease between the two trials. The SBP showed a statistically significant decrease of 7 mmHg in the pre-exercise measurements and 11 mmHg in the post-exercise measurements between the two trials, while the DBP mean decreased by 1 mmHg between the two trials in both pre-exercise and post-exercise measurements. The body mass remained almost unchanged between the two MSWT assessments, whereas the mean waist circumference for trials 1 and 2 decreased by 0.77 cm.

Table 3.6. Physiological responses and physical characteristics at the two assessments (trial 1 and trial 2) (n=30)

Variable	Trial 1		Trial 2		Mean Difference (95%CI)	t-test	Sig.(2-tailed) *P* value
	Mean	(SD)	Mean	(SD)			
MSWD (m)	502	(161)	509	(146)	-7 (-44 *to* 29)	-0.41	0.685
Maximal walking speed ($m \cdot sec^{-1}$)	1.65	(0.29)	1.70	(0.25)	-0.05 (-0.12 *to* 0.03)	-1.31	0.199
METs achieved	5.45	(0.77)	5.57	(0.73)	-0.12 (-0.33 *to* 0.09)	-1.19	0.245
RPE score	14.5	(1.4)	13.9	(1.5)	0.6 (-0.12 *to* 1.18)	1.69	0.103
Maximum HR (bpm)	128	(18)	127	(18)	1 (-3.99 *to* 5.64)	0.35	0.727
Resting HR (bpm)	68	(11)	68	(17)	0 (-5.87 *to* 5.25)	-0.11	0.910
HR recovery (bpm)	36	(17)	34	(17)	2 (-5.08 *to* 9.43)	0.61	0.544
Time to recovery (min)	6.12	(4.17)	4.88	(4.31)	1.24 (0.36 *to* 2.12)	2.88	0.007
Pre-exercise SBP (mmHg)	143	(19)	136	(22)	7 (0.92 *to* 12.25)	2.38	0.024
Pre-exercise DBP (mmHg)	79	(8)	78	(10)	1 (-2.26 *to* 4.13)	0.60	0.555
Post-exercise SBP (mmHg)	180	(30)	169	(29)	11 (4.51 *to* 16.66)	3.57	0.001
Post-exercise DBP (mmHg)	83	(14)	81	(13)	1 (-2.12 *to* 4.32)	0.70	0.488
Body mass (kg)	77.8	(12.7)	77.5	(12.6)	0.25 (-0.86 *to* 0.67)	0.78	0.442
Waist Circumference (cm)	96.1	(11.6)	95.4	(11.2)	0.77 (-3.67 *to* -0.20)	2.37	0.025

Definition of abbreviations: *MSWD=modified shuttle walk distance; bpm=beats per minute; METs=metabolic equivalents; RPE=Borg rating of perceived exertion; HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure.*

3.3.2. Test–retest reliability

3.3.2.1. Correlations

Correlation alone is not a good measure of reliability, as it cannot measure variance (how much variability there is) among patients (Bartko *et al.,* 1991). It has, however, been used in previous studies and so is included here for reasons of comparability (Bradley *et al.,* 2000; Fowler *et al.,* 2005).

Table 3.7 presents the correlations for each of the physiological variables between the two incremental assessment tests. There were significant and strong correlations between trials for MSWD (Pearson's r=0.80; $p<0.001$), maximal walking speed (Pearson's r=0.76; $p<0.001$), maximum HR (Pearson's r=0.76; $p<0.001$) and time to recovery (Pearson's r=0.85; $p<0.001$); while a moderate non-significant relationship was recorded for HR recovery (Pearson's r=0.35, $p=0.06$). There was no significant correlation between the two MSWTs for the RPE score. These relationships are represented by the plots shown in figure 3.2.

Table 3.7. Correlation between the 2 trials (trial 1 vs. trial 2) (n=30)

Variables	**Pearson r**	***P* value**
MSWD (m)	0.80	<0.001
Maximal walking speed ($m \cdot sec^{-1}$)	0.76	<0.001
RPE score	0.28	0.135
Maximum HR (bpm)	0.76	<0.001
HR recovery (bpm)	0.35	0.06
Time to recovery (min)	0.85	<0.001

Definition of abbreviations: MSWD=modified shuttle walking distance; RPE=Borg rating of perceived exertion; HR=heart rate; bpm=beats per minute

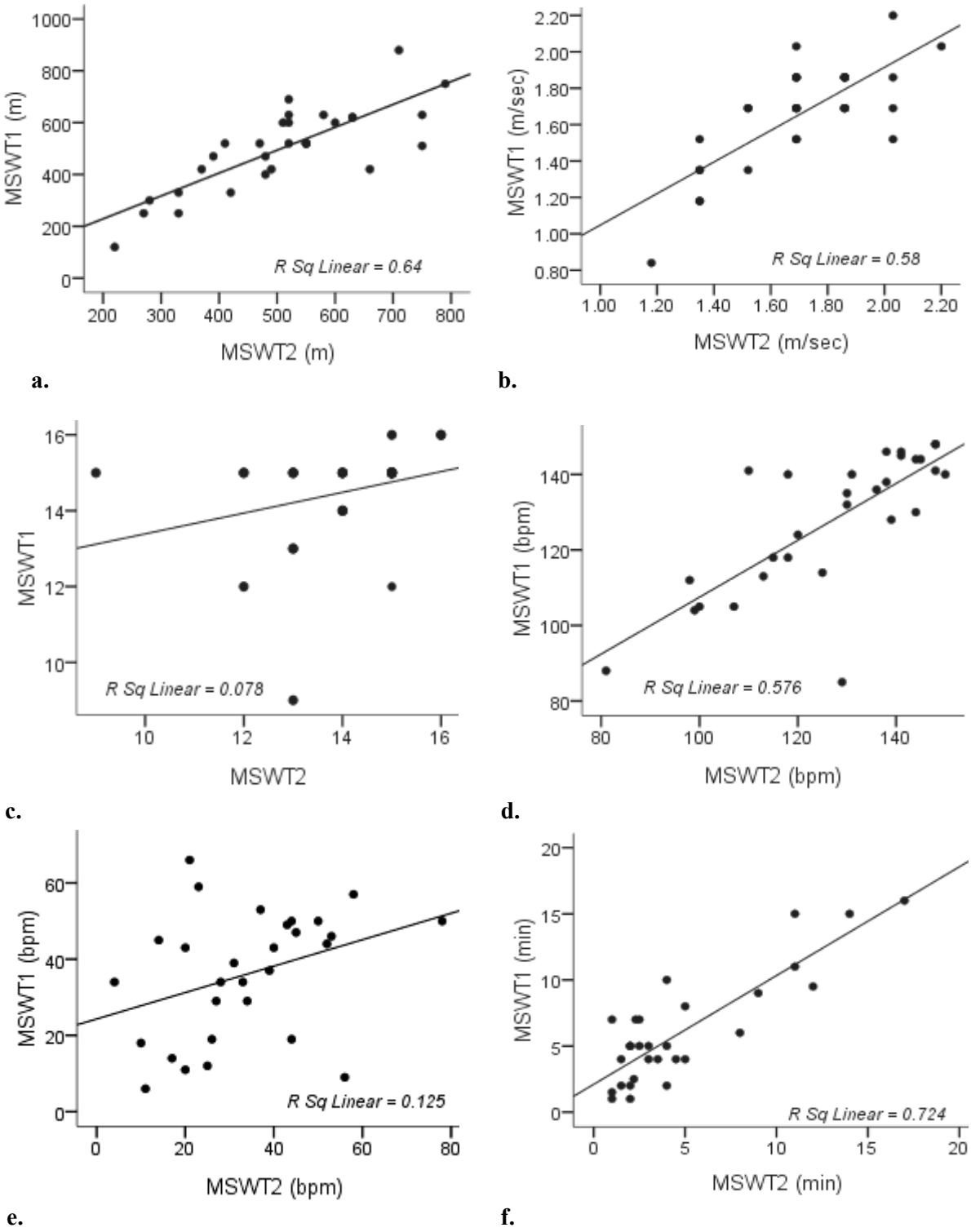

Figure 3.2. (a, b, c, d, e). Regression line for the relationship of each variable in the two modified shuttle walk tests.
a. total distance, **b.** maximal walking speed, **c.** peak Borg rating of perceived exertion (RPE scale), **d.** maximal heart rate, **e.** heart rate recovery and **f.** time to recovery.

MSWT= modified shuttle walk test 1;bpm=beats per minute.

3.3.2.2. Test–retest reliability and agreement

There were no statistically significant differences in the MSWD between the first and second assessment (see table 3.6). Table 3.8 shows test–retest reliability in terms of the ICC with 95% confidence intervals for each variable (MSWD, maximum HR, RPE, HR recovery in 1 minute, and total HR recovery time). The ICC was high for MSWD (0.80), maximal walking speed (0.76), maximum HR (0.77) and time to recovery (0.85); while it was low for maximum RPE value (0.28) and HR recovery (0.35) (see table 3.8).

Table 3.8. Reliability statistics: Test–retest reliability of the modified shuttle walking test (n=30)

Variables	**ICC**	**95% confidence intervals (CI)**		***P* value**
		Lower Bound	**Upper Bound**	
MSWD (m)	0.80	0.62	0.90	<0.001
Maximum walking speed ($m \cdot sec^{-1}$)	0.76	0.55	0.88	<0.001
RPE score	0.28	-0.08	0.58	0.064
Maximum HR (bpm)	0.77	0.55	0.88	<0.001
HR recovery (bpm)	0.35	-0.01	0.63	0.028
Time to recovery (min)	0.85	0.71	0.93	<0.001

Definition of abbreviations: MSWT=modified shuttle walking test; RPE=Borg rating of perceived exertion; m=metres; bpm=beats per minute

The within-subject standard deviation, the repeatability coefficients and the limits of agreement plots (for MSWD) are shown in table 3.9 and figure 3.3, respectively. The coefficients of repeatability for the repeated MSWT were 196 m for MSWD, 0.38 $m \cdot sec^{-1}$ for maximal walking speed, 3.4 units for RPE score, 24 bpm for maximum HR and 38 bpm for HR recovery. A repeatability coefficient of 196 m for MSWD between trials indicates that the difference in a

patient's performance between the two assessments could be expected to be within -44 m and 29 m.

The test (see figure 3.3) showed a mean test–retest bias of -7 m with LoA from -203 m to 189 m, for MSWD; and a mean test–retest bias of -0.05 m·sec^{-1} with LoA from -0.43 m·sec^{-1} to 0.33 m·sec^{-1}, for maximal walking speed. This indicates that, in a retest situation, 95% of patients exposed to this protocol would be expected to walk distances ranging from 203 m less to 189 m more than a baseline score.

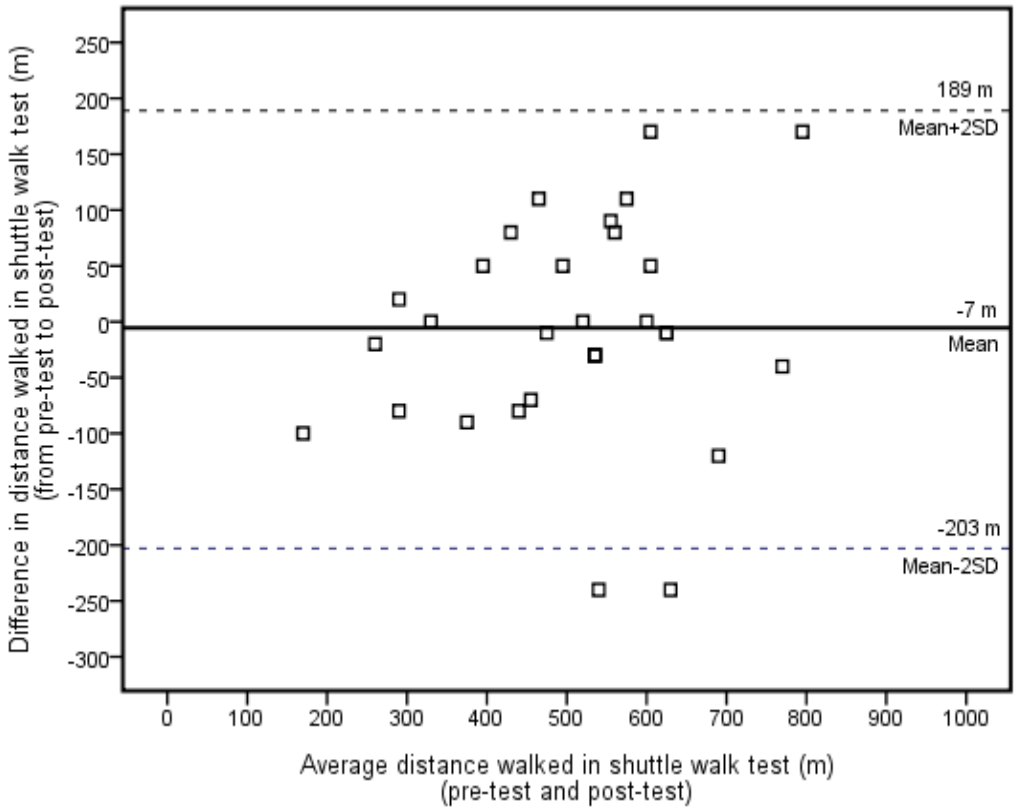

Figure 3.3. Limits of agreement plot (Bland and Altman plot). Intraindividual differences between performances on two incremental shuttle walking tests (test MSWT vs retest MSWT) plotted against the mean of the sum scores, in phase IV cardiac rehabilitation. The central line represents the mean of the intraindividual differences and the flanking lines represent the 95% limits of agreement.

Table 3.9. Agreement statistics: Mean difference (95% confidence intervals) and repeatability coefficient for trial 1 vs. trial 2

	Mean (SD) difference	95% confidence interval	Repeatability coefficient (RC)	Limits of agreement (mean±RC)
MSWD (m)	-7 (98.2)	-44 to 29	196	-203 to 189
Maximal walking speed ($m \cdot sec^{-1}$)	-0.05 (0.19)	-0.12 to 0.03	0.38	-0.43 to 0.33
RPE score	0.5 (1.7)	-0.1 to 1.1	3.4	-2.9 to 3.9
Maximum HR (bpm)	1 (12)	-1 to 1	24	-23 to 25
HR recovery (bpm)	2 (19)	0 to 1	38	-36 to 40
Time to recovery (min)	1.2 (2.3)	0.4 to 2.1	4.6	-3.4 to 5.8

Definition of abbreviations: MSWD=modified shuttle walking distance; RPE=Borg rating of perceived exertion; HR=heart rate; bpm=beats per minute

3.4. Discussion

Measurements of exercise performance are essential in order to assess the functional capacity of CR patients and to evaluate the intervention or changes brought about by CR programmes. Conventional clinical or laboratory-based measurements are the gold standard for measuring VO_{2max} but tend to be complicated, expensive and time consuming. Many alternative exercise tests have been developed in order to make cardiorespiratory assessment simpler. The SWT is an affordable alternative to treadmill testing, but its reliability has only been tested over short test–retest durations (Singh *et al.,* 1992; Bell *et al.,* 1995; Jolly *et al.,* 2008).

All participants were patients with cardiovascular disorders, including MI survivors, angina, post-revascularisation interventions (CABG, PCI), HF, arrhythmias, hypertension; only 7% were chronic obstructive pulmonary disease patients. All were attending phase IV CR, and all had at least one cardiac risk factor and were clinically stable. Some attended the phase IV CR programme more regularly than others. Some had joined more than two years previously with others had attended for just ten weeks. These differences may not have affected the final experimental results since phase IV is a follow-up CR programme for maintaining exercise performance, which was expected to have been built up during phase III CR. Physical activity patterns are usually established by the end of phase III CR, and remain stable during phase IV (Woolf-May and Ferrett 2008). Thus, the long-term reliability of the MSWT can be assessed in phase IV CR, as this is a maintenance phase in which no significant improvements in functional capacity are expected (Woolf-May and Ferrett 2008). Due to the nature of the programme, it is unlikely that significant, systematic gains in functional capacity will occur in groups of patients. The functional capacity of individual patients is, however, likely to vary due to many factors, including comorbidities, motivation and changes in other exercise training they may undertake.

3.4.1. Total distance versus maximal walking velocity: which is the most valid outcome measure for the modified shuttle walking test performance?

Total distance covered and/or maximal walking speed constitutes the test's score (Singh *et al.,* 1992). In daily life, routine walking distance is an important factor. Walking speed also plays an important role in performing everyday activities, and both elements have proven to be significant factors in estimating clinical status and mobility (Van Herk *et al.,* 1998).

In contrast with the 6-MWT, equal distances in the MSWT do not necessarily represent equal levels of exertion. For instance, it is harder to 'cross' a stage than to complete an additional shuttle within a stage. For instance, going from shuttle 40 (7^{th} shuttle in level 7) to shuttle 42 (last shuttle of level 7) requires no change in speed. It is, therefore 'easier' to do this than to go from shuttle 42 to shuttle 43 (1^{st} shuttle of level 8) (see table 3.4). The latter change requires the participant to be able to walk at a greater speed (with a greater physiological demand) but would provide only 30 m extra to the score, as opposed to the 60 m gain seen in the first example, which requires no change of speed. Distance, in this case, when it is measured over an incremental course, should not be considered as interval scale data but ordinal.

Walking speed seems the obvious measure by which to evaluate functional capacity and has been used to describe MSWT performance. However, as previous MSWT reliability studies report only on distance walked (MSWD in metres) (Fowler *et al.,* 2005; Campo *et al.,* 2006; Jolly *et al.,* 2008), this metric will be used here to discuss the results of this study for purposes of comparability.

3.4.2. Comparison of results with previous data

The distance covered and the maximal walking speed achieved at the end of the test was used to prescript the MSWT score. In this study, the mean MSWD was 502 (±161) m in the trial 1 and

509 (±146) m in the trial 2. In other studies, undertaken using patients with pulmonary disorders (chronic obstructive pulmonary disease, chronic airflow limitation) as the sample, lower scores for MSWD were found, with mean values of 378 m (Singh *et al.,* 1992), 375 (±137) m (Singh *et al.*, 1994), and 307 (±89.3) m (Rosa *et al.,* 2006). Studies with cardiac patients as a sample recorded higher values in total distance, in contrast with pulmonary studies; however, the rates were still lower than the present results.

Lewis *et al*. (2001) studied a sample of patients following heart transplantation achieved a maximum mean MSWD of 401.3 (±129) m in the third assessment. Fowler *et al.*'s (2005) sample of patients who had undergone CABG surgery recorded a highest mean distance of 487 (±147.6) m after three assessments made using the SWT. Arnold *et al.* (2007) used the SWT to investigate the effects of once- versus twice-weekly CR and found that the post-rehabilitation (twice weekly intervention) mean distance was 557 (±171) m. Sandercock *et al.* (2007) found a mean total distance of 597 (±235) m in the second SWT assessment, in a CR population. Woolf-May and Ferrett's (2008) sample, of post-MI patients who attended phase IV CR programmes, measured a mean total distance of 430 (±109) m in the first assessment. Jolly *et al.* (2008) recorded the highest mean distance of 414.8 (±157.5) m in a cardiac population in the second assessment using the SWT.

The mean MSWD of 505 m seen here is comparable with other studies of cardiac patients (Fowler *et al.,* 2005; Arnold *et al.,* 2007; Sandercock *et al.,* 2007; Woolf-May and Ferrett 2008). The present study, however, is the first to assess long-term (>10 week) attendees of phase IV CR. It was necessary for the research design, clinically stable patients to attend a maintenance phase of exercise training, in which it would have been unlikely to show significant gains in functional capacity.

3.4.3. Reasons for test termination

In the present study only 40% and 37% of the total number of patients, for the first and second assessment respectively, reached their maximum predicted HR, as determined by the age-related formula 85%×[210-(0.65×age)]. Breathing disorders and fatigue were the most common reasons that led the patients to terminate the test. Ventilator factors in combination with cardiovascular factors can limit exercise tolerance in typical patients with cardiovascular disorders. This agrees with data from Verschuren *et al.* (2006), who stated that cardiovascular tests are good tools for measuring cardiorespiratory capacity.

3.4.4. The reliability of the modified shuttle walking test

The short-term reliability of the SWT has been assessed previously in both pulmonary and cardiac populations (Singh *et al.,* 1992; Arnott 1997; Bradley *et al.,* 2000; Fowler *et al.,* 2005). The results of the present study showed no statistically significant difference in the MSWT score between the two assessments. There was a small, non-significant increase (7 m) in MSWD and maximal walking speed (0.05 $m \cdot sec^{-1}$) between the trials. RPE and maximum HR were decreased by 0.6 units and 1 bpm respectively; there were no changes in the resting HR. Although some changes were noticed in respect of the MSWT results, they were only small changes and not statistically significant. A statistically significant difference between the two MSWTs was noticed only in the recovery time rates and the SBP (pre- and post- exercise) measurements, which might be due to test familiarisation.

Strong, significant correlations were recorded between trial 1 and trial 2 for MSWD and maximal walking speed, maximum HR and total time to recovery. These results agree with Fowler *et al.* (2005), who carried out a piece of research using three MSWTs and an incremental treadmill test over the course of one week, in order to assess the reliability and validity of SWT.

They found strong correlations between the distances in the two tests; however, higher RPE and HR scores were achieved for the treadmill test and these might be the result of greater cardiorespiratory stress during that test.

In the present study, high long-term reliability (8 weeks) was observed for the same variables (MSWD, maximal walking speed, maximum HR and total time to recovery). There was also a high internal consistency for the MSWT score measured by Cronbach's alpha. The ICC values for MSWD, maximal walking speed, maximum HR and total time to recovery were 0.80, 0.76, 0.77 and 0.85 respectively, while the ICC values were low for RPE score and HR recovery. The results indicate that each of the MSWT's outcome variables (MSWD, maximum HR, RPE, HR recovery and recovery time) has different repeatability. However, no reports of the ICC of the MSWT over long periods of testing were available in the literature.

3.4.4.1. Reliability and learning effects

The test–retest reliability of any measurement is challenged by both systematic bias (i.e., practice effects) and random error (i.e., measurement error, biological variation). The ICC values for MSWD (R=0.80) and maximum walking speed (R=0.76) are both in excess of the critical value (R=0.70) deemed to indicate reliability in previously research (Fowler *et al.,* 2005). The ICC is a dimensionless coefficient and is prone to inflation if there is a wide range of mean scores, as in the present study. ICC suggested the test was reliable, but these data were also analysed using the LoA. LoA was used because it assesses both systematic and random variation in MSWD, and because it provides 'real world' values for test–retest changes in distance for use by clinicians and researchers.

The systematic bias from test to retest was low (-7 m), indicating that there was no learning effect between trial 1 and trial 2. These data are in agreement with those of Arnott *et al*. (1997)

and refute the findings of studies (Singh *et al.,* 1992; Fowler *et al.,* 2005; Jolly *et al.,* 2008) suggesting the need for a practice test to obtain reliable MSWT results.

The creators of the test demonstrated that a practice test was necessary to secure the reliability of the results in chronic obstructive pulmonary disease patients (Singh *et al.,* 1992). This means clinicians can ensure a reliable output if they suggest that patients perform at least one practice SWT. Arnott (1997), however, found no significant changes in distance walked when the SWT was repeated in cardiac patients, and noted that practice tests for the SWT were unnecessary for obtaining reliable measurements of functional capacity in cardiac patients. Later, Bradley *et al.* (2000) suggested that test practice is not necessary if it is used to assess functional capacity in adult patients with stable cystic fibrosis who are familiar with the test.

Fowler *et al.* (2005) suggested the learning effect may influence SWT results and that the potential benefits of CR interventions may not always be identified. Thus, a practice walk was recommended by the authors (Fowler *et al.,* 2005), in order to overcome the natural variability of the test and to ensure the reliability of the output. Jolly *et al*. (2008) utilised a practice SWT and a second SWT to assess cardiac patients and to explore if the recommended practice test was necessary. They recommended the need for a practice walk before the assessment; they also noticed an improvement in the MSWD after a practice walk.

What must be borne in mind from the above: firstly, the issue over whether or not a practice SWT is necessary had not been resolved; and secondly, these studies used short (day to day) or very short (within day) test–retest protocols. Patients retested over such short periods will remember previous test scores and may set goals to beat previous scores. Furthermore, SWT is a field test devised for clinical application. In a clinical setting, it is unlikely that practice tests will be used. It would be noted that the results of this study intend to be clinically valid and,

therefore, use a simple test–retest design, as this is what is most commonly used in a clinical setting.

As no systematic bias was shown, the present study suggests that no practice effect was present when the tests were used at clinically valid intervals (eight weeks). Several patients needed the test protocol explaining again from the start for the purposes of the retest. It seems unlikely that these patients would remember their performance measures over such a long period.

In order that test–retest reliability is deemed satisfactory, the LoA should be smaller than the minimum expected difference in MSWD which the test will be used to detect. From previous studies (Fowler *et al.,* 2005; Arnold *et al.,* 2007; Sandercock *et al.,* 2007), it was determined that a 100 m improvement in MSWD could be expected over a six to eight week outpatient phase III CR programme.

The large LoA (-203 m to 189 m) were greater than values from previous test–retest studies, that did not use practice walks (Bradley *et al.,* 2000; Fowler *et al.,* 2005), and are well in excess of the proposed 100 m critical value. Unfortunately, this seems to be the first time where this 'critical value' was calculated and was mentioned. These data suggest, in the population studied here at least, that the MSWT contains too much random variation in MSWD to be used, successfully, to monitor changes in functional capacity.

The lower test–retest reliability is most likely due to assessing long-term reliability, as opposed to day-to-day variation in MSWD as in previous studies (Fowler *et al.,* 2005; Campo *et al.,* 2006; Jolly *et al.,* 2008). The wide LoA show that individuals' MSWD varied considerably from trial 1 to trial 2. Despite no mean group change (systematic bias), some patients' MSWD greatly improved, while the MSWD of others clearly declined. The long test–retest duration undoubtedly allowed greater physiological and psychological variation in the patients. Between

the trials, some patients attended CR sessions more regularly than others; patients missed sessions due to illness, musculoskeletal problems, holidays or, in one case, a minor operation. Just as, it is conceivable that such factors may negatively influence MSWD, it is equally conceivable that some of individuals, whose MSWD greatly improved, may have increased their training volume between trial 1 and trial 2. Such individual variations in behaviours that may affect MSWD are a limitation of the current study.

There was no systematic variation from test to retest in terms of learning effect or homoscedascity. The LoA plot shows that six patients' MSWD changed by less than one shuttle (10 m) between the two assessments while others declined by over 200 m. It is beyond the scope of this study to identify changes in individuals that may have been associated with such changes in MSWD, but it seems that the two patients outlined above may be outliers. In accordance with Bland and Altman's (1986) instructions, these two outliers were excluded and the analysis repeated. The repeatability coefficient was still large at ±146 m.

Changes were also found in resting blood pressure and total time to HR recovery from test to retest in some but not all patients, possibly indicating that the notion of a clinically stable patient may be a misnomer. Psychological variables might also have had an impact on MSWD.

3.4.5. Study limitations

The lack of a practice test could also be perceived as a weakness of this study, but it is also possible that this actually increased the study's generalisability. There is good evidence for a short-term learning effect on the MSWT, meaning that a practice walk is preferable. In a clinical setting, it is unlikely that time or money would be available for a practice walk prior to a patient's pre-rehabilitation assessment. Certainly, studies that have used the MSWT to monitor

changes in functional capacity during CR have not used a practice walk (Fowler *et al.*, 2005; Arnold *et al.*, 2007).

We made no psychological measures prior to either test and so cannot comment on such factors as motivation of fear, but they may also have had an impact on MSWD. Neither were individual variations in behaviours such as habitual walking or exercise taken to into account. These also may have affected test performance and reliability.

3.5. Conclusion

Previous studies had demonstrated the reliability of the SWT for patients with CVD by using only short-term tests (same day trials, day-to-day trials, up to a maximum of one week). This study examined the long-term reliability of an incremental MSWT in stable cardiac patients who were clients in phase IV CR. The results showed small changes in the mean MSWD between the two assessments, a good long-term reliability (ICC) of the MSWT and large LoA between the two assessments.

In conclusion, clinicians can be confident that they can use the MSWT to monitor changes in functional capacity in groups of CR patients. The lack of systematic bias suggests that only one MSWT trial pre- and post-CR is needed to monitor changes in CR. A practice walk is not required to assess long-term changes in functional capacity. Monitoring of individuals may be difficult, especially if there are potential factors that may impede performance on the test. Changes in symptoms, muscle pain, changes in medication, frequency of exercise training and motivation may all play a role in creating the large random variation in performance (MSWD) seen here in clinically stable cardiac patients. Thus, further studies to elucidate other physiological and potential psychological factors, which may predispose such patients to large variations in performance (MSWD), are warranted.

This study has been published as: 'Pepera, G. McAllister, J. Sandercock, G. (2010). Long-term reliability of the incremental shuttle walking test in clinically stable cardiovascular disease patients. Physiotherapy, ***96****, 222-227'.*

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CHAPTER 4. BIOMECHANICAL PREDICTORS OF THE MODIFIED SHUTTLE WALKING TEST PERFORMANCE IN PATIENTS WITH CARDIOVASCULAR DISEASE

4.0. Abstract

The shuttle walking test is a reliable measure of cardiorespiratory capacity. There are a number of biomechanical parameters that may affect the performance score. The purpose of this study was to evaluate the influences of biomechanical parameters on a modified shuttle walking test (MSWT) in clinically stable cardiovascular disease patients, and to provide a preliminary reference equation to account for biomechanical (dis)advantage when performing the test.

Sixteen cardiac patients (56% males, 44% females, mean age: 69.1±7 years), who were attending a phase IV (UK classification) cardiac rehabilitation programme, volunteered for the study. All the patients were assessed twice (with 8 weeks between assessments) using the MSWT. Modified shuttle walking distance (MSWD) was used as the outcome performance variable. Anthropometric data (mass, stature, body mass index [BMI], waist circumference, leg length) were recorded prior to the start of the first test. During the test, the number of steps taken in every shuttle was recorded and then the step length was calculated. Patients' balance was assessed on a Kistler force plate, with eyes open and closed. Gait and ground reaction force data were collected during the MSWT through video recordings and the force plate measurements. Pearson's product–moment correlation coefficients were calculated to assess the biomechanical correlates of test performance. Stepwise linear regression analysis was used in order to identify the predictors of test performance (m).

The mean MSWD was 479 (±139) m in trial 1 and 499 (±138) m in trial 2. MSWD correlated most strongly with step length measured at the 2/3rd of total test (trial 1 and 2: r=0.83, p<0.05)

and stature (trial 1: r=0.74, trial 2: r=0.69; $p<0.05$) in both trials. Step length was the best predictive measure of MSWD, followed by stature. Stepwise regression revealed step length as the best independent predictor. Given the rarity of step length assessment in clinical practice, the next most powerful predictor of performance, stature, was entered in a subsequent model, which explained 55% of the variance found in the test performance.

This study demonstrated that taller patients can be expected to perform better on the MSWT than shorter patients with similar clinical characteristics. The regression equation generated here could be used to predict an individual's performance and remove some of the bias towards taller patients.

4.1. Introduction

Cardiovascular disease (CVD) patients usually present with levels of functional capacity, exercise tolerance and daily physical activity that are lower than age-matched controls (Ades *et al.,* 2006). Low functional capacity may be more a result of decreased activity levels in chronic CVD than part of the disease aetiology. Most rehabilitative cardiovascular exercise programmes focus on increasing the patient's functional capacity and muscular strength (Darnley *et al.,* 1999).

Gait and mobility can play an important role in the assessment of both musculoskeletal and cardiopulmonary systems. Functional walk tests, such as the six-minute walking test (6-MWT) (Guyatt *et al.,* 1985) and the incremental shuttle walking test or modified shuttle walking test (MSWT) (described in Chapter 3, see '*Long-term reliability of the modified shuttle walking test in clinically stable cardiovascular disease patients*'), were originally developed to evaluate functional capacity and the ability to cope with activities of every day life (Singh *et al.,* 1992).

Walk tests are typically used as measurements of functional status to record progression during rehabilitation.

In British CVD patients, the most commonly used functional capacity test is the shuttle walking test (SWT), originally developed by Singh *et al.* (1992) as the 12 stage incremental SWT, which was subsequently modified to the 15 level version used today (Bradley *et al.,* 1999, 2000). Initially the SWT was developed for evaluating functional capacity in patients with chronic obstructive pulmonary disease, whereas it has been demonstrated recently that the test is reliable when compared with the gold standard test – the Maximal Graded Treadmill Exercise (Singh *et al.,* 1994; Lewis *et al.,* 2001; Fowler *et al.,* 2005).

4.1.1. The modified shuttle walking test

As outlined in Chapter 3, the incremental or modified SWT (MSWT) is now routinely used in cardiovascular and pulmonary rehabilitation centres (Singh *et al.,* 1992; Tobin and Thow 1999; Francis *et al.,* 2000; Morales *et al.,* 2000; Lewis *et al.,* 2001; Solway *et al.,* 2001; Zwierska *et al.,* 2004; Fowler *et al.,* 2005; Campo *et al.,* 2006; Jolly *et al.,* 2008; Woolf-May and Ferrett 2008). The SWT can be used to evaluate the functional capacity of individuals and, by this means, the effectiveness of different rehabilitation treatments; it can also be used to determine prognosis of cardiopulmonary disease (Singh *et al*., 1992, Morales *et al.*, 2000; Lewis 2001; Solway *et al*., 2001). Cardiorespiratory conditions, functional capacity, habitual exercise and age are all variables, which may influence SWT performance (Singh *et al.,* 1992; Payne and Skehan 1996; Lee *et al.,* 2005). What has not been thoroughly examined is whether MSWT performance is also related to gait parameters, despite their importance in the analogous 6-MWT.

There is some evidence of biomechanical influences on the 6-MWT in healthy adults (Enright and Sherrill 1998; Troosters *et al.,* 1999; Gibbons *et al.,* 2001; Enright *et al.,* 2003; Camarri *et*

al., 2006; Chetta *et al.,* 2006; Poh *et al.,* 2006; Jenkins *et al.,* 2009); however, there are no published reports concerning the anthropometric and gait variables associated with MSWT performance. The studies noted above were limited to collecting simple anthropometric data and have not evaluated the potential associations between gait parameters and walk test performance. The primary outcome measure of the MSWT is the distance walked (MSWD), and it is possible that anthropometric and gait parameters may affect the MSWD.

Biomechanical inefficiencies in walking are common among the elderly (Payne and Skehan 1996). Enright and Sherrill (1998) conclude that the gradual reduction of muscular mass and strength and the increase of pathologies that occurs with ageing are responsible for low performance in the 6-MWT. The 6-MWT protocol is less strictly standardised than other exercise tests, creating a degree of measurement variability (Revill *et al.,* 1999). The 6-MWT allows rest periods for patients with severe cardiorespiratory problems (such as heart failure [HF] patients), whereas the MSWT requires participants to increase their exercise intensity output until pre-determined termination criteria are met. The MSWT provokes graded cardiovascular responses, which are not produced by the 6-MWT (Turner *et al.,* 2004). Due to these differences, and because the British Association of Cardiac Rehabilitation (BACR) suggests the use of the 10 m SWT as the major assessment component in a cardiac rehabilitation (CR) programme, the SWT was used here to evaluate performance stable CVD patients who exercise regularly.

4.1.2. Biomechanical components of modified shuttle walking test

In contrast with the gold standard assessment (graded exercise treadmill test), the MSWT requires patients to change direction through 180^{o} at regular intervals, making the test more difficult than treadmill walking (Revill *et al.,* 1999) and creating very different biomechanical demands. Such turns occur every 10 m during the test, which may influence performance.

Turning is a gait parameter found in many everyday activities, but it may prove difficult, especially for the elderly or for people with particular neuromuscular disorders, because of the demands it places upon balance. Other biomechanical parameters may also influence the MSWT performance score and these clearly warrant further investigation.

An exercise test with many turns, like the MSWT, requires proficient balance control. The faster a patient walks, the greater the deceleration required before turning in order to re-orientate the centre of mass, and the greater the propulsive impulse required to accelerate the body in the new direction (Seeley *et al.,* 2008). Hence, the more biomechanical inefficient a person is, the more difficult it will be to undertake a test involving many turns.

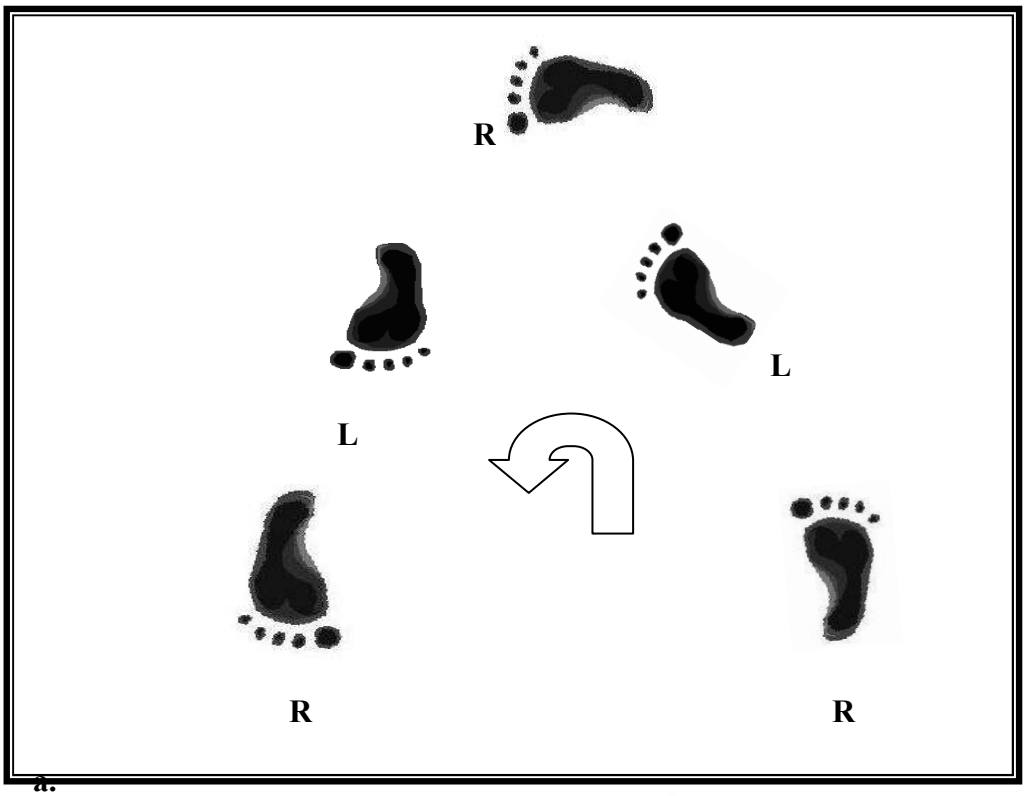
Solway *et al.* (2001) conducted a systematic review of cardiorespiratory tests, such as the 6-MWT and the MSWT. They concluded that it was controversial to compare performance on these tests, where the participant walks along a hallway and numerous turns are performed, with exercise performance on a treadmill, in which no turning is involved. This is because energy expenditure and performance results seem to vary between protocols. It is clear that both practices have their own advantages (Solway *et al.,* 2001), however; the treadmill, for example, does not require the participant to turn, but some of the participants are unaccustomed to walking on a moving belt where they cannot control the pace.

In order to clarify how biomechanical factors (turning time, number of steps needed to turn, turning strategy, balance, stature, leg length and step length) may affect MSWT results, a separate analysis of these gait parameters will be undertaken. In the two following subsections, turning variables (turning time, number of steps to turn, turning strategy) and balance will be described.

4.1.2.1. Turning

Turning is used during everyday activities, where two turns are usually required for every ten steps taken in daily life. Turning is a complex manoeuvre: the participant needs to decelerate the forward motion, select one of the two turning strategies (step turn or spin turn), rotate the body laterally, use the forward leg as an axis towards the turning direction and, finally, make the step in that direction, while accelerating again (Hase and Stein 1999; Taylor *et al.,* 2005) (see figure 4.1). The foot that is planted on the ground in front of the body during the deceleration effort controls the timing of muscle activities for producing the braking force (Fy). Different mechanisms of deceleration are used to decrease the speed of walking before turning, depending on the timing within the step cycle and the nature of the task (Yang and Winter 1985; Hase and Stein 1998, 1999).

Functional mobility and balance interact to achieve movements in everyday life (walking, standing, sitting, turning). They also interact with a number of variables, such as the type of turning, the speed, the turning time and the number of steps needed to complete the turn (Hase and Stein 1999; Demura and Uchiyama 2007). Healthy people, either without or with few chronic conditions (chronic obstructive pulmonary disease, diabetes, HF, CHD) tend to have better mobility (Gorgon *et al.,* 2007). These people may perform turning tasks more easily than those with a high number of chronic complications. For instance, elderly cardiac patients with several pathologies usually have poorer mobility due to attenuated functional locomotion system performance. Being elderly is associated with a decrease in functional mobility. Changes in gait characteristics occur to reduce the risk of falling. Older people usually decrease gait speed, cadence and step length, while increasing their turning time and the number of steps used during turning (Laufer 2005; Demura and Uchiyama 2007).



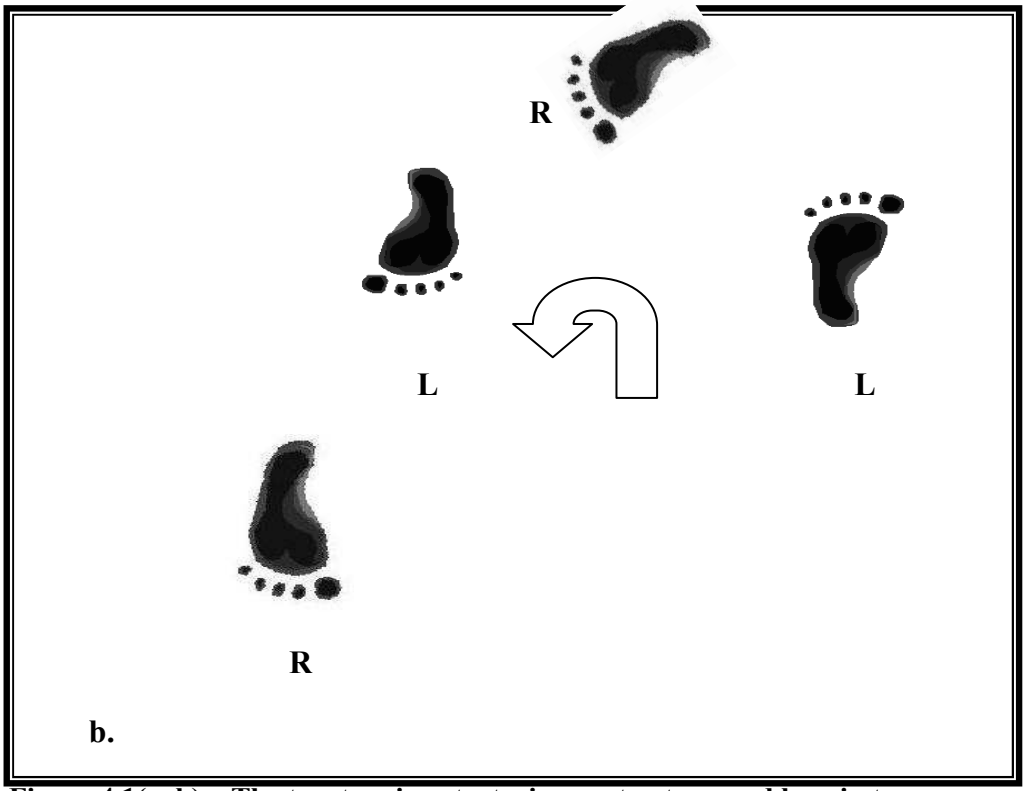


Figure 4.1(a, b). The two turning strategies; **a. step turn and b. spin turn**
(R: Right foot, L: Left foot)

4.1.2.1.1. Turning time and number of steps to turn

Turning time is used as an index of mobility (Imms and Edholm 1981). These authors assessed the mobility of 70 participants (aged 60–90 years) with different activity levels and pathologies (post-stroke, post-myocardial infarction or the weakness associated with age), by involving them in different tasks. Turning time on a walkway showed a high correlation with walking speed (Pearson's r=-0.824; $p<0.001$; n=51), the time taken to complete the task (Pearson's r=0.584) and the number of gait abnormalities during the effort (Pearson's r=0.491), but not age. People with several pathologies in daily life needed more time to complete a task and more time to turn. As turning is a feature of almost all daily activities, this population may find difficult to cope with everyday tasks. This may lead to reduced physical activity and, therefore, poor functional capacity.

Shkuratova *et al.* (2004) compared 20 healthy young participants (mean age: 25±6 years) with 20 healthy older participants (mean age: 72±5 years) in terms of several walking tasks, with and without turns. There was a significant negative relationship between age and walking speed, but no significant relationship between age and turning. Older people did not increase their speed and step length during walking as much as young adults, which was proposed as a potential strategy for older people to maintain their balance.

Van Herk *et al.* (1998) compared two walking protocols in a sample of patients with mobility disabilities following a stroke; a straight walking course for 10 m and a 5 m walking course with turns. Patients required significantly more time for the turning task than the 10 m straight walk ($p<0.001$). Patients took an average of 3.2 seconds longer to complete the 2 x 5 m walk task with turn, compared with the 10 m straight course. The walking speed varied considerably between conditions; some patients required less time to complete the turning task than the straight walking task. The authors suggested that a 10 m task created greater psychological stress in some patients, resulting in reduced walking speed, in order to complete their task safely. The 5 m task

appeared easier for some of the patients and resulted in faster gait speeds. Van Herk *et al*. (1998) found that a 5 m walk with turns was an acceptable alternative to 10 m straight walking for these patients. Such data suggest that, in a test like the MSWT, with repeated turns, participants may take more time to complete the test because of the extra time and effort spent during turning.

Turning influences walk performance by requiring more time and more effort from the participant to complete a turning task. Because turning is an important feature of walking, the next section will discuss turning strategies and the effect that these might have on walking performance.

4.1.2.1.2. Turning strategy

During most turns, humans use one of two turning strategies – the step turn or the spin turn (Hase and Stein 1999). These strategies are classified depending on the action of the leg the participant uses for braking. For example, when turning left, the step turn is a strategy by which the right foot is placed in front of the participant in order to turn left. The base of support is on the right leg first, and then shifts to the left; the participant rotates the left hip, steps to the left leg, then to the right, completes the turn and continues walking (see figure 4.1.b).

The spin turn is a turning strategy in which the participant begins with their left foot in front and turns left by spinning the body around the left leg. It is named the "spin turn" because the body spins around one foot, which is the axis for turning (see figure 4.1.b) (Hase and Stein 1999). Furthermore, the spin turn can be divided into two sub-turning strategies: the crossover and the pivot turn (Taylor *et al.,* 2005). Both of these turns move towards the same side as the stance limb. The crossover turn occurs when the stance limb remains 'rooted' to the ground as the contralateral limb is swung in the new direction. The pivot turn is more dynamic and the stance

limb pivots about the ball of the foot, rotating the whole limb and body towards the new direction.

The step turn is easier and provides better stability than the spin turn, as well as having lower neuromuscular demand. This is why most people prefer to use this strategy in everyday functional activities with turns. The improved stability is due to a wider base (wider steps) with the centre of gravity always between its boundaries; this turn retains a larger contact surface with the floor. This is at the cost of an increase in turning time and the number of steps taken during turning. A step turn requires less muscular effort and joint angular displacement than the spin turn, as well as less rotation speed of the upper body and less push-off power by the soleus (Patla *et al.,* 1991; Hase and Stein 1999; Taylor *et al.,* 2005).

For anyone with poor balance or decreased mobility, a step turn is usually the safest way to turn. In middle-aged (26- to 57-year old) healthy participants, both of the processes (step turn and spin turn) are so smooth that, at the end of the turn, the walking procedure continues with few or no disturbances in timing or to walking speed (Hase and Stein 1999). So, it is clear that there are many strategies and that CVD patients with heterogeneous levels of functional capacity are likely to turn in different ways.

Turning increases the motor control requirements and, therefore, the risk of falling in the elderly adults (Tinetti *et al.,* 1988). During turning, the body must work harder against gravity to maintain an upright posture (Huxham *et al.,* 2001; Kirtley 2006). The mechanism that keeps the body stable is the balance or postural control system (Karlsson and Frykberg 2000).

4.1.2.2. Balance

Balance control or stability is the ability of the body to keep its centre of mass within the boundaries of the base support after a perturbation. Everyday examples of such perturbations include walking and turning (Karlsson and Frykberg 2000). Ageing and pathologies such as neurological and muscular disorders interact with the balance system, which create increases in body sway; a decline in balance control and stability inevitably changes the dynamics of motion and posture (Hase and Stein 1999; Karlsson and Frykberg 2000; Huxham *et al.,* 2001). Poor balance and postural stability are related to visual conditions, such as low-lighting levels and visual disorders – glaucoma and hyperopia, for example. Such conditions lead to an increase in postural sway and risk of falling (Lord and Menz 2000; Black *et al.,* 2008; Friedrich *et al.,* 2008).

Choy *et al.* (2003) demonstrate that body sway and postural stability are significantly related to age and visual stimulation. Their study shows a decreased ability to balance when the visual input is removed (when eyes are closed). The literature suggests that body sway, balance control and falls are significantly related to age, visual stimulation and other visual disorders. In the elderly, visual disorders are commonplace, provoking an increase in postural sway and the risk of falls. Balance changes with aging, and people with impaired balance tend to change their gait characteristics (such as step length, cadence and walking speed), and need more time to walk and turn. Gait characteristics, balance and turning seem to relate to each other and together they affect walking performance.

4.1.3. Relationships between biomechanical variables (balance, step length, cadence, walking speed, braking force, total vertical impulse and turning)

Pathologies of the locomotor system may affect gait parameters such as step length and walking speed. Particularly, patients with Parkinson's disease walk with reduced cadence, step length and

walking speed because of balance impairment. They spend more time in the double-support phase of walking, utilise a greater number of steps and need more time to turn, compared with healthy controls (Carpinella *et al.,* 2007). Thus, turning appears to increase hypokinetic characteristics in elderly Parkinson's disease patients, in order to increase stability.

Imms and Eoholm (1981) showed that turning time correlated poorly with age but was negatively and very strongly correlated with walking speed (Pearson's r=-0.824, $p<0.001$). They found that elderly people without pathology of the locomotor system preferred to change their step length instead of their cadence. This infers that older people may prefer to make wider steps in order to obtain a wider base of support to prevent falls.

The process of turning requires the deceleration of walking speed a few steps before the turn. In order that the walker decelerates properly and maintains body stability, the direction of the turn should be known at least one step before turning (Patla *et al.,* 1991; Hase and Stein 1999). In the MSWT, both the direction and the turning movement are known to the participant; thus, they may be able to better adapt to the turning effort by preplanning and taking more steps to turn.

To summarise, balance is attenuated in the elderly, affecting a decrease in the step length, turning time, the number of steps needed to turn, gait speed and gait cadence. The next section will discuss how balance can affect MSWT in elderly patients.

4.1.4. Does turning affect walking test performance?

Walk tests are commonly used to evaluate functional capacity. Most field tests, however, include several turns and thus studies have focused on examining the effect of turning on test performance.

Beaumont *et al.* (1985) compared the results of two self-paced 12 minute walking tests, performed on different 'courses' (a hospital corridor including a turn and a flat treadmill) in pulmonary patients. They found no significant difference in distance walked, step length or average speed. The use of two very different protocols (corridor and treadmill) makes the interpretation of the results difficult. There is no information given about how long the corridor was or how long participants had to walk before turning. Participants may have been unfamiliar with the treadmill, while walking along a corridor is closer to an everyday situation.

Swerts *et al.* (1990) used the twelve-minute walking test in pulmonary patients and found that patients performed better (significantly higher distance walked and walking speeds) along a 100 m corridor than on a treadmill. The result was independent of any difference in heart rate, indicating that the intensity of exercise was similar across the two trials. Stevens *et al.* (1999) supported these findings by showing that the majority of patients who undertook the 6-MWT walked further along a hallway than on a treadmill. Both studies concluded patients were more familiar with walking along a corridor than accelerating on a treadmill, which required more effort to utilise supplementary voluntary movement.

Conversely, Revill *et al.* (1999) found that patients with chronic obstructive pulmonary disease walked further on a treadmill than along a corridor, when performing the endurance SWT (externally controlled, constant paced test) at all intensities. In this study, patients were asked to perform three endurance SWTs, three treadmill endurance tests and an incremental SWT. The intensity of these endurance tests was calculated individually for each patient and related to 75%, 85% and 95% of each patient's maximum incremental SWT performance. Again, the heart rate responses provoked during the endurance SWT were similar to those achieved during the treadmill endurance test. The difference in distance covered between the two tests was explained in terms of the smaller amount of energy expended on the treadmill, as the belt that is used on it

assists in the backwards movement of the foot. Another explanation would be that the SWT along the corridor is more biomechanically demanding than the treadmill test, due to the turning, decelerations on corners, lateral displacements and accelerations; however, the authors were unable to determine among these factors.

A further study of the 6-MWT involved 761 patients with obstructive pulmonary disease (Sciurba *et al.,* 2003). There was no effect of course length on the 6-MWT for straight courses (range: 15-50 m). There was, however, an effect of course layout. Patients who performed the test on continuous courses (circular or oval corridors, ranging in length from 56 to 121 m) walked 28 m further than those tested on straight corridors. The layout of the course and thus, the different biomechanical parameters (turns), may affect performance. Nevertheless, different groups of patients with different clinical characteristics were used in each trial, creating limitations in design and reducing generalisability of the results.

The American Thoracic Society (ATS) a medical association whose standing is recognised globally– hence the use of ATS protocols here. Recently (2002), the ATS recommended that when the 6-MWT is performed along straight, short corridors; patients need more time to reverse direction, reducing the total walking distance. This might be because of the time and effort required to turn. The ATS guidelines suggest, therefore, that the 6-MWT should be performed along a straight corridor course at least 30.5 m long, in order to limit the number of turns (American Thoracic Society 2002).

More recent studies have compared the 10 m SWT with the 6-MWT in terms of chronic obstructive pulmonary disease patient performance. The significant difference in distance covered between the two tests may provide an opportunity to analyse the effect of the different designs of the two tests. Rosa *et al.* (2006) compared performance on the 10 m incremental SWT

and the 6-MWT (performed along a 28 m corridor), in a sample of elderly pulmonary patients. The authors compared patients' performance at the two different tests. They found a significant difference in the mean distance covered; with the incremental SWT, the mean score was 307 (±89.3) m and with the 6-MWT, the mean score was 515.5 (±102.3) m (p<0.001). The 6-MWT was found to produce more stress on the cardiovascular system (as measured by higher heart rates and higher levels of dyspnoea), despite the 10 m SWT requiring double the number of turns compared with the 6-MWT along a 28 m hallway. This might be explained by the different layout of the two tests: the 10 m SWT is an incremental test, which requires the patient to exercise intensively for a relatively shorter period of time, while navigating many turns along the course.

In a comparison between a 6-MWT along a flat 30 m walkway and a 10 m endurance SWT in patients with cardiopulmonary disorders (Pepin *et al.,* 2007), the SWT was more physiologically demanding than the 6-MWT. Mean walking speed was similar for both tests, but patients found it more difficult to maintain walking speed on the 10 m SWT, as this test required more alterations in direction and more numerous accelerations and decelerations compared with the 6-MWT performed on a 30 m course. Patients found the SWT more demanding, but were able to increase their endurance time and thus cover more distance in SWT. The authors concluded that it was easier for patients to increase endurance time than to increase walking speed, due to the different biomechanical test designs, which effects bronchodilation responsiveness. The mechanism by which bronchodilation may have an impact on patients with respiratory disorders is, however, unclear. Difference in the findings between the two studies mentioned above cannot be explained only in terms of test design. Different methodologies of the tests must also be considered. Due to its incremental and externally paced structure, physiological responses to exercise can vary.

The SWT requires the participant to make a 180º turn every 10 m and this seems to require an additional effort in order to maintain their balance and posture stability. Anthropometric characteristics, such as: stature and leg length, may affect gait and, by extension, these factors may influence test results.

4.1.5. Aim and hypothesis

The aims of this study were to investigate the influence of these anthropometric (stature, leg length, step length) and gait parameters (turning time, steps needed to turn, braking force, vertical impulse) on MSWD in clinically stable CVD patients. This work is intended to provide a preliminary reference equation to account for biomechanical (dis)advantage when performing the test.

The results and discussion of this chapter will attempt to reference the following hypothesis: Gait and anthropometric parameters can predict a significant proportion of variance in MSWD, in clinically stable CVD patients.

4.2. Methods

4.2.1. Participants

Sixteen adults (9 males and 7 females) aged 55 to 80 years volunteered for this study. All were members of a phase IV (UK classification) CR programme, the 'Phoenix Club', which is held at the University of Essex (same population as Chapter's 3 population). All participants had been enrolled in the community-based, long-term maintenance CR programme for a minimum of ten weeks. All the participants were patients with cardiac disorders; they were either involved in revascularisation intervention (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]) or had been affected by an MI, or they had had both an MI and cardiac

surgery. Some patients joined the CR programme because of HF, stable angina and arrhythmias. The patients had finished phase III CR at a local Colchester Hospital or been referred to phase IV CR by their general practitioner. All patients were defined as clinically stable (asymptomatic), according to the BACR (2006) criteria. The patients were supported by medication (β-blockers, nitrates, aspirin, statins), and they were free from lower limb injuries, musculoskeletal or neurological disorders, illness or post-operative limitations. The descriptive characteristics and baseline measurements of the patients are presented below (see table 4.1).

Patients were briefed verbally and in writing on the procedure, and they gave written informed consent. The study was approved by the Ethics Committee of the University of Essex and conformed to the declaration of Helsinki (World Medical Association 2009) guidelines for research with human participants. Criteria for exclusion from the study included lower limb injuries, neurological disorders, illness or post-operative limitations, all of which could affect gait. The patients continued taking their medication throughout the study. The study took place between January 2008 and September 2008.

Table 4.1. Descriptive characteristics and baseline measurements of participants

Clinical characteristics and baseline measurements	Values
Number of patients	16
Age (years) (mean ± SD)	69.1 ± 7.0
Sex (%)	Males= 9 (56%) – Females=7 (44%)
Body mass (kg) (mean ± SD)	81.7 ± 10.94
Stature (cm) (mean ± SD)	167 ± 10
Median value (25th percentile)	162
Median value (75th percentile)	176
BMI ($kg \cdot m^{-2}$) (mean ± SD)	29.3 ± 3.7
Leg Length (cm)	88 ± 8
Medical History/Reason for joining CR	
MI	n=2 (13%)
Stable Angina	n=5 (31%)
Surgical procedure (CABG, PCI)	n=11 (69%)
Heart Failure	n=2 (13%)
Arrhythmias	n=2 (13%)
Medication	
β-blockers	n=10 (63%)
Nitrates	n=4 (25%)
Aspirin	n=7 (44%)
Statin	n=4 (25%)
Other	n=5 (31%)

Definition of abbreviations: *BMI=body mass index; MI=myocardial infarction; CABG=coronary artery bypass graft; PCI=percutaneous coronary intervention*

4.2.2. Protocol

All patients were assessed twice, with eight weeks between assessments; during this period they continued to attend phase IV CR. Each of the patients performed both the balance test and the modified shuttle walking test (MSWT), as described below. In order to ensure consistency, each patient was given a primary assessment prior to testing, which required them to fill in a Pre-Exercise Health Questionnaire; this was followed by an interview on their medical, pharmacological and family history.

4.2.2.1. Anthropometric Assessment

First anthropometric measurements were taken including: stature, body mass and leg length. Stature was recorded using a stadiometer (Seca 240 stature measuring rod) and body mass was recorded with a weight scale (Seca 888 Class III Floor Scale) without shoes. From these measurements, BMI was calculated as: body mass (kg)/stature^2 (m^2). Waist circumference was measured at the level of the natural waist (the narrowest place between ribs and the iliac crest [Lohman *et al.,* 1988]). Leg length was recorded by assessing the distance between anterior superior iliac spine and the medial malleolus, as shown in figure 4.2 (Hof 1996). There is an equation to estimate stature from leg length; both stature and leg length were, however, measured to provide more accurate results.

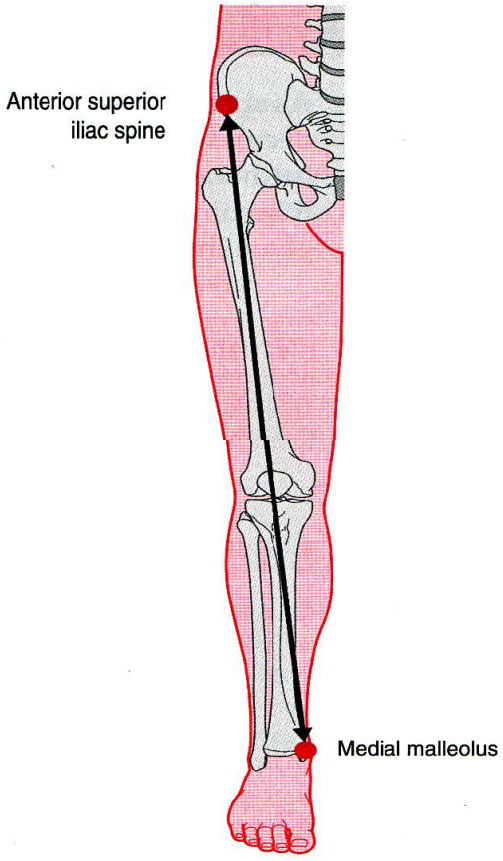


Figure 4.2. Leg length measurement points (Kirtley 2006)

4.2.2.2. Balance test

In order to assess the stability status for each patient in the sample, static body sway tests with eyes open and eyes closed were performed before the MSWT test. These evaluated the visual effect on balance control and followed standard practice for balance testing.

The balance test was performed on a Kistler piezoelectric force plate (Kistler 9281C, Kistler Instruments AG, Winterthur, Switzerland). Data were collected for 30 seconds, using a frequency of 50 Hz. The patients were advised to stand comfortably on the force plate with both feet within the plate's boundaries and their arms held loosely by their sides. They wore their own shoes. Two types of visual input (eyes open and eyes closed) were used to activate different sensory conditions. When the patients stood with their eyes open, they were advised to look at a spot placed in front of them at eye level (Karlsson and Frykberg 2000). The balance test was used only once, before the second assessment.

There are several methods available for assessing postural balance. Here, a decision was taken to estimate postural balance by calculating the standard deviations of the centre of pressure, x-y, during the balance test with eyes open and eyes closed respectively, because this method is reliable, valid and frequently used in clinical practice (Middleton *et al.,* 1999; Era *et al.,* 2006). Bioware Software (version 3.21, Kistler Instrument Corporation) was used for the data uploading.

4.2.2.3. Modified shuttle walking test procedure

In this study, the shuttle walking test was modified slightly, so that the patients walked in an anticlockwise direction (see figure. 4.3). The MSWT was performed by each patient, as described in Chapter 3 (pp.130-131).

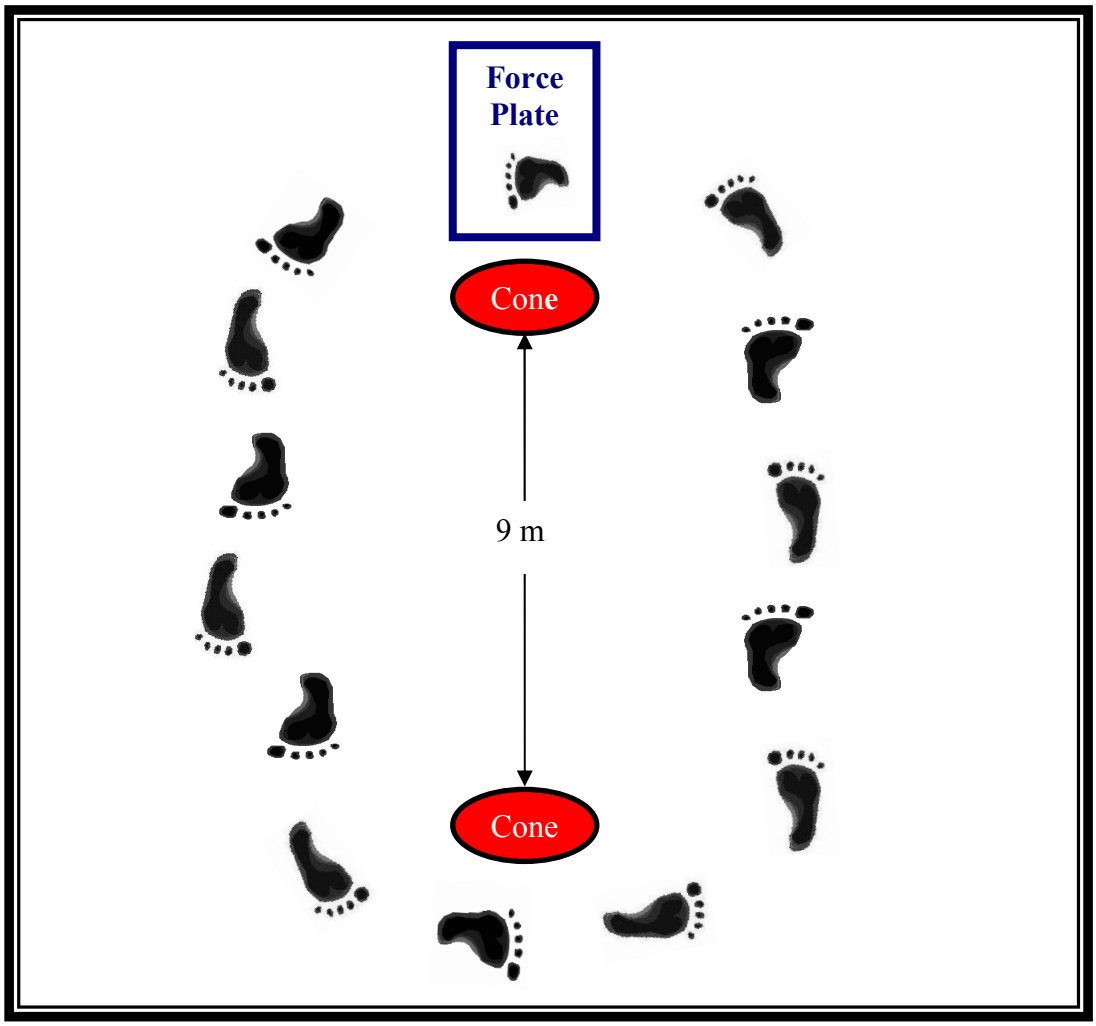


Figure 4.3. Diagram of the modified shuttle walking test - Turn in an anticlockwise direction

During the test, the number of steps taken in every shuttle was recorded. Step length was estimated by dividing the length of the course (nine metres – the straight portion of the course) by the number of steps in each shuttle (Hof 1996).

4.2.2.4. Turning: force plate data

A piezoelectric force plate (Kistler 9281C, Kistler Instruments AG, Winterthur, Switzerland) was used to record the peak braking force (F_y) and the total vertical impulse (I_z) at the end of the 10 m walkway. The vertical impulse gives an indication of support during gait (Seeley *et al.,* 2008) and turning (Strike and Taylor 2009). Horizontal ground reaction force (GRF) data were not included in the analysis because, for turning, this requires reorientation of the GRF reference

frame with the centre of mass (determined from the kinematic data) body reference frame (Glaister *et al.,* 2007). The force plate was positioned at the end of the 10 m walkway and was set to work at a frequency of 500 Hz for periods of 5 seconds. Fy was defined as the minimum recording of the Fy curve, where Iz was the area under the vertical force (Fz) curve (see figure 4.4). The data were recorded on a computer connected to the force plate. Bioware (version: 3.21, Kistler Instrument Corp.) software was used for the force plate data recording.

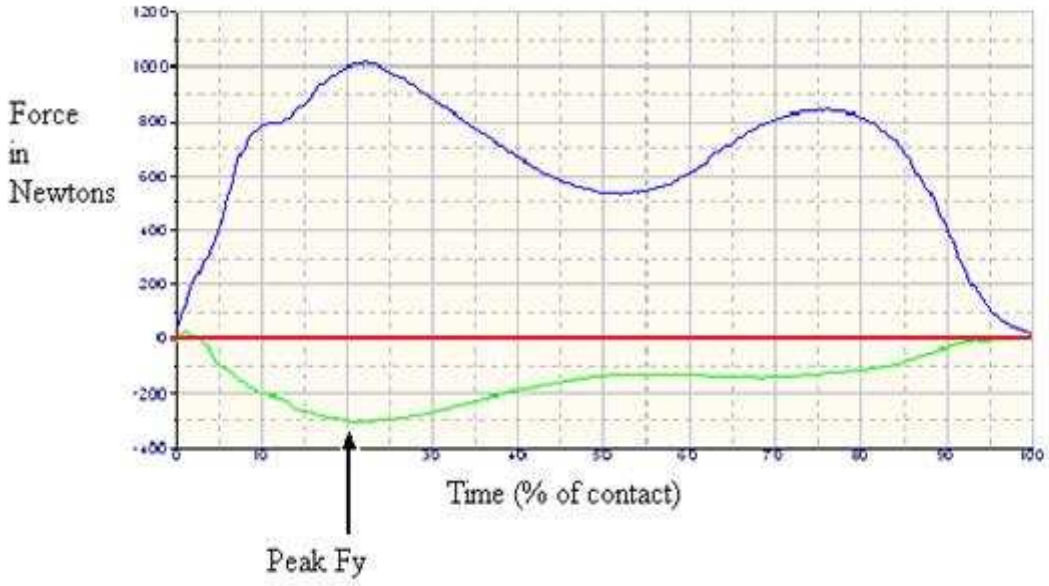


Figure 4.4. Illustration of raw I_z (area between the blue line and the zero) and peak raw peak F_y (green line)

Patients were asked to walk freely along the 10 m walkway and to turn on the flush-mounted force plate. To ensure that the data were not affected by changes, patients requested not to alter their gait. Three satisfactory measures (first, middle and last shuttle) were collected at each speed (see table 4.2). Satisfactory measures were those which recorded only clean, full foot strikes. Any footfalls that fell outside the boundaries of the plate or data resulting from double support were ignored (Kirtley 2006) (see figure 4.5).

Table 4.2. The shuttles at which the ground reaction force data were recorded

Levels	No of shuttles	Shuttles recorded
1	3	1, 3
2	4	2, 4
3	5	2, 4
4	6	1, 3, 5
5	7	1, 3, 5, 7
6	8	2, 4, 6, 8
7	9	2, 4, 6, 8
8	10	1, 3, 5, 7, 9
9	11	1, 3, 5, 7, 9, 11
10	12	2, 4, 6, 8, 10, 12
11	13	2, 4, 6, 8, 10, 12
12	14	1, 3, 5, 7, 9, 11, 13
13	15	1, 3, 5, 7, 9, 11, 13, 15
14	16	2, 4, 6, 8, 10, 12, 14, 16
15	17	2, 4, 6, 8, 10, 12, 14, 16

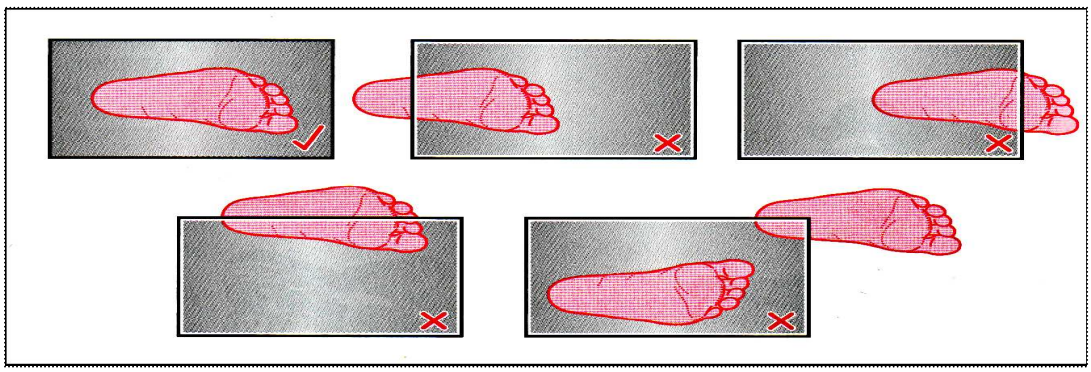


Figure 4.5. Clean full step on the force plate (Kirtley 2006)

4.2.2.5. Video recording

Every turn on the plate was recorded with a Sony CCD-TRV20E camera, mounted on a tripod, level with the force plate. From the video data, the turning style, the turning time, and the number of steps needed to complete the turn were obtained.

Two turning strategies were used to interpret the turning style of the patients – the step turn and the spin turn. As mentioned in the introduction, turning strategies are differentiated by the leg that the participant uses in front for braking. In the step turn, patients used the right foot in front, in order to turn left; while in spin turns, the patient had the left foot in front and turned left by spinning the body around the left leg (Hase and Stein 1999).

Turning time and number of steps used for turning were recorded one step before turning, from either foot heel strike, until the end of the turn. 'End of the turn' was defined as the first heel strike with all toes, pelvis and thorax facing the hallway directly opposite the cone (Hase and Stein 1999). The software used for the video analysis was SiliconCoach Pro (version 6.1.5.0, SiliconCoach Ltd, New Zealand).

4.2.2.6. Data processing

Prior to the analysis, step length was normalised to leg length by dividing step length by leg length, to control its influence on step length (Hof *et al*., 1983). Ground reaction force data were averaged (Fy and Iz) across the three satisfactory trials for each speed, and then they were converted to dimensionless quantities in order to remove the effect of body size. Peak braking force (Fy) was divided by body mass, and the vertical impulse (Iz) was divided by the sum of body mass and the square root of l/g, where g is the acceleration due to gravity ($g=9.81\ m{\cdot}s^{-1}$) and l is leg length (Kirtley 2006; Seeley *et al.,* 2008).

4.2.2.7. Variables used

The independent variables were divided into three categories: static variables (age, stature, leg length), dynamic variables (step length, braking force –Fy, total vertical impulse -Iz, number of steps to turn, turning time, turning style) and normalized dynamic variables (step length

normalised to leg length). The dynamic variables and normalized dynamic variables were analysed during the 1/3rd, 2/3rd, penultimate and final levels of the test, in order that the analysis should be less complicated. Thus, the analysis of these variables was divided into four parts: 1/3rd, 2/3rd, antepenultimate and the last level of the test (see table 4.3).

Dependent variables were the maximum walking speed achieved and the total distance covered (MSWD). Braking force (Fy) and total vertical impulse (Iz) were normalised as described, prior to performing the analysis.

Table 4.3. Variables used in the study

Static variables	Dynamic variables	Normalized dynamic variables
Age	Step length	Step length normalized to leg length
Stature	Balance	
Leg Length	Braking force (Fy)	
	Total Vertical impulse (Iz)	
	Number of steps needed to turn	
	Turning time	
	Turning style	

4.2.3. Statistical analysis

Data were presented as means and standard deviations. The median value of stature was also calculated. Stature data were divided into three quartiles (25th, 50th, 75th percentile of the distribution).

Differences between the two MSWTs were evaluated using the paired-samples t-test. The paired-samples t-test examined the difference between the two balance tests. Relationships and statistical significance for each of the variables measured during the two tests were evaluated using Pearson's product moment coefficient. This statistical method was used first because of

low participant numbers (n=16). According to Tabachnick and Fidell (2007), a sample of n≥138 patients (n>50+[8×m], where m=number of independent variables used) would actually be needed.

After determining which variables were most strongly related to test performance, stepwise linear regression analysis was performed. The stepwise model was chosen in favour of other models because the objective was to identify the lowest number of variables that influenced the test results most greatly. Two stepwise models were used: model one contained all the independent variables, which show at least some correlation with performance (r>0.3); (regression analyses were performed separately for each of the trials). To establish a clinically useful equation, a second regression analysis was performed, containing only variables that were both strongly correlated with performance and routinely recorded in CR. Colinearity diagnostics were performed for all predictor variables (Meyers *et al.*, 2006). The lower limit of normal (LLN) in MSWT performance was determined by using the lower 5^{th} percentile of a normal distribution (Pellegrino *et al.,* 2005).

Statistical analysis was performed using SPSS version 16.0 (SPSS inc., Chicago, IL, US), whereas calculations were carried out in Microsoft Office Excel 2003 (Microsoft Corporation**,** Washington, US). The statistical significance was set at level 0.05.

4.3. Results

4.3.1. Differences in variables between trial 1 and trial 2

Table 4.4 provides descriptive values for the measurements of the two assessments, made eight weeks apart during phase IV CR using the MSWT as an assessment tool. None of the patients completed the 15-level protocol MSWT (1500 m). The MSWD ranged from 210 to 750 m. The MSWD and the maximal walking speed that was achieved at termination of the test were used to prescript the MSWT score. In this study, the mean MSWD was 479 (±139) m in trial 1, and 499 (±138) m in trial 2; the mean maximal walking speed was 1.65 (±0.23) $m \cdot sec^{-1}$ and 1.65 (±0.25) $m \cdot sec^{-1}$. No significant difference was observed in the MSWT score (MSWD, maximal walking speed) between the two assessments ($p>0.05$).

The only variable that showed significant differences between trials was the step length. Step length was significantly longer in trial 2 at the $1/3^{rd}$ and $2/3^{rd}$ stages but not at the penultimate and final stage.

Table 4.4. Modified shuttle walking test: Comparison of the two trials (trial 1 vs. trial 2)

	trial 1				trial 2			Sig
	n	MEAN	SD	N	MEAN	SD	t	(2-tailed)
Maximum walking speed ($m \cdot sec^{-1}$)	13	1.65	0.23	16	1.65	0.25	<0.001	1.000
MSWD (m)	13	479	139	16	499	138	-1.8	0.092
Balance eyes opened to eyes closed	0	-	-	11	0.0051	0.0022	-	-
Balance -eyes closed-	0	-	-	11	0.0065	0.0024	-	-
1/3rd of maximal level								
No of Steps to turn	11	4.27	0.47	16	0.41	0.2	0.335	0.221
Turning time (sec)	11	2.7	0.63	16	2.5	0.28	1.33	0.212
Step length (m)	16	0.61	0.078	16	0.70	0.079	-4.75	<0.001
Normalized Step length	16	0.69	0.069	16	0.79	0.067	-4.36	0.001
Fy (N/kg)	10	-1.66	0.45	14	-1.95	0.42	2.15	0.064
Iz (*1/3 of total test*)	10	6.52	0.85	15	6.51	0.77	0.067	0.948
2/3rd of maximal level								
No of Steps to turn	9	4	0	16	3.9	0.17	1	0.347
Turning time (sec)	9	2.26	0.37	16	2.24	0.21	0.148	0.886
Step length (m)	15	0.72	0.11	16	0.76	0.095	-3.029	0.009
Normalized Step length	15	0.81	0.078	16	0.86	0.066	-3.14	0.007
Fy (N/kg)	9	-2.69	0.65	15	-2.56	0.42	-0.69	0.51
Iz	9	6.04	0.84	15	5.55	0.68	1.19	0.268
Penultimate level								
No of Steps to turn	12	4.08	0.29	16	3.84	0.28	2	0.07
Turning time (sec)	12	1.82	0.43	16	1.91	0.23	-0.825	0.427
Step length (m)	16	0.77	0.14	16	0.8	1.12	-1.78	0.096
Normalized Step length	16	0.87	0.11	16	0.90	0.082	1.33	0.208
Fy (*penultimate level*) (N/kg)	13	-2.98	0.68	15	-3.17	0.63	1.083	0.302
Iz (*penultimate level*)	13	5.23	1	15	5.08	0.41	0.449	0.662
Maximal level								
No of Steps to turn	10	4.05	0.16	16	3.87	0.43	1.15	0.279
Turning time (sec)	11	1.7	0.23	16	1.8	0.25	-1.068	0.311
Step length (m)	16	0.77	0.17	16	0.82	0.13	-1.4	0.175
Normalized Step length	16	0.87	0.14	16	0.92	0.09	-1.51	0.153
Fy (maximal level) (N/kg)	10	-3.3	1.02	15	-3.8	0.95	1.27	0.237
Iz (maximal level)	11	4.63	0.55	15	4.8	0.59	-0.775	0.456

Definition of abbreviations: MSWD=modified shuttle walking distance; Fy=braking force; Iz= vertical impulse

4.3.2. Correlations

Due to the exploratory nature of this chapter, this section only discusses those statistical findings that are particularly noteworthy (that is, they show statistical significance). This is because a large number of potential variables were examined, meaning that the initial correlation analysis output was rather large.

4.3.2.1. Correlations for step length

Patients' stature and leg length were correlated with their step length at all stages of the test. The correlations tended to increase from the 1/3rd level of the total test to the penultimate level, where they were strongest for both variables in both trials. In general, the correlations were also slightly stronger in trial 2 compared with trial 1 (see table 4.5). When the step length was normalised for leg length, there were no significant correlations with any of the potential step length predictors.

Table 4.5. Correlations for the "step length" variable in the two trials

Level	Variables	trial 1			trial 2		
		N	Pearson r	*P* value	N	Pearson r	*P* value
1/3rd of total test	Step length-Stature	16	0.519	0.04	16	0.601	0.014
	Step length-Leg length	16	0.639	0.008	16	0.707	0.002
2/3rd of total test	Step length-Stature	15	0.618	0.014	16	0.703	0.002
	Step length-Leg length	15	0.746	0.001	16	0.817	<0.001
	Step length- Iz	9	NS	NS	15	0.741	0.002
Penultimate level	Step length-Stature	16	0.680	0.004	16	0.747	0.001
	Step length-Leg length	16	0.824	<0.001	16	0.812	<0.001
	Step length-Number of steps to turn	11	NS	NS	16	-0.541	0.03
	Step length-Fy	9	NS	NS	15	-0.710	0.003
Maximal level	Step length-Stature	16	0.649	0.007	16	0.702	0.002
	Step length-Leg length	16	0.78	<0.001	16	0.781	<0.001

Definition of abbreviations: MSWT=modified shuttle walking test; Fy=braking force; Iz=vertical impulse; NS=non significant

4.3.2.2. Correlations for turning

Turning was evaluated by recording the number of steps that the patients needed to turn and the turning time. Correlations between turning variables and other biomechanical measures were mainly found in trial 2. Significant associations were found between the number of steps that the patients needed to turn and turning time at the penultimate level of the MSWT.

Numbers of steps needed to turn

The number of steps required for turning correlated significantly with braking force at the penultimate level, while the number of steps required for turning was found to have a negative association with the patient's stature and leg length at the 2/3rd level of the total test and at the penultimate level respectively (see table 4.6).

Turning time

Braking force and total vertical impulse were correlated with the time that the patients needed to turn at the initial and last levels of the test. Patient's posture was associated significantly with turning time at the penultimate level of the test (see table 4.7).

Preferred turning strategy

The patients generally performed a step turn in the 1/3rd and 2/3rd stages of the test, while they used a spin turn at the penultimate and maximal level where the walking speed increased, which resulted in a step length increase and the 'other' foot landing on the plate, resulting in a spin turn. Furthermore, it was noted that most of the patients carried out a step turn if they were starting the turn with their right foot, and a spin turn if they were using their left foot. Thirteen of the patients used the step turn as the dominant strategy. However, in terms of performance, no difference was observed between groups in terms of a preferred turning strategy.

Table 4.6. Correlations for the "number of steps" variable in the two trials

Level	Variables	trial 1			trial 2		
		N	**Pearson r**	***P* value**	**N**	**Pearson r**	***P* value**
2/3rd of total test	No of Steps to turn-Stature	9	NS	NS	16	-0.607	0. 013
Penultimate level	No of Steps to turn- Turning time	12	NS	NS	16	0.753	0.001
	No of Steps to turn- Fy	11	NS	NS	15	0.577	0.024
	No of Steps to turn- Step length	12	NS	NS	16	-0.541	0.03

Definition of abbreviations: MSWT=modified shuttle walking test; Fy=braking force; Iz= vertical impulse; NS=non significant

Table 4.7. Correlations for the "turning time" variable in the two trials

Level	Variables	trial 1			trial 2		
		N	**Pearson r**	**P value**	**N**	**Pearson r**	**P value**
1/3rd of total test	Turning Time-Fy	10	NS	NS	14	0.648	0.012
	Turning Time-Iz	10	0.64	0.046	15	0.603	0.017
Penultimate level	Turning Time- Stature	12	NS	NS	16	-0.502	0.047
	Turning Time-Number of steps to turn	12	NS	NS	16	0.753	0.001
	Turning Time-Fy	11	NS	NS	15	0.561	0.03
Maximal level	Turning Time-Iz	10	NS	NS	15	0.644	0.01

Definition of abbreviations: MSWT=modified shuttle walking test; Fy=braking force; Iz= vertical impulse; NS=non significant

4.3.2.3. Correlations for balance

Static balance was measured only in the second assessment (trial 2) and did not show any significant correlation with any of the other variables. Moreover, balance did not correlate significantly with age (see table 4.8).

Table 4.8. Correlations for the "balance" variable in the second assessment

Variables	Trial 2		
	N	**Pearson r**	***P* value**
Balance eyes open- age	11	NS (r=0.373)	NS (p=0.259)
Balance eyes closed-age	11	NS (r=-0.370)	NS (p=0.263)

Definition of abbreviations: NS=non significant

4.3.2.4. Correlations for test performance (modified shuttle walking distance)

The predictors of test performance were divided, as noted, into three groups: static measures, dynamic measures and normalized dynamic variables. Measurements of the lower extremities taken during physical examination were referred to as static measurements, while biomechanical measurements recorded during gait analysis were referred to as dynamic variables (McMulkin *et al.,* 2000).

Static measurements

The static measurements, stature and leg length, were the ones that correlated with test performance in both of the trials (see table 4.10).

Dynamic measurements and normalized dynamic measurements

Dynamic measurements and normalized dynamic measurements– step length, Fy and Iz, and number of steps taken to turn – were the only ones that showed a significant correlation with MSWT performance. In particular, step length and step length normalised to leg length were both significantly associated with the MSWT score at all stages of the test. The associations tended to decrease from the 1/3rd level of the total test to the penultimate level in trial 1. Total vertical impulse was associated with test performance in the 1/3rd and 2/3rd levels of the total test in the second assessment, while braking force was found to have a negative association with the trial 2 score at the penultimate level. The number of steps taken when turning correlated negatively at the 2/3rd level of the total test in the second assessment (see table 4.9).

Table 4.9. Correlations between gait and anthropometric parameters and modified shuttle walking distance in the two trials, in phase IV cardiac rehabilitation

Level	Variables	trial 1			trial 2		
		N	Pearson R	P value	N	Pearson r	P value
	MSWD – Stature	16	0.741	0.001	16	0.688	0.003
	MSWD - Leg length	16	0.808	<0.001	16	0.762	0.001
	MSWD - Age	16	0.051	0.852	16	-0.016	0.954
1/3rd of total test	MSWD - Step length	15	0.826	<0.001	16	0.563	0.023
	MSWD – Iz	10	NS	NS	15	0.526	0.044
2/3rd of total test	MSWD - No of Steps to turn	9	NS	NS	16	-0.587	0.017
	MSWD - Step length	15	0.826	<0.001	16	0.826	<0.001
	MSWD - Step length normalized	15	0.593	0.02	16	0.523	0.038
	MSWD – Iz	9	NS	NS	15	0.708	0.003
Penultimate level	MSWD - Step length	16	0.724	0.002	16	0.813	<0.001
	MSWD - Step length normalized	16	0.512	0.042	16	0.574	0.020
	MSWD – Fy	13	NS	NS	15	-0.632	0.012
Maximal level	MSWD - Step length	16	0.651	0.006	16	0.765	0.001
	MSWD - Step length normalized	16	0.471	NS (0.065)	16	0.535	0.033

Definition of abbreviations: MSWT=modified shuttle walking test; Fy=braking force; Iz=vertical impulse; NS=non significant

4.3.3. Multiple linear regression analysis

Stepwise linear regression analysis was used to assess the ability of selected variables to predict patients' MSWT performance. The variables selected for this analysis were significantly correlated (r>0.3) with test performance (MSWD and maximal walking speed) (Pallant 2007). Walking speed seems the obvious measure by which to evaluate functional capacity and has been used to describe MSWT performance. Previous MSWT studies report only MSWD (Fowler *et al.,* 2005; Campo *et al.,* 2006; Jolly *et al.,* 2008), this metric was, therefore, used to analyse the biomechanical predictors of the MSWT, for comparability.

The regression used only those independent variables for which the coefficient correlation with the other independent variables was less than 0.75, in order to minimise multicollinearity and avoid high correlation between the variables (Meyers *et al.,* 2006). The probability of F for entry was set at 0.05 and for removal at 0.1; these counted as the statistical criteria that the dependent variables needed to attain in order to be included in the analysis.

4.3.3.1. Prediction of test performance

Trial 1

Using MSWD as the dependent variable, the only variables that met the assumptions described above were step length (at the 1/3rd, 2/3rd, penultimate and maximal levels of the test) and step length normalised to leg length (at the 2/3rd, penultimate and maximal levels of the test). Ultimately, however, stepwise analysis included only step length at the 2/3rd stage of the whole test, since this was the only variable that met the statistical criteria for inclusion. In this model, 68.3% of MSWD was explained by step length at the 2/3rd stage of the whole test, with a

standard error of 74 m on the estimation. The coefficient (β value) was found to be 997.1 m. The intercept value (A) was -230.6 m.

Trial 2

In the second trial, MSWD was correlated with stature, leg length, step length (at the 1/3rd, 2/3rd, penultimate and maximal levels of the test), number of steps to turn (2/3rd stage of the whole test), normalised step length (2/3rd, penultimate and maximal levels), Iz (at the 1/3rd and 2/3rd stages of the test) and Fy (at the penultimate level). Ultimately, however, the stepwise analysis only included step length (at the 2/3rd stage of the whole test) since this was the only variable to meet the statistical criteria for inclusion. In this model, 68.2% of MSWD was explained by step length at the 2/3rd stage of the test, with a standard error of 85.37 m. The β value was 1203.9. The intercept value (A) was -415.7.

4.3.3.2. Validating predictors of modified shuttle walking test performance

Stepwise regression analysis indicated that step length at the 2/3rd level of maximal test performance was the best predictive measure for performance, followed by stature, in both trials.

As step length is a dynamic measure, it is probably not practical to measure this in routine clinical assessment. In order to measure step length, a practice MSWT would be neccesary and the relatively complex procedures outlined here would need to be followed. The variable next most highly correlated with performance in regression analysis was stature. Regression analysis was repeated using only stature to predict performance; data from trial 1 were used (see equation 4.1a). This model explained 55% of the variation in performance.

The accuracy of the prediction equation was assessed by predicting performance in trial 2. The predicted result was calculated by using the regression equation $Y=A+(B\times X)$, where Y is the

predicted value on the dependent variables (the predicted MSWD in metres), A is the Y intercept (the value Y when the X value is zero), X indicates the rate of the independent variable (stature) and B are the coefficients assigned to each of the independent variables in the regression analysis. Y value can be predicted for each patient, as the patient's own X values were entered (Tabachnick and Fidell 2007).

Actual MSWD showed a high correlation with predicted MSWD (Pearson's r=0.69, p=0.003) when stature was entered into the equation model. Predicted MSWD was computed by using the equation form for each individual. The 5th percentile of MSWT performance distribution of trial 1 was 200 m, so the lower limit of normal range (LLN) was computed by subtracting 200 m from the equation (see equation 4.1b).

Equation 4.1a. MSWD = (10.7 × stature, $_{cm}$) – 1316
Equation 4.1b. $MSWD_{(LLN)}$ = (10.7 × stature, $_{cm}$) – 1116
where: MSWD=distance walked in modified shuttle walk test (m); LLN=lower limit of normal range

4.4. Discussion

The SWT is used in the evaluation of the majority of remaining CVD populations, while it includes a number of biomechanical parameters that might influence SWT performance. Many researchers have used the 10 m SWT to gain information on potential deficiencies in the locomotor system (Bradley *et al.*, 1999; MacSween *et al.,* 2001; Chown *et al.,* 2008). There is no way, however, to determine whether biomechanical predictors (anthropometric features, balance and turning characteristics, for instance) affect SWT results. This study aimed to investigate which biomechanical predictors affect the MSWT score, how they are associated with test performance and how these findings can be used in clinical CR practice. As far as it has been possible to ascertain, the present study is the first to examine the biomechanical predictors and effect on MSWT performance.

The findings of this chapter will be subdivided and each subsection will discuss individual predictors of; step length, turning and test performance. Finally, this section will present and justify the biomechanical variables that can predict MSWT performance and discuss the importance of this finding for the clinical CVD population will be analysed.

4.4.1. Biomechanical predictors of the modified shuttle walking test

In order to assess the influence of these variables on the MSWT, a series of correlations was initially tested between various biomechanics variables and the MSWT outcome measures of distance walked (MSWD) and maximum walking speed. Total distance covered and maximal walking speed constituted the test's score, whereas static (stature, leg length, balance) and dynamic (number of steps to turn, turning time, turning strategy) biomechanical measures were studied for their association with the MSWT performance.

Walking speed is the obvious measure for MSWT performance; MSWD was used to analyse the test's biomechanical predictors, and this will be further examined in this discussion. This is because previous SWT studies used the distance walked to describe SWT performance (Fowler *et al.,* 2005; Campo *et al.,* 2006; Jolly *et al.,* 2008), which is probably due to its use in self-pacing 6-MWT. Also, MSWD refers to real numbers, is more tangible and shows improvement in patients. Thus, MSWD was used as the outcome performance measure for reasons of comparability. The following sections will follow the division given in the results section and will discuss the predictors of step length, turning and test performance (MSWD).

4.4.1.1. Step length associations

Unsurprisingly, stature and leg length were associated with step length at all levels of the MSWT in both assessments. It is logical that anthropometric variables such as stature and leg length

would express a linear relationship with step length (Owings and Grabiner 2004). Murray *et al.* (1964) reported that while walking short people have the shortest stride and tall people have the longest; however, the relationship between people's stature and walking speed remains ill-defined and thus it will be discussed in the following subsections according to the findings of this research.

4.4.1.2. Turning associations

The nature of the MSWT protocol means that it is not simply a walking test. It involves turning every 10 m during the test. Turning might also, therefore predict of MSWD. At faster walking speeds, the number of steps required for turning was significantly correlated with turning time and braking force (Fy); while turning time was significantly correlated with both braking force (Fy) and total vertical impulse (Iz). This means that as the number of steps taken for turning increases, more time is required to complete the turn. Thus, greater deceleration and acceleration forces are being produced to maintain stability and turn the body to continue with the walking task.

Turning variables, such as number of steps and turning time, were correlated throughout the test with anthropometric characteristics, including stature and step length, suggesting that taller people tend to have longer step lengths and thus need less steps to complete a turn. Taller people are perhaps able to cope better with the increase in speed needed in the latter stages of the test than those with shorter step lengths. Turning speed seems to follow walking speed, which was controlled by the test, and on the later levels of the test, taller patients spent less time and took fewer steps to turn.

Turning strategy did not seem to be change at different test levels and the different required turning speeds. The most of the patients performed a step turn at the first stages of the test, while

they used a spin turn for the last levels. That is, when walking speed was increased. Thus, the 'other' foot will land on the plate and a spin turn will be used in order to turn quickly, rather than an extra step taken to ensure a step turn. In general, though, the step turn strategy was observed more often during the MSWTs.

In the present study, and in common with the results of previous studies (Hase and Stein 1999; Akram *et al.,* 2010), the step turn was preferred by the elderly participants, as it is simpler, biomechanically less demanding and a more stable strategy compared to the spin turn. Step turns are characterised by greater muscle activation and better deceleration control before turning. Taylor *et al*. (2005) used a three-dimensional analysis to compare the two turning strategies. They concluded that participants used the step turn strategy more often, as it is simpler, less demanding on the muscles, provides a greater base of support, greater safety and stability.

In this study, the turns were standard and planned; the patients were advised to turn to the left at the end of the 10 m walkway. In previous studies (Hase and Stein 1999; Taylor *et al.,* 2005), where both turning directions (right and/or left) were used, the direction of turning does not, however, seem to play an important role in the results.

4.4.1.3. Predictors of test performance (modified shuttle walking distance)

Three categories of potential MSWT predictors were examined in the present study; turning parameters, balance and finally anthropometric characteristics. These are described below.

4.4.1.3.1. Effect of turning on walking test performance

The recording of turning parameters has been used as an assessment of mobility (Imms and Edholm 1981). The results of the present study showed that turning variables are not associated with MSWD. Imms and Eoholm (1981) found a high level of association between turning time

and the time taken to complete functional tasks in participants with different pathologies (post-stroke, post-myocardial infarction or weakness associated with chronological age). The authors divided the participants into subgroups based on their activity level, but the absence of a control group (such as young adults with normal gait and mobility, or adults who exercise regularly) with which results can be compared is a limitation in this study.

Van Herk *et al.* (1998) found that patients with mobility disorders (post-stroke) require more time to complete a turning task than a straight walking task. However, the walking speed varied considerably between conditions: some patients required less time to complete the turning task than the straight walking task. This might be explained by the different daily activities of each patient, or by the different psychological effects that each of the test conditions may create. The sample of patients in the present study consisted of cardiac patients with normal gait who exercised regularly for long periods of time. The turning issue seems only to affect pathologies that include mobility disorders. Thus, it is logical that these findings did not show any significant correlation with turning, because the present sample was free from locomotor limitations. The present results are in agreement with previous data (Beaumont *et al.,* 1985), which demonstrated that the 12-minute walking test performance does not relate to turning in pulmonary patients. This study used two different walkways (a hospital corridor with a turning, and a flat treadmill).

Studies in the literature have compared functional walking tests (such as the 6-MWT, the twelve-minute walking test and the SWT) performed along a corridor and on a treadmill (Swerts *et al.,* 1990; Revill *et al.,* 1999; Stevens *et al.,* 1999). Two studies found that patients reached higher scores when they had to walk along a corridor rather than on a treadmill (Swerts *et al.,* 1990; Stevens *et al.,* 1999), while another showed the opposite (Revill *et al.,* 1999). This significant variation in results might be due to the fact that some patients may be more familiar with walking along a corridor than with speeding up on a treadmill, and vice versa. Above all these

factors, and according to the results of this research, it can be suggested that turning parameters are not related to MSWD in stable CR patients.

4.4.1.3.2. Effect of balance on walking test performance

Different features of a task may increase or decrease posture stability, when balance is defined as the capacity of the body to control acceleration forces (Massion 1996; Huxham *et al.,* 2001). During demanding movements, such as turning, increased acceleration forces affect the body in general, resulting in changes to biomechanical parameters. During turning, the body's centre of mass lies near the extreme of the base support for most of the task and therefore the body's balance control system works to maintain the centre of mass as much as possible within the limits of base support, ensuring postural stability (Winter 1995; Huxham *et al.,* 2001).

Because of this, balance was assessed while patients stood silently with eyes open and with eyes closed. No statistically significant relationships were found between balance with turning variables (number of steps taken to turn, turning time) and MSWT score (maximal walking speed, total distance). Paquette *et al.* (2008) observed age-related changes in turning variables during the turn task in healthy adults. These authors also noted a reduction in walking speed during turning, and an increase in turning time and step length for older people, compared with young adults. They suggested that older people are more cautious about foot placement because of their impaired balance and locomotor abnormalities, preferring to use a hip strategy, especially during difficult tasks (where many biomechanical parameters are presented), such as turning. The patients in the present study, who were older people, seemed to use a similar (or the same) kinematic strategy; thus, no special skills in balance control are needed to achieve better scores in the MSWT.

Carpinella *et al.* (2007) compared patients with Parkinson's disease with healthy elderly people and found that the former took more steps during the turning task and required more time to turn. In their protocol, patients had to walk straight for 2 m, reach the force plate, make a 90º turn and continue walking in the new direction for 2 more metres. It must be remembered, though, that Parkinson's disease is a neurological disorder with special clinical features, causing disabilities in mobility, which cannot necessarily be compared with the effects of other diseases (such as cardiovascular and cardiopulmonary disease).

The correlations between balance and biomechanical variables during turning (Fy, Iz) were also very weak at all levels of measurement. No significant interaction between balance and age was found. The present results agree with those of Shkuratova *et al.* (2004), who found no statistically significant relationships between age and turning parameters, although they did find that older people had a shortened stride and lower walking speed as compared with younger adults. Kang and Dingwell (2008) also arrive at the same result. Older people utilise a specific strategy (shorter step length and lower walking speed) in order to maintain their posture stability, especially during more demanding tasks.

As noted by Huxham *et al.* (2001), the absence of any statistically significant correlation between balance and MSWT variables (including the biomechanical turning parameters) underlies the difficulty of balance assessment. Especially with samples such as those used in the present research, where patients were all members of a long-term follow-up training CR programme and are accustomed to exercise, the evaluation of balance and the selection of the most appropriate balance test to administer becomes more difficult.

In addition, the present results did not show any significant difference between the two balance tests, which took place with and without visual input (eyes open and eyes closed). Body sway

and postural stability decrease with age, that various pathologies accompany ageing (Hase and Stein 1999; Karlsson and Frykberg 2000), and that the sensory system (vision) is related to the balance and stability of the body (Lord and Menz 2000; Black *et al.,* 2008; Friedrich *et al.,* 2008). The visual system is responsible for the proactive balance mechanism that is mostly utilised during active movement rather than in silent standing (Huxham *et al.,* 2001). In removing visual help during standing, balance does not appear to be influenced to any great extent.

Above all, the current study suggests that balance is not significantly related to MSWD. The present work used the static balance test, as is commonly used with elderly people; however, turning strategies require a dynamic balance. Several studies have shown that both static and dynamic clinical balance tasks are reliable and can identify the state of the balance control system (Heitmann *et al.,* 1989; Allum *et al.,* 2001; Gill *et al.,* 2001).

4.4.1.3.3. Association of anthropometric and gait parameters with walking test performance

In contrast with turning gait variables, several anthropometric characteristics (stature, leg length and step length) supported the hypothesis regarding predictors of MSWD. Step length throughout the test, particularly, was highly correlated with MSWD. This was true even when step length was normalised to leg length as the relation with walking distance remained significant. Corrected step length values were only correlated with MSWD during the latter test stages.

At the beginning of the test, patients walked at an artificially slow pace; to do so they took small steps. Later on in the test, they felt more at ease and were able to walk as normal; they approached their normal walking speed. During latter test levels, when the speed was increased,

patients who were able to make longer steps managed to reach the markers on time; and, thus, they could continue to the next stage. Patients who took small steps during the latter test levels either voluntarily withdrew due to fatigue, or the experimentor stopped them, as they were unable to increase their speed and performed the shuttle on time. These patients, who managed to increase their step length at the later stages of the test, obtained better scores in the MSWT.

Taller patients had longer step length and appeared better able to cope with the increases in walking speed needed at the later stages of the test. Shorter patients were less able to increase walking speed by increasing step length during latter test stages, resulted in poorer MSWD. This can be theoretically illustrated by calculating the Froude number for the MSWTs based on ± 1SD of the mean leg length. The Froude number (v^2/gl; where v is velocity, g is gravitational acceleration and l is leg length) provides a dimensionless number which normalises walking speed to leg length (Steudel-Numbers and Weaver 2006). By calculating this number based on leg length we can see that tall patients walked at a lower Froude number as the shuttle speed (level) increased compared to short patients. Thus the taller patients were walking at a relatively lower proportion of their maximal velocity than short patients, and the walk to run transition speed (0.5 Froude) (Gatesy and Biewener 2009) occurred approximately one shuttle later. This model can also be used to predict maximal walking speed and again shows a bias toward the taller patient. Therefore taller patients, who could continue to increase step length at later stages of the test, were more able to obtain better scores in the test.

This finding is partly in agreement with Imms and Eoholm (1981), who found that walking speed correlated very strongly with stature, leg length and step length. As the MSWT is incremental in nature, walking speed is always positively associated with distance walked (Singh *et al.,* 1992). Hence, characteristics such as long step length and greater stature, which are associated with greater maximal walking speed, are likely to result in better MSWD. Walking

speed is determined by variations of both step (stride) length and cadence. In the present study, cadence (number of steps per minute) was not recorded. Imms and Edholm (1981) noted that the variation of step length in their elderly population was greater than the variation in cadence. Thus, the increase in walking speed in the population of the present study may be due more to the changes in step length than to alterations of cadence.

There was no difference in the MSWD between the two trials. Longer step length during the initial levels of the test was the only variable that was significantly different between trials. This may indicate some adaptation or learning response to the test protocol. Step length, however, correlated with MSWD in both trials. This demonstrates, once more, that cardiac patients who exercise regularly may need some time or more practice to walk in a normal way, especially at the first levels of the test, where the movement is not physically demanding. Walking at speeds slower than those preferred can lead to inefficient or 'awkward' gait patterns (Nymark *et al.*, 2005). Some patients may need a practice MSWT to adapt their gait speed (Fowler *et al.,* 2005; Jolly *et al*., 2008), however it has been argued in Chapter 3 that these potential gait adaptations via a practice MSWT do not influence MSWD.

4.4.1.3.4. Which is the best predictor of modified shuttle walking test performance?

Despite measuring a number of walking and turning gait parameters, only one gait parameter and two anthropometric characteristics predicted MSWD. Step length at 2/3rd of individual maximal walking speed, stature and leg length were all independently associated with MSWD. Regression analysis showed that step length was the most important predictive value for MSWD, but that stature was also significantly correlated with MSWD. In routine clinical assessment, stature is easily assessed, as it is a static measure. Step length, however, is a changeable, dynamic biomechanical characteristic, which cannot be easily measured in clinical practice, especially

amongst the elderly. This is because they display great variability in their step length during walking – a fact that has been attributed to their decreased muscular strength, especially in the leg muscles, resulting in frequent changes in step length during walking, and higher risks of falls (Brach *et al.,* 2001; Kang and Dingwell 2008).

Thus, it was decided that although step length is the best overall predictor of MSWD, a second stepwise linear regression analysis should be carried out, omitting step length. Given that step length is closely related to leg length and stature, a final regression analysis was performed, using only stature to predict MSWD. The use of stature as the predictor of MSWD has clinically utility, because it is easy to measure and is used in the calculation of BMI.

This finding is in agreement with other studies, which have used only static variables (stature, age and body mass, or BMI) in their equation for predicting 6MWD in healthy adults (Enright and Sherrill 1998; Troosters *et al.,* 1999; Gibbons *et al.,* 2001; Enright *et al.,* 2003; Camarri *et al.,* 2006; Chetta *et al.,* 2006; Poh *et al.,* 2006; Jenkins *et al.,* 2009). Particularly, Enright and Sherrill (1998) established predictive equations to estimate the expected distance walked in the 6-MWT for healthy adults (see equation 4.2). Enright (2003) suggested that lower scores correlated significantly with factors such as shorter stature (shorter step length), participants being elderly, higher body mass, female sex, a shorter course distance (more turns), cardiopulmonary diseases and musculoskeletal disorders. Enright and Sherrill (1998), however, studied a healthy population and it needs revalidation in CVD patients, while the findings cannot be generalised from the 6-MWT to the MSWT.

Equation 4.2. Enright and Sherrill (1998)

men: $6MWD = (7.57 \times stature_{,cm}) - (5.02 \times age_{,yrs}) - (1.76 \times body\ mass_{,kg}) - 309$

women: $6MWD = (2.11 \times stature_{,cm}) - (5.78 \times age_{,yrs}) - (2.29 \times body\ mass_{,kg}) + 667$

where: 6MWD=distance walked in six-minute walking test (m)

In the present study, stature accounted for 55% of the variance in the MSWD. Each additional 1 cm of stature predicts that patients will complete an additional shuttle during the test. The mean stature for women (n=7) and men (n=9) in the present study were 159 cm and 174 cm respectively. Using the prediction equation generated here, in a population with similar clinical characteristics to the present sample, it could be suggested that male CVD patients can walk, on average, 160.5 metres more (i.e., 16–17 more shuttles) in the MSWT than women, due to stature differences between the two sexes.

It appears obvious that taller cardiac patients have an advantage over shorter patients when performing an MSWT. In CR programmes, patients usually present with a number of co-morbidities. CVD patients often prefer to walk slowly, while it is not very easy for them to speed up, even though they are fit. The MSWT is an incremental test, which increases in speed gradually at each level. During the later levels, the speed gets quite fast, allowing to the patients to run if they are able to do so. The findings show that taller people benefit more in contrast with shorter ones, as the former are able to obtain longer strides and complete the shuttle. According to phenomenon of regression towards to the mean suggestion, CVD patients who are high performers >610 m (75^{th} percentile) can only improve marginally, whereas low performers <370 m (25^{th} percentile) can improve much more. This phenomenon, in combination with these results, means that tall cardiac patients >176 cm (75^{th} percentile) are likely to improve their MSWD only slightly, in contrast with short patients <162 cm (25^{th} percentile), who can improve greatly after a particular intervention (for example, with CR in the form of exercise activities) (Ostermann *et al.,* 2008).

These findings indicate that the interpretation of MSWD is not accurate and the MSWT is unfair, without taking stature into account. For instance, if the MSWD is not corrected to stature, (i) short patients, who are more likely to attain low scores in MSWT, may be prescribed low-

intensity training in CR; (ii) while tall patients won't be able to show real improvement in their functional capacity after an exercise intervention. Surprisingly, no one has ever examined the association of stature with MSWT in cardiac population.

4.4.2. Study limitations

The application of the above findings might be limited by some methodological issues. One limitation of this study is the sample used, which was relatively small to demonstrate statistically significant relationships between weakly associated pairs of variables. This sample does, however, represent typical participants in a long-term CR programme. Moreover, as far as has been ascertained, no other study in the literature examines the biomechanical predictors for MSWT in the cardiac population. This study may serve as the basis for further studies with larger samples. Furthermore, the patients were all members of a long-term follow-up (phase IV) training CR programme and are accustomed to exercise. Less conditioned patients, such as those entering earlier phases of rehabilitation (phase III CR, UK classification) may demonstrate different associations between gait predictors and MSWD.

Another limitation is the measurement of the balance test, which was conducted only once for eyes open and once for eyes closed. It might be more accurate to perform three measurements for each test, with periods of rest in between, so that the mean value can be used for the measurements. It remains problematic, however, to select an appropriate way of assessing the balance for patients who are accustomed to exercise.

4.5. Conclusion

Previous research has attempted to demonstrate the usefulness of the MSWT in assessing functional capacity. There have been attempts to establish an MSWT threshold, for CVD

mortality; however, the participants in these studies were patients with HF, meaning that their results cannot be generalised to all CVD patients. There are no existing data on biomechanical parameters that may affect patient's MSWD. The MSWT is one of the most popular functional assessment tests for cardiac patients and it is important that these biomechanical parameters should be identified as they relate to the performance of this test. There are a few studies that have demonstrated that stature is associated with 6MWD, suggesting that taller people can walk further than shorter people, for the purposes of this test. The problem is that the study refers to healthy people and thus the results cannot be generalised for the CVD population.

The findings of the present study are important with regard to clinical practice in CR. These data show that tall patients have an advantage in the MSWT and that practitioners should account for stature when interpreting MSWD. By interpreting distance as a percentage of the stature-predicted value, practitioners would gain a more meaningful assessment of individual patient's functional capacity on his/her admission to a CR programme. Adding this simple, predictor (stature) to the standard assessment of functional capacity may help clinicians to provide more realistic expectations and functional improvement targets after a treatment (such as CR). Such modified targets may also make prescribed exercise intensity more accurate and, therefore safe as well as allowing the CR patient to experience real success.

These pilot data are the first to provide specific regression equations to estimate MSWD. While there is a clear need for a larger study to independently validate the present findings, these data may enhance the use of the MSWT as a prognostic tool in stable cardiovascular patients. This study has, however, potentially eliminated the need to further investigate certain gait parameters (turning variables, balance) which are time consuming and expensive. This small study may allow for a larger, more economical study to be conducted using the simple anthropometric predictors of performance (MSWD) identified here.

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CHAPTER 5. PREDICTORS OF THE SIX-MINUTE WALKING TEST PERFORMANCE IN HEART FAILURE PATIENTS

5.0. Abstract

The six-minute walking test (6-MWT) is a simple, safe and inexpensive measure, used to evaluate functional capacity, effects of interventions and to provide prognosis in heart failure (HF) patients. The purpose of this research was to identify the routine, simple measures associated with 6-MWT performance and to establish a reference equation to predict 6-MWT performance.

Seventy-one HF patients (82% males, 18% females, mean age: 76.3±8.6 years, mean body mass index: 28.7±5.1 $kg \cdot m^{-2}$), who were enrolled in a chronic disease assessment programme, completed the 6-MWT. Baseline clinical assessment took place prior to testing and included stature, body mass, body mass index, medical and pharmacological history, ventricular function and New York Heart Association (NYHA) functional class. Patients walked along a 15 m corridor between two cones for six minutes. Patients were allowed to rest if necessary. The number of steps taken in every 15 m shuttle was recorded, and step length was calculated. The total distance walked during the 6-MWT (6MWD) was used to indicate performance. The relationship between 6MWD and potential predictors was assessed using Pearson correlation and multiple stepwise regression analysis. Multinomial logistic regression was used to determine the factors associated with poor 6MWD (≤300 m). Threshold values were identified for dependent (total distance 300 m) and independent variables (age >/< 75; stature >/< 172 cm; body mass index >/< 25 $kg \cdot m^{-2}$; step length >/< 0.63 m; walking pace index >/< 50%; resting heart rate >/< 80 $beats \cdot min^{-1}$; left ventricular ejection fraction >/< 45%). Odds ratios with 95% confidence intervals (CI) were calculated.

The mean 6MWD was 319 (±126) m for males and 253 (±95) m for females. For males (n=58), significant correlations were observed between 6MWD, stature (r=0.254) and age (r=-0.376) for $p<0.05$. For females (n=13), significant correlations were observed between 6MWD and stature (Pearson's r=0.598, $p<0.05$) only; age (Pearson's r=-0.416, $p=0.16$) and body mass (Pearson's r=0.366, $p=0.218$) were correlated moderately with 6MWD but not significantly. Univariate multinomial logistic regression analysis showed that body mass index >25 $kg \cdot m^{-2}$ (OR=12.7, 95% CI=1.45 – 111) and age >75 years (OR=4.9, 95% CI=1.24 – 19) were independent predictors of poor 6MWD (<300 m). Sex-specific regression equations using age and anthropometric data explained 40% and 52% of the variance in 6MWD in males and females, respectively.

Clinical variables such as ventricular function were unrelated to 6MWD in HF patients. Age, stature, body mass index/or body mass were independent predictors of 6MWD; these should be taken into account when the test is used to assess HF patients' functional capacity. These variables appear particularly important when 6MWD is used to categorise patients according to known prognostic cut-off points.

5.1. Introduction

As discussed in Chapter 2 (see '*Introduction to cardiovascular diseases and cardiac rehabilitation: a review in the literature*'), heart failure (HF) is a major cause of death and hospitalization worldwide (Majeed *et al.*, 2005; Papadopoulos *et al.* 2008; Levitan *et al.,* 2009). The European Society for Cardiology (ESC) guidelines state that the prevalence of HF is between 2% and 3% in the general population; this increases with age and reaches 10-20% by 70 to 80 years old (Dickstein *et al.*, 2008). In the UK, the prevalence of HF is 8.3 per 1000 population, increasing with age from 0.02% at the age of 35 years to 12.5% in those over 85 years old (Majeed *et al.*, 2005). According to these epidemiological statements, it is clear that HF is a

medical condition that affects a large part of the population, accounts for most hospital readmissions and relates to poor quality of life for these patients (Jaarsma *et al.*, 1999; Hobbs *et al.*, 2002). A serious, progressive disorder such as HF demands new investigations in the assessment, prognosis and treatment of the disease.

5.1.1. Heart failure: definition

Heart failure may be caused by several disorders, resulting in loss or dysfunction of myocardial muscle tissue. HF is indicated as a syndrome when the left ventricle is unable to maintain cardiac output, meaning that the oxygen supply in the body is insufficient. According to SIGN (the Scottish Intercollegiate Guideline Network 2007) and ESC guidelines (Dickstein *et al.*, 2008), HF is characterised as a syndrome having the following typical features:

- breathlessness at rest or during exertion, fatigue, ankle swelling;
- signs of fluid retention, such as tachycardia, tachypnoea, pulmonary congestion, oedema;
- objective evidence of cardiac dysfunction at rest.

In terms of clinical symptoms and cardiac function, HF is usually progressive (Heart Failure Society of America 2006).

5.1.2. Heart failure: classification

There are many categorisations of HF. This is carried out according to either side of the heart involved, the symptoms and the degree of functional impairment. HF may affect one or both sides of the heart; being characterised as either left-sided (left ventricular dysfunction [LVD]) or right-sided HF (right ventricular dysfunction [RVD]). The effects of LVD, in which the left ventricle of the heart is functionally impaired, are insufficient blood supply to the systemic circulation, reduced left ventricular ejection fraction (LVEF), limited blood return into the pulmonary circulation and increased pressure on the pulmonary capillaries (Hunt *et al.*, 2005;

SIGN 2007; Dickstein *et al.*, 2008; Hunt *et al.*, 2009). The signs of LVD are exertional dyspnoea, pulmonary oedema, short breath, cyanosis, cold skin and hypertension. RVD, in which the right ventricle of the heart is functionally impaired, is usually the result of advanced LVD. When the left ventricle fails to work properly, blood often returns back to the lungs, triggering pulmonary circulation disorders and thus RVD. The results of RVD are a variety of pathologies, like pneumonia, pulmonary embolism and acute right ventricular infarction (Hunt *et al.*, 2005; Dickstein *et al.*, 2008; Hunt *et al.*, 2009).

LVD may then be sub-divided into two further types: left ventricular systolic dysfunction and left ventricular diastolic dysfunction. Left-ventricular systolic dysfunction refers to a syndrome where the left ventricle is unable to contract enough to pump oxygen-rich blood into the systemic circulation; while in left ventricular diastolic dysfunction, the left ventricle loses the ability to fill with enough blood during the relaxation period between each beat. This often occurs due to increased left ventricle muscle stiffness or mitral valve damage.

Clinicians usually assess HF severity using the NYHA functional classification system (American Heart Association 1994; Heart Failure Society of America 1999; Heart Failure Society of America 2006) (see table 5.1). This classification is based on symptoms observed during everyday activities.

The European Society of Cardiology (ESC) guidelines (Dickstein *et al.*, 2008) classify HF in relation to three categories, according to duration and the severity of the symptoms: a) new onset HF describes new symptoms; b) transient HF refers to recurrent symptomatic HF, and c) chronic heart failure describes persistent HF, which might be stable or might worsen, leading to hospital admission in most cases (80%).

Table 5.1. NYHA functional classification in patients with heart failure (AHA 1995; HFSA 1999, 2006)

Class	Severity according to symptoms and functional capacity
Class I (Mild)	Patients with cardiac disease who are able to do any physical activity without discomfort. Regular physical activity does not cause fatigue, palpitation or dyspnea.
Class II (Mild)	Patients with cardiac disease, but with slight limitation of physical activity. They feel comfortable at rest. Regular physical activity results in fatigue, palpitations, or dyspnea.
Class III (Moderate)	Patients with cardiac disease with marked limitation of physical activity. They feel comfortable at rest. Minimal physical activity causes fatigue, palpitation or dyspnea.
Class IV (Severe)	Patients with cardiac disease with inability to carry on any physical activity without discomfort. They have symptoms of cardiac insufficiency present at rest (angina symptoms). If any physical activity is undertaken, discomfort is increased.

5.1.3. Heart failure risk factors

Hypertension and previous MI are the major risk factors for HF, increasing the likelihood of HF occurrence by 2 to 3 times (Gottdiener *et al.*, 2000; He *et al.*, 2001; Wilhelmsen *et al.*, 2001; Abramson *et al.*, 2001a, 2001b; Schocken *et al.*, 2008). The Framingham Heart Study demonstrated that hypertension increases the risk for developing HF two-fold in men and three-fold in women (Levy *et al.*, 1996; Schocken *et al.*, 2008). An increased systolic blood pressure and an increased HR predict HF development than an increased diastolic blood pressure (Haider *et al.*, 2003). Hypertension promotes an increase in afterload, triggering abnormal myocyte cell growth (hypertrophy), myocardial fibrosis and loss of myocardial contractile function. All these parameters decrease the functional myocyte reserve myocardial blood flow and flow reserve (Gradman and Alfayoumi 2006; Schocken *et al.*, 2008).

Diabetes mellitus is an independent risk factor for HF, increasing the risk of HF development by 2 to 3 times (Kannel *et al.*, 1974; Abramson *et al.*, 2001a, 2001b; Wilhelmsen *et al.*, 2001;

Kenchaiah *et al.*, 2004b; Schocken *et al.*, 2008). Every 1-mmol·l^{-1} -higher fasting plasma glucose, creates a 1.1 fold increase in the risk of HF hospitalisation (Held *et al.*, 2007).

Obesity is an independent risk factor for HF, due to increased cardiac demand, preload and afterload, neurohormonal upregulation, sleep-disordered breathing and chronic kidney disease observed in obese patients (Kannel *et al.*, 1974; He *et al.*, 2001; Kenchaiah *et al.,* 2002, 2004a, 2004b). Obese people have double the risk of HF than normal-weight people (Kenchaiah *et al.*, 2004a; Schocken *et al.*, 2008). Findings from the Framingham Heart Study showed that, for each unit increase in body mass index (BMI), there is a 5% increase in the risk of HF in men and 7% in women (Hubert *et al.,* 1983). More recent studies demonstrate that normal-weight HF patients have a higher incidence of morbidity and mortality than obese HF patients (Curtis *et al.*, 2005; Fonarow *et al.*, 2007). This apparently paradoxical outcome may be due to unmeasured markers (such as plasma norepinephrine, brain natriuretic peptide concentrations) (Curtis *et al.*, 2005) or increased catabolic stress that occurs in underweight or normal-weight HF patients (Fonarow *et al.*, 2007). However, further investigation is needed on this topic to investigate the mechanisms by which a high BMI appeared to be protective against hospitalization and morbidity in HF patients.

Several other risk factors associated with HF to a lesser extent than those listed above include: smoking, excessive alcohol consumption, dyslipidemia, sleep-disordered breathing, chronic kidney disease, albuminuria, C-reactive protein homocysteine, natriuretic peptides, anaemia, unhealthy dietary habits, increased heart rate (HR), low socioeconomic status, psychological stress and genetic factors (Schocken *et al.*, 2008). The presence of these traditional risk factors for CHD is associated with a progression of asymptomatic LVD, contributing to the development of HF.

The prevalence of HF increases with age. Particularly in women, the incidence of HF increases more than two-fold between 65 and 85 (Kannel *et al.*, 1999; Kitzman *et al.*, 2001; Levy *et al.*, 2002; Kenchaiah *et al.*, 2004b). Men have an increased overall incidence of HF in contrast with women, because of their increased risk of CHD (Gottdiener *et al.*, 2000; He *et al.*, 2001; Wilhelmsen *et al.*, 2001; Abramson *et al.*, 2001a, 2001b; Schocken *et al.*, 2008).

5.1.4. Prevention of heart failure

Coronary heart disease constitutes the major cause of HF disease; due to atherosclerotic CHD, less blood is supplied to the heart, damaging the heart muscle and so the cardiac pump performance. Thus, the prevention of HF should be focused firstly on CHD prevention, via management of hypertension, dyslipidemia and diabetes (McKee *et al.*, 1971; Gottdiener *et al.*, 2000; He *et al.*, 2001).

5.1.5. Clinical assessment of patients presenting with heart failure

Early diagnosis of HF is crucial for effective treatment (Lewis 1933). ESC 2008 guidelines and the updated ACC/AHA 2009 guidelines recognise that the information obtained from the patient interview and physical examination are usually the main tools for identifying the presence, aetiology and severity of HF. The interview assessment is based on clinical symptoms, signs and medical history. The physical examination includes assessment of body mass, stature, BMI calculation, pulse, orthostatic blood pressure, jugular venous distension, peripheral oedema, lung function (respiratory rate, rales, pleural effusion) and third and fourth heart sounds (Dickstein *et al.*, 2008; Hunt *et al.*, 2009).

Laboratory tests are also used to identify the presence and level of the disorder. The most common diagnostic tests are electrocardiogram (ECG), echocardiogram, chest X-ray and blood

tests. Resting ECG is regarded as the gold standard in detecting left ventricular remodelling or hypertrophy, or previous myocardial infarction (Hunt *et al.*, 2005; Dickstein *et al.*, 2008). Atrial and ventricular arrhythmias are common findings in patients with HF (Wenger *et al.*, 1990). Atrial fibrillation is usually prognostic marker for the severity of HF (Stevenson and Stevenson 2004).

An echocardiogram is an ultra-sound test, which measures the left ventricular size, volume, function and wall thickness. LVEF is one of the most commonly clinical parameter that is usually taken during an echocardiogram and is used to evaluate the left ventricular function. The ESC (2008) characterised an LVEF <45–50% as left ventricular systolic dysfunction. Also, left ventricular end-diastolic diameter (LVEDD) >55–60 mm, and left ventricular end-systolic diameter (LVESD) >45 mm refer to HF abnormality.

A chest x-ray may also be used to detect cardiac enlargement, pulmonary congestion or pleural fluid accumulation. Blood tests, including serum electrolytes, blood glucose, liver function tests, lipid profile and thyroid function, are also commonly used in HF diagnosis (Hunt *et al.*, 2005; Dickstein *et al.*, 2008). Taken together, these tests provide useful information about heart muscle function. The NYHA classifications use functional capacity in their definition of HF, and one of the key observable features of the HF patient is low functional capacity. Because of this, there has been much scientific interest in assessing functional capacity in HF patients (Hunt *et al.*, 2005).

5.1.6. Functional capacity assessment of patients presenting with heart failure

Cardiac insufficiency due to HF means there is a decreased oxygen supply to the whole body, including the skeletal muscles. HF patients can present dyspnea, muscle fatigue and exercise intolerance. These symptoms usually affect the patient's functional capacity. Functional capacity refers to the capability of performing aerobic activities and tasks, which requires additional effort

of the cardiovascular system to deliver oxygen into the muscle tissues. The assessment of functional capacity and cardiac (in)sufficiency can provide diagnostic and prognostic information about patients with suspected HF (Fleg *et al.,* 2000).

At the initial assessment, the patient is usually asked to describe activities that they would like to carry out but are not able to perform. Sometimes the clinician asks the patient to perform some specific tasks, like walking and climbing stairs. Many methods have been investigated to describe the functional limitation of HF patients. One of the most common is the NYHA functional classification, described above (Hunt *et al.*, 2005). Both individually administered questionnaires and NYHA classification are unable to measure functional capacity accurately. However, both tests are based on the patient's self-assessment, and because they cannot measure exercise tolerance accurately their accuracy in assessing the functional capacity of HF patients is also limited.

Exercise testing of HF patients is a practical assessment tool for delivering a variety of outcome measures, which can be interpreted in many ways. The interpretation of exercise testing outcomes not only provides diagnostic and prognostic information about HF patients, but also shows responses to treatment and can assist in the selection of cardiac transplant candidates (Aaronson *et al.*, 1997; Osada *et al.*, 1998; Ramos-Barbon *et al.*, 1999; Lewis *et al.*, 2001).

The gold standard assessment of the functional capacity test is typically a laboratory-based cycle ergometer, or treadmill exercise protocols, due to their ability to provide a direct and easy measurement of maximal functional capacity via expired gas analysis (maximal oxygen uptake [VO_{2max}]) (Weber *et al.*, 1982). Treadmill exercise appears to be more valid than the cycle test in determining VO_{2max} in patients with HF. Cycle ergometer exercise typically results in a 10% lower VO_{2max} than the treadmill test, due to local muscular fatigue and the recruitment of a

smaller muscle mass during cycling (Page *et al.*, 1994; Lainchbury and Richards 2002). Treadmill walking tests involve exercise with both upper and lower body muscles. HF patients reach higher levels of oxygen uptake during the treadmill test than during cycle ergometer test, which involves only the lower body muscles in exercise (Jondeau *et al.*, 1992).

As well as the practical differences between the two protocols (treadmill and cycle ergometry), both have some disadvantages that make them difficult to use in HF patients who typically presents with multiple disorders. Familiarisation with the equipment and the protocol are important in order for participants to satisfactorily perform these tests. Most HF patients are elderly and often not accustomed to cycling or treadmill walking. Often, such patients do not feel comfortable enough to exercise with a mask and a nose clip when the test is used for gas analysis, as well (Page *et al.*, 1994; Lainchbury and Richards 2002). It should also be emphasised that maximal cardiopulmonary tests are not used frequently in patients with a severe disease, such as HF, as patients are often unable to cope with maximal effort tests (SEOSI Investigators 1997; Demers *et al.*, 2001).

For all these reasons, and others referred to in Chapter 3 (see '*Long-term reliability of the modified shuttle walking test in clinically stable cardiovascular disease patients*'), alternative, practical, inexpensive and simple functional capacity tests based on walking have been developed. The six-minute walking test (6-MWT) is one of the most used functional capacity assessment tests for HF patients. It has been tested for its reliability, validity, use in HF prognosis and is discussed below (Peeters and Mets 1996; Enright *et al.*, 2003).

5.1.6.1. Six-minute walking test

5.1.6.1.1. Development

As mentioned in Chapters 3 and 4, the 6-MWT was originally developed by Guyatt *et al.* (1985a) and is a functional capacity sub-maximal test for patients with HF. This test has been used to assess patients with pulmonary diseases (Steele 1996; Redelmeier *et al.*, 1997) and cardiovascular diseases patients (CVD) (Faggiano *et al.*, 2004; De Feo *et al.*, 2009). The 6-MWT is a functional capacity assessment test used for patients with severe cardiac dysfunction or who cannot be assessed with maximal exercise tests (such as treadmill or cycle ergometer tests) (Guyatt *et al.*, 1985a; Peeters and Mets 1996; Larsen *et al.*, 2001). Such traditional maximal exercise assessment protocols may be difficult and uncomfortable (for the reasons referred to above) for elderly and severely limited patients, such those with HF (Guyatt *et al.*, 1985a).

During the original 6-MWT protocol, the participants are instructed to walk repeatedly shuttles of a 33 m course and to cover as much distance as possible in six minutes (Guyatt *et al.*, 1985a). They are allowed to determine their own pace and are permitted short rest periods during the test if necessary. At the end of a 6-min period, the test is terminated, and the distance walked during the 6-MWT (6MWD) is calculated by the tester. A functional capacity test should, also, be both valid and reliable for appropriate use in clinical practice.

5.1.6.1.2. Six-minute walking test: validity, reliability and sensitivity

Reliability and validity are two necessary features of any test of functional capacity. A third feature, linked to validity, is sensitivity, which is the ability of the test to detect changes in functional capacity if they are present. Most studies suggest that the 6-MWT is a valid, reliable,

sensitive assessment of functional capacity in patients with HF. These studies are discussed below.

Validity and reliability

Zugck *et al.* (2000) evaluated the validity of the 6-MWT in patients with stable HF (n=113), by comparing 6MWD with a symptom-limited cycle ergometer exercise test during which VO_{2max} was recorded. Ten patients repeated the 6-MWT three times within three days. The results showed high reliability of the 6-MWT with an intraclass correlation coefficient of R=0.96. The authors also examined the ability of 6-MWT to predict individual $VO_{2max.}$ They demonstrated a high correlation between distance covered during the 6-MWT and both the actual (r=0.68, $p<0.01$) and the predicted VO_{2max} (r=0.61, $p<0.01$). Over a follow-up period (381±170 days), both 6-MWT and cycle exercise test were performed two times by 28 patients and three times by 14 patients. Thus, the authors suggested an equation form for follow-up performance in stable HF patients, based on the 6-MWT and the cyclo-ergometer test (see equation 5.1).

Equation 5.1. Zugck *et al.* (2000)

VO_{2max} (at follow-up) = [VO_{2max} (at initial visit)] × [6MWD (at follow- up)/6MWD (at initial visit)]

where: VO_2max=maximal oxygen uptake ($ml \cdot min^{-1} \cdot kg^{-1}$); 6MWD=distance walked in six-minute walking test (m)

These authors (Zugck *et al.*, 2000) recommended this equation for individual prognosis in HF. They demonstrated that HF patients with VO_{2max} <10 $ml \cdot min^{-1} \cdot kg^{-1}$ have almost double the risk of mortality than those with VO_{2max}=10-14 $ml \cdot min^{-1} \cdot kg^{-1}$, at 1-year. This equation, however, is not routinely used in clinical practice as it requires the performance of two different exercise tests. This process is time consuming, while the cycle ergometer test may be unsuitable for elderly HF patients, as explained above.

Kervio *et al.* (2004) assessed the validity of the 6-MWT by comparing it with a symptom-limited treadmill exercise and its reliability in patients with moderate HF (n=24). The 6-MWT was reliable and gave similar results to a sub-maximal treadmill exercise test, equal to nearly 90% of VO_{2max}. The authors found differences in VO_{2max} and maximal HR values at different times of day, and suggested that such daily differences are critically important for the accurate assessment of functional capacity in HF patients. The authors also suggested that the 6-MWT should be performed at a consistent time of the day in order to evaluate VO_2 and HR with more accuracy. They also recommended validation of the results across a larger sample and the assessment of daily 6-MWT reliability in patients with severe HF.

Roberts *et al.* (2006) validated the 6-MWT against a treadmill exercise test, using 38 clinically stable patients (post-MI or post-revascularisation). Patients were assessed twice (before and after 8 weeks of exercise training) using both the sub-maximal treadmill test and the 6-MWT. The exercise intensity of the 6-MWT was lower than the treadmill test: a higher HR was observed at the end of the treadmill test. Neither test was able, however, to identify improvements in cardiovascular function and workload achievement after the exercise programme. The authors concluded that the 6-MWT was a valid and safe assessment tool, which can give the same results as a sub-maximal treadmill exercise test of nearly 85% of the age-predicted maximum HR.

Reliability

Demers *et al.* (2001) examined the reliability of the 6-MWT by assessing the effects on this test of drug treatments such as angiotensin II receptor antagonist and β-blockers. The authors reported high reliability of the 6-MWT after assessing 768 HF patients twice at baseline, and then again at 18 and 43 weeks. Each set of measurements was averaged. It was concluded that the 6-MWT is a highly reproducible (ICC=0.91 after 43 weeks) assessment tool for HF patients and it is not sensitive to changes after taking β-blockers or placebo pills. This was the first study

that examined the reliability of the 6-MWT over such a long-term (12 months), however, the clinical conditions (such as co-morbidities of hypertension, diabetes mellitus, chronic obstructive pulmonary disease) were not controlled.

Ingle *et al.* (2005) described the 6-MWT as a convenient test of functional capacity in HF patients, by demonstrating the long-term (1 year) reliability in this patient group. The authors used a questionnaire to assess perceived symptoms during physical exertion. The authors took into account the patients' clinical conditions; patients who reported unchanged symptoms after a 1-year follow-up evaluation were used for the reliability analysis. The 6-MWT was sensitive enough to detect self-perceived symptom changes, and that when the symptoms did not change, the 6MWD was reproducible. Ingle *et al.* (2005) used a large cohort of patients (n=1,077) at the initial assessment; the reproducibility analysis, however, was only based on 7% of the cohort (n=74), and it seems likely that this is a very selective subsample, from which it may not be easy to generalise. One limitation of the study was the large variation in 6MWD observed, especially in women. This is might be due to many factors not measured in their protocol, including psychological status. Psychological impairment (i.e., distress, depression) is a common condition in HF and is associated with deterioration of HF symptoms, functional capacity and quality of life over time (Steptoe *et al.*, 2000; Rumsfeld *et al.*, 2003; Opasich *et al.*, 2008). These psychogenic symptoms may affect 6MWD (Gottlieb *et al.*, 2009).

Sensitivity

Meyer *et al.* (1997) used the 6-MWT and a symptom-limited cycle ergometer test to assess hospitalised patients (n=18) with severe HF enrolled in a three-week exercise programme and in a three-week activity restriction programme. There was a significant (65%) increase in walking distance after exercise training but a non-significant decline after activity restriction. The improvements in 6MWD showed a significant correlation with VO_{2max} measured during cycle

ergometer test. The authors concluded that the variation in 6MWD can be used to identify the short-term effects of exercise interventions in patients with severe HF.

A randomized controlled study (Owen and Croucher 2000) examined the effects of a twelve-week exercise programme involving elderly HF patients with an average age of 81 years. The 6-MWT was used to evaluate functional capacity and showed a significant (20%) improvement in 6MWD: an increase in walking distance of 40 m. A control group showed a significant decrease in their 6MWD after twelve weeks, which the authors described as being a result of the natural development of the disease. This was despite no significant change in their NYHA classification or quality of life as assessed by the Living With Heart Failure Questionniare (LWHQ). This indicates the high sensitivity of the 6-MWT in investigating not only improvement but also deterioration in the functional capacity of HF patients after an exercise programme.

A waiting list controlled study (Wright *et al.,* 2001) of 239 CVD patients, suggested the 6-MWT was a simple and effective test which can be used to diagnose an improvement in the functional capacity of CVD patients who embarked on a specific six-week cardiovascular exercise programme. This study of 209 patients, who entered the CR programme, and a control group of 30 patients, who delayed joining the CR programme for six weeks, showed that CR improves significantly 6MWD in the cardiac population ($p<0.001$). There were no follow-up data to assess the reliability of the 6-MWT or longer term changes in 6MWD.

It is clear from this discussion that the 6-MWT is reliable, valid and has a justified role in measuring functional capacity and limitation in HF patients. The test is easy to perform, and the results are easy to interpret (Larsen *et al.*, 2001). Functional capacity is an excellent prognostic tool when derived from maximal laboratory-based tests (Kwok *et al.*, 2002; Mora *et al.*, 2003;

Jouven *et al.*, 2005). A number of studies have also focused on the 6-MWT as a potential prognostic marker of mortality for the HF population, and these are discussed below.

5.1.6.1.3. Heart failure and prognosis: the role of the six-minute walking test

A number of variables can be used in the prognostic evaluation of patients with HF. Some are clinical measures tests, such as type-B natriuretic peptide, C-reactive protein (blood tests) or LVEF (echocardiography) (de Groote *et al*., 2004; Anand *et al.*, 2005). Others are measured during clinical exercise testing, such as peak oxygen consumption, ventilatory efficiency, HR response and the 6-MWT (Francis *et al.*, 2000; Davies *et al.*, 2006; Kubrychtova *et al.*, 2009).

de Groote *et al.* (2004) found that plasma levels of type-B natriuretic peptide (BNP), in combination with VO_{2max}, were independent prognostic indicators of risk stratification in patients with stable HF. They reported that patients with a BNP $\geq$109 pg·ml^{-1} and VO_{2max} $\leq$7 ml·kg^{-1}·min^{-1} had a greater likelihood of mortality within two years; they had double the likelihood of cardiovascular mortality compared with patients with a BNP <109 pg·ml^{-1}. Anand *et al.* (2005) demonstrated that C-reactive protein (CRP) was an independent predictor of HF and mortality. They reported that higher levels of CRP were associated with adverse clinical outcomes (a worse hemodynamic and neurohormonal profile, increased risk of ischaemic/non-ischaemic events) and increased risk of mortality.

The prognostic capability of VO_{2max} determined from treadmill exercise is well established in HF patients. There is significant variation in prognostic VO_{2max} cut-off points. Reduced VO_{2max} is typically associated with poor prognosis in HF patients. For example, low VO_{2max} threshold ($\leq$10 ml· kg^{-1}·min^{-1}) implies a bad prognosis, while a high VO_{2max} threshold ($\geq$18 ml·kg^{-1}·min^{-1}) implies a good prognosis, within 2 years with medical treatment in patients with HF (Opasich *et al.*, 1998; Francis *et al.*, 2000; Gitt *et al.*, 2002).

Such clinical prognostic markers are valuable in laboratory assessments, because they are predictive in detecting the severity of HF disease. Such measures are not easy to obtain in routine clinical practice; they are costly and time consuming. Conversely, the 6-MWT offers an easy, quick, low-cost prognostic measurement. The prognostic value of 6-MWT in HF patients is well established; and will be discussed below. However, it would be worthwhile identifying the parameters (clinical and non-clinical measures) associated with 6MWD and individual cardiovascular prognosis. For instance, some non-modifiable factors (anthropometric, age, sex) might be able to overestimate or underestimate the individual patient's prognosis. In this case, the prognostic cut-off points or individual walking performance should be corrected to these prediction parameters.

5.1.6.1.3.1. Analysis of prognostic studies

The Left Ventricular Dysfunction Study (Bittner *et al.*, 1993) was one of the first large-scale (n=898) studies to demonstrate that the 6-MWT could be used as a prognostic marker in patients with HF. Distance walked in the 6-MWT correlated significantly with 1-year mortality; patients who achieved MSWD scores of less than 300 m had a higher risk (OR=1.77, 95% CI=1.38 – 2.26) of dying or being hospitalised over one year compared with patients who achieved >300 m.

Cahalin *et al.* (1996) evaluated patients with advanced HF (n=45) who had been referred for heart transplantation evaluation. The patients underwent both a symptom-limited cycle ergometer test and a 6-MWT. Distance walked was related to VO_{2max} and they devised the relevant equation (see equation 5.2).

Equation 5.2. Cahalin *et al.* (1996)

$VO_{2max} = (0.03 \times 6MWD) + 3.98$

where: VO_2max is maximal oxygen uptake ($ml \cdot min^{-1} \cdot kg^{-1}$) and 6MWD=distance walked in six-minute walking test (m)

The authors (Cahalin *et al.,* 1996) also reported that a 6MWD of less than 300 m increased the likelihood of death or hospital admission for inotropic or mechanical support for transplantation within the next 6 months (40% versus 12%, p=0.04). Walking a distance of more than 300 m in the 6-MWT failed to predict long-term or event-free survival, in this group of patients. This finding was in contrast with the VO_{2max}>14 $ml \cdot min^{-1} \cdot kg^{-1}$, which was a significant predictor of long-term survival.

Roul *et al.* (1998) found that poorer 6MWD (≤300 m) could predict mortality and morbidity (hospitalisation for HF) in patients with mild-to-moderate HF (NYHA class II or III). The study was performed in 121 patients followed over 1.53 (±0.98) years using a symptom-limited cycle ergometer test with VO_{2max} and a 6-MWT. The 6MWD correlated significantly with the VO_{2max} from the cycle ergometer test. When a distance of 300 m was used as a threshold, the 6-MWT was a significant prognostic indicator for mortality and morbidity in this population. They demonstrated that the percentage of short-term (500 days) event-free survivals were almost 75% for patients who walked between 370 m and 450 m and 50% for patients who walked ≤370 m in the 6-MWT. Similarly, Rostagno *et al.* (2003) investigated whether the 6-MWT could be used as a simple and reliable tool for prognosis of cardiac death in patients with mild to moderate HF (n=214). They found that patients with a 6MWD of less than <300 m had higher mortality rates at 36 month follow-up compared with those who scored >300 m (82% versus 62%, p=0.01).

Curtis *et al.* (2004) found that HF patients who walked <200 m in the 6-MWT had an increased risk of death over a 32-month period compared with those who walked >200 m (43.9% versus 23.3%, p<0.001). They suggested that 200 m was a preferable threshold point for mortality prognosis in HF patients. This is in opposition to most other studies which have recommended 300 m. Curtis *et al*. (2004) found that although all-cause mortality for patients who walked <200 m was higher than those walked >200 m, the mortality rates among those patients who walked

more than 200 m (201-300 m, 301-400 m, and >400 m) were similar. Similar results were confirmed in more recently study (Arslan *et al.,* 2007), when stable mild-to-moderate HF patients (n=43) were studied. The death risk was higher in patients who walked ≤300 m in the 6-MWT and in patients whose LVEF was ≤0.30%. There were several limitations to this study (Arslan *et al.,* 2007), including a small sample size and the fact that a significant percentage of the initial patients were lost in the follow-up (30%) and the relatively short study duration. Despite this, the 6-MWT was found to be a reliable and independent predictor of cardiac death.

Conversely, Opasich *et al.* (2001) found that, in 315 patients with moderate-to-severe HF, 6-MWT distance did not correlate with cardiac function (haemodynamic data), while it was moderately correlated with functional capacity measured by cycle ergometer. The 6-MWT did not provide additional useful prognostic information in this population and could not be used to complement or replace VO_{2max} measurements and NYHA classification. There were methodological differences between this and other studies, which may explain different findings. The participants were patients with more severe HF than those who participated in the above studies. Moreover, the authors reported that no encouragement was given to patients during the test, while the test was repeated twice, with only a 30 min interval between test administrations, and the average score was taken as the walking performance distance for each patient. Factors such as learning effect, tiredness resulting from the shortness of the interval between the two tests and the lack of encouragement, might have created limitations in terms of the participants being able to reach their anaerobic threshold during the 6-MWT. Nevertheless, assessment in routine clinical practice differs from laboratory assessment, since it usually includes only one 6-MWT – thus avoiding these problems.

Ingle *et al.* (2006) investigated clinical values related to poor 6MWD in 571 HF patients. Being older, of female sex, having a higher BMI, lower haemoglobin concentration, increased resting

HR, elevated serum creatinine and NT-proBNP were all associated with poor 6MWD. The authors attempted to demonstrate the relationship between clinical measures and functional capacity, but failed to clarify which variables were 'cause' and which were 'effect'. This might be due to methodological limitations, such as a lack of detailed examinations of their patients' medical histories. The results remain valuable because poor 6MWD (<300 m) relates to a high incidence of morbidity and mortality in HF patients and thus all the clinical measures associated with poor 6MWD can also aid prognosis. Ingle *et al.* (2007) also performed a follow-up study at 36.6 months (initial population of 1,592 HF patients), and demonstrated that the 6-MWT was an independent predictor of mortality in this population. This was true especially for patients with severe left ventricular systolic dysfunction. NT-proBNP was the strongest independent predictor of mortality in this population.

Measures of LVEF are considered important prognostic indicators in HF. Traditionally low LVEF (≤50%) provides poor prognosis in HF (Ahmed *et al.*, 2002; Gottdiener *et al.*, 2002). New guidelines suggest that left ventricular systolic dysfunction is diagnosed only when LVEF is <45% (ESC 2008). Recent data showed that preserved LVEF (≥50%) does not necessarily imply freedom from increased risk of mortality, while they suggested that reductions in HF mortality risk are higher in patients with low LVEF (≤50%) (Bhatia *et al.*, 2006; Owan *et al.*, 2006). A variety of alternative clinical (cholesterol, triglycerides, hypertension and diabetes mellitus) and non-clinical (sex, age) variables describing the HF population also influence the likelihood of mortality.

Assessment of such clinical predictors requires specialist equipment and advanced training for clinicians and is thus not easy to carry out in daily clinical practice. In this case, reliable, simple and easily used measures, like the 6-MWT, can be used as a simple prognostic marker of cardiac death in HF. It seems that a walking distance of 300 m in the 6-MWT is a useful cut-off value

and prognostic indicator of mortality and morbidity (hospitalisation) in patients with mild-to-moderate and advanced HF. Other clinical measures can also be used as determinants of poor 6MWD and, thus, of a poor prognosis. Clinical measures, like LVEF, are not associated with poor 6MWD (Ingle *et al.*, 2007). There seem to be other factors influencing the 6MWD.

A review of the literature reveals an absence of research regarding how simple measures, including anthropometry, gait characteristics or basic clinical measures, may affect 6MWD in an HF population. In particular, researchers have not studied the effect that anthropometric and gait measures, such as step length and pacing index, might have on 6MWD in the HF population. Prognostic studies have not considered non-clinical factors (anthropometric and gait), when determining thresholds for 6-MWT in HF patients. These shortcomings in the clinical literature exist, despite established evidence that such factors influence walking test performance. These data are discussed below.

5.1.6.1.4. Associations between anthropometric variables and six-minute walking test performance in healthy adults

There is good evidence for associations between anthropometric variables and 6MWD in healthy adults (Enright and Sherrill 1998; Troosters *et al.*, 1999; Gibbons *et al.*, 2001; Enright *et al.*, 2003; Camarri *et al.*, 2006; Chetta *et al.*, 2006; Poh *et al.*, 2006; Jenkins *et al.*, 2009). In all of these studies, age and stature were included as independent predictors of 6MWD. Within these studies, it is acknowledged that taller and younger healthy people can walk further in the 6-MWT than shorter and older people; but it is not known whether taller and younger HF patients can walk further in the 6-MWT than shorter and older patients. Creating prediction equations in healthy adults might be useful, but authors have assumed that the same basic parameters (age, sature, sex, weight, BMI) influence 6MWD in HF patients. There is only one similar study in a clinical population (Ingle *et al.*, 2006). These authors did not, however, include stature in their

prediction equations. Further discussions of these studies will appear in the discussion section (see section 5.4).

Given that exercise prescription and even some clinical decisions may rest on a patient's 6MWD, it would seem important to know whether anthropometric and gait parameters significantly influence 6MWD. This study will clarify whether the predictors of 6MWD are the same as those in healthy adults. These issues should be investigated further to help in the improvement of cardiac assessment, rehabilitation and prognosis in this population.

5.1.7. Aims

The results and discussion of the findings in this chapter will discuss the two aims of this study.

i. to identify whether routinely measured, non-clinical (sex, age, anthropometric and gait parameters) and clinical characteristics can predict 6MWD in HF patients.
ii. to establish a reference equation for individual prediction of 6-MWT distance in patients with HF.

These indicators can be used to describe the 6MWD more efficiently in the individual patient, on his/her admission to a CR programme.

5.2. Methods

5.2.1. Participants

Seventy one adult volunteers (58 males and 13 females; aged 52 to 91 years) with stable HF volunteered for the study. Of these, 93% had left ventricular systolic dysfunction (LVEF ≤ 40%) ; 7% had diastolic HF. All patients were in stable NYHA functional classes I-III. The functional capacity of 16 patients was class I, 42 were in class II and the remaining 13 were in class III. All

the patients were taking treatment for stable HF, including angiotensin-converting enzyme (ACE) inhibitors, diuretics, β-blockers, statins, cardiac glycoside, aspirin, anticoagulants and others. Table 5.2 summarises the clinical characteristics of the study population.

Patients were recruited from a community HF clinic and were clinically reviewed as part of a routine screening appointment. Inclusion criteria were evidence of left ventricular systolic dysfunction and symptoms of HF (NYHA class I-IV). Patients had suffered from the disease for at least six months before the study. Patients were studied when they were clinically stable, without any changes in medication during the previous three weeks. Patients with severe locomotor limitations were excluded from this study. Heart failure was defined in accordance with guidelines from the National Institute for Clinical Excellence (NICE) (2003) and the European Society of Cardiology (Remme and Swedberg 2002).

The study conformed to the declaration of Helsinki (World Medical Association 2009) guidelines for research with human participants. The protocol was approved by the Hull and East Riding ethics committee. Informed written consent was obtained from all patients before enrolment.

Table 5.2. Clinical characteristics and baseline measurements of the heart failure patients (n=71)

Variable	Value
Age (years) (mean ± SD)	76.3 ± 8.6
Sex	
Males	58 (82%)
Females	13 (18%)
Cause (%)	
Left ventricular systolic dysfunction	93
Diastolic heart failure	7
NYHA class (mean ± SD)	2 ± 0.6
Class I (%)	23
Class II (%)	59
Class III (%)	18
Body mass (kg) (mean ± SD)	84.2 ± 17.6
Stature (cm) (mean ± SD)	171 ± 9
Median value	172
BMI ($kg \cdot m^{-2}$) (mean ± SD)	28.7 ± 5.1
LVEDD (mm) (mean ± SD)	46.8 ± 9.1
LVEF (mean ± SD) (%)	42.2 ± 12.1
LVESD (mm) (mean ± SD)	47.1 ± 11.3
ECG rhythm	
Sinus	47 (66%)
Atrial fibrillation	16 (23%)
Vetricular pacing	3 (4%)
Other	5 (7%)
Resting HR (bpm)	67 ± 13
ACE inhibitors	n=53 (75%)
β-blockers	n=57 (80%)
Diuretics	n=55 (78%)
Statin	n=46 (65%)
Aspirin	n=38 (54%)
Cardiac glycoside (Digoxine)	n=12 (17%)
Anticoagulant (Warfarin)	n=23 (32%)
Other	n=64 (90%)

Definition of abbreviations: *NYHA=New York Heart Association; BMI=body mass index; LVDD=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction; LVSD=left ventricular end-systolic diameter; HR=heart rate; bpm=beats per minute; ACE=angiotensin-converting enzyme*

5.2.2. Protocol and measurements

Patients were assessed once as described below. Each participant was given a primary assessment prior to the 6-MWT, which required them to fill in a Pre-Exercise Health Questionnaire, followed by an interview to establish their medical and pharmacological history.

5.2.2.1. Anthropometric assessment

Before the test, anthropometric measurements of stature and body mass were made. Stature was recorded using a stadiometer (Seca 240 stature measuring rod) and body mass was recorded, without shoes, using a weight scale (Seca 888 Class III Floor Scale). From these measurements, BMI was calculated as follows: body mass (kg)/stature^2 (m^2).

5.2.2.2. Cardiovascular assessment

Cardiovascular assessment included medical history of any heart problem, pharmacological history, NYHA functional class (I-IV), an electrocardiogram (ECG) (model: Cambridge Heart Inc, US), a comprehensive transthoracic echocardiogram (model: Vivid 7 dimension, GE Healthcare, US) and the 6-MWT. Current use of diuretic, antihypertensive, antiarrhythmic and anticoagulant medications was recorded. A 12-lead electrocardiogram recorded participants' resting HRs and heart rhythms.

Left ventricular function, including LVEDD, LVESD and LVEF were determined from two-dimensional echocardiography. LVEF was calculated using Simpson's formula from measurements of end-diastolic and end-systolic volumes on apical two-dimensional views, following the guidelines of Schiller *et al.* (1989); left ventricular systolic dysfunction was considered when LVEF was <45% (Dickstein *et al.*, 2008).

5.2.2.2.1. Six-minute walking test procedure

The 6-MWT was conducted according to the standardised protocol of Guyatt *et al.* (1985a) except that a 15 m course was used instead of the recommended 33 m course (Guyatt *et al.*, 1985a). A 15 m course was used, as this is commonly reported in clinical settings. Patients were instructed to walk, at their own maximal pace, along the 15 m flat, obstacle-free corridor, with chairs placed 0.5 m from the end of the course. The test was supervised by a trained research assistant and a cardiologist was present throughout. Patients were instructed as follows: 'Turn 180° every 15 m, and cover as much distance as possible during the six minutes'. Patients were allowed to take rest stops if they needed them, but they were instructed to continue walking as soon as they felt able to do so. Time remaining was called every second minute. Standardised verbal encouragement was provided after 2 minutes and 4 minutes (American Thoracic Society 2002). Patients walked unaccompanied so as not to influence walking speed. After six minutes, patients were instructed to stop and total distance covered was calculated to the nearest metre. Patients who failed to complete the test (walking for six minutes) were asked provide a reason for stopping. The total distance covered during the 6-MWT was recorded in metres.

5.2.2.2.1.1. Gait analysis

The numbers of steps was counted every 15 m during the test. Step length series (per 15 m) were calculated by dividing the course length (15 m) by the number of steps walked along the course. Subsequently, for each patient's step length series, the mean and standard deviation step length were calculated.

The mean and standard deviation values used only four step length series, which were recorded between 60 m and 120 m. The first two and the last step length series were removed from this analysis, to minimise any potential acceleration and deceleration effects (Beauchet *et al.*, 2005).

The time taken to walk each 15 m course was recorded, and the average speed for each 60 m was calculated. The pacing index was calculated as the percentage decline from peak walking speed: Pacing Index=[minimum speed in 60 m ($m \cdot sec^{-1}$) /maximum speed in 60 m ($m \cdot sec^{-1}$)] × 100.

5.2.3. Statistical Analysis

Data were presented as means and standard deviations. The median values of age, stature and step length were calculated. Stature data were divided into three quartiles (25^{th}, 50^{th}, 75^{th} percentile of the distribution). Relationships and statistical significance for each of the variables measured (total distance covered, age, stature, BMI, step length, LVEF, resting HR and pacing index) were tested using Pearson's product moment coefficient. An independent-samples t-test was also conducted to compare the 6MWDs for males and females.

The outcome measure for the 6-MWT was the distance walked in metres (6MWD). After using the correlation to determine which variables were most strongly related to 6MWD, the next stage involved performing a stepwise linear regression analysis to assess the combined associations. Independent variables significantly associated with 6MWD were entered into a model to predict 6MWD. Finally, regression analysis was repeated, and reference equations were constructed separately with the data split by sex. The stepwise model was chosen in favour of other models because the objective was to identify the lowest number of variables that had most influence on the test results. The regression used only those independent variables for which the coefficient correlation with the other independent variables was $r<0.75$, in order to minimise multicolinearity and to avoid high correlation between the variables (Meyers *et al.* 2006). The probability of F for entry was set at 0.05 and for removal at 0.1; these counted as the statistical criteria that the dependent variables needed to attain in order to be included in the analysis. The following

potential predictors were examined: sex, age, stature, BMI, step length, LVEF and pacing index. The dependent variable was the 6MWD.

Multinomial logistic regression was also performed to determine factors associated with poor 6MWD (≤300 m). Threshold values were identified for dependent (total distance 300 m) and independent variables (age 75; stature 172 cm; BMI 25 $kg \cdot m^{-2}$; step length 0.63 m; pacing index 50%; resting HR 80 bpm^{-1}; LVEF <45%) (see table 5.3). Dependent and independent variables were encoded by using 0 and 1 for this analysis (see table 5.4). Results were expressed as odds ratios with 95% confidence intervals (CI).

Statistical analysis was carried out using SPSS version 16.0 (SPSS inc., Chicago, IL, US), whereas calculations were illustrated in Microsoft Office Excel 2003 (Microsoft Corporation**,** Washington, US). The statistical significance was set at the 0.05 level.

Table 5.3. Threshold points for dependent and independent variables

Variables	Threshold values	Identifications
6MWD (m)	300 (Bittner *et al.,* 1993; Roul *et al.,* 1998; Rostagno *et al.,* 2003; Ingle *et al.,* 2006; Arslan *et al.,* 2007)	≤ 300: poor performance > 300: good performance
Age (median; yrs)	75	≥ 75: old < 75: young
Stature (median; m)	172	≥ 172: tall < 172: short
BMI ($kg \cdot m^{-2}$)	25 (World health organization 1998)	> 25: overweight ≤ 24.9: normal-weight
Step length (median; m)	0.63	≥ 0.63: long step < 0.63: short step
Pacing index	50%	≥ 50%: non-deceleration < 50%: deceleration
Resting HR (bmp)	80 (Ingle *et al.*, 2006)	> 80: high HR ≤ 80: normal HR
LVEF (%)	45 *(ESC 2008)*	≥ 45: good LVEF < 45: poor LVEF

Definition of abbreviations: BMI=body mass index; HR=heart rate; LVEF=left ventricular ejection fraction; bmp=beats · min^{-1}

Table 5.4. Dependent and independent variables encoding

Variables	Code '0'	Code '1'
6MWD	low performance	good performance
Sex	Male	female
Age	Older	younger
Stature	Short	tall
BMI	Overweight	normal-weight
Step	short step	long step
Pacing index	Deceleration	non-deceleration
Resting HR	high HR	normal HR
LVEF	poor LVEF	normal LVEF

Definition of abbreviations: 6MWD=six-minute walking distance; BMI=body mass index; HR=heart rate; LVEF=left ventricular ejection fraction

5.3. Results

5.3.1. Descriptive analysis

Table 5.1, above, presented some of the baseline descriptive characteristics of the HF group. Of the 71 patients, 54 (76%) completed the 6-MWT. The mean 6MWD was 319 (±126) m for males and 253 (±95) m for females (for the group overall: 6MWD=307±123 m, range: 90-530 m).

5.3.2. Predictors of test performance (distance walked)

5.3.2.1. Correlations between clinical measurements and six-minute walking test performance

Stature was significant and positively associated with 6MWD, while age had a significant but negative association with 6-MWD (see table 5.5).

Table 5.5. Correlations between total distance achieved during the 6-MWT and independent variables (for all heart failure patients)

Variables	6-MWT		
	N	**Pearson r**	***P* value**
6MWD – Age	71	-0.422	0.000
6MWD – Stature	71	0.351	0.003
6MWD – Body mass	71	0.031	0.801
6MWD – BMI	71	-0.163	0.174
6MWD – Step length	67	0.094	0.448
6MWD – Pacing index	57	0.15	0.283
6MWD – Resting HR	52	0.009	0.947
6MWD – LVEF	60	-0.116	0.378

Definition of abbreviations: 6MWD=six-minute walking distance; BMI=body mass index; LVEF=left ventricular ejection fraction; HR=heart rate

Data were divided by sex, and the correlations were repeated. In male HF patients (n=58), significant correlations were observed between 6MWD, stature (Pearson's r=0.254, *p*=0.045) and age (Pearson's r=-0.376, *p*=0.004). Respectively, for females (n=13), significant correlations were observed between 6MWD and stature (Pearson's r=0.598, *p*=0.031) only; age (Pearson's r=-0.416, *p*=0.157) and body mass (Pearson's r=0.366, *p*=0.218) were correlated moderately with 6MWD but not significantly (see table 5.6).

Table 5.6. Correlations between total distance achieved during the six-minute walking test and independent variables (for males and females separately)

Variables	Males			Females		
	N	**Pearson r**	***P* value**	**N**	**Pearson r**	***P* value**
6MWD – Age	58	-0.376	0.004	13	-0.416	0.157
6MWD – Stature	58	0.254	0.045	13	0.598	0.031
6MWD – Body mass	58	-0.122	0.362	13	0.366	0.218
6MWD – BMI	58	-0.233	0.078	13	0.117	0.704
6MWD – Step length	56	0.089	0.515	11	-0.247	0.464
6MWD – Pacing index	46	0.193	0.199	9	-0.224	0.562
6MWD – Resting HR	48	-0.050	0.737	12	-0.003	0.992
6MWD – LVEF	42	0.019	0.904	9	0.055	0.888

Definition of abbreviations: 6MWD=six-minute walking distance; BMI=body mass index; LVEF=left ventricular ejection fraction; HR=heart rate

The independent-sample t-test showed no statistically significant difference in 6MWDs between males (319±126 m) and females (253±95 m), t (71)=1.77, *p*=0.08 (two-tailed). The magnitude of the difference between the means (mean difference=66 m, 95% CI: -8.36 to 140) was, however, moderate: d=0.59 (Cohen 1988).

5.3.2.2. Regression Analyses

5.3.2.2.1. Multiple Linear Regression Analysis

Variables correlated ($r>0.3$) with 6MWD were further analysed using multiple stepwise linear regression analysis to identify which were independently associated with 6MWD. Regression analysis used only those variables for which the coefficient of correlation with other variables was $r<0.75$, to minimise multicollinearity and avoid high correlation between the variables (Meyers *et al.*, 2006).

Age and stature were the only variables entered into the regression analysis. Stepwise analysis showed that age was the only variable that met the statistical criteria for inclusion. In this model, 42.2% of 6MWD was explained by age, with a standard error of estimation of 113 m. The β value was -6. The intercept value (A) was 762.1 m. (see equation 5.3). Predicted results were calculated using the regression equation $Y=A+(B\times X)$, where Y is the predicted value of the dependent variables (predicted 6MWD, m), A is the Y intercept (the value Y when the X value is zero), X indicates the rate of the independent variable (age) and B are the coefficients assigned to each of the independent variables in the regression analysis (Tabachnick and Fidell 2007).

For 6-MWT the equation for predicting 6MWD is:

Equation 5.3.

$$6MWD = 762 - (6 \times age,_{yrs})$$

where: 6MWD=distance walked in six-minute walking test (m)

The regression analysis was extended to include category variables such as sex. In the sex-specific equation models, 40% of variance in 6MWD was accounted for by age and stature in males, and 52% was accounted for by age, stature and body mass in females (see equation 5.4). For the 6-MWT, the sex-specific equation for predicting 6MWD was:

Equations 5.4.

For males: 6MWD = 142 + (3.1 × stature, $_{cm}$) - (4.9 × age, $_{yrs}$)
For females: 6MWD = 259 + (4.6 × stature, $_{cm}$) - (6.6 × age, $_{yrs}$) – (2.9 × body mass, $_{kg}$)
where: 6MWD=distance walked in six-minute walking test (m)

5.3.2.2.2. Logistic regression analysis

Direct logistic (multinomial logistic regression) was performed to determine the factors associated with poor 6MWD (≤300 m). The model contained eight independent variables (sex, age, stature, BMI, step length, pacing index, resting HR, LVEF). The threshold values that were identified for dependent and independent variables are shown in table 5.3.

The overall model was statistically significant (p=0.008) and explained 25.3% (Cox and Snell R square) and 34.8% (Nagelkerke R squared) of the variance in 6MWD. The model could correctly classify 74.6% of cases. As shown in table 5.7, only two of the independent variables (age and BMI) made a statistically significant contribution to the model. Independent predictors of poor 6MWD (≤ 300 m) included high BMI>25 kg·m^{-2} (OR=12.7; 95% CI: 1.45 to 111) and age>75 years (OR=4.9; 95% CI: 1.24 to 19). These indicate that overweight HF patients (BMI>25 kg·m^{-2}) were 12.7 times more likely than normal-weight patients (BMI<25 kg·m^{-2}), and older HF patients (≥ 75 years) were 4.9 times more likely than younger patients (< 75 years), to achieve less than 300 m in the 6-MWT. LVEF did not make a significant contribution to the model; however, the odds ratio (OR=0.52; 95% CI: 0.15 to 1.82) showed that patients with LVEF<45 mm were 48% less likely to achieve less than 300 m in the 6-MWT than patients with normal LVEF (> 45%).

Table 5.7. Logistic regression predicting the likelihood of achieving less than 300 m in the six-minute walking test

	Odds Ratio	95.0% C.I.for Odds Ratio		*P* value
		Lower	Upper	
Sex (male vs. female *)	0.82	0.15	4.63	0.822
Age (older vs. younger *)	4.86	1.24	19.01	0.023
Stature (short vs tall *)	1.23	0.31	92	0.764
BMI (overweight vs. normal-weight *)	12.73	1.45	111.82	0.022
Step length (short step vs. long step *)	0.72	0.22	2.38	0.584
Pacing index (deceleration vs. non-deceleration *)	2.96	0.19	46.64	0.440
Resting HR (high HR vs. normal HR *)	1.05	0.31	3.61	0.934
LVEF (poor LVEF vs. normal LVEF *)	0.52	0.15	1.82	0.307

BMI=body mass index; LVEF=left ventricular ejection fraction; HR=heart rate

** The referent value (OR=1) in each variable respectively is: female; younger; tall; normal-weight; long step; non-deceleration; normal LVEF).*

The analysis was repeated with the same variables, except that age (expressed as a continuous variable) in years was used as a covariate. Table 5.8 shows that again only two of the independent variables (age and BMI) made a statistically significant contribution to the model. The odds ratio for age indicates that for every additional year the patients were 1.13 times more likely to walk <300 m when controlling for other independent factors in the model. This set of variables explained 28% (Cox and Snell R square) and 38.6% (Nagelkerke R squared) of the variability in 6MWD.

Table 5.8. Logistic regression predicting the likelihood of achieving less than 300 m during the six-minute walking test, using age as a continuous variable

	Odds Ratio	95.0% C.I. for Odds Ratio		
		Lower	Upper	*P* value
Sex (male vs. female *)	0.997	0.16	6.11	0.997
Stature (short vs. tall *)	1.27	0.31	5.19	0.739
BMI (overweight vs. normal-weight *)	11.73	1.34	102.51	0.026
Step length (short step vs. long step *)	0.62	0.18	2.18	0.458
Pacing index (deceleration vs. non-deceleration *)	4.42	0.21	91.33	0.336
LVEF (poor LVEF vs. normal LVEF *)	0.63	0.17	2.30	0.487
Resting HR (high HR vs. normal HR *)	1.13	0.33	3.92	0.847
Age (continuous variable)	1.13	1.03	1.23	0.009

BMI=body mass index; LVEF=left ventricular ejection fraction; HR=heart rate

** The referent value (OR=1) in each variable respectively is: female; younger; tall; long step; non-aceleration; normal LVEF).*

5.4. Discussion

5.4.1. Introduction

According to the American Thoracic Society (ATS 2002) guidelines, the 6-MWT is a useful self-paced functional capacity assessment test for patients with moderate to severe pulmonary or cardiac diseases. The 6-MWT is an easily administered tool, used to evaluate the results of post-operative or non-operative interventions (Meyer *et al.*, 1997; Gualeni *et al.*, 1998; Opasich *et al.*, 2004; Fiorina 2007; Nilsson *et al.*, 2008). Most studies use the 6-MWT to analyse the effects of an intervention in a cardiac population (Guyatt *et al.*, 1985a; Wright *et al.*, 2001; McKelvie *et al.*, 2002; Moalla *et al.*, 2005).

Distance walked during the 6-MWT is used to identify HF patients with severe functional impairment, to provide prognosis for those patients who have fewer complications and to show change due to interventions. The ATS (2002) stated that there was no definitive result on which would be the best choice to describe the changes in 6MWD after an intervention: absolute value, percentage change or change in the percentage of predicted value. Since there were no studies in the field, they recommended that 6MWD can be expressed as an absolute value until relevant research is published.

The ATS (2002) also stated that descriptive values, such as age, stature, body mass and sex, are independently associated with 6MWD in healthy adults (Enright and Sherrill 1998; Troosters *et al.*, 1999; Gibbons *et al.*, 2001; Enright *et al.*, 2003; Camarri *et al.*, 2006; Chetta *et al.*, 2006; Poh *et al.*, 2006; Jenkins *et al.*, 2009). This suggests that such variables should be carefully considered by clinicians when they try to determine patients' functional capacity by analysing single measurements from the 6-MWT. Despite these recommendations, none of the prognostic studies (Bittner *et al.*, 1993; Cahalin *et al.*, 1996; Roul *et al.*, 1998; Rostagno *et al.*, 2003; Curtis *et al.,* 2004; Arslan *et al.,* 2007) have corrected their prognostic cut-off values to age and anthropometric variables.

Fiorina *et al.* (2007) reported 6-MWT results with both absolute values (in metres) and percentages of predicted values by using Enright and Sherrill's (1998) equation form based on anthropometric variables. They suggested that expressing functional capacity as a percentage of predicted value was more accurate, because anthropometric limitations could be excluded. The implications of HF on 6MWD were not taken into consideration, since the equation was based on a healthy population. In this case, the accuracy of their results is open to question. There are associations between anthropometric variables and 6MWD (Enright and Sherrill 1998; Troosters

et al., 1999; Gibbons *et al.*, 2001; Poh *et al.*, 2006; Jenkins *et al.*, 2009), but data are only available in relation to healthy populations.

In light of the ATS recommendations, and the gap in the existing literature, the primary aim of the present study was to identify simple, measurable determinants (sex, age, anthropometric, gait parameters or clinical characteristics) of 6MWD in HF patients. This is of great importance for clinical practice, as clinicians may be able to use simple measurable values to predict expected functional capacity in patients with HF. Individual 6MWD can then be expressed as a percentage of predicted value in populations with similar demographic characteristics to the present sample.

As mentioned in Chapter 4 (see '*Biomechanical predictors of the modified shuttle walking test performance in patients with cardiovascular disease')*, both the modified shuttle walking test (MSWT), which is an incremental functional capacity test, and the 6-MWT can be used to measure the functional capacity of CVD patients. The 6-MWT is a less rigid protocol, ideal for use in severe CVD patients, such as the HF patients in the present sample. In this study, the 6-MWT was used with HF patients, and the cut-off point was a 6MWD of 300 m. This is because this value is a prognostic indicator of mortality and morbidity in HF patients (Cahalin *et al.*, 1996; Rostagno *et al.*, 2003; Arslan *et al.*, 2007).

5.4.2. Comparison of current results with previous data

Distance walked during the 6-MWT has been used to determine the functional capacity of many HF patients. The mean 6MWD in this sample was 305 (±123) m, in patients with an average LVEF of 42%. The mean 6MWD in HF patients ranges between 310 m in patients with a mean LVEF of 20% (Cahalin *et al.*, 1996) and 466 m in patients with a mean LVEF of 19% (Rostagno *et al.*, 2003). Most studies report 6MWDs between these values, for mild to severe HF patients (Zugck *et al.*, 2000; Rostagno *et al.*, 2003; Ingle *et al.*, 2006; Passantino *et al.*, 2006; Arslan *et*

al., 2007). The recorded mean 6MWD is lower than that to be found in most other studies, while it seems to be close to the results found by Cahalin *et al*. (1996) and Passantino *et al*. (2006). Reasons for this variability in results between studies are discussed below.

The variability in 6-MWT results among studies may be due to internal (i.e., LVEF, severity of HF) or external (design and layout of test) factors. Faggiano *et al.* (1997) stated that patients with severe HF (i.e., NYHA class IV) walk typically less than 335 m in the 6-MWT, while patients with milder HF (i.e., NYHA class II) tend to walk more than 500 m. Patients in the present study had mild to severe HF, which may partly explain the low mean MSWD, less than 335 m (307±123 m). Other factors may also be associated with 6MWD.

Possible external factors creating variability include course layout, encouragement and instructions (Guyatt *et al.*, 1985b; Sciurba *et al.*, 2003; Bansal *et al.*, 2008). The present research used the shortest length track among several studies (see table 5.9). It might be logical to think that more turns relate to lower values for 6MWD. It has been shown previously, however, that course length does not have any significant effect on 6MWD (Sciurba *et al.*, 2003). This concurs with data from Chapter 4, where turning variables were found not be associated with distance walked in MSWT. The MSWT is broadly comparable to the 6-MWT in terms of its physical demands.

Track layout (circular, oval or straight) can influence 6MWD (Sciurba *et al.*, 2003; Bansal *et al.*, 2008). The present study used a straight track layout and standardised instructions and encouragement (Guyatt *et al.*, 1985a). Previous researchers gave no encouragement to participants (Cahalin *et al.*, 1996; Opasich *et al.*, 2001; Zugck *et al.*, 2000). Guyatt *et al.* (1985a) made the original investigations into use of the 6-MWT, but they did not suggest the use or non-use of encouragement during test administration. They stated that encouragement should be taken

into consideration, and the same standardised protocol should be used for both HF and chronic obstructive pulmonary disease patients. The ATS suggests the use of standardised phrases for encouragement during the test (American Thoracic Society 2002). These recommendations were used in the present study.

Internal factors that can influence the variability of 6-MWT results include general characteristics (age, stature, sex, BMI, nationality), physiological (severity of HF, exercise habits and medication) and psychological factors (motivation, fear). This research showed that age and stature were associated significantly with 6MWD. The average age of the HF patients in this study was higher than other studies with HF patients (see table 5.9). The present sample was similar to those of Ingle *et al.* (2006), however, and the 6-MWT results are in close agreement with their studies. It is possible that the low mean 6MWD reported, in the present study, was due to the high mean age of the present research group in contrast with other studies. Increased age related to lower functional capacity (6MWD). The high mean age of the study group is a possible reason for the variation in 6MWD among studies.

The correlations between age, stature and 6MWD, are consistent with findings in healthy populations (Enright and Sherrill 1998; Troosters *et al*., 1999; Gibbons *et al.,* 2001; Poh *et al.*, 2006; Jenkins *et al.*, 2009). These studies aimed to establish prediction equations for 6-MWT based in healthy adults that can be used by the clinicians to provide patients with a measure of their expected 6MWD in the absence of disease. The mean 6MWD in these studies was 545 (±129) m, and the mean 6MWD in the present study was 307 (±123) m. The large difference in mean 6MWD between these two groups (healthy cohorts-present HF cohort, mean difference=238 m) is mainly due to different health conditions. HF is characterized by progressive loss of functional capacity (Kokkinos *et al.,* 2000; Pina 2010). The above discussion confirms that HF patients are likely to cover less distance in 6-MWT than healthy populations;

thus, the findings of healthy cohorts cannot easily be generalised to the clinical population. Moreover, estimation of the expected 6MWD in the absence of disease, for HF patients, is probably not clinical useful. HF is considered a chronic progressive progressive disorder (Kokkinos *et al.*, 2000), and HF patients may not be expected to restore functional impairment to the levels of healthy adults.

Regression equations based on HF population, that could estimate the expected 6MWD for these patients are essential, because they could show the real magnitude of an individual's functional limitation and performance expectations when compared to similar cases. As far as this research has been able to ascertain, the present study is the first that aims to identify anthropometric and gait predictors of 6MWD and provide the relevant equations for prediction of 6MWD, in HF population.

In the present study not all the patients completed the six minutes duration in the walking test. The following sub-section briefly presents the common reasons that led patients to terminate the test.

Table 5.9. Review of six-minute distance walked for heart failure patients

Reference	Patient characteristics	* Variables: Age (years), Stature (cm), BMI ($kg \cdot m^{-2}$)	LVEF (%)	6-MWT: track length (m)	6MWD (m)
Cahalin *et al.* (1996)	Severe HF, n=45	Age: 49 ± 8	20 ± 6	51	310 ± 100
Zugck *et al.* (2000)	Mild to Severe HF, n=113	Age: 54 ± 12	19 ± 7	132	466 ± 107
Opasich *et al.* (2001)	Moderate to Severe HF, n=315	Age: 53 ± 9	26 ± 8	34	389 ± 9.88
Rostagno *et al.* (2003)	Mild to Severe HF, n= 214	Age : 57.9 ± 9.8	Class I: 52.5± 12.8 Class II: 42.7±15.1 Class III: 33.1±14.2	25	Class I: 427 ± 71 Class II: 367 ± 90 Class III: 242 ± 100
Ingle *et al*. (2006)	Moderate HF, n=571	Age: 70 ± 11 Stature: 168 ± 10 BMI: 28 ± 5	32.1 ± 8.4	15	337 ± 103
Passantino *et al.* (2006)	Severe HF, n=476	Age : 63.6 ± 11.9 BMI: 26.7± 5.2	29.8 ± 9.7	60	326 ± 107
Arslan *et al.* (2007)	Stable HF, n=43	Age: 62 ± 10	35 ± 6	25	400 ± 108
Present study	*Mild to Severe HF, n=71*	*Age:* 76 ± 9 *Stature: 171 ± 9* *BMI: 28.7 ± 5.1*	*42.2 ± 12.1*	*15*	*305 ± 123 m*

Definition of abbreviations: 6MWD=six-minute walking distance; HF=heart failure; BMI=body mass index

** Stature and BMI are not reported in all references*

5.4.2.1. Reasons for test termination

In the present study, 76% of the patients completed the 6-MWT by walking continuously for the full six minutes. The most common reasons that led patients to terminate the test were: breathlessness (61%), leg and back pain (44%), chest pain (11%) and tiredness (11%). HF is associated with loss of muscle strength and endurance (Witte and Clark 2008). Skeletal muscle contains ergoreceptors, which are sensitive to the level of work performed. When the intensity of exercise is progressively increased, a greater number of motor units are recruited, leading to increased ventilation and sympathetic activation (ergoreflex) until fatigue (Pepera *et al.*, 2008; Witte and Clark 2008). The exaggerated ergoreflex in HF patients can explain disordered breathing and fatigue (Witte and Clark 2008). Witte and Clark (2008) found that fatigue and breathlessness as reasons for exercise test termination during stress testing are unrelated to increased mortality in HF patients. This suggests that the main cause forcing the participant to stop the test is the individual's functional capacity. However, the research question arising from this is whether 6MWD is associated with other individual internal parameters (sex, age, anthropometric, gait or simple clinical characteristics) and how these parameters could predict an individual's 6MWD.

5.4.3. Predictors of the six-minute walking test in heart failure patients

The present analysis considered a number of clinical and non-clinical measures known or hypothesised to influence 6-MWT distance, including step length, resting HR, pacing index, LVEF and NYHA class. The results showed that functional capacity, as expressed by 6MWD, was associated with non-clinical variables. From linear stepwise and logistic regression analysis, it was concluded here that age and anthropometric variables (stature, body mass and/or BMI) are the most potent independent predictors of poor 6MWD (<300 m).

In particular, linear regression stepwise analyses showed that younger, taller (and thinner, for females) HF patients were expected to attain better scores in the 6-MWT than older and shorter patients. The fact that age and stature were associated with 6MWD is in agreement with a previous study (Ingle *et al.,* 2006), which reported that HF patients >75 years have an increased likelihood of poor functional capacity (<300 m).

Logistic regression analysis showed that HF patients aged >75 years and/or with a BMI>25 $kg \cdot m^{-2}$, have an increased likelihood of poor functional status (6MWD) than younger and normal-weight HF patients. These associations of age and BMI with 6MWD are in agreement with Ingle *et al.* (2006). Despite being more focused on clinical cardiovascular determinants of the 6-MWT, they showed that simple measures, age and BMI, predicted 6MWD well.

In view of the present results, it seems that the functional capacity of HF patients is independently associated with age, stature and overweight. The results show that functional capacity in HF patients is reduced in elderly (>75 years) and overweight people (BMI >25 $kg \cdot m^{-2}$). The gradual loss of muscle mass and strength observed with increased age and progressive HF is associated with poor exercise tolerance (Fleg and Lakatta 1988; Tolep and Kelsen 1993; Evans *et al.*, 1995). This age-related loss of exercise performance explains the shorter distance covered in HF patients >75 years. Being overweight increases the demand for blood flow to supply the tissues, increases cardiac workload and cardiac output, and results in reduced functional capacity and thus shorter 6MWD by those with a BMI >25 $kg \cdot m^{-2}$ (Enright *et al.*, 2003; Gallagher *et al.*, 2005).

These associations are important and have clinical relevance. For instance, the 300 m cut-off point is widely used in clinical practice. According to this reference equation model, the same 6MWD (i.e., 300 m) indicates severe reduction in functional capacity for a tall (>178 cm, 75th

percentile for males) 75-year-old male, suggesting that one therapeutic goal should be the increase of exercise tolerance for such an HF patient. Conversely, this performance is the expected 'well for age and stature' functional capacity for a short (<171 cm, 25th percentile for males) 75-year-old male, which suggests that a less intense, less stressful, safer and more inexpensive programme could be aimed at in relation to the maintenance of functional capacity for this HF patient.

This study demonstrates that sex, age and anthropometric variables (stature, body mass) must be considered when interpreting 6MWD. Until now, no study had determined whether the same factors are associated with 6MWD in HF patients. It was also expected that stature would be associated with 6MWD, based on the previous findings in relation to MSWT (see Chapter 4) and on the inclusion of stature in prediction equations based on healthy controls (Troosters *et al.*, 1999; Gibbons *et al.*, 2001; Enright *et al.*, 2003; Camarri *et al.*, 2006; Chetta *et al.*, 2006; Poh *et al.*, 2006; Jenkins *et al.*, 2009). Since the most of the HF patients were men, regression analysis of male-only data showed that age and stature both predicted 6MWD. The equation suggested a 3 m per cm of stature expected gain in 6MWD and a 5 m loss per increased year of age. This model explained 40% of the variance in 6MWD.

It was further hypothesised that gait parameters might influence 6MWD. Step length was measured, and a pacing index formulated to investigate this. A longer step length infers greater mechanical efficiency in a walking test (Donelan *et al.*, 2002), and a constant pace in stepping indicates a comfortable, submaximal work rate (Shephard *et al.*, 1968). That neither measure correlated with 6MWD is surprising. This was particularly so concerning step length, which correlates with stature, which predicted 6MWD well. The relatively small sample size and relative crudeness of these assessments may underlie this lack of association, but it should be noted that the correlations observed were very close to zero. It appears, therefore, that clinicians

do not need to account for variance in such measures when evaluating 6MWD. Clinically, this is good news; as such measures are laborious and time consuming, whereas both measures identified here are important predictors when taken as part of routine clinical assessment.

Another, complex measurement, LVEF was not included in the final multivariate model of regression analysis, meaning that it does not significantly predict 6MWD. This finding is in agreement with previous studies showing that LVEF is a poor indicator of exercise intolerance and functional capacity in HF patients (Franciosa *et al.,* 1981; Muller *et al.,* 1992; Lele *et al.,* 1996; Kudtarkar *et al.,* 2010). Ingle *et al.* (2007) demonstrated that while NT-proBNP was an independent predictor of poor 6MWD, LVEF was not. Both NT-proBNP and LVEF correlate with cardiac function; LVEF reflects cardiac output. The 6-MWT provides an assessment of functional capacity, whereas cardiac function is mainly assessed on clinical evaluation (i.e., echocardiography, blood tests) (Kuster *et al.,* 2002). The present study was designed to assess the functional capacity of HF patients and not their cardiac function.

Muller *et al.* (1992) measured cardiac output and regional blood flow at rest and in response to treadmill exercise test, in a group of HF (n=30) patients and healthy adults (n=10). They found that cardiac output in HF patients was lower than the healthy adults, at rest and during the test. The regional blood flow to the tissues was, also, reduced, but the proportion of blood flow did not remain the same to all organs, compared with the controls. Particularly, the proportion of blood flow to the gut and kidneys and tissues (skeletal muscles) was reduced, indicating that the blood flow to the cerebral and coronary arteries remained the same. The authors concluded that haemodynamic factors (i.e., cardiac output) do not correlate with exercise tolerance and symptomatic impairment, due to redistribution in blood flow. Because HF patients' symptoms (i.e., fatigue, dyspnoea) are related to skeletal muscle blood flow, the authors suggested that functional capacity assessment seems to be more important than haemodynamic factors in

identifying symptoms in this population. Overall, assessment of functional capacity is independently associated with great prognostic importance in HF patients (Kuster *et al.*, 2002), confirming the usefulness of the 6-MWT in this population.

5.4.3.1. Linear versus logistic models

Similar results were found with both linear regression and logistic analysis. In both the linear and logistic models there was a relationship between age and 6MWD. The linear analysis showed that stature and body mass statistically influence 6MWD in women, while logistic analysis showed associations between the ratio of body mass and stature (BMI) with MSWD for both sexes. This difference is probably due to the limitation of linear analysis, for homoscedasticity and normally distributed variables (Lawrence and Arthur 1990), and the fact that regression results were stratified by sex while logistic results were estimated in relation to both sexes combined.

With regard to the fit of the models to the data, the linear models explained 40% and 52% of the variance in males and females respectively. This is better than that achieved in the healthy population (Enright and Sherrill 1998; Enright *et al.*, 2003) it still leaves 60% and 48% of the variance unexplained, meaning that more predictor variables should be added to the equations. The logistic equation model fits the data better, as it correctly predicts 75% of the cases. Linear and logistic statistics differ in their nature; however, in this study, the logistic model seems stronger than the linear model and there is no similar study available to which these findings can be compared.

5.4.4. Comparison of the six-minute walking test prediction equation model with previously published equations

This is the first research to generate a regression equation of 6MWD based on simple non-clinical characteristics (age and anthropometric measures). The equation is intended to estimate

functional capacity in patients with mild to moderate HF. The use of such a prediction model has the potential to be important in clinical practice. Such models allow prediction of an individual's expected functional limitation due to factors beyond their control; they are mainly based on non-modifiable factors (age, stature). The predictive equations provide information about performance expectations and, through this, indicate the desired improvement in functional capacity following a therapeutic intervention (such as an exercise CR programme). In this instance, 6MWD can be expressed as a percentage of the predicted value based on anthropometric variables (American Thoracic Society 2002; Fiorina *et al.*, 2007; Jenkins *et al.*, 2009). A normalised 6MWD value is more realistic than an absolute value, because the clinicians can then evaluate the individual's 6MWD and extent of individual functional limitation, when compared to a relevant age-matched 'control'.

Overall, 48% to 60% of variance in 6MWD of the HF population remains unexplained by these sex-specific models. The unexplained variance may be due to many modifiable factors not measured here, including habitual daily activities, psychological status (i.e., motivation), differences in the severity of patients' medical condition and medication. Approximately, 80% and 75% of the patients were receiving β-blockers and ACE inhibitors respectively. Beta-blockers show no association with 6-MWT performance in HF patients; however, ACE inhibitors cause dyspnea on exertion and reduce exercise tolerance (Lipkin *et al.,* 1986), contributing likely to these differences of variation. However, the present analysis considered a number of clinical measures thought to influence absolute 6MWD, including LVEF and NYHA functional class but these were unrelated to 6MWD. The unexplained variance is, therefore, similar to that observed in healthy populations.

Several studies have published 6-MWT values in healthy populations with different age ranges, creating predictive equations based on sex, age and anthropometric variables (body mass,

stature) (Enright and Sherrill 1998; Troosters *et al.*, 1999; Enright *et al.*, 2003; Camarri *et al.*, 2006; Jenkins *et al.*, 2009). The unexplained variance in 6MWD, in these healthy populations, ranges from 34% to 80% (see table 5.10). These reference models were constructed from normal, healthy populations. Healthy populations can sometimes act as age-matched control values for HF patients; however, as it was mentioned above the results of a larger study based on HF patient groups would have more validity. These studies are described below.

Enright and Sherrill (1998) established equations for prediction in healthy adults, taking into account sex, age and BMI. They proposed that their equation models should apply for healthy Caucasian adults, aged 40 to 80 years old; when the participants perform the 6-MWT for the first time and have standardised encouragement during the test. Their reference equations, based on a single 6-MWT, account for only 40% of the variation in 6MWD. There was no revalidation of the results in the non-healthy population and their predictive models can not be generalisable to HF patients. Due to functional limitations, HF patients are expected to achieve lower scores (MSWD) in 6-MWT than healthy adults (it was reviewed above).

Troosters *et al.* (1999) found that sex, age, stature and body mass significantly influenced 6MWD in healthy adults, and that these factors can be used to judge functional capacity in healthy populations. The participants performed the 6-MWT twice, and they achieved a better 6MWD in the second test. The authors concluded that a practice 6-MWT was recommended in order for the results to be more accurate. The sample population was not large enough, however, to validate the results. According to the sample size calculation described by Tabachnick and Fidell (2007), a sample size larger than 122 should have been used in this study (Troosters *et al.,* 1999).

Gibbons *et al.* (2001) found that 6MWD was related to sex, stature and age in healthy young adults. Their regression model accounts for only 41% of the variance in 6MWD. They also found

that 86% of healthy adults had a better 6MWD after the first practice walk and proposed the necessity of two practice walks for people with cardiorespiratory disorders. They also proposed that the improvement in 6MWD was a result of a learning effect, which could be misinterpreted as an improvement in functional capacity after treatment.

Enright *et al.* (2003) used the 6-MWT to assess a large cohort of elderly people (2,281, including 122 participants with HF). The authors showed that participants with cardiovascular disorders did not walk as far as the other participants. They only reported predictive equations that took into account sex, stature, body mass and age, for healthy elderly people. This study produced the most clinical useful and valid findings of all the others, because their prediction equations based on a large cohort, including CVD patients. On the other hand, the study suffers from two important weaknesses. Firstly, there were no referred equation models for CVD patients and their reference equations might overestimate predicted 6MWD in CVD population. Secondly, their models explained only 20% of the total variance in 6MWD, which might be due to large variations in individual health status. Their sample included healthy subjects and patients with different medical conditions, such as CVD, pulmonary disease, stroke, arthritis, diabetes.

Camarri *et al.* (2006) found that sex, stature and FEV1 were independent predictors of 6MWD in healthy Caucasian males. Their equation explained 33.9% of the variance in 6MWD. The authors used the best performance from three 6-MWT trials. This fact complicates their results, since it is unclear how many practice walks are needed before the use of their reference equation form.

Chetta *et al.* (2006) investigated the predictors of 6MWD, including clinical (oxygen saturation, pulse rate, respiratory rate, breathlessness perception), sex, age and anthropometric measures (stature, body mass) in healthy Caucasian adults. The final equation accounted for 42% of the total variance and included only sex, age and stature. They claimed to have confirmed the

significant effect of anthropometric characteristics on clinical values in relation to 6MWD. However, the sample was of healthy, young to middle-age adults, and there is no further data for the older population.

Poh *et al.* (2006) established an equation including age, stature, body mass and percentage of predicted maximum HR, in order to estimate 6MWD in healthy Singaporeans adults. They found no significant relationship between BMI and 6MWD, which was probably due to the fact that only 8.6% of the participants were obese. They also suggested, as in previous studies (Troosters *et al.*, 1999; Gibbons *et al.*, 2001), the necessity of a practice walk for more reliable results. Their equation explained a high percentage of variance (78%), indicating that their equation model produced accurate results; nevertheless, there was no further revalidation of the results. This was the only study which explained higher variance in 6MWD than the present study. Their equation model, however, is very limited for three reasons. First, their sample was small and unrepresentative of the healthy adult population. Secondly, the cohort that they used was around 10–12 cm shorter than other populations (i.e., Caucasians) and, thus, it cannot be applied to other ethnic groups. Lastly, the equation model includes the variable $\%predHR_{max}$, so it is not possible to use it in individuals taking medication that influences the HR response (i.e., β-blockers).

Most recently, Jenkins *et al.* (2009) used sex, age and anthropometric data (stature and BMI) to predict 6MWD in healthy Caucasian adults, while also they compared their equation with existing equations. They reported that previous regression equations overestimated performance in females. Their predictive forms explained 40% to 43% of variance. There was, however, no revalidation of their results.

Table 5.10 shows several established prediction equations for the 6-MWT and demonstrates the difficulty in comparing reference values among different studies. Each study used different

methods and different populations. Clinicians should use normative values or equation forms that are suitable to the clinical characteristics (pathology, severity of the disease, age, race) of the participant and the method employed during the test (number of repetitions, encouragement, course layout).

The use of 6MWD predictive equations derived from healthy cohorts might not be accurate to predict performance in HF populations. In healthy populations, walking for six minutes rarely represents maximal exercise capacity. In the studies which produced the predictive equations in healthy populations, participants walked, continuously, for six minutes during the test (Enright and Sherrill 1998; Gibbons *et al.*, 2001; Enright *et al.*, 2003; Camarri *et al.*, 2006; Chetta *et al.*, 2006; Poh *et al.*, 2006; Jenkins *et al.*, 2009). This is often not the case in HF patients and was not so in the present study, where only 76% of the patients completed the 6-MWT. In HF patients, walking in the 6-MWT is usually maximal, and six minutes of continuous exercise often unachievable due to fatigue and dyspnoea (Clark *et al.*, 2000). Thus, prediction regression equations were developed in the present work, with a single 6-MWT, over a 15-m course, with standard encouragement to patients, and it is applicable to British HF (mild to severe) patients, aged 51 to 91 years.

Table 5.10. Prediction equations for the six-minute walking test

Reference	Sample characteristics	Country/Race	Reference equations for walk distance in meters *
Enright and Sherrill (1998)	Healthy adults, aged: 40-80 yrs, n=290 (F=117, M=173)	US	$6MWD_{male} = (7.57 \times stature) - (5.02 \times age) - (1.76 \times body\ mass) - 309$ $6MWD_{female} = 667 + (2.11 \times stature) - (5.78 \times age) - (2.29 \times body\ mass)$
Troosters *et al.* (1999)	Healthy adults, aged: 50-85 yrs, n=51 (M=29, F=22)	Belgium	$6MWD_{male} = 269.31 + (5.14 \times stature) - (5.32 \times age) - (1.80 \times body\ mass)$ $6MWD_{female} = 218 + (5.14 \times stature) - (5.32 \times age) - (1.80 \times body\ mass)$
Gibbons *et al.* (2001)	Healthy adults, aged: 20-80 yrs, n=79 (M=41, F=38)	Canada	$6MWD_{male} = 868 - (2.99 \times age)$ $6MWD_{female} = 793.3 - (2.99 \times age)$
Enright *et al.* (2003)	Elderly adults, aged: 73-83 yrs, n=1809 (M=715, F=1,094)	US	$6MWD_{male} = 510 + (2.2 \times stature) - (0.93 \times body\ mass) - (5.3 \times age)$ $6MWD_{female} = 493 + (2.2 \times stature) - (0.93 \times body\ mass) - (5.3 \times age)$
Camarri *et al.* (2006)	Healthy adults, aged: 55–75 yrs n=33 (M=33, F=37)	Caucasians	$6MWD_{male} = 216.9 + (4.12 \times stature) - (1.75 \times age) - (1.15 \times body\ mass)$ $6MWD_{female} = 182.86 + (4.12 \times stature) - (1.75 \times age) - (1.15 \times body\ mass)$
Chetta *et al.* (2006)	Healthy adults, aged: 20–50 yrs, n=102 (M=48, F=54)	Caucasians	$6MWD_{male} = 518.9 + (1.25 \times stature) - (2.816 \times age) - 39.07$ $6MWD_{female} = 518.9 + (1.25 \times stature) - (2.816 \times age)$
Poh *et al*. (2006)	Healthy adults, aged: 45-85 yrs, n=35 (M=16, F=19)	Singapore	$6MWD = (5.5 \times \%predHR_{max}) + (6.94 \times stature) - (4.49 \times age) - (3.51 \times body\ mass) - 473.27$
Jenkins *et al.* (2009)	Healthy adults, aged: 45-85 yrs, n=109 (M=48, F=61)	Caucasian Australians	$6MWD_{male} = 1005 - (5.68 \times age) + (0.89 \times stature)$ $6MWD_{female} = 602 - (2.97 \times age) + (2.05 \times stature) - (5.50 \times BMI)$
Present study	HF adults, aged: 56 – 91 yrs, n=71(M=58, F=13)	UK	$6MWD_{male} = 142 + (3.1 \times stature) - (4.9 \times age)$ $6MWD_{female} = 259 + (4.6 \times stature) - (6.6 \times age) - (2.9 \times body\ mass)$

Definition of abbreviations: M=values for males; F=values for females; 6MWD=six-minute walking distance; HR_{max}=maximal heart rate; BMI=body mass index

** stature in cm, body mass in kg, 6MWD in metres, FEV1 in litres*

5.4.5. Study strengths

All the data were gathered on HF patients, and it seems that this is the only study presenting equations for prediction of 6MWD that accounts for simple non-clinical variables. This work proposes that the determinants of poor performance in the 6-MWT – suggesting a bad prognosis for HF – depend on age and anthropometric variables such as stature and body mass (for females only); many of which are not under the control of the patient or the clinician. Overweight HF patients (BMI >25 $kg \cdot m^{-2}$) and patients older than 75 years are expected to cover less than 300 m in the 6-MWT. Overweight patients have an almost 13-fold increased likelihood and the elderly (>75 years) have a 5-fold increase, in the risk of poor prognosis and hospitalisation. It is suggested that 6MWD should be expressed not only as an absolute value but also as a percentage of predicted value in HF patients. The predicted value can be calculated by using only the individual's age and anthropometric characteristics as a variable.

These prediction variables have both scientific and clinical value. These variables should be taken into account by the prognostic studies. For instance, very short HF patients are more likely to walk ≤300 m in 6-MWT, which according to previous prognostic studies indicates poor prognosis. Stature is a non-modifiable predictive variable for 6-MWT in HF population. The prognostic cut-off pints should be adjusted for this variable and revalidated, then, in this population.

These results are, also, very important to clinical practice in the CR field for two main reasons. Firstly, the prognostic stratification of HF patients by using baseline non-clinical features – BMI and age – is useful, as it can divide patients into subgroups with different functional capacity expectations. These two basic non-clinical features, BMI and age, can detect whether a HF patient has low or high risk of morbidity and mortality. Secondly, the use of such sex-specific

prediction models could have significant potential for use in clinical practice. Such models allow prediction of an individual's expected functional limitation due to non-modifiable factors (age, stature and body mass); they also provide information about performance expectations after an exercise CR programme. In this case, 6MWD can be expressed as a percentage of predicted value based on age, stature and body mass (for females only) (American Thoracic Society 2002; Fiorina *et al.*, 2007). Having these simple measurable prognostic markers (age and BMI) already in the assessment will help the clinician to state realistic expectations and functional improvement targets after a therapeutic treatment (i.e., in CR), which will be safe and will allow the patient to experience real success.

A further valuable feature of this study is that it has eliminated a large number of gait parameters from the prediction of 6MWD. The results presented in Chapter 4 suggest that step length is a positive predictor of MSWT performance, and it was predicted that this might be the case in the present study. The analysis of gait was time consuming and labour intensive and would not be tolerated well by staff in routine clinical use. It is perhaps fortunate that none of the gait variables predicted performance. Gait analysis limited the overall sample size of this study, but as they now appear unimportant a larger study can be carried out, concentrating on predictions based on age, BMI and/or stature. Given that these are routinely available in patient records, such a study could be retrospective in nature with a large enough sample size to provide sex-specific equations. Even more useful would be the assessment of the prognostic value of 'adjusted' 6MWD values against raw scores. This could be achieved via re-analysis of existing data.

5.4.6. Study limitations

A limitation of this study could be the fact that there were no psychological measures in the protocol. Stress and depressive symptoms might explain the additional variance in 6-MWT

scores. Also, no physical activity habits were estimated before the test. It would be useful to identify how much variance in 6MWD this variable (physical activity) can predict. A physical activity level estimation would address more thoroughly the sources of 6-MWT variation.

Furthermore, the patients in this study were considered to be overweight (with an average BMI of 28.7 $kg \cdot m^{-2}$), meaning that the present prediction equations form is more applicable to the overweight or obese HF population. The equations presented here based on physical characteristics of a European population, and they may not be acceptable for application in populations with lower average BMI (i.e., Asian).

A last limitation of the present study is that the sample size did not allow revalidation of the predictive equations (using the split half method for example). Further investigations are required to address this limitation (i.e., revalidation of present equations to ascertain suitability for use in HF population).

5.5. Conclusion

This research is unique as it presents equations based on non-invasive, clinically available variables to predict 6MWD in HF patients. This study confirms that the predictors of 6MWD are the same as those in healthy adults. Non-modifiable variables (stature, sex) accounted for a large percentage of the variance in the 6-MWT. Thus, the clinicians can accept with confidence the existing prediction equations for 6MWD and interpret 6MWT performance in a meaningful way (percentage of predicted value). At present, such interpretation remains rare in the scientific literature. Prediction equations may also help to set a more effective, simple and safe CR treatment for HF patients.

The study was conducted with a set of complex variables in a small sample; thus it is essential that the study is continued and the results revalidated in a larger sample size with the second set of simpler variables identified here.

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CHAPTER 6. NORMATIVE VALUES FOR FUNCTIONAL CAPACITY TESTING IN CARDIAC PATIENTS AND THE INFLUENCE OF ANTHROPOMETRIC MEASURES ON PERFORMANCE

6.0. Abstract

Functional capacity testing provides an important prognostic tool. National guidelines recommend the use of functional capacity tests to evaluate improvements resulting from attending cardiac rehabilitation (CR) programmes. Previous chapter showed (see Chapter 4 '*Biomechanical predictors of the modified shuttle walking test performance in patients with cardiovascular disease'*) that anthropometric factors are likely to influence modified shuttle walking test (MSWT) performance in the cardiac population. The aims of this study were, firstly, to establish a validation of Chapter 4's prediction equation based on the phase IV CR (UK classification) population, and secondly, to improve this equation for use in phase III CR. A further focus of the current study was to determine prior to CR the normal values and ranges for improvement in functional capacity with the MSWT.

Distance walked in the MSWT (MSWD) was measured across 159 cardiac patients (77% males, 23% females, mean age: 68.1±9.4 years; mean body mass index: 81.8±15.7 $kg \cdot m^{-2}$), at the start of their programme and after six weeks of phase III CR. Anthropometric data (mass, stature, body mass index, waist circumference) and routine clinical measurements (resting blood pressure) were recorded prior to and after receiving CR. The assessment also included patients' primary diagnosis, type of cardiac surgery, time from event/intervention and time between pre- and post- rehabilitation assessment. Differences in pre- and post- rehabilitation values were evaluated with a paired-samples t-test. Pearson's correlation coefficients and stepwise linear regression analysis were used to identify factors that influence the pre-rehabilitation MSWD and

the magnitude of change in the MSWD during CR. The study cohort was divided into two groups – a development group and a validation group. An equation model for the prediction of pre-rehabilitation MSWD was developed with the development group and was validated using the validation group. Pearson's product moment coefficient, intraclass correlation coefficient (ICC) and limits of agreement were also used to assess the validation of the equation model developed in Chapter 4 (see equation 4.1a), and for the validation of the new equation model for prediction of pre-rehabilitation MSWD in the phase III CR population. Finally, an one-way anova was performed to investigate differences in MSWD and MSWD improvement, among patients with different surgical diagnoses.

Mean MSWD was 292 (±136) m in pre-rehabilitation assessment and 420 (±186) m in post-rehabilitation assessment. Validation analysis showed a low accuracy for equation 4.1a in the phase III CR cohort (ICC=0.16 and LoA=81 m). Stepwise regression indicated that age, stature and sex were the best predictive measures for pre-rehabilitation MSWD. The model explained 62.3% (SE=114 m) of the variance in MSWD. Validation analysis of this model showed a small systematic bias of 5 m but a low ICC of 0.28. Repeated stepwise regression analysis for the prediction of the magnitude of change in MSWD during CR showed that stature was the best determinant, explaining 37% of the variance. An analysis of the variance demonstrated a significant difference in the magnitude of MSWD change (p<0.005), between the group of patients involved in different surgical diagnoses.

Age, stature and sex were independent predictors of pre-rehabilitation MSWD, while stature was an independent predictor of the magnitude of MSWD change during CR. These factors should be accounted for when the MSWT is used to assess patients' functional capacity during phase III CR. They appear to be particularly important when MSWT performance is used to stratify

patients at the start of CR, and when decisions are being made about patients at discharge from CR, according to known prognostic standards.

6.1. Introduction

6.1.1. Cardiac rehabilitation service: difficulties and recommendations

Cardiac rehabilitation (CR) programmes after a cardiac event or surgery improve exercise capacity, psychological status and prolong survival (Oldridge *et al.*, 1988; O'Connor *et al.,* 1989; Jolliffe *et al.,* 2000). Despite almost universal acceptance of the health benefits of exercise-based CR for cardiac patients, and the established safety of CR programmes (see Chapter 7 '*Safety of exercise training and exercise testing for cardiac patients, in a supervised, community-based cardiac rehabilitation programme'*), only 25% of post-myocardial infarction (MI) patients, 75% of patients who had coronary artery bypass graft surgery (CABG), and 20% of patients who had undergone a percutaneous coronary intervention (PCI) were enrolled in a CR programme (Bethell *et al.*, 2007).

A national survey of 28 CR centres (Brodie *et al.*, 2006) demonstrated deficiencies in CR services including; insufficient staff numbers, unsuccessful service delivery, failure to meet patient needs, insufficient numbers of exercise sessions and a lack of exercise testing. In total, 79% of responding centres offered fewer sessions than suggested by SIGN (Scottish Intercollegiate Guidelines Network 2002). Two of the main reasons for the poor provision of CR were lack of financial support in many CR centres and lack of cooperation from cardiologists to persuade them to promote CR. According to Brodie *et al*. (2006), 71% of CR centres performed exercise capacity tests when the patients were enrolled in the programme, while only 39% of the centres assessed patients' exercise capacity at the end of the CR sessions. It is obvious that not all the CR centres in the UK use exercise testing to assess patients' exercise capacity, or to assess

the change in exercise status due to CR, as recommended (National Institute for Clinical Excellence [NICE] 2007).

6.1.2. The importance of exercise capacity evaluation and the use of normative values in cardiac rehabilitation service improvements

Both NICE (2007) and SIGN (2002) recommend the use of exercise capacity testing when a patient enters an exercise-based phase III CR programme to help prescribe exercise at the correct levels of intensity; they also recommend such testing at the end of the CR sessions to evaluate improvements resulting from programme attendance. Exercise capacity testing helps clinicians to prescribe an individualised, safe and effective CR programme.

The use of normative values of exercise capacity at the start of phase III CR programmes, and testing of exercise capacity improvement after a CR programme, can stratify patients by comparing their performance at the start of the programme against established norms; it would also set realistic expectations for improvement. Evaluating performance against normative data would allow CR programmes to be individualised, perhaps less stressful, less dangerous and potentially shorter or longer depending on patient need. CR services could be brought closer to patients' needs and potentially be less expensive. Moreover, established norms in exercise capacity improvement after a CR programme might provide motivation to patients who participate in such programmes (Ades *et al.*, 2006) and to cardiologists in giving higher priority to CR.

6.1.2.1. Normative values for exercise capacity in cardiac rehabilitation: incremental treadmill testing

Normative values and predictive nomograms for exercise capacity through maximal oxygen uptake (VO_{2max}) during treadmill testing were established by the American Heart Association

(AHA), (Ades *et al.*, 2006). Based on 2,896 coronary heart disease (CHD) patients entering CR, the AHA established predictive VO_{2max} equations, accounting for patient sex and age (see equation 6.1). They created nomograms of VO_{2max} stratified by age, sex and diagnosis. After normalisation of VO_{2max} for body mass, there was significantly lower VO_{2max} (22% for females and 39% for men) between age groups ranging from 40-80 years. VO_{2max} was lower in patients who had undergone CABG surgery (Mean values: males=15 $ml \cdot kg^{-1} \cdot min^{-1}$; females=21 $ml \cdot kg^{-1} \cdot min^{-1}$) than in those receiving PCI surgery without MI (Mean values: males=14 $ml \cdot kg^{-1} \cdot min^{-1}$; females=18 $ml \cdot kg^{-1} \cdot min^{-1}$). The latter might be due to longer hospitalisation and the longer recovery period required after CABG surgery. The authors re-assessed 504 of the patients who completed 36 CR sessions and showed an increase of 17% in exercise capacity. There are no comparable data provided for exercise capacity after CR nor examined the effect of stature on exercise capacity, which seems to be clinical important. The clinical importance of stature in the prediction of exercise performance in CVD population was proved in previous chapters (see Chapter 4 '*Biomechanical predictors of the modified shuttle walking test performance in patients with cardiovascular disease'* and Chapter 5 '*Predictors of six-minute walking test performance in heart failure patients*')

Equation 6.1. (Ades *et al.*, 2006)

For males: $VO_{2max} = 33.970 - (0.242 \times age_{,\,yrs})$
For females: $VO_{2max} = 21.693 - (0.116 \times age_{,\,yrs})$
where: VO_{2max}*=maximal oxygen uptake* ($ml \cdot kg^{-1} \cdot min^{-1}$)

These normative values (Ades *et al.*, 2006) are expressed as units of oxygen consumption normalised to body mass. Such values might be readily applicable to the US cardiac population, but they are less useful for a UK CR population. In the UK, exercise capacity for CR patients is more commonly expressed as metres of distance walked during specific walking tests (functional capacity). In particular, UK guidelines (SIGN 2002; British Association for Cardiac

Rehabilitation [BACR] 2006) recommend the use of the incremental shuttle walking test (SWT) or six-minute walking test (6-MWT) to assess functional capacity in cardiac patients.

As mentioned in Chapter 5, distance walked in 6-MWT can be converted into VO_{2max} (Cahalin *et al.,* 1996); while VO_{2max} and distance walked in the SWT can also be converted into an estimated value of metabolic equivalents (American College of Sports Medicine [ACSM] 2005). The metabolic equivalent (MET) is a widely used physiological unit and expresses energy cost of physical activities. It is defined as the ratio of metabolic rate during an activity to a standard metabolic rate while seated and resting (Byrne *et al.*, 2005). The definition of MET appears problematic in clinical populations, including CVD patients (Byrne *et al.*, 2005; Savage *et al.*, 2007). Savage *et al.* (2007) demonstrated that the widely accepted value of 1 MET=3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, overestimated resting oxygen consumption in 23-36% of CVD patients. This value depends on disease status, lean body mass, age and sex of the patient (Byrne *et al.*, 2005; Savage *et al.*, 2007).

Established MET values (ACSM 2005) appear accurate for healthy populations but less so for cardiac patients (Woolf-May and Ferrett 2008). Woolf-May and Ferrett (2008) measured 31 post-MI patients who participated in phase IV CR along with 19 healthy adults. All patients performed the SWT; healthy participants performed the SWT and a treadmill test using walking speeds derived from SWT. VO_{2max} was obtained during exercise testing. As expected, healthy adults walked further in the SWT than cardiac patients. MET values were significantly higher in cardiac patients compared with healthy participants, at each SWT level. In cardiac patients, MET values were similar at different walking speeds on the SWT and the treadmill. MET values may, therefore, underestimate exercise capacity (oxygen consumption) in CR patients. Woolf-May and Ferrett (2008) concluded that where direct measure of VO_{2max} is not taken, extra caution is needed when using MET values to prescribe exercise for CVD patients. The authors

recommended that, 'new cardiac patient-based reference MET values' should be established and validated for use in the CR population. This research has not been undertaken.

Given such problems, estimated functional capacity in METs may be inaccurate in CVD patients, when the equation for estimating METs is based on healthy participants. This suggests an even greater the need to establish normative values for functional capacity testing, measured in distance walked, for the most frequently used walking tests in the UK. Reference values exist for the 6-MWT in post-cardiac surgery patients (see 'Fiorina *et al.*, 2007' below) and although cardiac surgery patients (CABG, PCI) make up 78% of CR patients in UK (Bethell *et al.,* 2007) the 6-MWT is not routinely used.

6.1.2.2. Normative values for functional capacity in cardiac rehabilitation: the six-minute walking test

Fiorina *et al.* (2007) provided normative values for distance walked in the 6-MWT, based on 1,370 patients admitted for intensive CR following CABG, valve replacement or other cardiac surgery. Sex, age, diabetes mellitus and the type of cardiac surgery all significantly contributed to the prediction of 6-MWT distance. The distance walked was lower with increased age, while men walked 60-74 m further than women across all age groups. After CABG, patients walked significantly further in the 6-MWT than patients who had undergone other surgeries. CR was conducted twice daily for 2.1 (±0.4) weeks (mean 30 sessions). Following the CR programme, 348 patients were re-assessed, showing a 46% increase in distance walked. The authors did not consider the patients' medical treatment after cardiac surgery, nor changes during CR. Thus, it is unclear whether the medications used had an influence in terms of exercise tolerance. The CR programme used was also not consistent with current guidelines (SIGN 2002; BACR 2006), making it difficult to generalise the findings to patients enrolled in a more typical programmes.

The major limitation of this Italian study in terms of UK CR is that only 10% of CR services in the UK use the 6-MWT to assess functional capacity (Brodie *et al.,* 2006).

The 6-MWT is largely restricted to use in heart failure (HF) (Cahalin *et al.*, 1996; Faggiano *et al.*, 2004). The SWT is more physiologically demanding than the 6-MWT, due to the incremental increase in intensity during the test and its continuous nature. Thus, the SWT is more valid in assessing functional capacity in less severe cases of clinically stable CR patients. The SWT is recommended by UK clinical guidelines (SIGN 2002) as a valid and reliable measure for determining functional capacity before and after CR, in patients who have experienced an MI, and patients who have undergone cardiovascular surgery or pacemaker insertion (Payne and Skehan 1996; Tobin and Thow 1999; Francis 2000; Lewis *et al.,* 2001; Woolf-May and Ferrett 2008). Chapter 3 (see '*Long-term reliability of the modified shuttle walking test in clinically stable cardiovascular disease patients*') demonstrated, for first time, the long-term (>8 weeks) test-retest reliability of SWT.

Functional capacity has good prognostic value in CVD patients and is unique among CVD risk factors in that it can only be improved with exercise and not treated pharmacologically. A number of studies have demonstrated improvements in functional capacity when the SWT is performed after a CR programme, but there is a wide range of in performance values among the studies. It is necessary to establish performance indicators that measure the effectiveness of CR as a treatment to increase functional capacity. There appear to be no established normative values for the SWT in the literature to suggest what an expected or effective improvement in functional capacity might be after a CR programme.

6.1.3. Functional capacity assessment in phase III cardiac rehabilitation

6.1.3.1. Functional capacity in cardiac rehabilitation patients, assessed by the shuttle walking test

Next, is a brief review of the literature concerning SWT performance values in patients participating in phase III or centre-based CR. Table 6.1 summarises these studies, detailing patient cohorts, the number of CR sessions, the duration of the CR programme, its outcomes and improvement. Tobin and Thow (1999) found a significant improvement of 117 m in the SWT after a long (12 weeks) hospital-based CR programme. This was the largest increase among all studies reviewed (see table 6.1). The authors did not give clear details about patients' daily activities outside the class, which may have influenced their functional capacity, while the small sample (n=19) does not allow for broad generalisations. Fowler *et al.* (2005) found an increase of 82 m in SWT performance following an exercise-based CR programme. Unfortunately, the authors gave no information regarding the number of sessions patients attended. If, as is common, only one weekly session was attended (as is common in the UK), patients took part in only six sessions in total during the CR programme. This might explain the smaller improvement in functional capacity achieved.

Arnold *et al.* (2007) used the SWT to assess the effects of once- versus twice-weekly CR in post-MI patients and they demonstrated an improvement of 101 m and 89 m respectively. Over the six-week period, a small number of training sessions were as effective as a larger number of training sessions. The lower number of training sessions might be more economical, which is an important issue noted earlier. The patients were asked to record home activities diaries, but it is not clear how this information was included in the analysis or measured outcomes. Sandercock *et al.* (2007) showed larger improvements in functional capacity (109 m) following CR in CVD patients. The study included a control group of patients (n=23) who carried out no exercise and

did not perform the SWT. This study did not put restrictions on activities during the research period. These results suggest that training had induced a large improvement in functional capacity, in this population.

Continuing the theme of reducing CR costs, Robinson *et al.* (2009) used the SWT in 100 low risk CVD patients to determine whether they could be fast-tracked to community-based phase IV CR, instead of beginning phase III hospital-based programme. The patients were randomly divided into two groups. One group attended hospital-based phase III CR (n=54); the other a community-based phase IV CR group (n=46). The phase III group showed a mean improvement of 58 (±12) m and the phase IV group showed a mean improvement of 60 (±25) m after a six-week CR programme using the SWT. There was no significant difference in performance between groups ($p>0.5$). The authors concluded that both services were effective in improving functional capacity and suggested that the fast-track service is safe and encourages long-term exercise adherence. Despite these positive conclusions, this study reports the smallest improvement in functional capacity after CR among all the above studies (see table 6.1). The source of this difference in functional improvement between the above study (Robinson *et al.*, 2009) and previous studies (Tobin & Thow 1999; Fowler *et al.*, 2005; Arnold *et al.*, 2007; Sandercock *et al.*, 2007) is likely to be due to regression towards the mean suggestions (Ostermann *et al*., 2008) rather than by the treatment in question. According to the theory of regression toward the mean, patients with the highest baseline performance values (as in Robinson *et al.*'s study) tended to show less improvement at re-assessment following a CR programme (Ostermann *et al.*, 2008).

These studies highlight the effectiveness of CR exercise intervention by comparing pre- with post- intervention SWT performance. The training stimulus varied from six to twelve weeks (mean 8 weeks), comprising between 6 and 24 sessions (mean 11 sessions). The results of the

studies reviewed here are supported by a survey carried out across England in 28 CR centres. The survey showed that the mean length of the CR courses was 7.1 weeks, and the mean number of exercise sessions offered was 11.6 (Brodie *et al.,* 2006).

After exercise training, the mean improvement in SWT distance was 93 m, while the mean percentage of improvement is 19% (based on meters) or 9.5% (based on estimated METs). The magnitude of the differences in the means represents a moderate effect size of d=0.48 (Cohen 1988). Using the data presented in table 6.1 a Pearson's correlation showed that there was no significant association between functional capacity improvement and CR exercise duration, or between improvement and the number of training sessions (p>0.5). This seems to be consistent with Arnold *et al.*'s (2007) results, where no additional benefit was found in a 12-session CR exercise programme versus a 6-session programme. Both programmes had a similar influence on outcome measures.

To determine whether the MSWT is valid, it is necessary to compare it as an evaluative tool with other tests used in a similar way. The treadmill test is the most used in CR evaluation.

Table 6.1. Review of functional capacity improvement during centre-based outpatient cardiac rehabilitation, assessed by the modified shuttle walking test

Study	Patient cohort	Pre-rehabilitation SWD (m)	Pre-rehabilitation estimated METs (ACSM 2005; Woolf-May & Ferrett 2008)	Post-rehabilitation SWD (m)	Improvement				CR duration (weeks)	CR exercise sessions
					Metres	% (based on metres)	METs	% (based on estimated METs)		
Tobin & Thow (1999)	CABG n=19	N/A	N/A	N/A	117	N/A	N/A	N/A	12	24
Fowler *et al.* (2005)	CABG n=39	481 ± 138	5.5 ± 3.9	563 (SD N/A)	82	17	0.5	9.1	6	N/A
Arnold *et al.* (2007)	MI A: n=85 B: n=121	A: 409 ± 166 B: 469 ± 153	A: 5.0 ± 3.9 B: 5.5 ± 3.9	A: 510 ± 191 B: 557 ± 171	A: 101 B: 88	A: 25 B: 18.7	A: 0.5 B: 0.5	A: 10 B: 9.1	6	A: 6 B: 12
Sandercock *et al.* (2007)	MI, CABG, PCI n=38	488 ± 214	5.5 ± 4.2	597 ± 235	109	22.3	0.5	9.1	8	8
Robinson *et al.* (2009)	MI, CABG n=54	618 ± 165	6.0 ± 3.9	676 ± 177	58	9.4	0.6	10	6	6
Mean		*493*	*5.5*	*581*	*93*	*19*	*0.5*	*9.5*	*9.5*	*11*

*Definition of abbreviations: SWD=distance walked in shuttle walking test; MI=myocardial infarction; CABG=coronary artery bypass graft; PCI=*percutaneous coronary intervention; *N/A=non applicable*

6.1.3.2. Exercise capacity in cardiac rehabilitation patients, assessed by the treadmill test

Studies that used the SWT to evaluate functional capacity improvement in CR patients are limited. There are, however, numerous studies using treadmill testing, to demonstrate exercise capacity (measured as oxygen consumption) improvement during phase III CR. Table 6.2 highlights the main findings regarding changes in exercise capacity after hospital-based outpatient (phase III, UK classification) CR assessed by treadmill testing. Applying a meta-regression approach to the data presented in table 6.2, a Pearson's correlation showed a high negative correlation between exercise capacity improvement and duration of the CR programme. This was true when exercise capacity was expressed either as an absolute value in METs or as percentage improvement from baseline (r_1=-0.93, r_2=0.88, respectively; p<0.005).

Changes in exercise capacity were not significantly associated with the number of CR exercise sessions (p>0.5). These associations mean that shorter exercise programmes can be as effective as longer programmes, while the number of sessions does not relate to the programmes' effectiveness. This might be a result of large variance in CR programmes and in the cohorts used in different studies; some might have used a more intense but shorter exercise programme than others. Not all studies provided information regarding the mean number of sessions attended. Some of the studies, included in table 6.2, used a CR programme over eight weeks (Ades *et al.*, 1995; Lavie and Milani 1995; Balady *et al.*, 1996; Carlson *et al.*, 2000; Seki *et al.*, 2003; Adams *et al.*, 2008; Seki *et al.*, 2008; Onishi *et al.*, 2010); however, two studies have demonstrated that after six to eight weeks of outpatient phase III CR, patients do not further improve their exercise capacity (Woolf-May and Ferrett 2008; Robinson *et al.*, 2009).

Table 6.2. Review of exercise capacity improvement during centre-based outpatient cardiac rehabilitation, assessed by the treadmill test

Study	Patient cohort	Pre-rehabilitation exercise capacity (METs)	Improvement (METS)	Improvement (%)	Mean CR duration (weeks)	CR exercise sessions
Miller *et al.* (1984)	MI n=61	2.1 ± 1.4	2.0	N/A	8	24
Ades *et al.* (1995)	MI, CABG n=60	N/A	N/A	16	12	N/A
Lavie & Milani (1995)	CHD n=458	6.6 ± 2.2	2.4	38	14	36
Balady *et al.* (1996)	MI, CABG, PCI n=500	7.3± 3	N/A	36	10	N/A
Carlson *et al.* (2000)	MI, CABG, PCI n=78	6.7 ±1.7	0.4	6.3	24	72
Seki *et al.* (2003)	CHD n=38	6.7± 1.0	0.1	1.3	24	24
Adams *et al.* (2008)	MI n=210	6.6 ± 2.7	2.1	32	12	N/A
Seki *et al.* (2008)	CHD n=20	6.8 ± 1.0	0.5	7.7	24	24
Onishi *et. al.* (2010)	CHD n=37	6.4 ± 0.9	0.2	3.6	24	24
Mean		*6.1*	*1.1*	*17.6*	*17*	*34*

*Definition of abbreviations: MI=myocardial infarction; CABG=coronary artery bypass graft, PCI=*p*ercutaneous coronary intervention; N/A=non applicable*

6.1.3.3. Differences in exercise capacity improvement between studies performed using the treadmill test and those using the shuttle walking test

A comparison of the data in tables 6.1 and 6.2 shows that the mean exercise capacity improvement after CR, (as METs or percentage improvement), is higher in studies that used the treadmill test than those using the SWT. This might be due to many potential factors such as, the higher sensitivity of treadmill testing for detecting exercise capacity changes or walking speed differences between the two tests. For example, in the modified Bruce treadmill protocol the grade but not the speed is increased at each stage whereas for the SWT only the speed is increased at each stage. Differences may be attributable to lower baseline values for exercise capacity in studies used the treadmill test (regression toward the mean) or perhaps the inaccuracy of MET values in CVD cohorts (Savage *et al.*, 2007; Woolf-May and Ferrett 2008). There are also differences, however, in the training stimuli between the two groups of studies. The mainly US-based CR programmes which have used the treadmill test tend to be longer and contain a greater number of exercise sessions than the SWT studies.

Due to systematic differences in both the training stimulus and the exercise assessment protocols these two groups of studies are difficult to compare. A study using a UK training protocol (8 sessions over 8 weeks) that assessed changes in exercise capacity via treadmill testing would, however, rectify this situation.

6.1.4. How to improve the accuracy of exercise capacity assessment

Given the importance placed upon increasing exercise (functional) capacity in CR, it is surprising how few data are available to evaluate whether the 'typical' UK service is effective. Table 6.1 contains all the available data on UK CR services (n=356). Most are cohort studies (groups of patients who are members of a particular CR centre), and the ideal way to investigate

effectiveness of a CR system is to perform a service evaluation research. Service evaluation has been defined as 'the systematic collection of research data to assess effectiveness of organisations, services, and programmes (i.e., health service interventions) in achieving predefined objectives' (Shaw 1980, cited in Bowling 2002). Service evaluation research takes place in 'real-world' NHS settings and does not allow the researcher to control aspects of the research process to the same degree as do other research designs (such as randomised controlled trials). Service evaluation is usually performed to meet specific local requirements.

Service evaluation can also give important knowledge regarding normal values and ranges for improvement in functional capacity tests (i.e., SWT), in CR. Their use could improve patient care in CR and help practitioners make informed choices regarding their recommendations to patients at their discharge from the programme. For instance, if a patient's functional capacity has not improved during phase III CR, it may be decided that they should be retained on the programme or strongly encouraged to enrol in a phase IV programme.

There seems little doubt that if normative values for functional capacity tests are used to inform practice, could improve the accuracy of functional capacity assessment. In Chapter 5, an extended analysis was presented regarding data from previous studies, in which anthropometric variables were used to predict functional capacity test performance in healthy adults (Enright and Sherrill 1998; Gibbons *et al.*, 2001; Enright *et al.*, 2003; Camarri *et al.*, 2006; Chetta *et al.*, 2006; Poh *et al.*, 2006; Jenkins *et al.*, 2009), with only one study that evaluated anthropometric associations in a clinical population (Ingle *et al.*, 2006).

These studies all concerned the 6-MWT and no comparable data exist for the SWT. A pilot study has already been completed (see Chapter 4) with sixteen phase IV CR patients, where it was suggested that taller CVD patients have an advantage over shorter patients when performing the SWT, while the established prediction equation could be used to predict an individual's

performance and remove some of the bias towards taller patients. These results are very important to the clinical practice of CR. Methodological issues, such as small sample size, a non-validated equation and the nature of the CR cohort, indicated limited scope for generalisation. Taking into account the importance of the findings and the limitations derived from the pilot study, there is a need for further investigation in this area.

6.1.5. Aims and hypothesis

The two primary aims of this chapter are to determine normative values for functional capacity before and after CR, and the magnitude of change in functional capacity in phase III CR patients from a typical cohort. Secondary aims were to revisit Chapter 4 in a larger, phase III cohort and examine the anthropometric predictors of MSWT performance (distance walked in MSWT [MSWD]).

6.2. Methods

6.2.1. Participants

The sample comprised 159 (122 males and 37 females) patients aged 36 to 87 years. Data from the records of the previous 12 months (September 2009 – September 2010) for cardiac patients referred for CR at two UK NHS trusts (Broomfield hospital and West Cumberland hospital) were examined. The cardiac care providers (specialist CR nurses) working within each hospital were responsible for identifying patients. A list of patients, with access to their records, was provided by the CR nurse in charge of care provision. Patient records were assessed, including a description of CR services, patients' characteristics, time from operation or event to enrolment in the rehabilitation centre, pre-rehabilitation and post-rehabilitation assessment measurements, and time from pre-rehabilitation assessment to post-rehabilitation assessment. Table 6.3 summarises the descriptive characteristics and baseline measurements of the study population.

All procedures were approved by the University of Essex Ethics Committee, the National Research Ethics Service (NRES) and conformed to the declaration of Helsinki guidelines (World Medical Association 2009) for research with human participants.

Table 6.3. Descriptive characteristics and baseline measurements of participants

Clinical characteristics and baseline measurements	Values	
Number of patients	159	
Sex (%)	Males=122 (77%) – Females=37 (23%)	
Age (years) (mean ± SD)	68.1 ± 9.4	
Body mass (mean ± SD)	*Pre-rehab:* 81.8 ± 15.7 *Post-rehab:* 80.6 ± 15.0	
Stature (cm) (mean ± SD)	170 ± 8.5	
Median value (25th percentile)	165	
Median value (75th percentile)	175	
BMI (kg · m^{-2}) (mean ± SD)	*Pre-rehab:* 28.3 ± 4.4 *Post-rehab:* 28.0 ± 4.9	
Waist circumference (cm) (mean ± SD)	*Pre-rehab:* 78.1 ± 16.1 *Post-rehab:* 76.1 ± 21.8	
Medical primary diagnosis (%)		
CHD	n=103 (64.8%)	
NSTEMI	n=18 (11.3%)	
STEMI	n=7 (4.4%)	
Valvular heart disease	n=18 (11.3%)	
Other	n=6 (3.8%)	
No information	n=7 (4.4%)	
Surgical diagnosis		
CABG	n=98 (61.6%)	
PCI	n=29 (18.2%)	
Valve replacement	n=21 (13.2%)	
Other	n=1 (0.6%)	
None	n=10 (6.3%)	
Smokers	n=15 (9.4%)	
Diabetes	n=30 (18.9%)	
Time from surgical intervention procedure or event (weeks)	7.6 ± 4.6	
Time to retest (weeks)	7.2 ± 2.3	
Medication	*Pre-rehab*	*Post-rehab*
β-blockers	n=121 (76.1%)	n=117 (74.2%)
Statin	n=117 (73.6%)	n=120 (75.5%)
Aspirin	n=139 (87.4%)	n=144 (90.6%)
Clopidogrel	n=33 (20.8%)	n=33 (20.8%)
Ace Inhibitor	n=98 (61.6%)	n=101 (63.5%)
GTN	n=14 (8.8%)	n=14 (8.8%)

Definition of abbreviations: CHD=coronary heart disease; NSTEMI=non-ST-segment myocardial infarction; STEMI=ST-segment myocardial infarction; CABG=coronary artery bypass graft, PCI=Percutaneous coronary intervention; ACE=angiotensin-converting enzyme; GTN= glyceryl trinitrate

6.2.2. Cardiac rehabilitation exercise programme

All the patients had been enrolled in a hospital-based phase III CR (UK classification) programme for six weeks. The patients joined the CR programme at a mean of 7.6 (±4.6) weeks after an acute cardiac episode or surgical intervention. The CR programme followed the BACR guidelines (2006) and consisted of two supervised sessions per week, involving 12 exercise sessions over a period of six weeks. Supervisory personnel included (CR) specialised physiotherapists and exercise staff, who were trained in life support techniques. The sessions consisted of 60 minutes of circuit-based exercise, with 15-minutes warm-up, 30-minutes main conditioning component and 15-minutes cool down. The warm-up included mobility exercises and stretches; the main component of the session included cardiovascular and strength exercises using exercise equipment (an arm, cycle and rowing ergometers, progressive resistance equipment, balance equipment, steppers, free-weights) at an intensity of 60 to 75% of their age-predicted maximal heart rate (HR); the cool-down included gently paced recovery exercises, mobility exercises and stretches.

6.2.3. Cardiac rehabilitation assessment

Patients were referred to the CR programme by their cardiologists. Patients included in phase III CR underwent cardiac assessment at entry to and at the completion of the programme, with a mean of 7.2 (±2.3) weeks between the two assessments. The assessment included medical and pharmacological history, a primary health assessment (pre-exercise health questionnaire, resting HR and resting blood pressure measurement), anthropometric assessment and exercise testing. Anthropometric assessment included measurements of stature, body mass and waist circumference. BMI was then calculated as follows: mass (kg)/stature (m^2). All patients participated in the sub-maximal modified shuttle walking test (MSWT), as described in Chapter 3 (pp.130-131).

6.2.4. Statistical Analysis

Descriptive analysis was used to describe the sample under examination here. Data were presented as mean and standard deviations. The median value of stature was calculated; Stature data were divided into three quartiles (25^{th}, 50^{th}, 75^{th} percentile of the distribution). A paired-samples t-test was conducted to evaluate the changes in the functional capacity and the physiological variables during phase III CR.

In order to evaluate how well (validate) the prediction equation 4.1a, developed in Chapter 4 (pp.196), for estimating MSWD of patients ending phase III CR, a Pearson's product moment coefficient, an intraclass correlation coefficient (ICC) and limits of agreement (LoA) test (Bland and Altman 1986) were calculated. The Bland and Altman (1986) method sets limits of agreement and confidence intervals around the average difference between the actual and predicted MSWD. In order to use this method, first step was to calculate the difference in MSWD (predicted-actual) for each patient and then to plot these individual difference MSWDs against individual average MSWDs. The average MSWDs were calculated by summing the individual actual and predicted MSWD and then dividing this sum by two. The standard deviation (SD) of the difference MSWDs is used to set the upper (+2SD) and lower limits of agreement (-2SD). It would be expected most of the MSWDs (95%) to lie between ±2SD, if the difference MSWDs are normally distributed. The smaller the limits of agreement (the smaller the error variance), the greater the predictive accuracy of the equation (Heyward and Wagner 2004).

Due to low accuracy of equation 4.1a, another regression analysis based on the current phase III CR population was performed. The current population was randomly divided into two groups (development population and validation population). For this purpose, an electronic program which generates random numbers was used (www.random.org).

Relationships between variables measured during the pre-rehabilitation assessment were tested in the development population using a correlation coefficient (Pearson's product moment or Spearman's rank). After determining which variables were most strongly related to MSWD ($r>0.3$), stepwise linear regression analysis was performed to assess the combined associations in the development population. The accuracy of the new equation model was evaluated in the same way as was done for equation 4.1a (Pearson's product moment coefficient, ICC and LoA test).

In order to assess the factors that might associate with magnitude of change in functional capacity during phase III CR, stepwise regression analysis was performed. Prior to the regression analysis, difference in MSWD between pre- and post- rehabilitation assessment was calculated per each individual, and a correlation coefficient (Pearson's product moment or Spearman's rank) was used to determine which variables were most strongly related to MSWD ($r>0.3$).

In all cases, the stepwise linear model was chosen in favour of other models because the objective was to identify the lowest number of variables that most influenced the test results. The regression used, only, those independent variables for which the coefficient correlation with the other independent variables was less than 0.75, in order to minimise multicollinearity and to avoid high correlation between the variables (Meyers *et al.*, 2006). The probability of F for entry was set at 0.05 and for removal at 0.1; these were set as the statistical criteria that the dependent variables needed to attain in order to be included in the analysis.

After determining the predictors of the MSWT, the next step was to establish normative values for male and female patients separately. Thresholds values were identified for predictors and they were encoded by using 0 and 1. Then, mean values of MSWD for each subgroup were computed via univariate analysis. One-way ANOVA was performed to investigate differences in MSWD and MSWD improvement, among patients with different surgical diagnoses. Statistical

analysis was performed using SPSS version 16.0 (SPSS inc., Chicago, IL, US); calculations were presented in Microsoft Office Excel 2003 (Microsoft Corporation**,** Washington, US). The statistical significance was set at the 0.05 level.

6.3. Results

6.3.1. Changes in physiological measurements due to cardiac rehabilitation in phase III

Table 6.4 provides values for the physiological measurements taken before and after phase III CR. There was a statistically significant increase in MSWD, between the two assessments: $t=-12.1$, $p<0.001$ (two-tailed). Of particular note, there was also a significant increase in SBP (4 mmHg) between the two assessments: $t=-2.4$, $p<0.05$ (two-tailed). A small and non-significant decrease between the two assessments was found for body mass (0.17 kg) and waist circumference (0.7 cm).

Table 6.4. Physiological effects of phase III cardiac rehabilitation (n=159)

Variable	Pre- rehabilitation		Post-rehabilitation		Mean Difference 95%CI	t-value	*P* value
	Mean	(SD)	Mean	(SD)			
MSWD (m)	292	(136)	420	(186)	-128 (-148 *to* -107)	-12.1	<0.001
RPE score	11.4	(2.1)	11.7	(2.1)	-.3 (-1.3 *to* 0.6)	-0.65	0.518
Maximum HR (bpm)	88	(17)	89	(15)	-1 (-4 *to* 3)	-0.34	0.733
HR 5 min after the end of the test (bpm)	68	(13)	70	(12)	-2 (-5 *to* 1)	-1.55	0.130
Resting SBP (mmHg)	133	(19)	137	(19)	-3.74 (-6.81 *to* -0.67)	-2.40	0.017
Resting DBP (mmHg)	76	(9)	76	(9)	-0.23 (-1.69 *to* 1.22)	-0.32	0.752
Body mass (kg)	80.7	(14)	80.6	(15)	0.17 (-0.63 *to* 0.97)	0.43	0.668
BMI ($kg \cdot m^{-2}$)	28	(3.8)	28	(4.9)	-0.06 (-0.57 *to* 0.45)	-0.25	0.800
Waist Circumference (cm)	96.1	(11.6)	95.4	(11.2)	0.7 (-4.41 *to* 4.32)	-0.02	0.982

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test; RPE=Borg rating of perceived exertion; bpm=beats per minute; HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure.

6.3.2. Validating the prediction equation developed in Chapter 4

The correlation and level of agreement between actual and predicted MSWD, by using equation 4.1a, were weak. Due to the lengthy data analysis, the results of this section (6.3.2.) are included in appendix A1. Another regression analysis was, therefore, performed using the variables outlined in Chapter 6; a new MSWT prediction equation was created.

6.3.3. Predictors of the modified shuttle walking test in phase III cardiac rehabilitation

The cardiac population in this study was split randomly into two groups; development group (n=79) and validation group (n=80). In the development group, the mean MSWD was 287 (±142) m in the pre-rehabilitation assessment; in the validation group, the MSWD was 295 (±131) m. Sex, age and stature were the only variables that showed a significant correlation with MSWD in the development group. In particular, age was negatively and moderately associated with MSWD, while stature and sex showed a positive, moderate association with MSWD (see table 6.6).

Table 6.6. Correlations between independent variables and modified shuttle walk distance in the phase III cardiac rehabilitation (development group)

Variables	**N**	**Spearman rho**	***P* value**
MSWD – Sex *	79	0.508	<0.001
MSWD – Diabetes mellitus *	79	-0.153	0.178
Variables	**N**	**Pearson r**	***P* value**
MSWD – Age	79	-0.351	0.002
MSWD – Stature	77	0.412	<0.001
MSWD - Body mass	79	0.181	0.110
MSWD - BMI	77	-0.088	0.448
MSWD - SBPresting	79	-0.142	0.212
MSWD - DBPresting	79	0.100	0.378
MSWD - Time from procedure or event	75	- 0.117	0.318

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure

** Data were coded: for Sex- Male=1, Female=0; for Diabetes mellitus- Yes=1, No=0*

Next, the independent variables, sex, age and stature, which were correlated (r>0.3) with MSWD, were further analysed using multiple linear regression analysis (Pallant 2007). The regression used only those independent variables for which the correlation coefficient with the other independent variables was less than 0.75, in order to minimise multicollinearity and to avoid high correlation between the variables (Meyers *et al.*, 2006).

The regression analysis showed that age, stature and sex should be included in the final model. In this model, 62.3% of MSWD was explained by age, stature and sex, with a standard error of 114 m. The predicted result was calculated by using the following regression equation: $Y=A+(B\times X)$, where Y is the predicted value of the dependent variables (predicted MSWD in m), A is the Y intercept (the value Y when the X value is zero), X indicates the rate of the independent variable (age, stature, sex) and B are the coefficients assigned to each of the independent variables in the

regression analysis (Tabachnick and Fidell 2007). Predicted MSWD would be computed by using the equation form for each individual.

The intercept value (A) was -115 m. The coefficient (β value) for age was -6.1; the coefficient for stature was 4.4; and the coefficient for sex was 97 (see equation 6.1a). The 5th percentile of pre-rehabilitation MSWD distribution for development group was 60 m, so the lower limit of normal range (LLN) was computed by subtracting 60 m from the equation (see equation 6.1b). The predictive equation for MSWD produce was:

Equation 6.1a. $MSWD = (4.4 \times stature,_{cm}) - (6.1 \times age,_{yrs}) + (97 \times sex) - 115$

Equation 6.1b. $MSWD_{(LLN)} = (4.4 \times stature,_{cm}) - (6.1 \times age,_{yrs}) + (97 \times sex) - 175$

where: MSWD=distance walked in modified shuttle walking test (m); LLN=lower limit of normal range; sex: M =1, F=0

6.3.4. Validation of the prediction equation developed in the phase III cardiac rehabilitation cohort

The accuracy of the prediction equation developed in the phase III development CR population (development group) was assessed by predicting MSWD in the validation CR population (validation group). The predicted result was calculated by using the regression equation 6.1a.

6.3.4.1. Correlations between actual and predicted distance walked in the modified shuttle walking test in the validation population

Actual MSWD had a significant correlation with predicted MSWD (Pearson's r=0.307, p=0.006) when age, stature and sex were entered into the equation model. This relationship between predicted and actual MSWD is shown in figure 6.3. The standard error of estimation was 124 m.

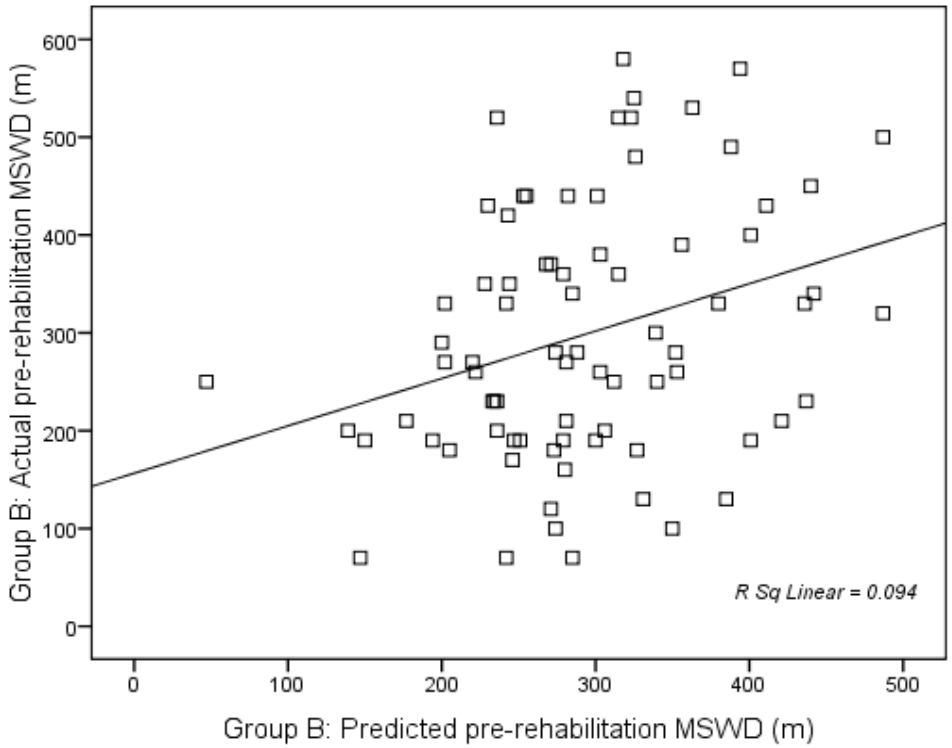

Figure 6.3. Regression line for the relationship between actual pre-rehabilitation and predicted pre-rehabilitation performance (using equation 6.1a)

6.3.4.2. Agreement between actual and predicted distance walked in the modified shuttle walking test, in phase III cardiac rehabilitation

The ICC between actual and predicted MSWD with 95% confidence intervals (post-rehabilitation MSWD) was low, at 0.28 (p=0.007). The mean difference and the limits of agreement (for MSWD) are shown in table 6.7 and figure 6.4. The standard deviation (130 m) of the difference MSWDs indicates that the difference between predicted and actual MSWD could be expected to be within -255 m and 265 m.

Table 6.7. Agreement statistics: Mean difference (95% confidence intervals) between predicted- and actual pre- rehabilitation distance walked in modified shuttle walking test (using equation 6.1a)

	Mean (SD) Difference	95% confidence interval from the mean difference	2SD	Limits of agreement (mean±2SD)
MSWD (m)	5 (130)	-24 to 35	260	-255 to 265

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test; SD=standard deviation

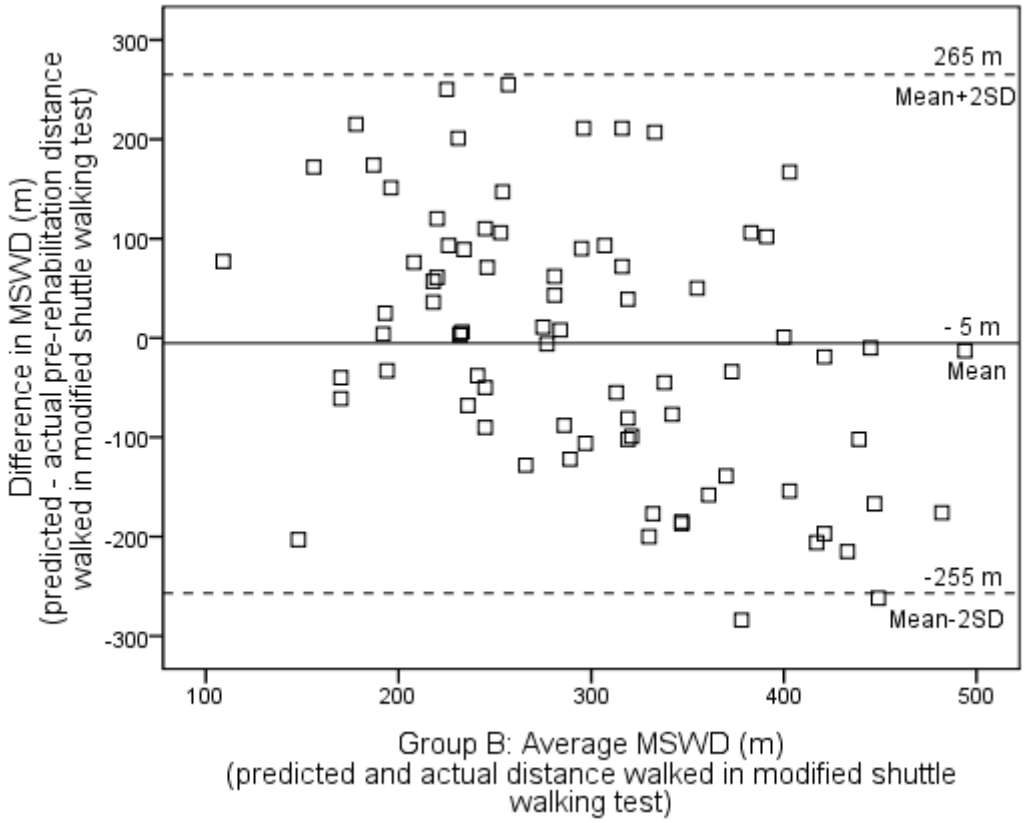

Figure. 6.4. Limits of agreement plot (Bland and Altman plot) (using equation 6.1a). Intraindividual differences between performances in walking-test scores (predicted-actual distance walked) plotted against the mean of the sum scores, in training group (phase III cardiac rehabilitation). The central line represents the mean of the intraindividual differences and the flanking lines represent the 95% limits of agreement.

6.3.5. Multivariate determinants of change in modified shuttle walking distance.

The difference in MSWD between pre- and post-rehabilitation assessment was calculated for each individual. The mean difference was 25 (±46) m. The correlations between independent variables and difference in MSWD are presented in table 6.8.

Table 6.8. Correlations between independent variables and change in modified shuttle walk distance in the phase III cardiac rehabilitation (n=159)

Variables	**N**	**Spearman rho**	**P value**
$MSWD_{change}$ – Sex*	149	0.030	0.718
MSWD – Diabetes mellitus *	149	-0.008	0.918
Variables	**N**	**Pearson r**	**P value**
$MSWD_{change}$ – Age	149	-0.277	0.001
$MSWD_{change}$ – Stature	145	0.190	0.281
$MSWD_{change}$ - Body mass	149	-0.139	0.091
$MSWD_{change}$ – BMI	145	-0.086	0.306
$MSWD_{change}$ – Waist circumference	46	-0.015	0.922
$MSWD_{change}$ - $SBP_{resting}$	149	-0.199	0.015
$MSWD_{change}$ - $DBP_{resting}$	149	0.003	0.973
$MSWD_{change}$ – Time to retest	123	0.168	0.064

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure

** Data were coded: for Sex- Male=1, Female=0; for Diabetes mellitus- Yes=1, No=0*

Since none of the variables had a correlation >0.3 with the change in MSWD, all the variables were first checked for multicollinearity and then entered into the stepwise regression analysis. Body mass was excluded from the analysis due to high collinearity with BMI (VIF>10) (Meyers *et al.*, 2006).

The linear regression analysis showed that only stature significantly predicted MSWD in the final model, explaining 37% of the variance. The intercept value (A) was found to be 764 m. The coefficient (β value) for stature was -4.2 (see equation 6.2a). The 5^{th} percentile of change in MSWD distribution was 40 m, so the lower limit of normal range (LLN) was computed by subtracting 40 m from the equation (see equation 6.1b).

For the MSWT, the equation for predicting change in MSWD in phase III CR is:

Equation 6.2a. $MSWD_{change} = 764 - (4.2 \times stature,_{cm})$

Equation 6.2b. $MSWD_{change(LNN)} = 724 - (4.2 \times stature,_{cm})$

where: MSWD=distance walked in modified shuttle walking test (m)

6.3.6. Normative values for functional capacity and magnitude of change in functional capacity during phase III cardiac rehabilitation

The threshold values that identified predictors are shown in table 6.9; they represent median values of normal distributions.

Table 6.9. Threshold points for predictors

Variables	Threshold values	Identifications
Age (median; yrs)	69	≥ 69: old
		< 69: young
Stature (median; cm)	Males: 172	Males:
		≥ 172: tall
		≤ 172: short
	Females: 160	Females:
		≥ 160: tall
		≤ 160: short

Tables 6.10, 6.11 and 6.12 present the normative values of pre-rehabilitation MSWD, post-rehabilitation MSWD and magnitude of change in MSWD, respectively. The highest values of MSWD (pre- and post- rehabilitation) and change in MSWD were recorded for males who were younger than 69 years and taller than 172 cm, while the lowest values were recorded by females who were older or equal to 69 years and taller or equal to 160 cm.

Table 6.10. Normative values for pre-rehabilitation modified shuttle walking test performance

	Male		Female	
	Young < 69 years	**Old ≥ 69 years**	**Young < 69 years**	**Old ≥ 69 years**
Short (M<172cm; F<160cm)	330 ± 111 m n=26	267 ± 114 n=29	176 ± 61 m n=8	236 ± 93 m n=7
Tall (M ≥ 172 cm; F ≥ 160 cm)	391 ± 114 m n=28	309 ± 156 n=39	221 ± 93 m n=9	147 ± 59 n=13

Definition of abbreviations: M=values for males; F=values for females

Table 6.11. Normative values for post-rehabilitation modified shuttle walking test performance

	Male		Female	
	Young < 69 years	**Old ≥ 69 years**	**Young < 69 years**	**Old ≥ 69 years**
Short (M<172 cm; F<160 cm)	484 ± 191 m n=25	408 ± 155 m n=27	332 ± 137 m n=8	330 ± 59 m n=7
Tall (M ≥ 172 cm; F ≥ 160 cm)	553 ± 234 m n=25	402 ± 158 m n=37	364 ± 91 n=8	233 ± 67 n=12

Definition of abbreviations: M=values for males; F=values for females

Table 6.12. Normative values for magnitude of change in modified shuttle walking test performance

	Male		Female	
	Young < 69 years	**Old ≥ 69 years**	**Young < 69 years**	**Old ≥ 69 years**
Short (M<172 cm; F<160 cm)	152 ± 119 m n=25	133 ± 94 m n=27	156 ± 124 m n=8	94 ± 61 m n=7
Tall (M ≥ 172 cm; F ≥ 160 cm)	168 ± 184 m n=25	86 ± 133 m n=37	158 ± 107 n=8	88 ± 73 n=12

Definition of abbreviations: M=values for males; F=values for females

6.3.7. Differences in modified shuttle walking test performance between patients with different surgical diagnoses

Patients were divided into four subgroups according to type of surgical intervention: 1) coronary artery bypass graft surgery (CABG), 2) percutaneous coronary intervention (PCI), 3) valve replacement (VR), 4) none. One-way between groups analysis of the variance was used in order to find the impact of different interventions/invasive treatments on pre-rehabilitation MSWD and on changes to MSWD during CR.

There was no statistically significant difference in pre-rehabilitation MSWD ($p>0.05$): F_1 (3, 154)=2.58, p=0.055, while there was a significant difference in the magnitude of MSWD change: F_2 (3, 145)=4.11, p=0.008, among the elective subgroups. The mean values for pre-rehabilitation MSWD are presented in table 6.13 and figure 6.5, while the mean values for MSWD change are presented in table 6.14 and figure 6.6, for the different elective subgroups. Higher mean values of MSWD (305±130 m) and MSWD change (146±123 m) were achieved by patients who had received CABG (see table 6.9 and 6.10).

Table 6.13. Distance walked during the modified shuttle walking test in pre-rehabilitation assessment related to surgical diagnosis

Surgical diagnosis	N	MSWD (m)	
		Mean	SD
CABG	98	305	130
PCI	29	304	148
VR	21	251	146
NONE	10	199	102

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test; CABG=coronary artery bypass graft; PCI=percutaneous coronary intervention; VR=valve replacement

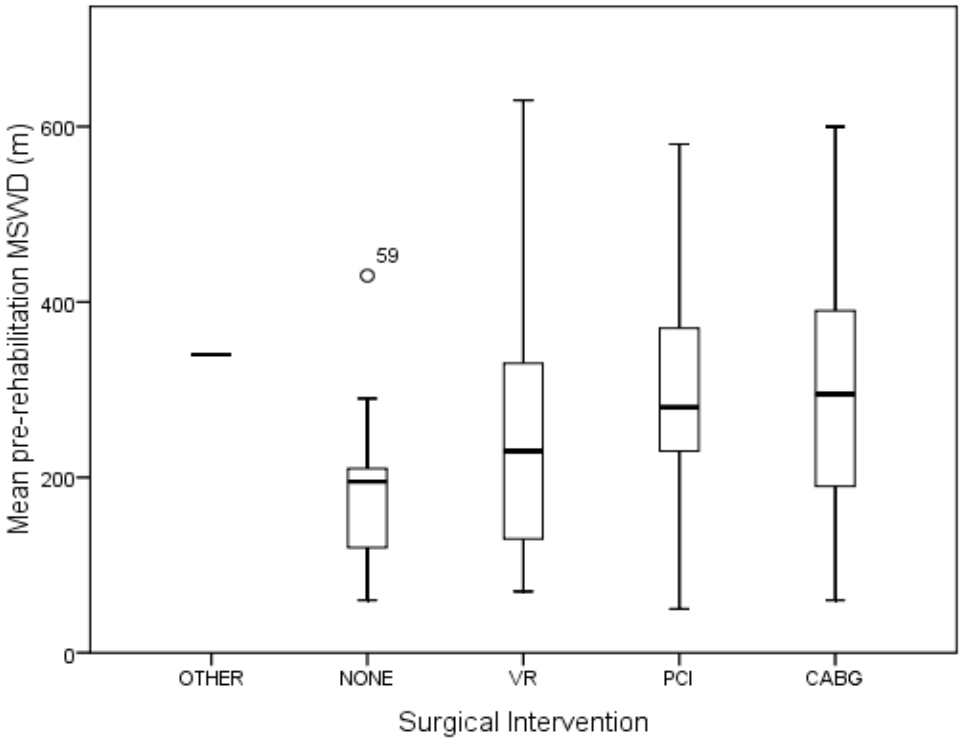

Figure 6.5. Box plot of differences in the pre-rehabilitation modified shuttle walking test performance (MSWD) among the surgical subgroups.

The upper edge of each box indicates the 75 percentile and the lower edge the 25 percentile of MSWD. The line in the box indicates the 50th percentile of MSWD (median value). The ends of the vertical lines (whiskers) indicate the minimum and maximum MSWD. The points outside the whiskers are outliers. Symbols are used to label outliers (o) and extremes (*). The label outliers range between between 1.5 and 3 box-lengths from the 75th percentile or 25th percentile. The extreme values are MSWD values more than 3 box-lengths.

MSWD=distance walked in modified shuttle walking test; CABG=coronary artery bypass graft surgery; PCI=percutaneous coronary intervention; VR=valve replacement

Table 6.14. Distance walked during the modified shuttle walking test in pre-rehabilitation assessment related to surgical diagnosis

Surgical diagnosis	N	MSWD (m)	
		Mean	SD
CABG	94	146	123
PCI	24	46	132
VR	21	137	115
NONE	10	131	144

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test; CABG=coronary artery bypass graft; PCI=percutaneous coronary intervention; VR=valve replacement

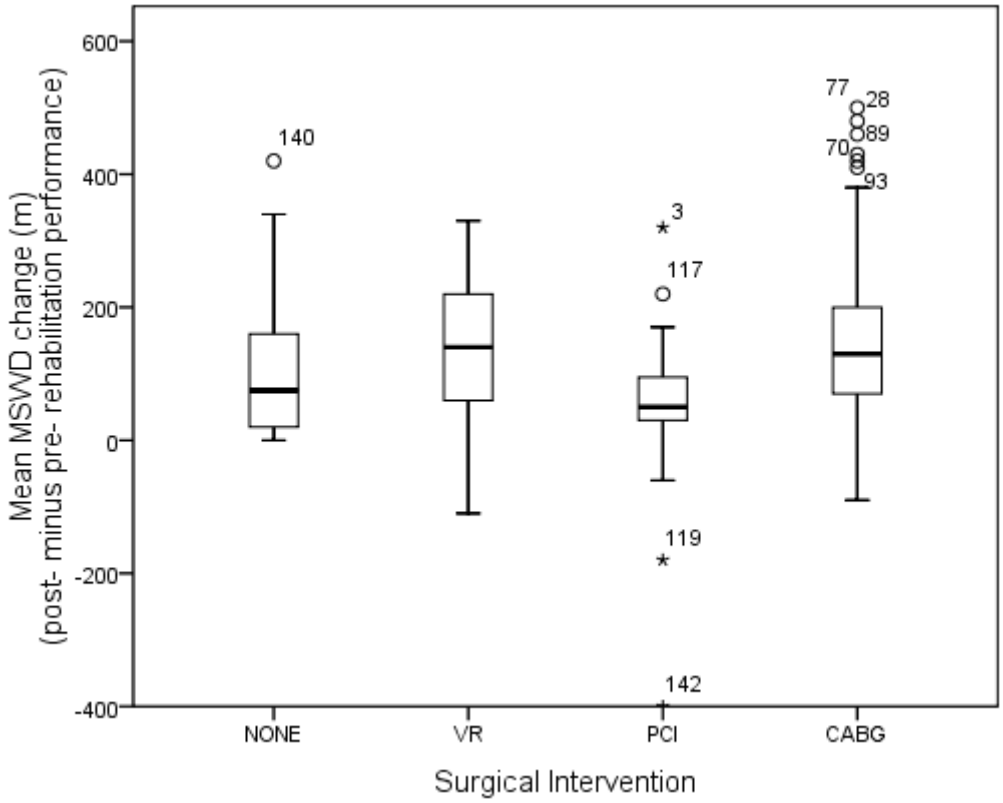

Figure 6.6. Box plot of differences in modified shuttle walking test performance (MSWD) change during phase III cardiac rehabilitation, among the surgical subgroups

The upper edge of each box indicates the 75th percentile and the lower edge the 25th percentile of MSWD change. The line in the box indicates the 50th percentile of MSWD change (median value). The ends of the vertical lines (whiskers) indicate the minimum and maximum MSWD change. The points outside the whiskers are outliers. Symbols are used to label outliers (o) and extremes (*). The label outliers range between between 1.5 and 3 box-lengths from the 75th percentile or 25th percentile. The extreme values are values more than 3 box-lengths.

MSWD=distance walked in modified shuttle walking test; CABG=coronary artery bypass graft surgery; PCI=percutaneous coronary intervention; VR=valve replacement

6.4. Discussion

There are a number of reasons for performing an exercise test in CR patients; to confirm diagnosis of CHD, to monitor disease progression, to determine prognosis, to prescribe treatment, to evaluate exercise capacity at baseline and after an exercise-based CR treatment (Kraus *et al.*, 2007). The MSWT is a common practical field test, in which the absolute value in metres is mainly used to assess patients' functional capacity and responsiveness to a CR

programme (Singh *et al.*, 1994; Fowler *et al.*, 2005), while its role in prognosis and exercise prescription has not been well investigated.

Research to date has not examined the anthropometric or clinical predictors of MSWD in a cardiac population, despite a wealth of data showing such variables predict 6MWD in healthy adults (Enright and Sherrill 1998; Gibbons *et al.*, 2001; Enright *et al.*, 2003; Camarri *et al.*, 2006; Chetta *et al.*, 2006; Poh *et al.*, 2006; Jenkins *et al.*, 2009). A pilot study was carried out on a phase IV population, (see Chapter 4). The present chapter aims to compensate for some of the limitations described in Chapter 4. Thus, one of the purposes of the present study was to validate the equation developed (see equation 4.1a) in a larger sample of CR patients.

The discussion of findings will be subdivided into subsections in order to address the multiple aims of the study. The primary aim was to construct a more fair evaluation system enabling a more effective prescription of exercise therapy, by refining the prediction equation for MSWD and by establishing normal values for the functional capacity of patients in CR.

6.4.1. Changes in functional capacity: comparison with previous data

The results of the current study showed that six weeks of phase III CR improves functional capacity, as assessed by the MSWT. Only five studies have previously evaluated the effectiveness of CR intervention using the MSWT (Tobin and Thow 1999; Fowler *et al.*, 2005; Arnold *et al.*, 2007; Sandercock *et al.*, 2007; Robinson *et al.*, 2009). Similar to the present findings, all these previous studies showed improvement in MSWD, but responses were relatively heterogeneous; ranging from 58 to 117 m after six to twelve weeks (6 to 24 sessions) of exercise-based CR.

The usefulness of the SWT as a predictor of prognosis and mortality in cardiac patients is not yet known. Using treadmill data, Franklin *et al*. (2003) demonstrated that a 1 MET increase in exercise capacity corresponds to a 10% reduction in mortality. When MSWD was converted to METs (Woolf-May and Ferrett 2008) the present study showed a mean improvement of 0.4 METs due to CR. The expression of functional capacity as METs may not be wholly accurate for CVD populations (Woolf-May and Ferrett 2008), but it still shows an improvement in functional capacity and a reduction in risk for CVD mortality. Direct measures of oxygen consumption during the SWT are not routinely taken in clinical practice, while estimates of $VO2_{max}$ are usually used when it is necessary. MET values were derived from the ACSM equations in healthy people as there are no established MET values for the various SWT stages derived from CVD population.

The improvements recorded here (128 m or 44% from baseline MSWD or 0.4 METs) were larger than in all the previously mentioned studies (see tables 6.1. and 6.2), which together, report a mean improvement of 93 m or 9.5% (based on estimated METs) from the baseline measurement (Tobin and Thow 1999; Fowler *et al*., 2005; Arnold *et al.,* 2007; Sandercock *et al*., 2007; Robinson *et al.,* 2009) (see table 6.1). Studies using treadmill tests report a mean improvement (measured in METs) of 17.6% (Miller *et al.*, 1984 Ades *et al.,* 1995; Lavie and Milani 1995; Balady *et al.,* 1996; Carlson 2000; Seki *et al.,* 2003, 2008; Adams *et al.,* 2008; Onishi *et. al.,* 2010) (see table 6.2). The large improvement in functional capacity observed in the present study may represent regression towards the mean, where patients with a low-baseline values show more improvement at the re-assessment following an intervention (Ostermann *et al.*, 2008).

The present data show lower pre- and post- rehabilitation values (292 m and 420 m, respectively) for MSWD than in previous studies (493 m and 581 m, respectively) (see table 6.1). The large

variation in MSWT outcomes between studies is probably due, amongst other factors, to different sampling strategies. In contrast with the present study, all previous studies, except that undertaken by Arnold *et al.* (2007), assessed volunteers. The present study was not a cohort study as participants did not volunteer to take part but gave an overview of outcome assessment issues in CR using service evaluation. It aimed to present realistic values from a non-selective CR population. There were no specific exclusion criteria for survey patients, and all patients eligible for the CR services evaluated were able to participate. It is likely that patients included in this study had a higher number of disorders than those in other studies. The present sample also has the highest mean age compared with previous data (see table 6.1). Plotting a regression line for the relationship between mean age and MSWT outcomes among different studies showed that age can explain 61% of the variance in MSWD (see figure 6.7).

Using younger patients than the present study, Arnold *et al.* (2007) recorded MSWT outcomes similar to those in the present study than in others. Participants were post-MI patients with a mean age of 62 years compared with the present mean age of 68 years; they were assessed at a time when the mean time from pre-rehabilitation testing to hospital discharge was five weeks, compared with the current mean time of 7.6 weeks. These findings are in agreement with the previous study, which demonstrated that post-MI patients can perform better in the MSWT than patients with some other types of heart disease (i.e., valvular heart disease); age is associated with poor MSWD; and the longer the time period that has elapsed between pre-rehabilitation assessment and hospitalisation, the poorer the expected exercise capacity (Ades *et al.*, 2005).

The present study has several strengths; it comprises a large CR data set from two different hospitals, obtained recently (between 2009 and 2010). This is the second largest study of pre- and post- programme MSWT data in a CR population. Arnold *et al.* (2007) assessed a large sample of 206 patients divided, however, into two groups who undertook different interventions,

as it was mentioned above. Jolly *et al.* (2009) assessed a larger cohort (n=179) using the MSWT; they were also involved in centre-based CR. These patients were assessed only at the end of the CR programme for safety reasons. The reason given for this was because they were recruited a few days after MI, but this cohort did not only include MI patients. The cohort was assessed after long-term (12 months) CR, and they recorded slightly lower post-rehabilitation outcomes than the present study. As the MSWT was not performed when patients started the CR programme, there are insufficient data here for comparison with the present findings.

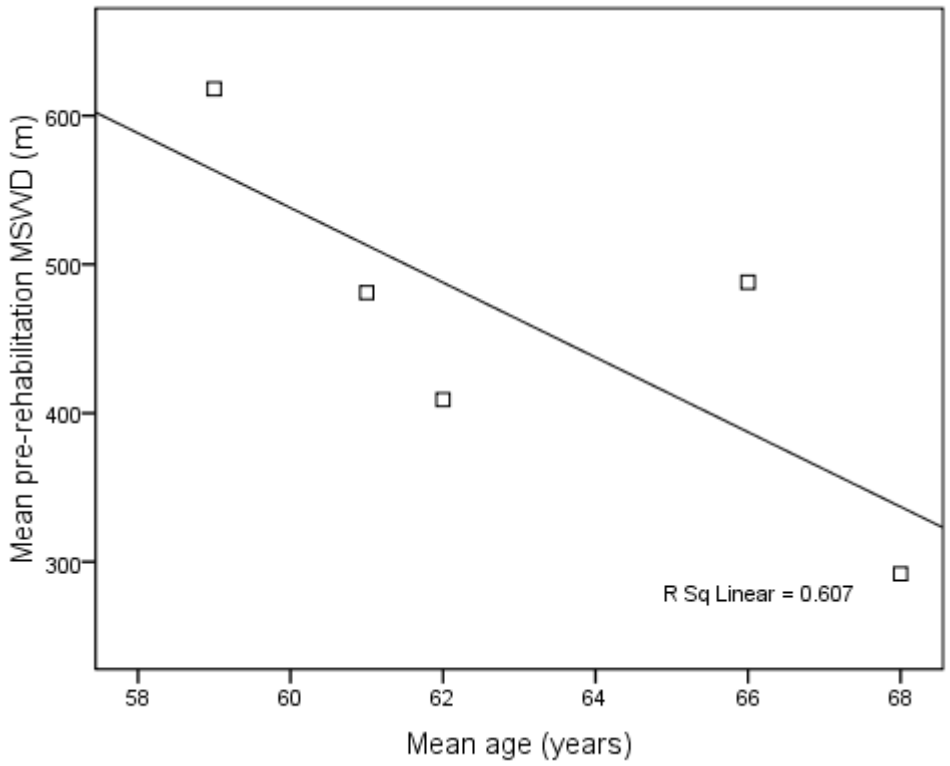

Figure 6.7. Regression line for the relationship between mean age and post-rehabilitation modified shuttle walking test performance, among different studies (Fowler *et al.*, 2005; Arnold *et a*l., 2007; Sandercock *et al.,* 2007; Robinson *et al.,* 2009, present study)

MSWD=distance walked in modified shuttle walking test

6.4.2. Testing the accuracy of the stature-based equation in predicting shuttle waking test performance in patients exiting phase III cardiac rehabilitation

The prediction equation developed in Chapter 4 (see equation 4.1a), based on the testing of phase IV CR patients, was examined for validation purposes using data from patients exiting phase III

CR. Post-rehabilitation data was used here, as an increase in functional capacity is usually established by the end of phase III CR and remains stable during phase IV (Woolf-May and Ferrett 2008). The present findings showed that the prediction equation developed in the pilot study did not yield similar estimates of MSWD as those reported in the validation sample. For brevity, these results have been excluded, but a further discussion of this subsection is included in appendix A2.

6.4.3. Predictors of shuttle walking test performance in cardiac patients entering hospital-based cardiac rehabilitation

The present study, addressed many of the limitations outlined in the pilot study of Chapter 4 (i.e., small sample and a well-trained group, who were accustomed to exercise). An attempt was made to improve the clinical validity of results by making a new prediction equation model for MSWD. The research was similar to Chapter 4 but repeated in a larger, less conditioned cardiac population who were entering an earlier phase of CR. The variables used in the current study were more easily measured than some of those used in the pilot study. The present study did not include a measurement of step length; it was previously stated that step length is a changeable and dynamic measure and clinicians need practical measurement procedures for regular use in clinical assessment. Only age, anthropometric and some clinical measures were taken in order to identify predictors of MSWD in phase III CR.

The results of this study showed that age, sex and anthropometric variables are significantly associated with MSWD. These can be used to predict MSWD in cardiac patients entering phase III CR. Age, stature and sex must be considered when interpreting MSWD as they explain 62.3% of the variance in MSWD. Stature was expected to be associated with MSWD, in accordance with findings from the pilot study (see Chapter 4) and as stature is included in prediction equations for estimating 6MWD (Enright and Sherrill 1998; Gibbons *et al.*, 2001; Enright *et al.*,

2003; Camarri *et al.*, 2006; Chetta *et al.*, 2006; Poh *et al.*, 2006; Jenkins *et al.*, 2009). This, in combination with the fact that the equation model based on the pilot study (see equation 4.1a) gave a lower variance in the results it predicted (55%), indicates that the present prediction equation had improved and has given more accurate results for MSWD.

Approximately 38% of variation in MSWD remains unexplained by the present equation. This variance is most likely to be due to many of factors not measured; cardiac function, daily physical activity, motivation and stress. The time elapsed from an event or surgical intervention until admission to phase III CR was not included in the final multivariate model of regression analysis, as it did not have significant predictive value for MSWD. The longer the time which had elapsed from leaving hospital to baseline assessment, the poorer the functional capacity recorded. Ades *et al.* (2005) also reported an age-associated decline in exercise capacity when assessed by the treadmill test which was particularly evident when a long time has elapsed between hospitalisation and testing. Of note was their finding that older cardiac patients delayed entry into CR after the event or intervention compared with younger patients.

There are three observations that can be made about the prediction equation generated here. First, it supports the conclusion reported in the pilot study that taller CVD patients have an advantage over shorter patients and that they generally perform better in the MSWT. Second, younger patients are expected to attain better MSWD than older patients. This is in agreement with the present results obtained by using the 6-MWT in HF patients. Third male CVD patients tend to walk 97 m further (approximately 10 shuttles) in the MSWT than females. This difference in MSWD between sexes is smaller than the one estimated in the pilot study (16 shuttles more in males than females). Due to the small number of patients, sex was not included in the analysis for the pilot study. The difference in performance was estimated after accounting for the mean difference in stature between sexes which may act as a surrogate variable for sex.

Specifically, the prediction model implies a 4.4 m gain in expected MSWD per cm of stature, and a 6.1 m loss per increase year of age. Validation of this equation showed a significant correlation but low test–retest reliability between actual and predicted MSWD. The LoA plot (see figure 6.4) shows that the relationships between the actual and predicted values seem not to be linear, and the equation model generated here tends to overestimate poor performers and underestimate good ones. A more complex statistical technique may be needed, but this cannot be carried out within the remit of the current thesis due to its already wide scope.

6.4.4. Predictors of magnitude of change in shuttle walking test performance, due to phase III cardiac rehabilitation

Stature was the only variable able to predict change in MSWT. The stature-based equation for the prediction of the magnitude of change in the MSWD (see equation 6.2a) suggests 20 m (approximately) less expected improvement in MSWD due to CR, per 5 cm of patient stature. Taller CVD patients are, therefore, more likely to attain higher initial MSWT scores than shorter patients, shorter patients are expected to record more improvement in a re-assessment with MSWT after CR. This suggestion had been assumed in Chapter 4 and was revalidated here. While 37% of the MSWD change can be explained by this equation, 63% remain unexplained. This variance is likely due to individual differences in response to exercise training. This variation in individual response may arise from internal or external sources, such as individual clinical characteristics, health condition or even physical activity habits outside the class.

Marchionni *et al.* (2003), used treadmill tests to assess change in exercise capacity after an eight-week (40 sessions) CR programme in post-MI patients (n=161) and confirmed that age, sex and the type of exercise programme (home-based or hospital-based) could predict changes in exercise capacity. The authors assessed a number of independent variables; but interestingly did not include stature in their regression analysis, as the present study was done. They did not

provide information concerning the percentage of variance explained by their equation model, and the overall goodness of fit of their model is not known.

The association between stature and the magnitude of change in MSWD across phase III CR was significant. Moreover, men and women are expected to have the same improvement in functional capacity during CR, even though it is assumed that men will show higher MSWD in the pre-rehabilitation assessment. Short CVD patients (i.e., 165 cm: 25th percentile) are expected to improve by 42 m, or by a factor of 2.5 more than tall CVD patients (i.e., 175 cm: 75th percentile) from start to finish of six weeks of phase III CR. Also, the equation model 6.2 suggests that MSWD improvement dropped steadily by 42 m per 10 cm increase in stature, while patients taller than 182 cm are not expected to improve their functional capacity with the MSWT during an exercise-based CR programme.

Time from test to retest did not have significant predictive value for the magnitude of change in MSWD observed during CR. However, it was shown that the longer the time that had elapsed between pre- and post- rehabilitation assessment, the higher the change expected in MSWD. This suggests that a longer duration of phase III exercise-based CR might facilitate greater improvements in functional capacity, without necessarily increasing the number of exercise sessions. Some patients delayed the time for post-rehabilitation assessment due to holidays. There was no control group in the present study and so there was no way to investigate that functional capacity improvement was absolutely due to exercise and not due to simply natural recovery.

Overall, aside from environmental factors, it would be interesting to analyse the impact of therapeutic factors on the magnitude of change in MSWD and the pre-rehabilitation MSWD in this cohort.

6.4.5. Is there any difference in modified shuttle walking test performance among patient groups with different surgical diagnoses?

Different surgical interventions (CABG, PCI, VR, none) had no significant association with pre-rehabilitation MSWT outcomes, but did show significant associations with the magnitude of improvement in the MSWT after CR. Patients receiving CABG had both the highest initial MSWD values and MSWD changes after six weeks of CR than patients who had undergone other surgical interventions.

Fiorina *et al.* (2007) found absolute distance walked in the 6-MWT was higher in CABG patients than in patients who had undergone other cardiac surgeries (i.e., valvular replacement). They also found significantly lower 6MWD in post-surgical patients compared with post-MI patients who had not undergone surgical intervention. The 6-MWT was performed within 2 weeks of surgery, meaning that post-surgical factors such as prolonged bed rest, post-sternotomy pain and respiratory dysfunction, could have affected these results. In the present study, baseline assessment was performed a mean of 7.6 ± 4.6 weeks after the event or surgical intervention. This is sufficient time for post-surgical wounds to heal and for physical activity to have taken place.

In contrast with the present findings, Ades *et al.* (2006) found significantly lower pre-rehabilitation treadmill test performance in CABG patients compared with those receiving PCI or suffering MI. The authors suggested this may be because CABG patients are usually hospitalised longer and thus they need longer recovery time than post-MI or PCI patients. There are a number of methodological differences between the present study and that of Ades *et al*. (2006). Ades *et al.* (2006) recorded oxygen consumption, not physical work capacity, as was done here. Furthemore, different locations may use differing treatment protocols that might

explain the difference in performance between the two studies. The study population consisted of UK cardiac patients, whereas Ades *et al.* (2006)'s study consisted of US cardiac population.

6.4.6. The utility of the developed prediction equation models and normative values, in clinical practice

Predictive equations and normative values were developed in the current study. Clinicians may prefer to use normative tables or equations to estimate patients' expected functional capacity. Both methods provide similar performance expectations. Development of nomograms, that could quickly provide an accurate individualized estimate of predicted functional capacity, might also be a useful tool to develop for the clinicians. To be accurate, such nomograms would need to be based on a larger sample size or a more varied approach than the present study. Particularly the population should include more females.

6.4.6.1. Utility of predictive equation models

The equation models developed in this chapter can be used to estimate the percentage of predicted functional capacity in patients entering phase III CR, and the percentage of predicted functional capacity improvement during phase III CR.

Estimating functional capacity at the start of CR (see equation 6.1)

The percentage of predicted functional capacity recorded on the MSWT can be determined using only age, stature and sex. Any result higher than 100% demonstrates better than average functional capacity, meaning that the patient could potentially be 'fast-tracked' to community-based phase IV CR, omitting phase III CR, in order to save time, money and speed the return to work. On the other hand, any result lower than 100% indicates a reduction in functional capacity,

suggesting that the main focus of exercise should be an increase in functional capacity for that patient.

Estimating functional capacity at the end of CR (see equation 6.2)

By using only stature and functional capacity improvement, assessed by the MSWT after phase III CR, the percentage of predicted change in functional capacity for stature can be ascertained. In this case, any result higher than 100% shows that the goal for functional capacity improvement has been achieved, and the patient can continue on to a maintenance (phase IV) CR programme. Any result lower than 100% indicates low improvement during the exercise programme and it could be decided that the patient should be retained on the programme, while encouragement could also be given for an increase in home activities.

6.4.6.2. Utility of normative values

The normal values shown here give ranges of functional capacity (pre- and post-rehabilitation) and ranges of improvement after a CR programme, based on age, sex and stature. Such values are used by clinicians to interpret raw scores of metres walked. These values show that younger and taller patients have an advantage when performing the MSWT.

In female patients, the lowest pre-rehabilitation MSWDs were recorded in older patients who were shorter in stature, while the highest post-rehabilitation MSWDs and highest change in MSWD were similar to those for males, that is, they were achieved by younger and taller patients. This is in contrast with equation 6.1, which shows that taller and younger patients, independent of sex, can perform better in the MSWT at their entrance to CR. This difference might be due to the number of female patients, which was not sufficient to make normative values.

The normative values for men and women clearly demonstrate the difference between the sexes, while they can also show the difference in achieved MSWD for any age or stature group. In general, the younger and taller a patient, the greater MSWD improvement due to CR is expected across sexes. These findings are in contrast to the idea related to the regression towards the mean, and outlined in Chapter 4; that short CVD patients can record more improvement in MSWD after CR intervention, in contrast with tall CVD patients. One possible explanation would be that taller CVD patients are always better able to cope with the increases in walking speed needed at the later stages of the test, and they obtain better MSWD than shorter patients.

6.4.7. Study limitations

A significant limitation of this study was that the prediction equation models were created from data collected only from two hospital-based CR centres in the UK. The present cohort showed low pre-rehabilitation functional capacity in comparison with previous studies, and there is no available information about whether the patients had followed any recommended exercise programme after hospitalisation, or whether they came directly into phase III CR. Moreover, no details regarding patients' physical activity outside the class were recorded, which may influence functional outcomes. However, even though some previous studies referred to collecting information on patients' home activities, there is no evidence that the authors integrated this recorded information into the final statistical analysis or measured outcomes. The failure to use this information in the analysis might be due to its potential complexity. Some patients' records lacked complete medical information, such as left ventricular ejection fraction (LVEF). This may have benefited the present study, however, previous chapter (see Chapter 5 '*Predictors of six-minute walking test performance in heart failure patients*') showed that clinical variables, such as the LVEF, did not have any significant prognostic value for distance walked in the 6-MWT.

A further limitation is the small number of females involved in this study. It would be ideal if the number of male and female patients was equal; however, the data were retrieved from two sets of hospital-based CR records and the patients did not take part in any selective participation. Thus, this population represents real CR participation. The lack of a gold standard test (treadmill tests or cycle ergometer tests) to compare the MSWT against could also be perceived as a weakness of this study. This comparison would be useful in order to check the validity of the MSWT in this cohort. Also, as it was mentioned above, this study used a single cohort design. The lack of a "usual care" comparison control group could be accounted as a limitation of the study. However, the present study does not contain cohort data but real national CR data from different hospitals. Each CR centre evaluates the functional capacity of CR patients through only a particular exercise test. Thus, it was not really possible to have a control group; also, it was not possible to have both MSWT and treadmill/cycle ergometer test records from the same CR cohort.

A further limitation involves the nature of the data set used to validate the reference equation for the prediction of pre-rehabilitation MSWD; the validation group were members of the same cohort as the development group. The validation process confirmed non-linear relationships between actual and predicted values, suggesting that a more complex statistical analysis might be required, which was not carried out here because of space constraints. The equation model generated here tends to overestimate or underestimate MSWD. All data were drawn from two CR centres, meaning that the patients would be likely to have similar characteristics. It would be useful to revalidate the reference equation developed here across other CR cohorts.

A final limitation involves the nature of the test protocols used. Following hospital discharge the target heart rate in CR might be based on the patient’s MSWD. It seems obvious that if the MSWT is used in prescription of exercise in CR, tall cardiac patients should be set higher MET-based workloads during the CR programme. Despite a higher workload, tall patients are still

expected to improve their MSWD during CR less than short patients. This might be a limitation of the test; however, the target of CR is to help the cardiac patients to reduce their cardiovascular risk by increasing their functional capacity levels. Unfortunately, except the data of Lewis *et al.* (2001), collected in a HF population, no studies have addressed the role of MSWT as prognostic predictor in cardiac patients. As yet, there is no clear MSWT performance threshold associated with improved survival in the general cardiac population. This seems not to be a real problem, because according to the above findings each individual can have his or her own functional capacity targets based on the normative values developed here.

6.5. Conclusion

Previous studies have provided prediction equations and reference values for functional capacity that could be used to stratify the population by comparing them against a known standard. However, the already published data are based either on a healthy population or on a different type of test (the treadmill or 6-MWT). The MSWT is recommended by UK guidelines as the most popular assessment; it is a reliable, simple exercise test for the CVD population. Reference values of functional capacity expressed in METs should be avoided, as they underestimate aerobic capacity in the CR population.

The current study is unique and has a number of clinical implications. Firstly, 159 MSWTs were performed at the entrance to and after six weeks of phase III CR in a CVD cohort. Only one MSWT was performed pre- and post- rehabilitation, since Chapter 3 indicated no need for a practice test to obtain reliable results. It is assumed this represents a valid assessment in this patient cohort. The present results showed that the mean pre-rehabilitation MSWD was lower than in previous studies, while the improvement in mean MSWD was higher than in all previous studies. These findings imply that CVD populations with high functional impairment can benefit

the most from a CR programme. Second, the reference equations generated here show that age, stature and sex should be accounted for in the estimation of functional capacity at the entrance of the patient into phase III CR; while only stature should be accounted for in the estimation of functional capacity improvement during CR. Using these equations, functional capacity at the start of CR and functional capacity improvement can be expressed as a percentage of predicted value, which can help practitioners in making informed choices regarding their recommendations to patients. Third, the normative values developed here can be used as reference points to predict functional capacity and the magnitude of functional capacity improvement, in a group of male or female patients, within specific cut-off limits for age and stature.

This is the first investigation to provide normative values for MSWT performance (MSWD) in a CR population. The research revealed a number of areas that would benefit from future investigation. The recommended step is to update the normative values in a larger cohort derived from several hospital-based CR records in the UK, in order to reduce any possible interference from investigators that might influence results. Data from Chapters 4 and 6, suggest that taller CVD patients can always record greater MSWD improvement due to CR than shorter patients. Further studies are required to confirm this hypothesis.

6.6. References

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CHAPTER 7. SAFETY OF EXERCISE TESTING AND EXERCISE TRAINING FOR CARDIAC PATIENTS, IN A SUPERVISED, COMMUNITY-BASED CARDIAC REHABILITATION PROGRAMME

7.0. Abstract

Exercise is well recognised as a tool for assessment, prevention and management of cardiovascular disease. Cardiac patients are encouraged to join in supervised exercise cardiac rehabilitation programmes after cardiac risk stratification based on their functional capacity test performance. However, the cardiovascular safety of supervised functional walk testing and exercise training in a community-based cardiac rehabilitation centre has not been clearly justified. The aim of this study is to identify cardiovascular events that might occur during the shuttle walking test and exercise training in a community-based cardiac rehabilitation programme.

Eleven cardiac patients (55% males, 45% females, mean age: 67.2±6.9 years – testing group) and twenty-two cardiac patients (59% males, 41% females, mean age: 66.3±8.6 years – training group) were assessed through ambulatory electrocardiogram monitoring during the modified shuttle walking test (MSWT) and exercise training in a phase IV (UK classification) cardiac rehabilitation programme, respectively. During assessment, testing group patients were required to walk up and down a 10 m course at increasing speeds using the 15 level MSWT; training group patients were required to participate in an exercise-based cardiac rehabilitation programme. All of them were regular members of phase IV cardiac rehabilitation. A cardiologist verified the presence or absence of a cardiovascular event. Frequency of the cardiovascular events was reported for the two groups. Patients were divided into an event-free subgroup and a cardiac event subgroup. Differences in functional capacity between the two subgroups were examined using a two-sample t-test. A chi-square test was performed to determine associations

between incidences of cardiovascular events with poor functional capacity (distance walked in MSWT <450 m).

No major cardiovascular event related to hospitalisation was detected in testing or training group. The most clinically important event was silent myocardial ischaemia, which occurred in 27.3% of the testing group patients, and in 18% of the training group patients. There was no significant difference in functional capacity between the event-free subgroup and the subgroup with cardiovascular events in both testing and training groups (p>0.05). A chi-square test showed no significant association between poor functional capacity and risk for cardiovascular events in either testing group or training group [Testing group: x^2 (11)=0, p=0.99, phi=0.24; Training group: x^2 (22)=2.1, p=0.15, phi=-0.42]. Among patients with poor functional capacity, minor cardiovascular events were found in half of those who were assessed during exercise testing with the MSWT, and in all of those who were assessed during exercise training.

The results confirm that there is no risk of major cardiovascular events during exercise testing with the MSWT or exercise training in phase IV CR patients. This is probably due to the overall good functional capacity of patients involved in programmes designed for CR maintenance. Poor functional capacity does not seem to be associated with the risk of a cardiac event during exercise. It is suggested that the MSWT and exercise training can be carried out safely in supervised phase IV CR settings.

7. 1. Introduction

Numerous investigations have demonstrated the utility of cardiovascular evaluation during physical exertion in diagnosis, prognosis and management of coronary heart disease (CHD). Physical exertion is a common physiological stressor of the cardiovascular system, able to derive cardiovascular abnormalities that are not produced at rest (Chaitman 1986; Mark *et al.,* 1991;

Morris *et al.,* 1991; Gordon and Kohl 1993; Franklin *et al.,* 1998; Fleisher *et al.,* 2007). The use of an electrocardiogram (ECG) during rest or exercise remains the gold-standard non-invasive diagnostic tool in the identification of cardiovascular diseases (CVD).

7.1.1. Basic uses of the electrocardiogram and ambulatory electrocardiogram monitoring

The use of an ECG involves the analysis of the recording of electrical signals during rest, which gives information on the heart's activity. Traditional ECG is used to identify arrhythmia, and it is crucial for identifying changes in the cardiac rhythm associated with myocardial ischaemia and infarction, the dysfunction of cardiac pacemakers, pericarditis, cardiomyopathy and electrolyte imbalances. A detailed analysis of the ST-segment can identify the location and the extent of damaged myocardium; it can also identify the type of pathology – myocardial infarction (ST-segment elevation) or ischaemia (ST-segment depression) (Fisch 1989).

Ambulatory ECG is used extensively in clinical practice, during exercise testing or cardiac exercise programmes, in order to evaluate the response of the heart rhythm to exercise activity in patients who have heart disease (i.e., previous MI). It can be used to identify cardiovascular events during exercise, which may improve the evaluation and stratification of patients at the start of a CR exercise programme (Cantwell and Fletcher 1974; Savage *et al.,* 1979; Pavy *et al.,* 2006).

7.1.2. Risk of cardiovascular events during exercise testing in cardiac rehabilitation

Exercise testing is a common, useful cardiovascular assessment tool both in diagnosis and rehabilitation. Exercise testing is usually performed either to identify exercise-induced ischaemia as a diagnosis of CHD or to assess functional capacity and exercise tolerance in patients with already diagnosed CHD (Saha *et al.,* 2007). The ACSM (American College of Sports Medicine

2000) recommends the use of ECG-monitored exercise testing for older people entering a vigorous exercise programme, in order to minimise exercise-induced cardiovascular events.

Treadmill and cycle ergometer exercise tests are the most common exercise testing methods. As mentioned in previous chapters, functional capacity exercise tests, such as the shuttle walking test (SWT) and the six-minute walking test (6-MWT) are frequently used to evaluate functional capacity in patients with cardiovascular dysfunction.

Exercise testing is considered to be a safe assessment procedure when conducted by experienced, well-trained and appropriately qualified medical staff that is able to recognise abnormalities during exercise. There remains some concern over cardiovascular events during exercise testing due to increased myocardial work, which may cause an imbalance between myocardial oxygen demand and supply. The risk of severe cardiovascular events during exercise testing is historically low, especially in those using continuous ECG monitoring (Haskell 1978). Other studies demonstrate that although the incidence of major cardiovascular events during exercise testing is low, the prediction of these events is difficult in most cases and independent of ECG monitoring or non-monitoring techniques (Van Camp and Peterson 1986; Pavy *et al.,* 2006).

Gibbons *et al.* (1989) examined the risk of cardiovascular events during treadmill testing over a period of 16 years. They reported only five severe cardiovascular events and one death among almost 72,000 tests. These events were recorded during the first eight years of the survey, and no events or deaths were observed during the last 45,000 tests. The authors demonstrated that exercise-induced events in a test environment are rare, and that exercise testing is a safe cardiovascular assessment when it occurs under medically supervised administration. Most of the participants in this survey were, however, healthy adults, while only a very small percentage of participants had a confirmed diagnosis of CHD before the exercise testing. The authors state

that the use of exercise testing is safer in healthy adults than in CHD patients. Coronary heart disease is the most common pathological factor in sudden death during exercise, due to atheromatic plaque rupture and thrombosis in the coronary arteries (Thompson *et al.,* 2007).

Gordon and Kohl (1993) summarised an analysis of eight published surveys and reported estimated rates of sudden death or acute myocardial infarction (MI) during exercise testing ranging from 0 to 5 per 100,000 tests in patients with CHD. The authors reported that the risk of cardiovascular events was higher in post-MI patients and in those with potentially malignant ventricular arrhythmias.

Pavy *et al.* (2006) surveyed 42,419 exercise stress tests in 65 cardiac rehabilitation (CR) centres and found that the risk of cardiovascular events during exercise stress testing was 1.4 per 10,000 tests. They recorded only five events in patients who had been recently involved in a percutaneous coronary intervention (PCI) with stent and one cardiac arrest, which was resuscitated, while no deaths occurred during exercise testing. The main event during exercise testing was ischaemia in patients with coronary artery stenting over the short term after surgery, and the authors concluded that the events were caused because of previously untreated coronary artery stenosis.

According to this brief review of the literature, it is obvious that cardiovascular events during laboratory-based exercise testing are rare, but they do still occur and are somewhat unpredictable. As mentioned in previous chapters, the traditional laboratory-based cycle ergometer or treadmill exercise protocols have commonly been replaced in daily clinical practice by reliable functional capacity tests (i.e., the SWT, or 6-MWT). There is, however, little information regarding the safety of these functional capacity exercise tests when used to assess a CVD population. Tobin and Thow (1999) used ECG monitoring during the SWT in 19 post-

CABG (coronary artery bypass graft) patients among whom they noted only one episode of >1 mm ST-segment depression. The very low number of cardiovascular events during exertion in Tobin and Thow's (1999) study leads to important queries about whether this was the result of low individual effort during exertion, producing less stress on the cardiovascular system, or the result of the successful treatment of coronary arteries during surgical intervention. These queries, combined with the fact that their study focused on a small and very selective subsample (post-CABG patients), increase the necessity for new studies in this field.

Table 7.1. Summary of event rates during exercise testing

Study	Patients	Exercise tests	Cardiovascular incidence rates per 10,000 exercise tests
Gibbons *et al.* (1989)	34,295	71,914 treadmill tests	overall events: 0.83 nonfatal event: 0.70 fatal event: 0.14
Pavy *et al.* (2006)	25,420	42,419 bike or treadmill tests	overall events: 1.42 nonfatal event: 1.18 resuscitated cardiac arrests: 0.24 fatal event: 0
Tobin and Thow (1999)	19	19 shuttle walking tests	overall events: 1 per 19 tests

7.1.3. Risk of cardiovascular events during exercise training in cardiac rehabilitation

Cardiac patients are usually encouraged to participate in a programme of increased physical activity and programmed exercise due to the benefits derived from exercise training in this population (Haskell 1978).

The benefits of exercise training, as part of a CR programme, were described in detail in Chapter 2 (see '*Introduction to cardiovascular diseases and cardiac rehabilitation: a review in the literature*'). Exercise prescribed as part of a comprehensive CR programme acts as cardioprotective tool. There is evidence that regular exercise modifies cardiac risk factors,

improves quality of life and reduces morbidity and mortality in the cardiac population (Gill *et al.,* 2000; Hambrecht *et al.,* 2000; Pasquali *et al.,* 2001). Data from two meta-analyses of more than 4,000 patients each estimated that the total mortality for CHD patients who participate in exercise-based CR was significantly reduced by 20% to 27%, when compared with patients not involved in programmes (O'Connor *et al.,* 1989; Jolliffe *et al.,* 2000).

Increased myocardial oxygen delivery and improved myocardial contractility are some of the main benefits of exercise training. However, increased myocardial work due to exercise can cause an imbalance between myocardial oxygen supply and demand in the heart, which is a trigger for myocardial ischaemia or cardiac arrest in patients with established CHD (Haskell 1978). There is some evidence documenting major cardiovascular events during exercise among CVD patients (see table 7.1).

Haskell *et al.* (1978) surveyed 30 exercise programmes in North America, commencing on average 9 weeks after MI or cardiac surgery, with a mean of three exercise sessions per week. The programmes contained mainly aerobic types of exercise, such as walking, jogging, games and calisthenics. Twenty-eight exercise programmes included pre-training assessment with a health questionnaire, a resting ECG recording and blood pressure measurements. In two exercise programmes, patients were monitored with telemetry ECG during exercise using a cycle machine, treadmill walking or rowing. The authors found the following cardiovascular event rates during participation in these supervised exercise programmes.

The total number for all events (fatal and nonfatal) was 47, representing an event rate of 1 per 26,715 patient hours. In particular, there was one nonfatal event per 34,673 patient hours and one fatal event per 116,402 hours. Both fatal and nonfatal events were significantly lower in the two ECG monitored exercise programmes (ratios fatal/nonfatal ranges: 1/1 to 4/1) than the rates

recorded in the 28 non-monitored programmes (ratios fatal/nonfatal ranges: 10/1 to 35/1). According to the authors, however, the medical supervision of the 28 non-monitored programmes was not close enough to identify changes in patients' symptoms and prevent them from developing cardiovascular events. The highest number of cardiovascular events (72%), especially cardiac arrest, occurred during warm-up or cool down or at the end of the session. However, there were differences among the programmes that were not mentioned, while there is no information on the intensities at which the different programmes were used. The reduction of the occurrence of events with the use of ECG-monitoring, and the fact that there was no information on exercise intensities during training, do not make it clear whether the programmes' characteristics had any effect on these cardiovascular events.

Van Camp and Peterson (1986) surveyed 167 medically supervised CR exercise programmes; and they estimated that the cardiovascular event rates per million patient exercise hours were 8.9 for resuscitated cardiac arrests, 3.4 for MIs and 1.3 for fatal events. The low rate of fatal cardiac arrests was associated with the medically supervised CR programmes and the immediate activation of emergency cardiac care.

Franklin *et al.* (1998) examined the incidence of cardiovascular events during medically supervised exercise in a CR programme over a 16-year period, where they showed a lower incidence of cardiac arrests (3.4) but a higher incidence of nonfatal MI (8.9) than previous study (Van Camp and Peterson 1986). The CR exercise programme was medically supervised, and all cardiac arrests were successfully resuscitated. Franklin *et al.* (1998) recorded cardiovascular events among moderate-to-high-risk patients, and highlighted the importance of risk stratification to identify those patients at increased risk for exercise-related cardiovascular events. The authors also reported that the presence of a physician during exercise training is not always necessary but that the most important safety measure was the risk stratification of

patients before their induction into an exercise programme. Medical supervision and ECG monitoring during exercise may be obligatory only in high-risk situations (Wenger *et al.,* 1995).

Pavy *et al.* (2006) surveyed 65 CR programmes and reported a risk of cardiovascular events during exercise of 20.2 per million patient exercise hours. During exercise training, overall 15 events were induced: 47% of them were angina, 27% arrhythmias, 6.7% pericarditis, 6.7% ventricular tachycardia, 6.7% cardiac tamponade and 6.7% resuscitated cardiac arrest. Neither fatal incidences nor MI were reported in this study. The authors found a low rate of cardiovascular events, which may again be due to the combination of effective risk stratification of the patients prior to entering into the rehabilitation programmes and the well-supervised sessions by specialised staff able to offer emergency medical treatment when required.

It is obvious from the research outlined above, that the incidence rates during exercise are lower in more recent studies which are based on supervised CR exercise programmes. During CR, the overall cardiovascular event rates range from 12.3 to 37.4 per million patient hours of exercise. Fatal cardiac events are more rarely reported, and range from 8.6 per million patient hours of exercise in 1978 to zero in the present day (2006) (see table 7.2).

Nevertheless, most of the studies above examined cardiovascular events during exercise-based outpatient (UK phase III) rehabilitation. According to UK guidelines, phase III typically begins four weeks after MI or six weeks after heart surgery and usually consists of clinically well-supervised sessions, which take place in hospital settings (Thompson *et al.,* 1996; Bethell *et al.,* 2009). Phase IV CR, following phase III, is a long-term community-based exercise programme where the goal is the maintenance of physical activity and life-style changes in cardiac patients (Bell *et al.,* 1995; British association for cardiac rehabilitation [BACR] 2006). Phase IV CR can consist of a supervised, organised programme or a self-assisting patient group, where the cardiac

risk stratification of the patients before entering this phase has not always been carried out. Usually, patients who finish phase III CR proceed directly to phase IV CR. There is little information concerning the risk of cardiovascular events during phase IV CR, leaving it unclear how necessary cardiac risk stratification is, alongside monitoring and medical supervision during exercise training and testing in this phase of CR.

Table 7.2. Summary of event rates during exercise based cardiac rehabilitation

Study	Patients	Patients exercised hours	Exercise programme	Cardiovascular incidence rates per million patient hours of exercise
Haskell *et al.* (1978)	13,570	1,629,634	30 supervised exercise programmes, aerobic exercise, mean sessions=3/week	overall event rate: 37.4 nonfatal event: 28.8 fatal event: 8.6
Van Camp & Peterson (1986)	51,303	2,351,916	167 supervised CR exercise programmes aerobic exercise	overall event rate: 12.3 nonfatal MIs: 3.4 resuscitated cardiac arrests: 8.9 fatal event: 1.3
Franklin *et al*. (1998)	3,335	292,254	1 supervised CR exercise programme, - Phase 2: aerobic (50min), 3/week, - Phase 3: aerobic and resistance exercise, 1/week	overall event rate: 12.3 nonfatal MIs: 10.3 resuscitated cardiac arrests: 6.8 fatal event: 0.0
Scheinowitz and Harpaz (2005)	3,511	338,688	1 supervised CR exercise programme, aerobic exercise (60–90 min), 2/ week.	overall event rate: 17.0 nonfatal event: 32.5 nonfatal MIs: 0.0 resuscitated cardiac arrests: 3.0 fatal event: arrest: 3.0
Pavy *et al.* (2006)	25,420	743,471	65 supervised CR exercise programmes, aerobic exercise (60min), 3-7/week	overall event rate: 20.2 nonfatal event: 20.2 resuscitated cardiac arrest: 1.3 fatal event: 0.0

Definition of abbreviations: CR=cardiac rehabilitation; MI=myocardial infarction

7.1.4. Risk management in exercise testing and training

Although event rates during exercise testing and training are low, events still occur during exercise. Exercise testing seems to present a greater risk than exercise training. The higher risk rates estimated during exercise testing and exercise training were 0.37 per 10,000 patient hours of exercise and 1.42 per 10,000 tests, respectively.

In order, that cardiovascular events during exercise may be minimised, the American Heart Association (AHA) provides guidelines that can be used to grade patients according to their pathological and functional characteristics (Fletcher *et al.,* 2001; Myers *et al.,* 2009). Pre-training and pre-testing cardiovascular risk assessment – including medical history and physical examination – can reduce the likelihood of adverse events during exercise by identifying patients at greatest risk (Fletcher *et al.,* 2001). The AHA guidelines emphasise the importance of ECG monitoring during an exercise training programme, suggesting that moderate to high risk CVD patients should be medically supervised with ECG-monitoring during exercise training until it can be determined whether exercise training can safely be tolerated by the patient; at this point, safe individual intensity levels can be set (Fletcher *et al.,* 2001).

To summarise, exercise training has a well-established role in reducing overall risk of cardiac death in the CVD population. On the other hand, the risk of a sudden cardiac event is elevated during and after exercise. As mentioned above, the increased risk is not great when exercise occurs in supervised CR settings and when patients exercise regularly. Accordingly, exercise undertaken following specific guidelines seems to be safe for patients. Thus, it would be interesting to verify to what extent a common exercise testing programme and a regular exercise training programme are safe for CVD patients in a well-supervised maintenance CR setting.

7.1.5. Aim

There are clear benefits of functional capacity testing over laboratory-based exercise tests to risk stratify patients for CR. The importance of the role of exercise as a beneficial treatment for cardiac patients is not in question here. The aim of this study was to verify to what extent a recommended exercise testing protocol (SWT) and an exercise training session are safe for a mixed cohort of CR patients.

7. 2. Methods

7.2.1. Study population

Eleven CVD patients (6 males and 5 females, aged 56 to 78 years: testing group) were monitored whilst undertaking a sub-maximal MSWT; twenty-two CVD patients (13 males and 9 females, aged 52 to 78 years: training group) were monitored during phase IV CR exercise training. Seven of the twenty-two patients were monitored during both exercise testing and exercise training. All patients were considered clinically stable and low risk, according to BACR (2006) criteria. The patients had varying cardiac conditions. The majority of participants were post-vascularisation patients (CABG or percutaneous coronary intervention [PCI]). They also included patients with stable angina, patients who had suffered from an, or patients who had undergone both an MI and a surgical procedure on the heart. They were under medical treatment during the assessment (β-blockers, nitrates, aspirin, statins). The population's descriptive characteristics and baseline measurements are presented in table 7.3.

All the patients were enrolled in a Phase IV CR programme at the University of Essex. All had completed the ten-week phase IV rehabilitation programme and used the exercise classes to maintain gains in functional capacity realised here and in phase III rehabilitation. Exclusion criteria were based on patients with severe locomotor or neurological limitations and those who

had a defibrillator or pacemaker fitted. Patients were recruited by informing them both orally and with written information regarding the scope, methods and procedure of the study. Written, informed consent was then obtained from each participant. All procedures were approved by the University of Essex Ethics Committee and conformed to the declaration of Helsinki guidelines (World Medical Association 2009) for research with human participants. The study took place between March 2009 and January 2010.

Table 7.3. Descriptive characteristics and baseline measurements of patients

Clinical characteristics and baseline measurements	**Testing group: Values from patients monitoring during the MSWT**	**Training group: Values from patients monitoring during the exercise training**
Number of patients	11	22
Age (years) (mean ± SD)	67.2 ± 6.9	66.3 ± 8.6
Sex (%)	Males=6 (55%) Females=5 (45%)	Males=13 (59%) Females=9 (41%)
BMI ($kg \cdot m^{-2}$) (mean ± SD)	27.2 ± 2.6	28.1 ± 4.0
Waist circumference (cm) (mean ± SD)	95.5 ± 9.4	98.3 ± 10.3
Resting HR (bpm) (mean ± SD)	65.6 ± 11.7	65.1 ± 11.1
Resting SBP (mmHg) (mean ± SD)	126 ± 19	136 ± 22
Resting DBP (mmHg) (mean ± SD)	78 ± 10	76 ± 9
Medical History/Reason for joining CR MI Stable Angina Surgical procedure (CABG, PCI) Arrhythmias	 n=2 (13%) n=3 (27%) n=7 (64%) n=3 (27%)	 n=3 (14%) n=9 (41%) n=17 (77%) n=1 (4.6%)
β-blockers	n=9 (82%)	n=16 (73%)
Nitrates	n=2 (18%)	n=7 (32%)
Aspirin	n=4 (36%)	n=17 (77%)
Statin	n=2 (18%)	n= 10 (46%)
Other	n=3 (27%)	n= 7 (32%)

*Definition of abbreviations: BMI=body mass index; CR=cardiac rehabilitation; MI=myocardial infarction; CABG=coronary artery bypass graft; PCI=*percutaneous *coronary intervention*; HR=heart rate*; bpm=beats·min*$^{-1}$

7.2.2. Study design

Before the initial testing began, each participant received a primary health assessment (pre-exercise health questionnaire, resting heart rate and blood pressure measurement) and interview (medical and pharmacological history). Stature was recorded using a stadiometer (Seca 240 stature measuring rod) and body mass was recorded, without shoes, using a weight scale (Seca 888 Class III Floor Scale). Body mass index (BMI) was calculated as follows: body mass (kg) /stature^2 (m^2) (see table 7.3). Resting heart rate and blood pressure (systolic and diastolic) were measured, using an automated arm blood pressure monitor (Omron Digital Automatic Blood Pressure Monitor MX3 Plus, Omron Health Care Co., Ltd., Kyoto, Japan).

Before testing started, testing group patients who were to perform the MSWT were fitted with a Polar heart rate monitor (Polar Electro Sports Tester S810I, Heart Rate Monitor, Kempele, Finland) to determine heart rate frequency and their predicted termination point. All patients were monitored with an ambulatory ECG event monitor (C.NET5000, version 1.2, Cardionetics Ltd., United Kingdom), either during the MSWT (testing group) or during the CR class (training group). Three ECG electrodes on a monitor cable were applied to the chest at pre-determined locations, based on traditional clinical ECG monitoring. Before ECG electrode placement, the patient's skin was prepared by shaving any significant chest hair around the position of the electrode pads. The patient's shaved skin was then cleaned and wiped with a surgical alcohol wipe and was allowed to dry before electrode pad placement. As figure 7.1 shows, the three ECG electrodes were placed as follows: right upper sternum – just below the sternal angle (RA); left upper sternum – just below the sternal angle (LA); and left fifth intercostal space – the left midclavicular line (V4) (Cardionetics 2010). The device was placed into a pouch fitted to the patient's waist using a particular type of belt. Next, testing group received oral instructions for completing the MSWT, while training group was instructed to enter the Phase IV CR class.

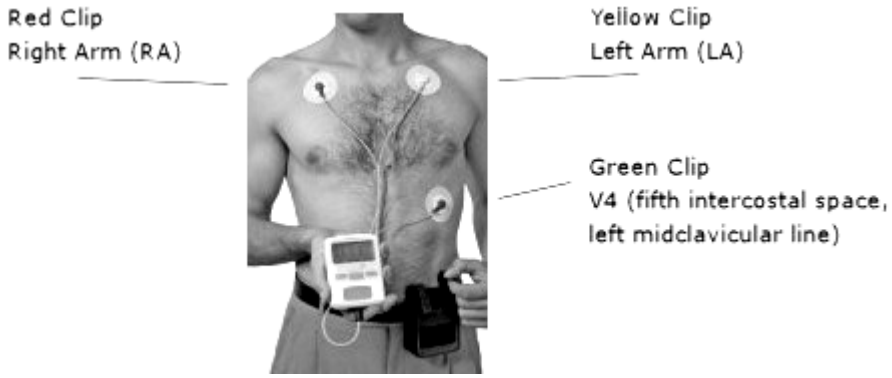

Figure 7.1. Electrode pads placement on the patient (http://www.cardionetics.com/electrodes.php)

Major cardiovascular events were defined as one of the following: MI requiring hospitalisation, ventricular fibrillation, ventricular tachycardia requiring treatment, atrial arrhythmias requiring treatment, asystole, stroke and death. Minor cardiovascular events were defined as: isolated ventricular arrhythmias or atrial arrhythmias not requiring intervention, chest pain and bradycardia not requiring intervention (Gibbons *et al.,* 1989).

7.2.3. Modified shuttle walking test procedure

The MSWT was performed according to the method described in Chapter 3 (pp.130-131).

The modified 15 level SWT, which was first developed by Singh *et al.* (1992), was used for the requirements of this study. This is analogous to the original incremental test (Singh *et al.,* 1992) but has 15 levels instead of 12. The modified version is useful for monitoring patient groups who may be able to complete the original 12 level protocol. Patients were required to walk on a gymnasium floor, which was marked by two cones set 0.5 m from either end of the 10 m course. During the first course, the operator was walking alongside the participant to maintain the correct pace.

The speed at which the patient was required to walk was indicated by an audio signal from a CD player. Initial walking speed, indicated by an audible signal, was 0.5 $m \cdot s^{-1}$ and increased by 0.13

$m \cdot s^{-1}$ each minute. A change in speed was indicted by a second audible signal. Instructors also reminded patients to walk faster after each minute. Patients were allowed to run at any time during the test. The MSWT was terminated when the patient (a) felt too breathless or fatigued to continue at the required speed, (b) failed to complete the shuttle within the allowed time, (c) reached 85% of the predicted maximal heart rate: 210-(0.65×age), (d) reached RPE ≥ 15 (Borg 1998), or (e) completed all the levels.

Heart rate was monitored during the test and was recorded at the end of each level, using short-range telemetry (Polar Electro Sports Tester S810i), while the Borg Perceived Exertion (RPE) scale (6-20) was used to determine the perceived exercise intensity at the end of each level (Borg 1982). During the procedure, a lap marker was indicated in the heart rate monitor by pressing the button of the Polar at the end of its level until the end of the test. At the end of the test, the maximum heart rate was recorded, while the patient was asked to sit on a chair. The patient was advised to relax and breathe in a normal way.

7.2.3.1. Heart rate data

Heart rate was recorded at the end of each level of the test. Heart rate data from the Polar monitor were transferred and filtered to remove signal noise associated with movement using a desktop computer and the Polar Precision Performance 3.0 training software, version 3.01.005.

7.2.4. Exercise training programme

The programme provides additional phase IV CR capacity in the local area and offers the opportunity of life-long supervised exercise. This programme consisted of two supervised sessions per week, made up of 60 minutes of circuit-based exercise classes. Patients were regularly (at least once per week) taking part in the programme. Supervisory staff included a

physiotherapist specialised in cardiac rehabilitation, also trained in immediate life support methods. The CR programme followed the BACR guidelines (2006) and was designed to maintain the functional capacity gains achieved in phase III CR. Exercise sessions comprised: a 15-minute warm-up, including mobility exercises and stretches; a 35-minute main conditioning component, including cardiovascular and strength exercises at an intensity of 60% to 80% of the age-predicted maximal heart rate, or at 12 to 15 on the RPE scale; and a 10-minute cooling down period, including gently paced recovery exercises, mobility exercises and stretches. During this component, patients had access to a variety of exercise equipment, such as arm ergometers, rowing ergometers, progressive resistance equipment, balance equipment, steppers and free weights.

7.2.5. ECG data from event monitoring

ECG data from the Cardionetics ambulatory ECG monitor was transferred, and event reports were collected using a desktop computer and the Cardionetics Connect software, version 2.0. At the end, a cardiologist verified the presence or absence of each cardiovascular event.

7.2.6. Data analysis

Data were presented as means and standard deviation, unless otherwise stated. Frequency of the events was reported for both groups. Patients were divided into an event-free versus cardiac event subgroups. Baseline differences in functional capacity between the two subgroups were examined using two-sample t-tests (for continuous variables) and chi-square tests (for nominal variables). A chi-square test was performed to determine associations between incidences of cardiovascular complications with poor functional capacity (SWT <450 m). The sample was also divided into groups based on their functional capacity assessed by a previous MSWT, using cut-points. The coding was done as follows: 0=event-free group and 1=cardiac event group; distance

walked in MSWT [MSWD] with 0=low functional capacity (MSWD<450 m), 1=good functional capacity (MSWD ≥ 450 m) (Morales *et al.,* 2000). For the patients (n=7) who were monitored during exercise training and exercise testing (MSWT), a binary logistic regression was performed to predict the incidence of cardiovascular events during the MSWT. Dependent and independent variables were encoded by using 0 and 1 for this analysis. The coding was done as follows: 0=no event and 1=event. The odds ratio was calculated. All statistical analyses were performed using SPSS version 16.0 (SPSS inc., Chicago, IL, US), whereas calculations were illustrated in Microsoft Office Excel 2003 (Microsoft Corporation**,** Washington, US). The statistical significance was set at the 0.05 level.

7.3. Results

The same data analysis process was used for the two study conditions (ECG recording during exercise testing and ECG recording during exercise training).

7.3.1. ECG event monitoring during exercise testing (modified shuttle walking test)

During exercise testing with the MSWT, 11 patients were recorded using ECG monitoring, involving 6 males (55%) and 5 females (45%) (mean age: 67.2±6.9 years). Most of the cardiac patients (64%) had had a surgical procedure involving their hearts (CABG, PCI). There were also patients with stable angina or arrhythmias (27%), while fewer patients (13%) had suffered a MI. According to the pharmacological history, all the patients were taking medication, while 82% of patients were taking β-blockers (see table 7.3).

7.3.1.1. Cardiovascular events using an ECG-recording system

According to the ECG recordings, 8 (73%) of the patients had cardiovascular events. These involved 5 males and 3 females (mean age: 64±9 years), with a medical history of heart surgery (CABG or PCI), angina, previous MI and arrhythmias, and with functional capacity levels assessed with the MSWT of 508 (±120) m (range: 370-750 m) or 5.6 (±0.8) METs (range: 4.6-6.6 m). Among these, the more important cardiovascular event was ischaemic ST-segment depression, involving 3 patients (2 females and 1 male) (mean age: 63±6 years) with a history of previous MI and heart surgery (PCI). Their recorded functional capacity levels during the MSWT were 445 (±106) m (range: 370-630 m) or 5.1 (±0.6) METs (range: 4.6-6.0 METs) (see table 7.4).

7.3.1.2. Event-ECG recordings verified by cardiologist

The ECG recordings were reviewed by a cardiologist, who found that 7 (64%) of the patients had cardiovascular events during the MSWT; the accuracy of the recordings was verified as 82% (the cardiologist was in agreement with 9 of the 11 event cases) (see table 7.5).

7.3.1.2.1. Frequency of cardiovascular events based on the cardiologist's review

According to the cardiologist's review of the ECG recordings, of the 11 patients, 5 (45.5%) had atrial ectopic beats, 4 (36.4%) had isolated ventricular ectopic beats, 3 (27.3%) had ischaemic ST-segment depression, 2 (18.2%) had an atrial fibrillation event, 1 (9.1%) had a bradycardia event (under 50 bpm), while 4 (36.4%) of the patients were free from cardiovascular events (see table 7.6).

Table 7.4. ECG event monitoring during the modified shuttle walking test performance (n=11)

Patient	Sex	Age (years)	Medical History	Pharmacological History	Functional Capacity		ECG event data	
					MSWD (m)	METs (ACSM 2005, Woolf-May & Ferrett 2008)	Event Y/N	Type of event
1	M	78	CABG	β-blockers, aspirin	480	5.5	Y	AEBs
2	M	70	CABG	β-blockers, other	710	6.6	Y	AEBs, bradycardia
3	F	60	MI, Angina, CABG, PCI, Arrhythmias	β-blockers, diuretics, nitrates	410	5.0	N	No event
4	M	64	CABG	β-blockers, aspirin	750	6.6	Y	AEBs, Isolated VEBs
5	M	69	PCI, arrhythmias	β-blockers, aspirin, statin	620	6.0	Y	AEBs, Isolated VEBs, AF, Ischaemic ST depression
6	F	69	Angina, arrhythmias	aspirin, ACE-inhibitor	520	5.5	N	No event
7	M	72	CABG	β-blockers, other	580	6	N	No event
8	F	67	MI	β-blockers, other	370	4.6	Y	AEBs, Isolated VEBs, Ischaemic ST depression
9	M	75	CABG	β-blockers, nitrates	660	6.6	Y	AEBs
10	F	59	MI, Hypertension	diuretics, statin	520	5.5	Y	AEBs, Ischaemic ST depression
11	F	56	Angina	β-blockers, aspirin	480	5.5	Y	Isolated VEBs, AF

Definition of abbreviations: M=values for males; F=values for females; Y=yes; N=no; AEBs=atrial ectopic beats; VEBs=ventricular ectopic beats; AF=atrial fibrillation

Table 7.5. ECG event monitoring during the modified shuttle walking test performance: cardiologist's verification (n=11)

Patient	ECG event data	ECG event data verification by Cardiologist	
		agree/disagree	**no event/major/minor**
1	AEBs	agree	minor
2	AEBs, bradycardia	disagree (no event)	no event
3	No event	agree	no event
4	AEBs, isolated VEBs	disagree (only isolated VEBs)	minor
5	AEBs, isolated VEBs, AF, Ischaemic ST-segment depression	agree	minor
6	No event	agree	no event
7	No event	agree	no event
8	AEBs, Isolated VEBs, Ischaemic ST-segment depression	agree	minor
9	AEBs	agree	minor
10	AEBs, Ischaemic ST-segment depression	agree	minor
11	Isolated VEBs, AF	agree	minor

Definition of abbreviations: *AEBs=atrial ectopic beats; VEBs=ventricular ectopic beats; AF=atrial fibrillation*

Table 7.6. Event rates during the modified shuttle walking test (n=11)

	ECG event data		Cardiologist's verification	
Event	**Frequency**	**% total event**	**Frequency**	**% total event**
Event-free	3	27.3 %	4	36.4 %
Atrial fibrillation event	2	18.2 %	2	18.2 %
Atrial ectopic beats	7	63.6 %	5	45.5 %
Isolated ventricular ectopic beats	4	36.4 %	4	36.4 %
Bradycardia event (under 50 bpm)	1	9.1 %	1	9.1 %
Ischaemic ST-segment depression	3	27.3 %	3	27.3 %

Definition of abbreviations: *bpm=beats per minute*

7.3.1.3. A comparison between cardiovascular events and functional capacity

The independent-samples t-test was conducted to compare functional capacity – expressed by the MSWD in metres – in the event-free group and in the group that experienced cardiovascular events. The cardiologist's ECG reviews were used here. Within the small group of patients, there was no significant difference in functional capacity between the event-free group (n=3, mean=503±86 m) and the group that experienced a cardiac event (n=8, mean=573±132 m); t (11)=-0.85, p=0.4. The mean difference between the two groups was -70 m, with 95% CI: -259 to 118 m. The magnitude of the difference between the means was moderate: d=0.63 (Cohen 1988).

A chi-square test for independence indicated no significant association between poor functional capacity and risk for cardiovascular events: x^2 (11)=0, p=0.99, phi=0.24. The phi coefficient value is considered a small effect between functional level and potential event (Cohen 1988). Also, half of the low performers (< 450 m in MSWT) and 77.8% of the high performers (≥ 450 m in MSWT) had an event recorded during the test (see table 7.7).

Table 7.7. Chi-square tests for exercise testing group (Crosstabulation)

		Event-free group	Group with cardiovascular events	Total
MSWD < 450 m	n	1	1	2
	% within MSWD	50.0%	50.0%	100.0%
	% within Potential Event	33.3%	12.5%	18.2%
	% of Total	9.1%	9.1%	18.2%
MSWD ≥ 450 m	n	2	7	9
	% within MSWD	22.2%	77.8%	100.0%
	% within Potential Event	66.7%	87.5%	81.8%
	% of Total	18.2%	63.6%	81.8%
Total	n	3	8	11
	% within MSWD	27.3%	72.7%	100.0%
	% within Potential Event	100.0%	100.0%	100.0%
	% of Total	27.3%	72.7%	100.0%

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test

7.3.2. ECG event monitoring during phase IV cardiac rehabilitation: programmed exercise session

During exercise training in phase IV CR, 22 patients were recorded, including 13 males (59%) and 9 females (41%) (mean age: 66.3±8.6 years). Most of the cardiac patients (77%) had undergone a surgical procedure on the heart (CABG, PCI), while there were a number of patients (41%) with stable angina; a few patients (17%) had been affected by a MI and one patient (4.6%) suffered from arrhythmias. According to the pharmacological history, all the patients were taking medication; 73% of patients were taking β-blockers (see table 7.3).

7.3.2.1. Cardiovascular events using the automated ECG-recording system

According to the ECG event monitoring reports, 18 (82%) of the patients had cardiovascular events. These involved 11 males and 7 females (mean age: 68±8 years), with a medical history

of heart surgery (CABG or PCI), angina, previous MI and arrhythmias, and with estimated functional capacity levels from a previous assessment using the MSWT of 473 (±117) m (range: 270-710 m) or 5.4 (±0.6) METs (range: 4.6-6.6 METs). Among all the patients, five significant cardiovascular events (ischaemic ST-segment depression) had occurred, involving 3 females and 2 males (mean age: 73±5 years) with a history of heart surgery (CABG or PCI), previous MI and angina. Their estimated functional capacity levels, assessed using a previously administered MSWT, were 486 (±135) m (range: 330-660 m) or 5.5 (±0.9) METs (range: 4.6-6.6 METs) (see table 7.8).

7.3.2.2. ECG event recordings verified by a cardiologist

The ECG recording was manually reviewed by a clinical cardiologist, who found that 16 (73%) of the patients had cardiovascular events; the cardiologist verified the accuracy of the recordings at 86% (the cardiologist was in agreement with 19 out of 22 event cases) (see table 7.9).

7.3.2.2.1. Frequency of cardiovascular events based on the manual review

According to the cardiologist's review of the ECG recordings, of the 22 study patients, 15 (68%) had isolated ventricular ectopic beats, 4 (18%) had atrial ectopic beats, 4 (18%) had ischaemic ST-segment depression, 1 (4.6%) had atrial fibrillation, while 6 (27.3%) of the patients were free from cardiovascular events (see table 7.10).

Ischaemic ST-segment depression

Ischaemic ST-segment depression occurred in 2 females and 2 males (age: 74±4 years) with a history of heart surgery (CABG or PCI) and angina. Their estimated functional capacity level, as

assessed with a previous MSWT, was 515 (±137) m (range: 330-660 m) or 5.7 (±0.8) METs (range: 4.6-6.6 METs) (see tables 7.8 and 7.9).

Cardiovascular events during programmed exercise

Taking into consideration the cardiologist's ECG analysis, 76.5% of the cardiovascular events were detected around the time of the main conditioning component of the exercise training, 11.8% during the warm up and 23.5% during the cool down.

Table 7.8. ECG event monitoring during phase IV cardiac rehabilitation exercise (n=22)

Patient	Sex	Age (years)	Medical CVD History	Pharmacological History	Functional Capacity		ECG event data	
					MSWD (m)	METs (Woolf-May&Ferrett 2008)	Event Y/N	Type of event
1	M	70	CABG	β-blockers, other	710	6.6	Y	AEBs, isolated VEBs
2	M	78	CABG	β-blockers, aspirin	480	5.5	Y	isolated VEBs
3	M	77	Angina	Nitrates, aspirin, other	280	4.6	Y	isolated VEBs
4	F	68	Angina, PCI	β-blockers, nitrates, aspirin, statin	520	5.5	Y	AEBs, ischaemic ST depression
5	F	78	PCI, Hypertention	aspirin, other	270	4.6	Y	isolated VEBs
6	F	60	Hypertention	β-blockers, other	420	5.0	Y	isolated VEBs
7	M	56	Angina, PCI	aspirin, statin	790	7.1	N	no event
8	M	55	MI, PCI	β-blockers, nitrates, statin, other	550	6.0	Y	isolated VEBs
9	M	64	CABG	β-blockers, aspirin	750	6.6	N	no event
10	F	78	CABG, PCI	β-blockers, aspirin, statin	330	4.6	Y	isolated VEBs, ischaemic ST depression
11	M	64	CABG	aspirin, other	390	5.0	Y	AEBs, isolated VEBs
12	M	76	Angina, 4CABG	β-blockers, nitrates, aspirin, statin	550	6.0	Y	AEBs, isolated VEBs, ischaemic ST depression
13	M	69	PCI, arrhythmias	β-blockers, aspirin, statin	620	6.0	Y	isolated VEBs
14	M	75	CABG	β-blockers, nitrates	660	6.6	Y	isolated VEBs, ischaemic ST depression
15	F	52	Angina	aspirin, statin	750	6.6	N	no event
16	F	64	PCI	β-blockers, aspirin	480	5.5	N	no event
17	M	68	Angina, CABG	β-blockers, aspirin, statin	550	6.0	Y	isolated VEBs
18	M	71	MI, 3CABG	aspirin, statin	470	5.5	Y	AEBs, VEBs
19	F	56	Angina	β-blockers, aspirin	480	5.5	Y	AEBs, isolated VEBs, AF
20	F	56	Angina, PCI	β-blockers, aspirin, nitrates, statin	470	5.5	Y	isolated VEBs
21	M	56	Angina, CABG	β-blockers, aspirin, nitrates	630	6.0	Y	isolated VEBs
22	F	67	MI	β-blockers, other	370	4.6	Y	AEBs, isolated VEBs, ischaemic ST depression

Definition of abbreviations M=values for males; F=values for females; Y=yes, N=no, CABG= coronary artery bypass graft; PCI=percutaneous coronary intervention; *AEBs=atrial ectopic beats; VEBs=ventricular ectopic beats; AF=atrial fibrillation*

Table 7.9. ECG event monitoring during phase IV cardiac rehabilitation exercise: cardiologist's verification (n=22)

Patient	ECG monitoring event	ECG event data verification by Cardiologist		
		Agree/disagree	**No event/ major/minor**	**When did it happen? (warm up/main component/cool down)**
1	Isolated VEBs	agree	minor	main conditioning component
2	Isolated VEBs	agree	minor	main conditioning component
3	Isolated VEBs	agree	minor	main conditioning component
4	AEBs, Ischaemic ST-segment depression	agree	minor	cool down
5	Isolated VEBs	agree	minor	main conditioning component
6	Isolated VEBs	agree	minor	warm up
7	No event	agree	no event	-
8	Isolated VEBs	agree	minor	cool down
9	No event	agree	no event	main conditioning component
10	Isolated VEBs, Ischaemic ST-segment depression	agree	minor	main conditioning component
11	AEBs, Isolated VEBs	agree	minor	main conditioning component
12	AEBs, Isolated VEBs, Ischaemic ST-segment depression	agree	minor	main conditioning component
13	Isolated VEBs	agree	minor	main conditioning component
14	Isolated VEBs, Ischaemic ST-segment depression	agree	minor	main component & cool down
15	No event	agree	no event	-
16	No event	agree	no event	-
17	Isolated VEBs	agree	minor	cool down
18	Isolated VEBs	disagree (no event)	minor	-
19	AEBs, VEBs, AF	agree	minor	main conditioning component
20	Isolated VEBs	disagree (no event)	no event	-
21	Isolated VEBs	agree	minor	main conditioning component
22	AEBs, VEBs, Ischaemic ST-segment depression	partly agree (only VEBs)	minor	warm-up & main component

Definition of abbreviations: AEBs=atrial ectopic beats; VEBs=ventricular ectopic beats; AF=atrial fibrillation

Table 7.10. Events rates during phase IV cardiac rehabilitation exercise (n=22)

	ECG event data		Cardiologist's verification	
Event	**Frequency**	**% total event**	**Frequency**	**% total event**
Event-free	4	18.2 %	6	27.3%
Atrial fibrillation event	1	4.6%	1	4.6%
Atrial ectopic beats	5	22.7%	4	18.2%
Isolated Ventricular ectopic beats	17	77.2 %	15	68.2%
Bradycardia events (under 50 bpm)	0	0 %	0	0 %
Ischaemic ST-segment depression	5	22.7%	4	18.2 %

Definition of abbreviations: *bpm=beats per minute*

7.3.2.3. Association between frequency of cardiovascular events and patient functional capacity

An independent-samples t-test was conducted to compare the functional capacity – expressed by the MSWD in metres – recorded during the MSWT in the event-free group, versus the group with cardiovascular events. The cardiologist's ECG reviews were used to group patients for this analysis. There was no significant difference in functional capacity between the event-free group (n=6, mean=618±160 m) and the group with cardiovascular events (n=16, mean=488±135 m); t (22)=1.92, *p*=0.069. The mean difference between the two groups was 130 m, with 95% CI: -11 to 271 m. The magnitude of the difference between the means was large: d=0.86 (Cohen 1988).

A chi-square test for independence indicated no significant association between poor MSWD and risk for cardiovascular events: x^2 (22)=2.1, *p*=0.15, phi=-0.42. The phi coefficient value indicates a moderate degree of interdependence between functional level and potential event (Cohen 1988). As can be seen in table 7.11, all patients with low functional capacity (<450 m in MSWT) and 60% of patients with good functional capacity (≥ 450 m in MSWT) had an event during the CR exercise.

Table 7.11. Chi-square tests for exercise training group (Crosstabulation)

		Event-free group	Group with cardiovascular events	Total
MSWD < 450 m	n	0	7	7
	% within MSWD	.0%	100.0%	100.0%
	% within Potential Event	.0%	43.8%	31.8%
	% of Total	.0%	31.8%	31.8%
MSWD ≥ 450 m	n	6	9	15
	% within MSWD	40.0%	60.0%	100.0%
	% within Potential Event	100.0%	56.2%	68.2%
	% of Total	27.3%	40.9%	68.2%
Total	n	6	16	22
	% within MSWD	27.3%	72.7%	100.0%
	% within Potential Event	100.0%	100.0%	100.0%
	% of Total	27.3%	72.7%	100.0%

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test

7.3.3. Comparison of event outcome data between the two conditions

Seven patients participated in both of the experimental protocols. Six of the seven patients (85.7%) had an event during exercise testing and during exercise training. The binary logistic regression analysis showed that patients who had a cardiac event during exercise training were over six times more likely to have a cardiac event during the MSWT than those who did not have any cardiac event during training (p=0.097).

7.4. Discussion

Previous electrocardiographic studies of CR patients have demonstrated that this is a reliable way to record the kinds of CVD events commonly evoked during exercise. These studies have shown that the frequency of cardiovascular events during medically supervised exercise testing and training is low in CR populations. However, there are few studies in the literature using

ambulatory ECG to record events during walking tests. The present study provides information regarding the safety of exercise training during the maintenance phase of phase IV community-based CR and exercise testing by using a functional walking test – the MSWT. The associations were observed between exercise and cardiovascular events in a number of stable CVD patients.

7.4.1. Risk of cardiovascular events during exercise testing and training

The exercise functional capacity MSWT, which was performed by patients who had already been enrolled in a CR programme, and the exercise training in phase IV CR, revealed some nonfatal cardiovascular events. According to cardiologist-verified ECG data only minor, nonfatal cardiovascular events were observed during both the SWT (with an event rate of 0.64 per patient per test) and in exercise training (with an event rate of 0.73 per patient per session). Contrary to the literature (Haskell *et al.,* 1978; Van Camp & Peterson 1986; Pavy *et al.,* 2006*)*, the present study showed that exercise training in phase IV CR is more risky than exercise testing with the use of the MSWT. Most of the previous studies used treadmill tests, while in Chapter 3 (see '*Long-term reliability of the modified shuttle walking test in clinically stable cardiovascular disease patients')*, it was stated that the MSWT provokes less stress on the cardiovascular system (less physiological stress) than the treadmill test (Singh *et al.,* 1994; Zwierska *et al.,* 2004; Fowler *et al.,* 2005). The MSWT seems to be a safe test, because it increases speed incrementally during walking.

The most clinical important event, silent ischaemia, was observed more often during the MSWT than during exercise training. This may indicate that the MSWT induces fewer yet potentially more serious cardiovascular complications than exercise training. This is likely due to differences in work rate and duration of exercise. For example, during the SWT the patients eventually achieve exercise at a higher intensity than during circuit-based exercise training, resulting in greater physiological stresses and thus major events.

Nevertheless, both exercise training and exercise testing in a phase IV CR setting seems to be safe, because despite the number of minor cardiovascular events observed, no major cardiovascular event was detected and no cardiac event related to hospitalisation, syncope episodes or fatality occurred in the present study. The findings agree with those of Hollenberg *et al.* (1998), who found no complex arrhythmias or symptomatic ischaemia during exercise. It should be noted, however, that the above study (Hollenberg *et al.,* 1998) was performed among people without suspected CVD. The nature of the observed cardiovascular events is discussed below.

7.4.1.1. Cardiovascular event: Myocardial ischaemia

The most clinically important event was silent (asymptomatic-painless) myocardial ischaemia with ST-segment depression, which was detected in patients with post-PCI, post-CABG, post-MI or angina. This event is likely associated with untreated coronary artery stenosis (Pavy *et al.*, 2006) or more likely, exercise-induced transient oxygen deprivation which results reversible perfusion defects (Franklin *et al.,* 1998).

The survival rate of a silent ST depression ischaemic event during ECG exercise testing was similar to non-ST and significantly better than symptomatic ST-changes, in CVD patients during a follow-up of 5 years (Mark *et al.,* 1989). This means that silent exercise-induced ST-segment depression should not be regarded as a severe cardiac event. A recent study found a significant association between silent myocardial ischaemia and sudden cardiac death in men with cardiac risk factors (Laukkanen *et al.,* 2009). The latter findings by Laukkanen *et al.* (2009) cannot be used in the present study due to different criteria for subject selection. They used a large sample, over 3,000, of middle-aged men without a history of CHD, but with a high number of risk factors (almost 30% of the patients were smokers); there was no evidence about participants' habitual

physical activity. On the other hand, the patients in the present study were CVD patients, who took the relevant treatment, minimised the cardiac risk factors and were enrolled in an exercise programme for a long period of time. Laukkanen *et al.* (2009) explained that the highly significant relationship between silent ischaemia and cardiac death found in their sample was associated with the large number of false positive diagnostic exercise tests. Previous studies demonstrated that according to Baye's rule the presence of false positive or negative exercise tests is more likely in asymptomatic (that is, without coronary risk factors) than symptomatic individuals (Miranda *et al.,* 1991; Lakka *et al.,* 1994). Thus, the presence of silent myocardial ischaemia does not necessarily signify a severe cardiovascular condition.

7.4.1.2. Cardiovascular event: Cardiac arrhythmias

The present study demonstrated a relatively high prevalence of ventricular and atrial arrhythmias in this low-risk cohort. These arrhythmias were not related to any major cardiac event during exercise. For instance, during exercise (testing and training), events such as non-complex ventricular ectopic activity, atrial ectopic and atrial fibrillation were detected in more than half (64% to 73%) of patients with PCI, CABG, post-MI or angina. Atrial ectopic beats and fibrillation are common events after cardiac surgery. They occur in 15%-40% of patients after CABG (Mathew *et al.,* 2004; Villareal *et al.,* 2004; Dogan *et al.,* 2007), 10%-11% of patients after PCI (Celik *et al.,* 2005; Gorenek *et al.,* 2007), 5%-10% after MI (Bhatia and Lip 2004), 37%-50% after a valve replacement (Asher *et al.,* 1998; Banach *et al.,* 2007) and 11%-24% after a cardiac transplantation (Creswell *et al.,* 1993; Pavri *et al.,* 1995). The above data were collected at rest, our study showed similar frequencies as atrial arrhythmias were detected in 45% of patients during the SWT and 23% of patients during exercise training. The high percentage of atrial arrhythmias may be explained by higher participation rates of post-

vascularisation patients and the fact that they were stress-induced arrhythmias (Bunch *et al.,* 2004).

Ventricular ectopic beats (VEBs) were observed in 36.4% of patients during the MSWT and in 68.2% during exercise training; these are common events of exercise (Dewey *et al.,* 2008). During exercise a number of important physiological changes occur, which interact with the cardiovascular system. These changes are reflected in an increase of sympathetic nerve activity and in the release of hormones and enzymes, such as catecholamines. Vigorous exercise is associated with a more than ten-fold increase in circulating catecholamines, a decrease in pH and a two-fold increase in serum potassium (Beckerman *et al.,* 2005). These changes can predispose people to arrhythmias, which are common and usually well tolerated during exercise.

Adabag *et al.* (2005) demonstrated that the ventricular arrhythmias shown on ambulatory 24-h Holter ECG traces were poor long-term predictors of sudden cardiac death in a cohort of low-risk patients with hypertrophic cardiomyopathy. The authors used a broad spectrum of ages (from 5 to 89 years old) with a mean patient age of 50 years old. It would be difficult to make a comparison with other groups, particular in terms of age group, such as 'elderly', which is the main cohort of the present study.

The prognostic value of exercise-induced VEBs also remains unclear (Gibbons *et al.,* 2002; Dewey *et al.,* 2008). There is some evidence that exercise-induced VEBs are independent predictors of CVD mortality in patients without a pre-existing diagnosis of CHD (Beckerman *et al.,* 2005). Beckerman *et al.* (2005) found that 17% of participants with VEBs induced during exercise testing died of cardiovascular causes during a mean follow-up of 6 (±4) years. Exercise-induced arrhythmias can occur after exercise, during the recovery period, because the levels of catecholamine usually continue to increase in the recovery period after exercise testing

(Dimsdale *et al.,* 1984; Fleg *et al.,* 1985). If any of these physiological changes occur during rest, there is an increased risk of cardiac arrest, particularly for patients with diagnosed CHD (Dimsdale *et al.,* 1984; Futterman and Lemberg 2006). Patients with resting VEBs, resting ST-segment depression and ischaemia during exercise testing are high-risk patients for profound CVD effects (Beckerman *et al.,* 2005).

The current study did not contain a resting ECG that could be used for comparison with the exercise data. It cannot be assumed, therefore, that the VEBs recorded were exercise-induced or associated with the severity of the CVD. The VEBs recorded in the current study were isolated, while 50% of those induced during the MSWT, and 27% of those induced during the exercise testing, also recorded an asymptomatic ischaemic ST depression episode. No episodes of transient ventricular fibrillation were observed, however, supporting the case that the VEBs were physiologically induced by exercise. Of note, the presence of isolated VEBs is not a contraindication for exercise (Gibbons *et al.,* 2002). Of more serious concern is the development of frequent complex VEBs, recommending a careful clinical follow-up.

The presence of VEBs can relate to elevated levels of exercise stress. There is a large variability in the occurrence of exercise-induced during treadmill testing and so the reproducibility of exercise-induced VEBs is low. A second exercise stress test is always required, since there is evidence that there is a decrease in the exercise-induced VEBs after the first practice test (Sheps *et al*., 1977). This finding was not explained by the authors (Sheps *et al*., 1977) as a learning effect; it seems to be an outcome of a decrease in myocardial oxygen consumption and a product of the pressure-rate, which has not been substantiated. In the present study, only one trial of the MSWT was used, since the target was to investigate events during exercise in clinically stable CVD patients who exercise regularly in a long-term CR programme.

7.4.2. Risk of cardiovascular events related to the components of an exercise training programme

The core components of CR/secondary prevention programmes, including a combination of exercise, psychological and educational intervention, were outlined in a Scientific Statement from the AHA and the American Association of Cardiovascular and Pulmonary Rehabilitation (Balady *et al.,* 2007). Following these recommendations, the exercise programme used in the present study included three components: warm-up, main conditioning and cool-down period.

Most of the events (76.5%) were detected during the main conditioning component of the exercise programme, which included moderate levels of aerobic and resistance exercise. When the exercise session during CR terminates rapidly, hypotension, bradycardia and arrhythmias are the most common events, which usually occur in response to the decrease in venous blood return to the heart (Barnard *et al.,* 1973). The current study did not show any major event after the end of the exercise session, which might be due to competing the recommended cool-down protocol at the end of the test (Balady *et al.,* 2007). Few events were recorded after the main conditioning component in the cool-down phase.

Consequently, it is possible that the relative safety of the exercise training experienced by the present study group was the result of a well-supervised exercise programme, which was risk stratified and gave special consideration to warm-up and cool-down elements (Balady *et al.,* 2007).

7.4.3. Is it possible to predict the risk of cardiovascular events considering the functional capacity level?

Low exercise capacity (less than 5 METs or 450 m in SWT) is used in risk stratification at entry into CR programmes, exercise prescription and prognosis of mortality (Morales *et al.,* 2000;

Lewis *et al.,* 2001). Patients who walked <450 m in the MSWT had no greater risk of cardiac events during exercise than patients who walked >450 m.

The present study showed no significant difference for cardiovascular events between patients with low and high functional capacity. This may be due to the lack of matched design and the low participant numbers. All patients with low functional capacity experienced a cardiac event, while only 60% of patients with a high functional capacity had any events. This suggests that patients in CR who performed in the MSWT at less than 450 m do not have an increased risk of cardiac event during exercise over patients who performed in the MSWT at more than 450 m; however, all the low performers will have an event (major or minor) during exercise training.

The fact that no significant association was found between event-rate and functional capacity may be due to the small sample and the fact that all the events recorded were minor. If major events with hospitalisation had been recorded, the minor cardiovascular events would have been excluded from the analysis. Moreover, the cut-off value of 450 m used may also be inappropriate for this population. It was originally used to categorise cardiac patients as high and low performers but was developed for use in heart failure patients. This group differ from the present cohort as they did not regularly exercise (Morales *et al.,* 2000; Lewis *et al.,* 2001) due to severe cardiorespiratory problems, exercise intolerance and fatigue (Troosters *et al*., 2004).

7.4.4. Study limitations

Within the present study, it is acknowledged that there is a lack of resting ECG data, which could have been used for comparison with the ECG during exercise (testing or training). Thus, the present study is unable to confirm whether the isolated VEBs recorded here are exercise triggered or related to cardiovascular pathology. The presence of isolated ventricular ectopic beats is not a contraindication to exercise. Either there was evidence that these arrhythmias are

exercise-induced or not, the recommended management of a patient with such events would be similar.

It is further acknowledged that the study monitored 11 patients during exercise testing and 22 patients during exercise training. The present sample size was relatively small, principally because ECG monitoring is not frequently used in the routine evaluation of low-risk, asymptomatic, CR patients in the UK. This sample included all non-paced patients attending the CR at the time of the study. This sample represents a typical cohort, participating in a long-term CR programme. Moreover, this study is based on individual evaluation and aims to point out potential events corresponding to patients' clinical characteristics. Therefore, it is useful here to note a brief clinical summary of a patient who had cardiovascular events during both testing and training.

7.4.5. Case study

The use of case studies in CR is an effective research approach, because it gives an opportunity to isolate and analyse an individual patient. It is used to explore in depth the clinical characteristics and medical history of a patient, the effectiveness of a CR programme and potential events during exercise or non-exercise tasks. A clinical case study provides the opportunity to make more accurate inferences by combining an individual's characteristics and outcome.

In this study, of particular interest was a 69-year-old man – stature 172 cm and BMI 27 $kg \cdot m^{-2}$ – who entered the CR programme after PCI surgery. He had a history of arrhythmias and he was used to regular exercise. He was under medication with β-blockers, aspirin and statins during exercise. During the MSWT the patient had isolated ventricular arrhythmias, atrial arrhythmias, atrial fibrillation and painless ischemic ST-segment depression, which required no further

intervention. He showed quite a high performance level in the MSWT (MSWD=620 m, 6.0 METs). The same patient had isolated VEBs during the exercise training in phase IV CR. Statin therapy usually decreases the risk of ventricular arrhythmias (Dewey *et al.,* 2008); however, in this case the patient had arrhythmias during both exercise testing and training.

Although in this study the overall incidence of cardiovascular events during the MSWT was lower than in exercise training in phase IV CR, for this patient more events were recorded in the MSWT than in exercise training. The results showed that almost 78% of the high performers in the MSWT >450 m had a cardiac event during the test, while only 60% of the high performers had an event during the exercise programme.

According to equation 4.1 (see Chapter 4 '*Biomechanical predictors of the modified shuttle walking test performance in patients with cardiovascular disease'*), the predicted MSWD for this patient, when his stature (172 cm) was entered into the equation model, was 524 m. He performed almost 100 m above this predicted MSWD. This might imply that the patient over-reached himself in an attempt to attain a higher score during the MSWT. This justifies Chapter 4's recommendations for using the prediction equation in order to set realistic and safe expectations for each individual patient in phase IV CR.

7.5. Conclusion

Some relevant studies already demonstrated the relatively low risks of cardiac events during supervised exercise. The present work adds to the body of information regarding the safety of exercise training and the MSWT in clinical stable CVD patients. The most important point to be drawn from this study is that in exercise-induced testing or training, complex arrhythmias or symptomatic ST-segment depression is not induced in cardiac patients enrolled regularly for more than 2.5 months in supervised CR maintenance programmes. Previous studies that

presented data from CR patients are not relevant to the present study cohort, or to the type of the exercise testing and the characteristics of the CR exercise programme used here.

The information that this study provides is that, in community-based settings, the assessment of functional capacity with the MSWT and exercise prescription, is safe for phase IV low-risk CR patients, if the contraindications for testing and training are followed. The minor cardiovascular events, such arrhythmias and silent ST depression, are not be ignored, but are a reason to suggest additional CVD assessment and risk modifications. Further investigations should address, firstly, the limitations of this work, and whether the presence of isolated ventricular arrhythmias is related to exercise; they should then examine the prognostic value of these minor cardiovascular events over a longer-term follow-up period.

Lastly, the present study was based on a cohort of low-risk CR patients. Cross-sectional studies should investigate further the possible cardiac complications during exercise among high-risk patients (i.e., HF patients, diabetics, patients with depression). Longitudinal study of patients who progress from high to moderate risk classifications would also be of great value.

7.6. References

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CHAPTER 8. THESIS CONCLUSION

This chapter is divided into two parts. The first part summarizes the most important features and outcomes of chapters 3 to 7. The second part describes the potential overall impact of the thesis results on clinical cardiac rehabilitation (CR) practice.

8.1. Main points of each chapter

Chapter 3. Long-term reliability of the modified shuttle walking test in clinically stable cardiovascular disease patients.

- Background: Cardiac rehabilitation aims to increase functional capacity. In order to verify such changes reliable functional capacity tests are needed. Clinical guidelines recommend the use of modified shuttle walk test (MSWT) and the six-minute walking test (6-MWT) to assess functional capacity in CR patients. Studies have only assessed its test–retest reliability in the short term.

- Aim: To examine long-term test-retest reliability of MSWT in clinically stable cardiac patients. Long-term reliability is important in CR because the MSWT is often administered to patients pre- and post- CR, a gap of four to twelve weeks.

- Methods: The MSWT was completed twice, by clinically stable phase IV CR patients (n=30), eight weeks apart.

- Conclusions:

- No systematic bias but a relatively large random variation in test performance over the test period.
- The test can be used effectively in CR and there is no need for a practice MSWT in both pre- and post- rehabilitation assessment.

Chapter 4. Biomechanical predictors of the modified shuttle walking test performance in patients with cardiovascular disease.

- Background: After determining the long-term reliability of MSWT, it was important to evaluate which factors influence MSWT performance. There was some evidence that performance on the 6-MWT is strongly influenced by age and stature of patients, but no comparable data were available for the MSWT.
- Aim: to evaluate the influences of anthropometric and biomechanical parameters on MSWT performance in clinically stable CVD patients.
- Methods: MSWT was completed twice, by clinically stable phase IV CR patients (n=16).
- Conclusions:

- Turning strategy, balance and ground reaction force data appear unrelated to MSWT performance.
- Step length is the most important mediator of MSWT performance, but stature acts as a suitable surrogate measure.
- An additional 1 cm of stature predicts that patients will complete an additional shuttle during the MSWT.
- Clinicians should correct MSWT performance for patient stature.

Chapter 5: Predictors of six-minute walking test performance in heart failure patients

- Background: The 6-MWT is used to evaluate; functional limitations, the effects of interventions and aid prognosis in heart failure (HF) patients. Anthropometric variables are determinants of 6-MWT performance in healthy adults. There is not much evidence whether the same variables can predict performance in HF patients.

- Aim: to identify if routinely-made measurements (anthropometric, gait and simple clinical) could predict 6-MWT performance in HF patients, in the same way as in healthy adults.
- Methods: 6-MWT was completed once, by clinically stable HF patients (n=71).
- Conclusions:

- Ventricular function is unrelated to 6-MWT performance in HF patients.
- Age and anthropometric variables (sex, stature, body mass) are independent predictors of 6-MWT performance, and they must be considered when interpreting performance in this population.
- 6-MWT performance may be better expressed as a percentage of normal population values which account for sex, age, stature and weight.
- The cut-off point of BMI> 25 $kg \cdot m^{-2}$ and age >75 years can be used for the prognostic stratification of HF patients.

Chapter 6: Normative values for functional capacity testing in cardiac patients and the influence of anthropometric measures on performance.

- Background: The cross-sectional study (Chapter 4) demonstrated that only anthropometric variables can be accounted for when MSWT is used to assess patients' functional capacity during phase IV CR.
- Aim: to determine normative values for functional capacity before and after CR, and the magnitude of change in functional capacity in phase III CR patients, through a longitudinal study.
- Methods: MSWT was completed twice (before and after six weeks of phase III CR programme), by clinically stable cardiac patients (n=159).

- Conclusions:

- Age, sex and stature are the best predictive measures for pre-rehabilitation MSWT performance
- Stature is the best predictor of magnitude of change in MSWT performance during phase III CR.
- Normative values can be used to estimate a normal improvement in functional capacity for CR patients.
- Clinicians can make better-informed decisions about patients at the entrance to or discharge from a CR programme when normative values are used to interpret test performance.

Chapter 7: Safety of exercise training and exercise testing for cardiac patients, in a supervised, community-based cardiac rehabilitation programme.

- Background: There was no information in the literature concerning the safety of exercise testing and training in phase IV community-based CR settings.
- Aim: To verify to what extent a recommended exercise testing protocol (MSWT) and an exercise training session are safe for a mixed cohort of CR patients during a long-term maintenance programme.
- Methods: Overall 33 cardiac patients underwent ambulatory electrocardiogram (ECG) monitoring during the MSWT (n=11) and exercise training (n=22).
- Conclusions:

- Poor functional capacity is not shown to be associated with the risk of a cardiac event during exercise.

- Supervised exercise testing and training are accompanied only by minor cardiovascular events and they can be carried out safely in community-based CR settings.

8.2. Clinical implications of thesis results

The findings of the present thesis are important with regard to clinical practice in CR. The present results provide several insights into the assessment of functional capacity in CR. This information can help clinicians to make the most efficient therapeutic decisions about CR patients.

The MSWT is a simple, cheap, valid and reliable test, which can be used to evaluate the functional capacity of patients enrolled in a CR programme. The present thesis (see Chapter 3) demonstrated its long-term reliability in a CR population for the first time. Clinicians can use the test to assess functional capacity improvement and they can feel confident that any improvement in patients' functional capacity is due to CR and not due to confounding variables such as learning effects. Clinicians should be confident that only one MSWT pre- and post-CR is sufficient to assess long-term changes in functional capacity with no need for a practice walk. Reducing the need for a practice functional capacity assessment can make clinical assessment more economical and less time consuming, both of which are important issues for CR.

The findings of this thesis (see Chapter 4, 5, 6) provided regression equations which can be used by clinicians to estimate MSWT and 6-MWT performance (distance walked). Clinicians should account for anthropometric parameters when interpreting distance walked. By interpreting distance as a percentage of the predicted value, practitioners would gain a more meaningful assessment of individual patient's functional capacity compared with distance alone. This can lead to better risk stratification and more accurate exercise prescription for patients entering CR when based on walk test performance.

Particularly, the percentage of predicted functional capacity recorded on the MSWT can be determined using only age, stature and sex (see Chapter 6). Patients who record higher scores than 100% of their predicted distance walked on MSWT at the entrance of phase III CR could be 'fast-tracked' to community-based phase IV CR. Patients who perform less than 100% of their predicted distance walked should be encouraged to join phase III CR and increase their habitual physical activity.

The BACR (2006) criteria for assessing the suitability of patients to exercise in phase IV CR community settings suggest patients should be able to sustain physical activities to a minimum level of 5 METS. Patients who perform less than 5 METs or walk <450 m in MSWT at the end of phase III CR are classified as high-risk patients and may not be allowed to join phase IV CR. However, according to the normative values and prediction equation derived in Chapter 6, males who are shorter than 172 cm and older than 69 years are actually expected to perform less than 450 m in MSWT at the end of phase III CR. Such patients, if they achieve this work rate should be considered for entry to phase IV CR. Clinicians should be more cautious, however, when making decisions for male patients who perform less than 450 m in MSWT, but are taller than 172 cm and younger than 69 years. Such patients can often walk >450 and should be encouraged to increase their functional capacity until they achieve the expected distance for their height and age. Tests should be interpreted and even clinical decisions made according to individual's anthropometric characteristics. In such ways, CR programmes could be tailored to better meet patients' needs while potentially becoming more economical.

The 6-MWT is commonly used to evaluate the functional capacity of patients with HF. The findings in Chapter 5 demonstrated that clinicians can use the gender-specific prediction models to evaluate individual's expected functional limitation in this population. 6-MWT performance can be expressed as a percentage of predicted value based on age, stature and weight (for females

only). It was known that the performance of 300 m in 6-MWT has clinical prognostic value. According to the reference equation model presented in this thesis for 6-MWT (see Chapter 5), the same distance walked (300 m) indicates severe reduction in functional capacity for a tall (>178 cm) 75-year-old male, suggesting that one therapeutic goal should be an increase in exercise tolerance for such an HF patient. Conversely, this performance is expected to be classed as doing 'well for age and stature' in terms of the functional capacity of a short (<171 cm) 75-year-old male, and a less intense, less stressful, safer and cheaper programme might be recommended, aimed at maintenance of functional capacity for such a HF patient.

There are many benefits of functional capacity assessment and clinicians should use the MSWT or 6-MWT to assess patients' performance at their start or discharge of a CR programme. These tests can be used with confidence but results appear more meaningful if clinicians are willing to look beyond the raw score of metres walked. Although, exercise can sometimes trigger symptoms in cardiac patients, the present thesis (see Chapter 7) showed that exercise prescription is safe for long-term supervised CR patients, if the contraindications to testing and training are followed. It is further suggested that when clinicians evaluate low-risk CR patients, there is no need for an ECG-monitoring during exercise in community-based CR settings. Patients can safely exercise in community-based CR settings.

These recommendations have the potential to enable clinicians or researchers to prescribe the most efficient, economical and safe exercise programme for each individual patient entering CR. We are currenlty conducting a longitudinal study based on CR records, taken from several UK hospitals, in order to update the normative values of the present study. The final aim is to develop functional capacity nomograms which can be easily used to predict patients' expected functional capacity in clinical practice.

APPENDIX A. VALIDATING THE PREDICTION EQUATION DEVELOPED IN CHAPTER 4

Appendix A1. Results

6.3.2. Validating the prediction equation developed in chapter 4

In order to validate MSWT performance (MSWD), prediction equation 4.1a (Chapter 4, pp.196), the correlations were first tested, and then the ICC and LoA between predicted and actual post-rehabilitation MSWD.

6.3.2.1. Correlations between actual and predicted distance walked in the modified shuttle walking test

Predicted MSWD was calculated using the equation based on stature (see equation 4.1a) for each individual. The mean MSWD in post-rehabilitation assessment was 420 (±186) m, while the mean of the predicted MSWD was 503 (±93) m. A significant but weak correlation was found between actual MSWD and predicted MSWD (Pearson's r=0.194; p=0.019), when stature was entered into the equation model. These relationships are represented by the regression equation shown in figure 6.1. The standard error of estimation was 184 m.

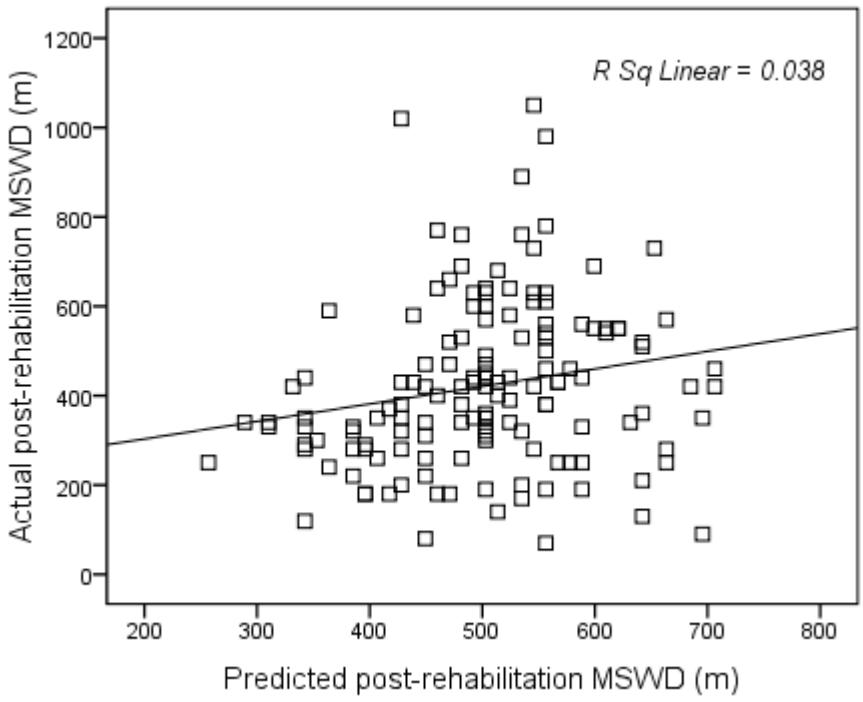

Figure 6.1. Regression line for the relationship between actual post-rehabilitation performance and predicted post-rehabilitation performance (using equation 4.1)

6.3.2.2. Agreement between actual and predicted distance walked in the modified shuttle walking test

The ICC between the actual and predicted MSWD, with 95% confidence intervals for MSWD (post-rehabilitation MSWD), was low 0.16 (p=0.031). The mean difference and the limits of agreement (for MSWD) are shown in table 6.5 and figure 6.2. The standard deviation (191 m) of the difference MSWDs indicates that the difference between predicted and actual MSWD could be expected to be within -301 m and 463 m.

Table 6.5. Agreement statistics: Mean difference (95% confidence intervals) between predicted- and actual pre- rehabilitation distance walked in modified shuttle walking test (using equation 4.1)

	Mean (SD) Difference	95% confidence interval	2SD	Limits of agreement (mean±2SD)
MSWD (m)	81 (191)	50 to 112	382	-301 to 463

Definition of abbreviations: MSWD=distance walked in modified shuttle walking test; SD=standard deviation

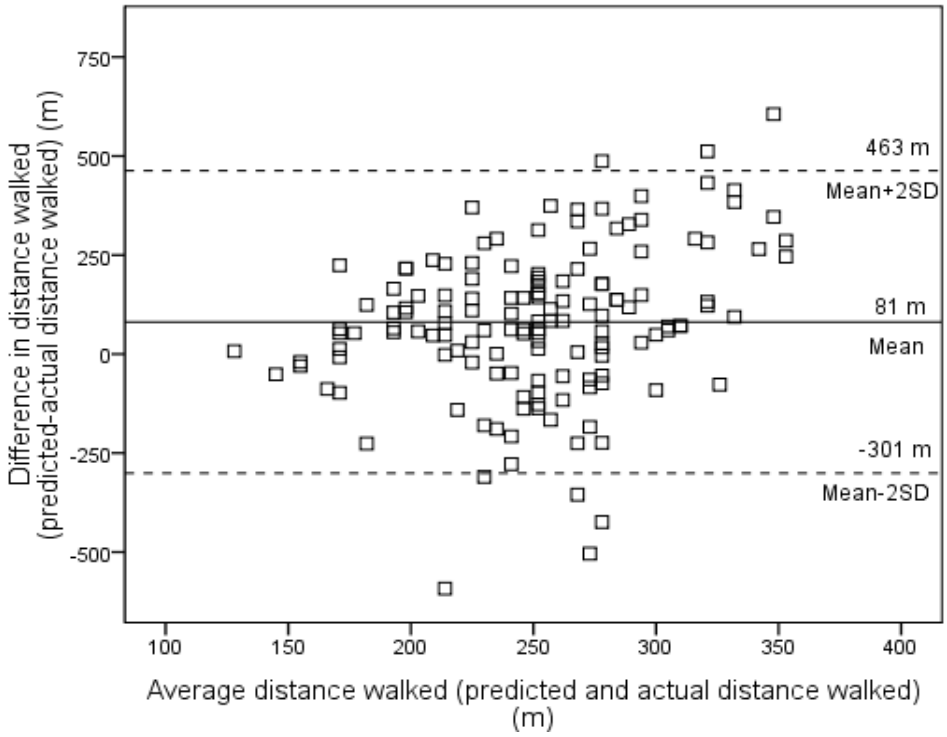

Figure 6.2. Limits of agreement plot (Bland and Altman plot) (using equation 4.1)**.** Intraindividual differences between scores (actual and predicted distance walked) in modified shuttle walking test, plotted against the mean of the sum scores. The central line represents the mean of the intraindividual differences and the flanking lines represent the 95% limits of agreement.

Appendix A2. Discussion

6.4.2. Testing the accuracy of the stature-based equation in predicting shuttle waking test performance in patients exiting phase III cardiac rehabilitation

The prediction equation developed in Chapter 4 (see equation 4.1a), based on the testing of phase IV CR patients, was examined for validation purposes using data from patients exiting phase III CR. Post-rehabilitation data was used here, as an increase in functional capacity is usually established by the end of phase III CR and remains stable during phase IV (Woolf-May and Ferrett 2008).

The present findings showed that the prediction equation developed in the pilot study did not yield similar estimates of MSWD as those reported in the validation sample. The correlation

between estimated MSWD (see equation 4.1a) and measured MSWD was significant but weak. Thus, it is suggested that equation 4.1a does not have application in the prediction of functional capacity achieved at the end of phase III CR. These findings suggest that the stature-based equation developed in the community based-group cannot be used to predict MSWD in a hospital based-group.

This may be explained by differences in patient recruitment strategies. Equation 4.1a was developed in relation to members of a long-term CR programme (10 weeks to over 2 years), who were accustomed to exercise. The absolute value of the difference of 82 m in the mean MSWD between the community-based group (479±139, 1st trial) and the hospital-based group (420±186 m, post-rehabilitation assessment) demonstrates differences in physical status between the two groups. The 59 m difference between predicted and actual MSWD is not within the acceptable difference-range, since the mean MSWD improvement after exercise training is 93 m (see table 6.1). An ideal case would be a zero difference between predicted and actual MSWD, whereas an acceptable difference might be less than half of mean MSWD improvement (i.e. <47 m).

The ICC and LoA for MSWD were low. The systematic bias between predicted MSWD to actual MSWD was 81 m, indicating that the prediction equation overestimates the MSWD and cardiovascular capacity levels of phase III CR patients. The mean of the predicted MSWD was 503 (±93) m. As mentioned earlier, this sample recorded lower mean values for MSWD than previous studies. Although the predicted MSWD is higher than the actual MSWD recorded in patients exiting phase III CR, it is still lower than in the results of previous studies (Fowler *et al.*, 2005; Arnold *et al.*, 2007; Sandercock *et al.*, 2007; Robinson *et al.*, 2009). The predicted mean value for MSWD is close to the results found in Arnold *et al*. (2007). The lower MSWT outcome in the present study compared with previous studies is explained by the very low-baseline physical status of the present sample when entering phase III CR. Unfortunately, there is no

information available in any of the studies regarding the habitual activities of the patients, which may influence patients' functional status.

To summarise, the stature-based equation developed in the pilot study (see Chapter 4) overestimates the measured MSWD for the majority of these phase III CR patients. Therefore, the stature-based prediction formula is not acceptable for application with a phase III CR population. It might, however, have clinical utility in a community-based group (phase IV CR, UK classification). The pilot equation needs to be revised using a population similar to that used in the pilot study.

Appendix A3. References

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APPENDIX B. RESEARCH ETHICS COMMITTEE APROVAL (FOR CHAPTER 6)

NHS
National Research Ethics Service
Cambridgeshire 4 Research Ethics Committee

Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

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03 February 2010

Dr Gavin Sandercock
Lecturer
School of Biological Sciences
University of Essex
CO43SQ

Dear Dr Sandercock

Study Title: **Normative values for functional capacity testing in cardiac patients and the influence of anthropometric measures on performance.**
REC reference number: **09/H0305/102**

Thank you for your letter of 22nd January 2010 responding to the Committee's request for further information on the above research.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
REC application	12414/73504/1/667	02 November 2009
Investigator CV	Dr Gavin Sandercock	
Protocol		
Response to Request for Further Information	Dr Gavin Sandercock	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0305/102	**Please quote this number on all correspondence**

Yours sincerely

pp. NStorey

Dr Leslie Gelling
Chair

Email: Nicky.Storey@eoe.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Ms Sarah Manning-Press
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APPENDIX C. PUBLICATIONS

Appendix C1. Long-term reliability of the incremental shuttle walking test in clinically stable cardiovascular disease patients (published)

ELSEVIER

Physiotherapy

Physiotherapy 96 (2010) 222–227

Long-term reliability of the incremental shuttle walking test in clinically stable cardiovascular disease patients

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Abstract

Objective The incremental shuttle walking test (ISWT) is a valuable tool for assessing changes in patients' functional capacity during cardiac rehabilitation. However, studies have only assessed its test–retest reliability in the short term. The purpose of this study was to examine long-term test–retest reliability of the ISWT in clinically stable cardiac patients.
Design Test–retest reliability assessment.
Setting Continuous, community-based phase IV cardiac rehabilitation centre.
Participants Thirty patients with cardiovascular disease (15 males, 15 females; age 55 to 80 years) volunteered to participate in the study.
Interventions Participants undertook two ISWTs, a minimum of 8 weeks apart.
Main outcome measures ISWT performance in metres.
Results Overall, the mean distance walked in the pre-test was 502 ± 161 m and this did not differ from test to retest. The intraclass correlation coefficient was 0.80, indicating good test–retest reliability. Using the Bland and Altman method, there was a small mean test–retest difference (−7 m). The 95% limits of agreement were large, ranging from −203 m to 189 m.
Conclusions Over long test–retest durations, there appears to be no learning effect in the ISWT, negating the need for a practice walk. The long-term random variation in the ISWT test is larger than in previous studies, probably due to greater physiological and psychological variation in the participants over 8 weeks compared with that seen in day-to-day testing. Factors influencing long-term test–retest reliability of the ISWT require further elucidation.

Keywords: Incremental shuttle walking test; Exercise test; Long-term test–retest reliability; Cardiovascular disease; Cardiac rehabilitation

Introduction

Functional capacity is an important predictor of mortality and morbidity in patients with cardiovascular disease (CVD). One aim of cardiac rehabilitation should be to increase functional capacity. However, to verify such changes objectively, there is a need for reliable functional capacity tests that can be carried out by nurses and physiotherapists.

Graded exercise tests aim to provoke a physiological response to continuously increasing incremental exercise levels [1,2]. The requirements of the cardiorespiratory system are challenged as the intensity increases, and the body's ability to cope with these demands can be investigated to provide an insight into aerobic capacity.

Several cardiorespiratory assessment tests and functional measurements have been developed to determine prognosis, prescribe exercise and assess the efficacy of cardiac rehabilitation. Several walk tests based either on a specific time (2-minute, 5-minute, 6-minute, 9-minute and 12-minute walk test), distance (100 m, half mile, 2 km walk test) or walking speed [self-paced, 6-minute and controlled-paced incremental shuttle walking test (ISWT)] are used to assess the functional capacity of cardiac patients, the effectiveness of a cardiac rehabilitation programme and the prognosis of CVD [3].

The British Association for Cardiac Rehabilitation (BACR) recommends use of the ISWT to assess and monitor functional capacity in patients with chronic heart failure,

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0031-9406/$ – see front matter
doi:10.1016/j.physio.2009.11.010

patients who have experienced a myocardial infarction, and patients who have undergone cardiovascular surgery or pacemaker insertion [4–8].

The ISWT has been used to track changes in functional capacity during cardiac rehabilitation programmes [8–11]. These studies typically use a single test at the beginning of rehabilitation and compare the distances walked with a post-rehabilitation test. While the ISWT appears to be able to assess changes in functional capacity in patients with CVD, only short-term (up to 7 days) test–retest reliability of the test has been assessed [9,12,13]. Given that cardiac rehabilitation programmes typically last for 6 to 12 weeks, long-term reliability is clearly of great importance.

If the ISWT is to be used to assess changes in functional capacity during cardiac rehabilitation, it is necessary to evaluate its long-term reliability. The primary aim of this study was to assess the test–retest reliability of a modified version of the ISWT over 8 weeks in clinically stable CVD patients.

Methods

Thirty CVD patients (15 males and 15 females; age 55 to 80 years) volunteered to participate in this study. Patients were verbally recruited by instructors prior to two consecutive exercise classes. All patients were defined as clinically stable, according to the BACR criteria [14].

All participants were attending a community-based phase IV cardiac rehabilitation programme at the University of Essex. The programme provides additional phase IV cardiac rehabilitation capacity in the local area, and offers the opportunity of life-long supervised exercise. The programme comprises twice-weekly, 60-minute circuit-based exercise sessions, in accordance with the BACR guidelines, and is designed to maintain functional capacity gains achieved in phase III cardiac rehabilitation. All participants had been enrolled on the programme for a minimum of 10 weeks. All participants met the inclusion criteria for the community-based phase IV cardiac rehabilitation programme, which excluded patients with severe locomotor limitations.

Each volunteer was provided with an information sheet which explained the procedures, risks and benefits of the study. Written, informed consent was then obtained. All procedures were approved by the Ethics Committee of the University of Essex, and conformed with the Declaration of Helsinki guidelines for research with human subjects.

Study design

Participants completed all elements of the study protocol twice, a minimum of 8 weeks apart. Before initial testing, each participant received a primary health assessment (pre-exercise health questionnaire) and interview (medical, pharmacological and family history). Stature was recorded using a stadiometer, and body mass was recorded without shoes. Body mass index (BMI) was calculated (kg/m^2). Waist circumference was measured with a tape at the level of the natural waist; the narrowest point between the ribs and the iliac crest. Table 1 summarises the participants' clinical characteristics and baseline measurements.

Table 1
Descriptive characteristics and baseline measurements of participants.

	Values
Number of participants	30
Age (years) (mean ± SD)	67 ± 8
Gender	15 males, 15 females
Body mass index (kg/m^2) (mean ± SD)	Test 1 M: 27.8 ± 2.6, F: 27.2 ± 4.7 Test 2 M: 28.0 ± 2.0, F: 27.0 ± 5.0
Waist circumference (cm) (mean ± SD)	Test 1 M: 100.1 ± 6.8, F: 92.6 ± 15.2 Test 2 M: 101.0 ± 6.0, F: 90.8 ± 13.5
Medical history/reason for joining cardiac rehabilitation (%)	
MI	17
Stable angina	30
Surgical procedure (CABG, PTCA)	60
MI and surgical procedure	10
MI and non-surgical procedure	7
Heart failure	10
Hypertension	17
Arrhythmias	7
COPD	7
Diabetic (%)	7
High cholesterol (%)	47
Alcohol (%)	27
Smoking (%)	7
Family history (%)	
Heart attack death	33
Heart failure	17
CABG	7
Angina	13
No family history	30
Medications (%)	
β-Blockers	53
Statin	47
Aspirin	43
Nitrates	20
Other	33

SD, standard deviation; M, male; F, female; MI, myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; COPD, chronic obstructive pulmonary disease.

ISWT procedure

The modified version of the original ISWT was used in this study. This is analogous to the original incremental test [15] but has 15 levels instead of 12. This test is useful for monitoring patient groups who may be able to complete the original 12-level protocol.

Participants were required to walk, on a gymnasium floor, between two cones, set 0.5 m from either end of a 10-m course. An initial walking speed of 0.5 m/second was

indicated by an audible signal from a CD player. Walking speed increased by 0.13 m/second each minute. A change in speed was indicted by a second audible signal. Instructors also reminded participants to walk faster after each minute. Participants were allowed to run at any time during the test.

Heart rate was recorded at the beginning of the test, at the end of each level of the test, at the end of the test and 1 minute after the end of the test using short-range telemetry (Polar Electro Sports Tester S810I, Heart Rate Monitor, Kempele, Finland Omron Digital Automatic Blood Pressure Monitor MX3 Plus, Omron Health Care Co., Ltd, Kyoto, Japan). Heart rate recovery was calculated as the difference between maximal exercise heart rate and heart rate 1 minute after termination of the test. Total heart rate recovery time (time to a heart rate ± 10 beats/minute of resting heart rate) was also recorded. Resting blood pressure was measured using an automated arm blood pressure machine (Omron Digital Automatic Blood Pressure Monitor MX3 Plus, Omron Health Care Co., Ltd.) before each test. Post-exercise blood pressure was measured within 1 minute of termination of the test. Ratings of perceived exertion were measured using the Borg (6–20) scale [16].

The ISWT was terminated when the participant: (a) was unable to continue the test because of breathlessness, other symptoms or unwilling to continue (voluntary withdrawal); (b) failed to reach the marker (by 0.5 m) on time; (c) achieved 85% of predicted maximal heart rate: 210 − (0.65 × age); (d) reached a rate of perceived exertion of 15 or more [17]; or (e) completed all the levels.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences Version 16.0 (SPSS Inc., Chicago, IL, USA). Data are presented as means and standard deviations. Differences between the two ISWT test sessions were evaluated using the paired-samples *t*-test for waist circumference, BMI, systolic blood pressure and heart rate recovery, with a *P*-value of less than 0.05 taken to represent significance.

The intraclass correlation coefficient (ICC) is the most common metric of reliability. In this study, the ICC (3.1) [18] and the limits of agreement test (Bland and Altman method) [19] were used to assess the test–retest reliability of distance walked and maximum walking speed. ICC values greater than 0.7 were taken to indicate good test–retest reliability [20].

Results

The mean age of participants was 67 ± 8 years. Most participants (60%) were elective post-revascularisation patients (coronary artery bypass graft or percutaneous transluminal coronary angioplasty), 17% were post-myocardial-infarction patients, and the other patients had stable angina or heart failure. Fifty-three percent of patients were β-blocked, but none of the participants changed their medication from pre-test to post-test (Table 1). Paired-samples *t*-tests showed that body mass remained unchanged from pre-test to post-test ($P = 0.442$), but waist circumference decreased significantly ($P < 0.05$). Both pre-exercise systolic blood pressure and total heart rate recovery time decreased significantly ($P < 0.05$) from pre-test to post-test (Table 2).

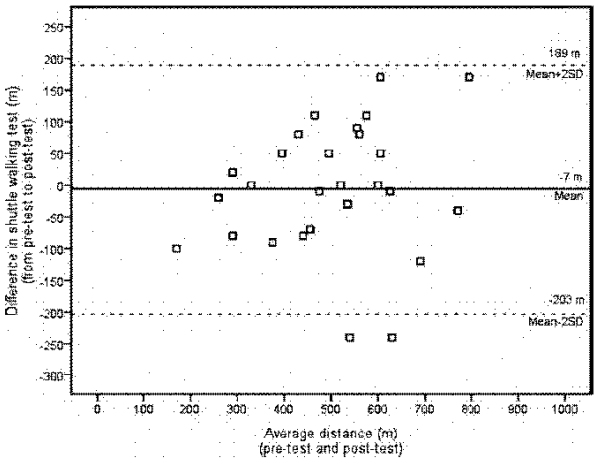

Fig. 1. Limits of agreement plot (Bland and Altman plot). Intraindividual differences between performances on two modified shuttle walking tests (from pre- to post-test) plotted against intraindividual average distance scores of the two tests (pre- and post-test). The central line represents the mean of the intraindividual differences, and the flanking lines represent the 95% limits of agreement. Six participants changed their performance by less than one shuttle (10 m) between the pre- and post-test.

The distance walked during the ISWT ranged from 120 to 880 m; no patients completed the protocol. There was no significant change in the mean distance from pre-test (502 ± 161 m) to post-test (509 ± 146 m). The ICC for distance covered was 0.80 [95% confidence interval (CI) 0.62 to 0.90]. The ISWT showed a mean test–retest bias of −7 m with limits of agreement from −203 m to 189 m. This indicates that in a retest situation, 95% of patients exposed to this protocol would be expected to walk distances ranging from 203 m less to 189 m more than their baseline score (Fig. 1).

The maximum walking speed during the ISWT ranged from 1.18 m/second to 2.20 m/second. There was no significant difference in maximum walking speed between pre-test (1.65 ± 0.29 m/second) and post-test (1.70 ± 0.25 m/second). The ICC for maximum walking speed was 0.76 (95% CI 0.55 to 0.88). There was a mean test–retest bias of −0.05 m/second with limits of agreement from −0.43 m/second to 0.33 m/second.

Discussion

Functional capacity patterns of CVD patients are usually established by the end of hospital outpatient (phase III) cardiac rehabilitation, and remain stable during community-

Table 2
Physiological responses and physical characteristics at the two assessments (Test 1 and Test 2) ($n = 30$).

	Test 1 Mean (SD)	Test 2 Mean (SD)	Mean difference (95% CI)	*P*-value
Mass (kg)	77.8 (12.7)	77.5 (12.6)	0.25 (−0.86 to 0.67)	0.442
Waist circumference (cm)	96.1 (11.6)	95.4 (11.2)	0.77 (−3.67 to −0.20)	0.025
Body mass index (kg/m^2)	27.30 (3.71)	27.33 (3.80)	−0.03 (−0.34 to 0.27)	0.823
Heart rate recovery (beats/minute)	36 (17)	34 (17)	2 (−5.08 to 9.43)	0.544
Time to recovery (minutes)	6.12 (4.17)	4.88 (4.31)	1.24 (0.36 to 2.12)	0.007
Pre-exercise SBP (mm/Hg)	143 (19)	136 (22)	7 (0.92 to 12.25)	0.024
Pre-exercise DBP (mm/Hg)	79 (8)	78 (10)	1 (−2.26 to 4.13)	0.555
Post-exercise SBP (mm/Hg)	180 (30)	169 (29)	11 (4.51 to 16.66)	0.001
Post-exercise DBP (mm/Hg)	83 (14)	81 (13)	1 (−2.12 to 4.32)	0.488
Distance walked (m)	502 (161)	509 (146)	−7 (−44 to 29)	0.685
Maximum walking speed (m/second)	1.65 (0.29)	1.70 (0.25)	−0.05 (−0.12 to 0.03)	0.199

CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

based phase IV cardiac rehabilitation [8]. Assessment of functional capacity in CVD patients is important for assessing the effectiveness of exercise interventions and in exercise prescription. The ISWT is an affordable alternative to treadmill testing, but its reliability has only been tested over short test–retest durations.

Phase IV cardiac rehabilitation offers a potential environment in which the long-term test–retest reliability of ISWT can be assessed, as this phase of rehabilitation is designed to maintain functional capacity [8]. Due to the nature of the programme, it is unlikely that significant, systematic gains in functional capacity will occur in groups of patients. However, the functional capacity of individual patients is likely to vary due to many factors such as illness, motivation and changes in other exercise training they may undertake. The test–retest reliability of any measurement is challenged by both systematic bias (e.g. practice effects) and random error (e.g. measurement error and biological variation). Walking speed seems the obvious measure by which to evaluate functional capacity, and has been used to describe ISWT performance. As previous ISWT reliability studies have only reported distance walked [9,12,13], this metric will be used to discuss test–retest reliability in the present study for purposes of comparability.

The mean distance walked was 502 ± 161 m in the pre-test and 509 ± 146 m in the post-test. The mean ISWT distance of 505 m is comparable with other studies in CVD patients [9–11,21]. However, the present study is the first to assess long-term (>10 weeks) attendees of phase IV cardiac rehabilitation. This was necessary for the study design to access clinically stable patients in a maintenance phase of exercise training, unlikely to show significant gains in functional capacity.

The ICCs for distance walked (0.80) and maximum walking speed (0.76) are both in excess of the critical value (0.70) deemed to show test–retest reliability [9]. The ICC is a dimensionless coefficient and is prone to inflation if there is a wide range of mean scores, as in the present study. Therefore, although the ICC suggested that the ISWT was reliable, the data were also analysed using the limits of agreement test (Bland and Altman method). The limits of agreement were calculated to provide an estimate of both systematic and random variation in test performance, and to provide values for test–retest changes in distance for use by clinicians and researchers.

The systematic bias from test to retest was low (−7 m), indicating that there was no learning effect between pre-test and post-test. These data are in agreement with those of Arnott *et al.* [22], and refute the findings of studies that have suggested the need for a practice test to obtain reliable ISWT results [8,13,15]. What must be borne in mind, however, is that all previous studies have used short (day-to-day) or very short (within-day) test–retest protocols. Patients retested over such short periods will remember previous test scores and may set goals to beat previous scores. In the present study, no learning effect was seen for the 8-week test–retest interval. Several participants required the test protocol to be explained 'as new' during the retest, and it seemed difficult for them to recall their performance measures over the 8-week interval.

For test–retest reliability to be deemed satisfactory, the limits of agreement should be smaller than the minimum expected difference in performance which the test will be used to detect. From previous studies [9–11], it was determined that a 100-m improvement in performance could be expected over an outpatient cardiac rehabilitation programme lasting 6 to 8 weeks.

The large limits of agreement values (−203 to 189 m) are greater than values from previous test–retest studies that have not used practice walks [8,23], and are well in excess of the 100-m critical value. These data suggest, in the population studied here at least, that the ISWT contains too much random variation in test performance to successfully monitor changes in functional capacity.

The low test–retest reliability is most likely due to assessing the long-term test–retest reliability as opposed to day-to-day variation in performance as in previous studies [9,12,13]. The wide limits of agreement show that individuals' test performances varied considerably from pre-test to post-test. Despite no mean group change (systematic bias), the performance of some patients greatly improved

while others clearly declined. The long test–retest duration undoubtedly allowed greater physiological and psychological variation in the participants. Between the tests, some participants attended cardiac rehabilitation sessions more regularly than others. Clients missed sessions due to illness, musculoskeletal problems, holidays or, in one case, a minor operation. Just as it is conceivable that such factors may have a negative influence on test performance, it is equally conceivable that some of the individuals may have increased their training volume between pre-test and post-test, leading to a large improvement in performance. Such individual variations in behaviours which may affect test performance are a limitation of the current study.

The lack of a practice test could also be perceived as a weakness of this study, but the authors consider that this actually increased its generalisability. There is good evidence for a short-term learning effect on the ISWT, indicating that a practice walk is preferable. In the clinical setting, it is unlikely that time or money would be available for a practice walk prior to a patient's pre-rehabilitation assessment. Certainly, studies which have used the ISWT to monitor changes in functional capacity during cardiac rehabilitation have not used a practice walk [8–10].

Despite the lack of a practice walk, there was no systematic variation from test to retest in terms of a learning effect or homoscedasticity. The limits of agreement plot (Fig. 1) shows that the performance of six participants changed by less than one shuttle (10 m) between the two assessments, while the performance of other participants declined by over 200 m. It is beyond the scope of this paper to identify changes in individuals which may have been associated with such changes in performance, but it seems that the two participants outlined above may be outliers. In accordance with Bland and Altman's [19] instructions, these two outliers were excluded and the analysis repeated. The repeatability coefficient was still large at ±146 m.

Changes in resting blood pressure and total time to heart rate recovery were also found in some but not all patients between test and retest, indicating that the notion of a clinically stable patient may be a misnomer. However, the small systematic bias (−7 m) in the group's ISWT score shows that the group of patients seem to be clinically stable. The fact that no psychological measures were collected prior to either test might have had an impact on performance.

In conclusion, the ISWT showed no systematic bias (learning effect) over an 8-week period; therefore, a practice walk is not required to assess long-term changes in functional capacity. This finding is in contrast with data regarding within-day test–retest reliability of shuttle walking [9,13]. In stable CVD patients attending community-based, phase IV rehabilitation, however, the random variation in distance walked and maximum walking speed achieved on the ISWT may be large. Biological variation such as changes in symptoms, frequency of exercise training and motivation may all play a part in creating this large random variation in performance in clinically stable CVD patients.

Further studies to elucidate further physiological and potential psychological factors which may predispose such patients to large variations in performance are warranted.

Ethical approval: University of Essex Ethics Committee (Ref. No. 2007/0132).

Sources of funding: This work was supported by the University of Essex Cardiac Rehabilitation Bursary Scheme.

Conflict of interest: None declared.

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Appendix C2. Biomechanical predictors of the shuttle walking test performance in patients with cardiovascular disease (peer-review)

Original article

Title: Biomechanical predictors of the shuttle walking test performance in patients with cardiovascular disease.

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Funding: No funding received for this work.

Conflict of Interest Statement: None declared

TEXT

ABSTRACT

Background & Purpose: Distance walked on shuttle walking test (SWT) is used clinically to estimate cardiorespiratory capacity. The purpose of this study was to evaluate the associations between anthropometric and gait parameters with distance walked during an incremental SWT.

Methods: Sixteen (9 males and 7 females) clinically stable cardiac patients performed the SWT on two occasions. Anthropometric data (mass, stature, body mass index, waist circumference, leg length) and gait characteristics (step length, turning gait) were collected. Linear regression analyses were used to identify the predictors of test performance (m).

Results: Distance walked correlated most strongly with step length (trial 1 and 2: r = 0.83, $p<0.05$) and stature (trial 1: r=0.74, trial 2: r=0.69; $p<0.05$) in both trials. Stepwise regression revealed step length as the best independent predictor. Given the rarity of step length assessment in clinical practice, the next most powerful predictor of performance, stature, was entered in a subsequent model which explained 55 per cent of the variance in test performance.

Conclusions: Taller patients perform better on the SWT than shorter patients with similar clinical characteristics. The regression equation generated here could potentially be used to predict an individual's performance and remove some of the bias toward taller patients.

Keywords: Incremental shuttle walking test; cardiovascular disease; predictors

INTRODUCTION

Functional walking tests are used to evaluate functional capacity in patients with lung disease,[1] heart failure[2] and ischaemic cardiovascular disease (CVD).[3] The functional outcome of these

tests can provide important information regarding patient's functional capacity, effectiveness of different rehabilitation treatments[4] and individual's prognostic expectations.[5]

There are two broad categories of test, those that are self-paced, such as the six-minute walk test[6] and those that are externally-paced protocols, such as the incremental SWT.[1] These field tests are reliable, inexpensive, easy to administer and use measures of distance walked to estimate functional capacity.[7-9] Patients often find walking tests preferable to the unfamiliarity of treadmill walking.[10] However, these shuttle-based protocols require patients to turn at regular intervals, making the test more difficult than treadmill walking[11] and creating different biomechanical demands compared to straight gait.[12]

People with high number of chronic complications (respiratory diseases, diabetes, chronic heart failure, coronary heart disease) commonly have lower mobility than those with low number of chronic events due to poorer functional locomotion system performance.[13] The more biomechanically inefficient a person is, the more difficult it will be for them to undertake such a test, like the SWT, which involves many turns.[14]

There are associations between anthropometric variables and walking test performance in healthy adults,[15-21] but there are no published reports concerning gait influences on test performance in clinical population. Only one study has evaluated anthropometric associations in a clinical population.[22] All these studies concern the six-minute walk test and no comparable data exist for the incremental SWT. Studies have also been limited to collecting simple anthropometric data and have not evaluated the potential associations between gait parameters and walking test performance.

Stature and thus leg length are likely to influence SWT performance and the ability to increase walking speed.[23] The aim of this study was to assess the associations between anthropometric measures, gait parameters and performance on the incremental SWT in clinically stable CVD

patients. Since walking speed is progressively increased during the SWT it was hypothesised that this will bias the taller patient toward an improved shuttle score, regardless of morbidity. Furthermore, we tested the hypothesis that gait and anthropometric parameters can predict SWT performance in this population.

METHODS

Participants

Sixteen clinical stable (clinically asymptomatic) CVD patients (9 males and 7 females; age 55-80 years), who were members of a community-based follow-up cardiac rehabilitation programme,[24] voluntarily participated in this study with informed consent. Prior to the study all procedures were approved by the appropriate ethical committee and conformed to the declaration of Helsinki guidelines for research with human subjects.[25]

All patients had been enrolled on a long-term maintenance, cardiac rehabilitation programme for a minimum of ten weeks. The programme comprises twice-weekly, 60-minute circuit-based exercise sessions, and is designed to maintain functional capacity gains achieved in outpatient cardiac rehabilitation (phase II, US classification).[24]

All the patients were free of severe locomotor limitations and completed the study protocol twice, a minimum of eight weeks apart. Before initial testing, a primary health assessment (pre-exercise health questionnaire, medical, pharmacological, family history) and anthropometric measurements including stature, body mass, waist circumference and leg length[26] were made.

Body mass index was calculated ($kg \cdot m^{-2}$). Table 1 summarises the patients' clinical characteristics and baseline measurements.

Procedure and data collection

Shuttle walking test procedure

Patients performed an incremental SWT[1] by walking back and forth on a corridor marked by two cones set 0.5 m from either end of a 10 m course. Initial walking speed was 0.5 $m \cdot s^{-1}$ and increased by 0.13 $m \cdot s^{-1}$ each minute, indicated by an audible signal. During the test, heart rate was recorded with a Polar heart rate monitor (Polar Electro Sports Tester S810I, Heart Rate Monitor, Kempele, Finland) and Ratings of Perceived Exertion (RPE) were measured using the Borg (6-20) scale.[27]

The SWT was terminated either when the patient (a) felt too breathless or fatigued to continue at the required speed, (b) failed to complete the shuttle within the allowed time, (c) reached 85% of the predicted maximal heart rate: 210- (0.65×age), (d) reached RPE ≥ 15 [20], or (e) completed all the levels.

Gait data

Each turn made at the end of the 10 m walkway was recorded with a a Sony CCD-TRV20E video camera and analyzed on SiliconCoach Pro software (version 6.1.5.0). From the video data the turning style (i.e., step turn or spin turn),[28] the turning time, and the number of steps needed to complete the turn were collected. Turning time and number of steps used in turning were recorded one step before turning, from either foot heel strike, until the end of the turn. End of the turn was defined as the first heel strike with the pelvis and thorax facing the opposite cone.

During the test, the number of steps taken in every shuttle was recorded. Step length was estimated by dividing the length of the course (nine meters – straight portion of the course) by the number of steps in each shuttle, and then normalized to leg length (step length/leg length).[26]

Statistical analysis

The independent variables were divided into two categories: static variables (age, stature, leg length) and dynamic variables (step length, step length normalized to leg length, number of steps to turn, turning time, turning style). The dynamic variables were analyzed during the 1/3rd, 2/3rd, penultimate and final levels of the test. Statistical analysis was implemented with SPSS (SPSS inc., Chicago, IL, US). Data were presented as means and standard deviation. The median value of stature was calculated. Differences between the two SWTs were evaluated by using paired-samples t-test. Pearson's correlation coefficients and stepwise linear regression analysis were used for the two tests (trial 1 and trial 2).

Two stepwise models were used: model one contained all the independent variables which correlated ($r>0.3$) with performance (regression analyses were performed separately for each of the trials). To build a clinically useful equation we built a second regression model containing only variables which were both; strongly correlated with performance, and routinely recorded in cardiac rehabilitation. Colinearity diagnostics were performed for all predictor variables.[29] The lower limit of normal (LLN) in SWT performance has been determined by using the lower 5th percentile of a normal distribution.[30]

RESULTS

Shuttle walking distance ranged from 210 to 750 m. There was no significant difference in mean performance between trial 1 (479 ± 139 m) to trial 2 (499 ± 138 m), t=-1.8, p=0.092. Shuttle walking test performances (m) were normally distributed in both trials. The static measurements: stature and leg length and the dynamic measurements: step length and number of steps to turn, showed significant correlation with performance, in both test trials (Table 2).

Stepwise regression analysis indicated that step length at the 2/3rd of maximal test performance was the best predictive measure for performance, followed by stature, in both tests. These models explained 68.3% (SE = 74 m) and 68.2% (SE = 85 m) of the variation of performance for trial 1 and trial 2, respectively.

As step length is a dynamic measure and probably not practical in routine clinical assessment. The variable next most highly correlated with performance in regression analysis was stature. Regression analysis was repeated using only stature to predict performance; data from trial 1 were used (equation 1). This model explained 55% of the variation in performance. The 5th percentile of SWT performance distribution of trial 1 was 200 m, so the lower limit of normal range (LLN) was computed by subtracting 200 m (equation 2).

$$\text{SWT (m)} = (10.7 \times \text{stature}_{cm}) - 1316 \quad (1)$$

$$\text{SWT (LLN) (m)} = (10.7 \times \text{stature}_{cm}) - 1116 \quad (2)$$

The accuracy of the prediction equation was assessed by predicting performance in trial 2. Actual distance walked in trial 2 was highly significant with predicted distance when stature was entered into the equation model (Pearson's r=0.69, p=0.003).

DISCUSSION

When assessing functional capacity with a standardized walking test in elderly clinical populations, non-clinical factors which may potential affect performance need to be considered in advance. This is the first prospective study to examine the effect of anthropometric and gait parameters on SWT in CVD patients.

Gait and anthropometric predictors of performance

Despite measuring a number of walking and turning gait parameters, we found only one gait parameter and two anthropometric measures which predicted SWT performance. Step length at 66% of individual maximal walking speed, stature and leg length were all independently associated with distance walked.

Taller patients had longer step length and appeared better able to cope with the increases in walking speed needed at the later stages of the test. Shorter patients were less able to increase walking speed by increasing step length during latter test stages, resulted in poorer test performance. This can be theoretically illustrated by calculating the Froude number for the shuttle tests based on the ±1SD of the mean leg length. The Froude number (v^2/gl; where v is velocity, g is gravitational acceleration and l is leg length) provides a dimensionless number which normalises walking speed to leg length. By calculating this number based on leg length we can see that tall patients walked at a lower Froude number as the shuttle speed (level) increased compared to short patients. Thus the taller patients were walking at a relatively lower velocity than short patients, and the walk to run transition speed (0.5 Froude)[31] occurred approximately one shuttle level later. This model can also be used to predict maximal walking speed and again shows a bias toward the taller patient. Therefore taller patients, who could continue to increase step length at later stages of the test, appear more able to obtain better scores in the test.

As the SWT is incremental in nature, walking speed is always positively associated with distance walked[1]. Characteristics such as long step length and greater stature, which are associated with greater maximal walking speed[32] are also likely to result in better test performance. Walking speed is a combination of step length and cadence, an increase in one or both results in an increase in speed. It is possible that the shorter patients would increase their cadence at higher

shuttles in order to complete the shuttle. Increases in cadence are limited in the elderly[32], patients will therefore need to increase step length to achieve higher walking speeds. This gives taller patients, a natural advantage in walking tests. A study in which cadence and step length are monitored during SWT would be needed to test this hypothesis.

The regression analysis showed that the step length recorded at 66% of maximal walking speed was the best predictive measure of performance. Step length is, however, a dynamic measure and changeable especially amongst the elderly,[33,34] while the clinicians need practical measurement procedures for regular use in clinical assessment. Stature was the next best predictor of performance. We chose, therefore, to use this in preference to step length, due to its simplicity and its existing high clinical utility (it is routinely collected for the calculation of body mass index as a CVD risk factor). Such a choice is consistent with previous studies, which used only static variables (stature, age and weight or body mass index alternatively) in their equation for prediction of six-minute walk test performance in healthy adults.[15-21]

The prediction equation generated here has three consequences. First, taller cardiac patients have an advantage over shorter patients and generally perform better in SWT. This is agreement with reference models already constructed for six-minute walk test in healthy populations.[15-21] The six-minute walk test is commonly used in chronic heart failure patients, while the SWT is recommended for the assessment of stable CVD patients.[1,6] Second, it is suggested that male CVD patients, can walk on average 160 metres further (i.e., 16 shuttles) in the SWT than women, due to stature differences between the two sexes (Table 1). Third, due to regression towards to the mean[35] CVD patients who are high performers >610 m (75th percentile of SWT performance, normal distribution) are likely to improve only marginally, whereas low performers <370 m (25th percentile) might improve to a much greater degree. Our results and the problem of regression to the mean imply that although tall >176 cm (i.e., 75th percentile of stature, normal

distribution) CVD patients are likely to attain higher initial SWT scores than shorter patients, short patients <162 cm (25th percentile) are expected to record more improvement in a re-assessment with SWT after a particular intervention (i.e., CR), in contrast with tall patients.

Approximately 45% of the variation in SWT performance remains unexplained. This figure is within the range of the unexplained variance in predicted 6-MWT in non-clinical populations (34-80%).[15-21] To our knowledge, no previous studies of either the 6-MWT or the incremental SWT have analysed spatial/temporal gait parameters. By performing this analysis we have demonstrated that it is useful to consider anthropometric but not gait parameters when interpreting SWT performance.

Effect of turning on walking test performance

Turning negatively affects walking test performance in housebound elderly patients compared with those with no limitations to their daily activity.[32] Despite the relatively high frequency and number of turns needed during the test, none of the turning variables we measured were associated with SWT performance. Of note, the present sample comprised CVD patients who regularly exercised and as such, were largely free from limitations to daily activities. Turning may be more important in less-able patients with greater orthopaedic limitations.

Study limitations

The application of the above suggestions might be limited by some methodological issues. The sample used was relatively small and may lack the statistical power to identify statistically significant relationships between more weakly associated pairs of variables. A larger sample would allow the generation of generalizable normative data to confirm the present findings. Future research should also independently validate the present equation.

Furthermore, the patients were all members of a long-term follow-up training cardiac rehabilitation programme and are accustomed to exercising. Less conditioned patients, such as those entering earlier phases of rehabilitation may show different associations between gait predictors and test performance. This is a potential avenue for further research.

CONCLUSIONS

The findings of the present study are important with regard to clinical practice in cardiac rehabilitation. These data show that tall patients have an advantage in the SWT and that practitioners should account for stature when interpreting distance walked. By interpreting distance as a percentage of the stature-predicted value, practitioners would gain a more meaningful assessment of individual patient's functional capacity compared with distance alone. This may lead to better risk stratification and more accurate exercise prescription when based on SWT performance.

These pilot data are the first to provide specific regression equations to estimate SWT performance, and there is a clear need for a larger study to independently validate the present findings. This study has, however, potentially eliminated the need to further investigate certain gait parameters which are time consuming and expensive. This small study may allow for a larger, more economical study to be conducted using the simple anthropometric predictors of performance identified here.

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Table 1. Descriptive characteristics and baseline measurements of patients

Clinical characteristics & baseline measurements	**Values †**
Number of patients	16
Age (years)	69 (9)
Sex (%)	Males: 56, Females: 44
Stature (cm)	167 (10) ; Males: 174, Females: 159
Median value (25^{th} percentile)	162
Median value (75^{th} percentile)	176
Body mass index ($kg \cdot m^{-2}$)	29.3 (3.7)
Leg Length (cm)	88 (8)
Medical History/Reason for joining CR (%)	
Myocardial Infarction	13
Stable Angina	31
Surgical procedure (CABG, PTCA)	69
Heart Failure	13
Arrhythmias	13

Abbreviations: CR, cardiac rehabilitation; CABG, coronary artery bypass graft; PTCA, Percutaneous transluminal coronary angioplasty*;* HR, heart rate

† Values are givens as means and standard deviations are in parentheses.

Table 2. Correlations between gait and anthropometric parameters and shuttle walking distance in the two trials

Level	Variables	Trial 1			Trial 2		
		N	Pearson r	P value	N	Pearson r	P value
	SWD - Stature	16	0.741	0.001	16	0.688	0.003
	SWD - Leg length	16	0.808	<0.001	16	0.762	0.001
1/3rd of total test	SWD - Step length	15	0.826	<0.001	16	0.563	0.023
2/3rd of total test	SWD - No. of steps to turn	9	NS †	NS †	16	-0.587	0.017
	SWD - Step length	15	0.826	<0.001	16	0.826	<0.001
	SWD - Step length normalized	15	0.593	0.02	16	0.523	0.038
Penultimate level	SWD - Step length	16	0.724	0.002	16	0.813	<0.001
	SWD - Step length normalized	16	0.512	0.042	16	0.574	0.020
Maximal level	SWD - Step length	16	0.651	0.006	16	0.765	0.001
	SWD- Step length normalized	16	0.471	NS †	16	0.535	0.033

Abbreviations: SWD, distance walked in shuttle walking test; NS, non-significant.

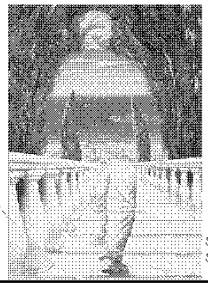
APPENDIX D. ORAL PRESENTATIONS

Appendix D1. 8th Annual Graduate Forum (2009), University of Essex, Colchester, United Kingdom

University of Essex

Centre for Sports & Exercise Science

BIOMECHANICAL PREDICTORS of the MODIFIED SHUTTLE WALKING TEST PERFORMANCE in patients with CARDIOVASCULAR DISORDERS



Student: Garyfallia Pepera
Supervisor: Dr. Gavin Sandercock

Shuttle Walking Test (SWT)

The shuttle walking test (SWT) is the most commonly used functional capacity test in UK CVD patients

- Initially: developed by *Singh et al. (1992)*
  12 level version incremental SWT
- Later: upgraded to the Modified SWT (MSWT)
  15 level version incremental SWT

Modified Shuttle Walking Test (MSWT)

Uses

- Measure cardiorespiratory capacity of CVD patients
- Determine prognosis
- Show the reaction of new CR treatments

Benefits

- **Safe** (Incremental)
- Reliable and valid
- Easy to perform & inexpensive

MSWT & Biomechanical Predictors

Gait parameters -turn every 10 m-

Anthropometric characteristics (stature, leg length)

Additional effort for balance and posture stability

may affect gait

INFLUENCE TEST RESULTS (?)

Aims of this study

- Evaluation of the influence of biomechanical (gait & anthropometric) parameters on MSWT performance in CVD patients.
- Build a preliminary reference equation which may predict individual MSWT performance

Participants

- 16 (9males and 7 females) cardiac patients
- Mean age: 69 ± 9 yrs
- Phase IV CR members, the 'Phoenix Club', University of Essex
- Medical History/Reason for joining CR
  - Surgical procedure (CABG, PTCA): 69%
  - Stable Angina: 31%
  - MI: 13%
  - Heart Failure: 13%
  - Arrhythmias: 13%
- Medication: β-blockers 63%

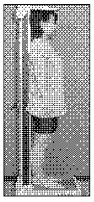
Background | Methods | Results | Discussion | Conclusion

Protocol

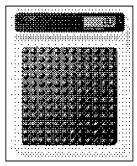
- Anthropometry
- Balance test
- Modified shuttle walking test (MSWT)

Background | Methods | Results | Discussion | Conclusion

Stature

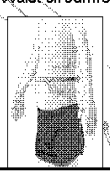


Body mass

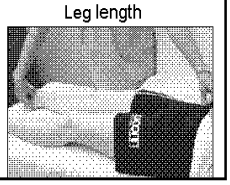


Anthropometry

Waist circumference



Leg length



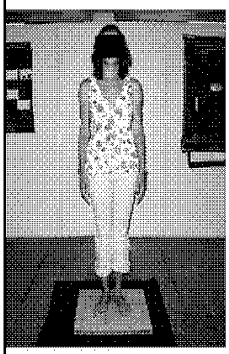
Background | Methods | Results | Discussion | Conclusion

Protocol

- Anthropometry
- Balance test
- Modified shuttle walking test (MSWT)

Background | Methods | Results | Discussion | Conclusion

Balance Test



Position of the body during the test.

- assess stability status
- Kistler force plate
- assessment with eyes opened and closed
- Data were collected for 30 seconds

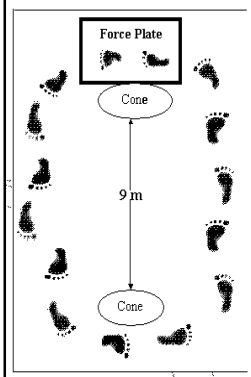
Background | Methods | Results | Discussion | Conclusion

Protocol

- Anthropometry
- Balance test
- Modified shuttle walking test (MSWT)

Background | Methods | Results | Discussion | Conclusion

MSWT procedure

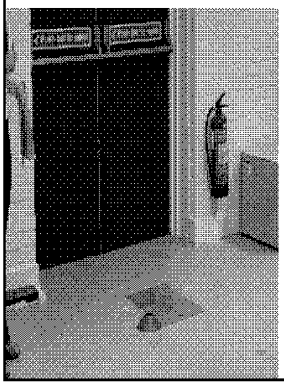


MSWT was performed twice
(8 weeks between assessments)

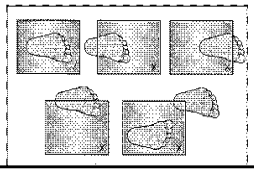
Test termination criteria:

✓voluntary withdrawal
✓ by the operator
✓ achievement:
a. *85%×HRmax=210-(0.65×age)*
b. *Perceived Exertion (RPE)* ≥ *15*
✓ all levels completed

Turning: Force Plate Data



- Gait and ground reaction force data were collected during MSWT
- Data collection (i.e. turning style, turning time, number of steps needed to turn) through video recordings and force plate measurements



Variables used

Stated variables	Dynamic variables	Dynamic variables calculated
✓ Age	✓ Step length	✓ Step length normalized to leg length
✓ Stature	✓ Balance	
✓ Leg Length	✓ Breaking force (Fy)	
	✓ Vertical impulse (Iz)	
	✓ Number of steps needed to turn	
	✓ Turning time	
	✓ Turning style	

Statistical Analysis

- Pearson's product-moment correlation coefficients to assess the biomechanical correlates of test performance.
- Stepwise linear regression analysis to identify the predictors of test performance (m).

MSWT Performance scores

- Mean distance walked$_{MSWT1}$= 479 m
- Mean distance walked$_{MSWT2}$=499 m
- No significant difference between MSWT1 and MSWT2 (P= 0.092)

Predictors of test performance (*distance walked*)

Static measures:
Stature & leg length

Dynamic measures:
Step length & step length normalized to leg length

Correlated *significantly with MSWT performance at all stages of the two tests* (*r*>0.60, *P*<0.05)

Validating predictors of MSWT performance with regression analysis

Although:

- "Step length" was the best predictive measure (followed by stature)
- step length is dynamic measure

not easy to use it in clinical practice assessment

Thus:

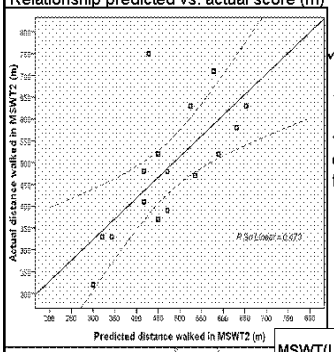
- Regression analysis was repeated by using only "stature" as independent variable
- The MSWT1 was used for the final regression analysis

Equation form for predicting MSWT performance:
MSWT = -1316 + (1070 × stature), m

Background | Methods | Results | Discussion | Conclusion

Stature as biomechanical predictor of MSWT performance

Relationship predicted vs. actual score (m)



✓ Highly significant *(CI=0.79, P=0.002)*

✓ Model explained 47% of variation

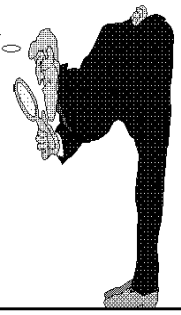
✓ Predicted MSWT score can be computed by using the equation form.

✓ Lower limit of normal range (LLN) can be computed by subtracting 99m.

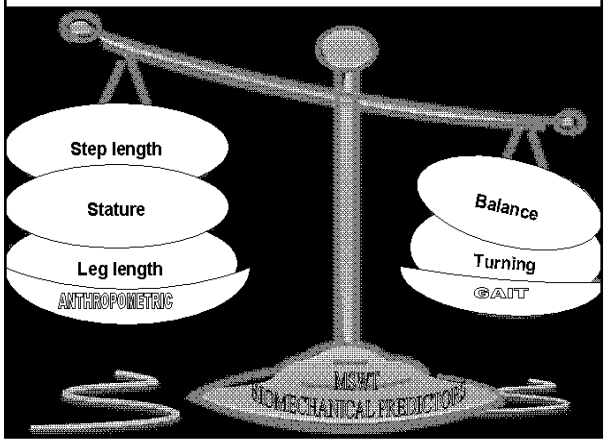
MSWT(LLN) = -1316 +(1070 × stature) - 99, m

Background | Methods | Results | Discussion | Conclusion

Finally..
Biomechanical (gait & anthropometric) parameters influence MSWT performance (?)



Background | Methods | Results | Discussion | Conclusion



Background | Methods | Results | Discussion | Conclusion

Taller patients had greater MSWT performance score than shorter ones.

..in agreement with results for 6MWT in healthy adults (Enright & Sherrill 1998)

Prediction equation suggests that male CVD patients would walk on average 160.5 metres (i.e. 16-17 shuttles more) more than women in MSWT

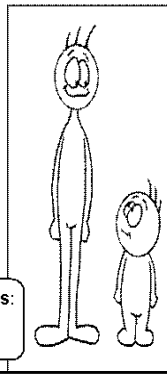
Our equation model explained 47% of the variation in MSWT, 53% unexplained.

..similar Enright & Sherrill (1998) found 60% of the variance unexplained in 6MWT by their suggested model

Background | Methods | Results | Discussion | Conclusion

Key points

- Stature: biomechanical predictor of MSWT
- Taller vs. shorter CVD patients expected better MSWT performance
- The reference equation might be used to:
  - reduce some of the bias toward taller patients
  - predict individual's MSWT performance (m)
  - predict individual's CVD prognosis



Reference equation for MSWT distance in CVD adults:
MSWT = -1316 + (1070 × stature), m
Subtract 99m for the LLN

Background | Methods | Results | Discussion | Conclusion

Further research

Next step:

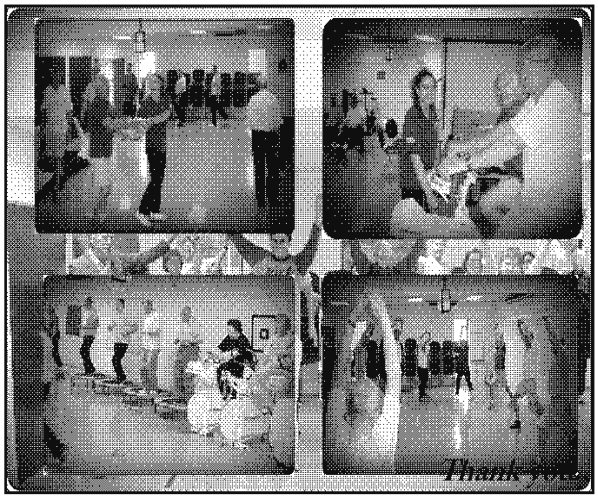
Continue the study with larger patients groups

This pilot, as it was the first one which examines the biomechanical predictors on MSWT in stable CVD population, provides a step closer to use the MSWT as a prognostic tool in this population.

Acknowledgements

People contributed on this study:

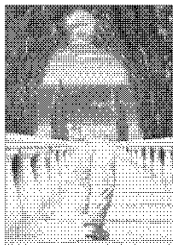
- Dr. Gavin Sandercock
- Dr. Matthew Taylor
- Argiris Peristeropoulos
- Joanne McAllister
- Peter Benson



Appendix D2. 5th International Meeting of the Onassis Cardiac Surgery Center (2010), Athens, Greece.

University of Essex

Simple determinants of six-minute walk test performance in heart failure patients



Garyfallia Pepera [1], Lee Ingle [2], Gavin Sandercock [1]

[1] Department of Biological Sciences, University of Essex, UK

[2] Carnegie Faculty of Sport and Education, Leeds Metropolitan University, UK

Background | Methods | Results | Discussion | Conclusion

Six minute walk test (6MWT)

Role

- Assess cardiorespiratory capacity
- Determine prognosis
- Show effectiveness of a therapeutic intervention

6MWT *vs* traditional treadmill test

- Easy to administer & perform
- Inexpensive
- Safe (self-paced)
- Distance walked (6MWD): understandable measure

Background | Methods | Results | Discussion | Conclusion

6MWD<300 m: Prognostic marker of mortality in HF [1]

Determinants in healthy adults: anthropometric variables [2]

Determinants of poor performance (?)

Ingle *et al.* (2006) identified clinical predictors of 6MWT in HF

clinical populations ?

clinical predictors require specialist equipment

exercise prescription & some clinical decisions rest on patient's 6MWT performance

influence 6MWT performance

Anthropometric, gait & simple clinical (?)

1. Bittner *et al.* 1993; Rostagno *et al.* 2003

2. Enright *et al.* 1998; Gibbons *et al.* 2001; Camarri *et al.* 2008; Chetta *et al.* 2006; Poh *et al.* 2006; Jenkins *et al.* 2009

Background | Methods | Results | Discussion | Conclusion

Aims

- Identify if routinely measures (clinical and non-clinical measures) could predict 6MWT performance in HF patients
- Establish a reference equation to predict 6MWT performance in HF population

Background | Methods | Results | Discussion | Conclusion

Participants

- 71 (82% males) HF patients
- Mean age: 76 ± 9 yrs
- Chronic disease assessment programme
- Medication: β-blockers 80%

Background | Methods | Results | Discussion | Conclusion

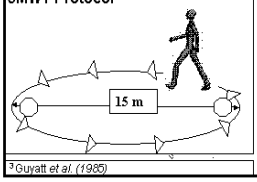
Protocol & measurements

- Anthropometry
  - stature
  - body mass
- Cardiovascular assessment
  - Clinical history
  - NYHA functional classification (I-IV)
  - Electrocardiography: resting HR, heart rhythm
  - Echocardiography: Left ventricular function
    LVEDD, LVESD, LVEF (LVEF ≤ 45%: left ventricular systolic dysfunction)
- Six-minute walking test (6-MWT)

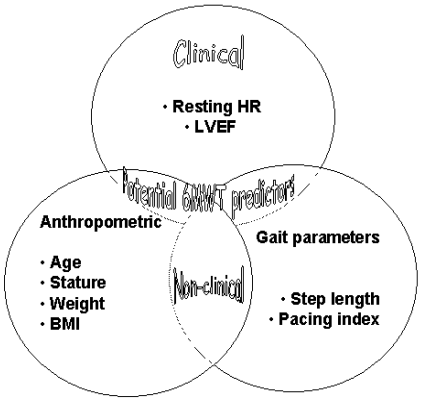
Gait Analysis & calculations

- Number of steps per shuttle
  - Step length: 15m / step number (from 60 m - 120 m).
- Time taken to walk per shuttle
  - average speed over each 60 m
    - Pacing index = (min speed / max speed) × 100

6MWT Protocol [3]

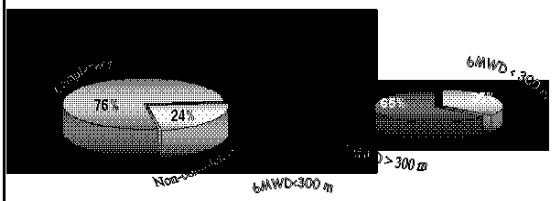


[3] Guyatt *et al. (1985)*

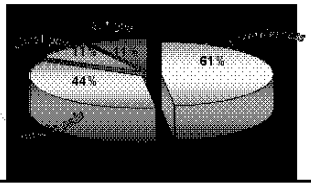


Statistical Analysis

- Pearson correlation, followed by stepwise multiple regression analysis to assess relationships between 6MWT performance and potential predictors
- Multinomial logistic regression to determine factors associated with poor performance (≤300 m) in 6MWT



Reasons for test termination



Correlations between 6MWT performance and independent variables

Independent Variables	Males (N=58)		Females (N=13)	
	Pearson r	*P* value	Pearson r	*P* value
Age	-0.376	0.004	-0.416	0.157
Stature	0.254	0.045	0.598	0.031
Weight	-0.122	0.362	0.366	0.218
BMI	-0.233	0.078	0.117	0.704
Step length	0.089	0.515	-0.247	0.464
Pacing index	0.193	0.199	-0.224	0.562
Resting HR	-0.050	0.737	-0.003	0.992
LVEF	0.019	0.904	0.055	0.888

Predictors of 6MWT performance
with
stepwise regression analysis

Anthropometric measures: age, stature, weight,

Equation forms for predicting 6MWT performance

males: 6MWD (m) = 142 + (3.1 × stature, cm) - (4.9 × age)

females: 6MWD (m) = 259 + (4.6 × stature, cm) - (6.6 × age) – (2.9 × weight, kg)

Background | Methods | Results | Discussion | Conclusion

Predictors of 6MWT performance with logistic regression analysis

Independent predictors of poor 6MWT performance (<300 m):

- high BMI > 25 kg·m^{-2} (OR = 12.7; 95 % CI: 1.45-111)
- age > 75 years (OR = 4.9; 95 % CI: 1.24-19)

Background | Methods | Results | Discussion | Conclusion

Predictors of absolute performance (linear model)

Prediction of meeting clinical cut-point (logistic model)

only Anthropometric variables

Males: age & stature 40% of the variance

Females: age, stature, weight 52% of the variance

Poor prognosis (6MWD<300 m)
- **Overweight** 13-fold increased
- **Old (>75 yrs):** 5-fold increased

75% of the variance

Logistic model stronger vs linear

Background | Methods | Results | Discussion | Conclusion

Highlights of this study

Cut off points: BMI > 25 kg·m^{-2}, age > 75 years

- Prognostic stratification of HF patients
- divide patients into different functional capacity expectations

The gender-specific models based on anthropometric variables can:

- predict individual's expected functional limitation
- realistic expectations

- 6MWT performance expressed as a percentage of predicted value (normalized performance)

- desired improvement after therapeutic intervention

Background | Methods | Results | Discussion | Conclusion

Case: HF patient, 75 yrs old male, 6MWD = 300 m

indicates

Tall>178 cm → severe reduction in functional capacity → Goal → ↑ exercise tolerance

Short<171 cm → 'well for age and stature' → Goal → maintenance of physical capacity

less intense, stressful, dangerous and expensive programme

Background | Methods | Results | Discussion | Conclusion

Key point:

The determinants of 6MWT depends on non-clinical, anthropometric factor

step length: positive predictor of SWT performance [4]

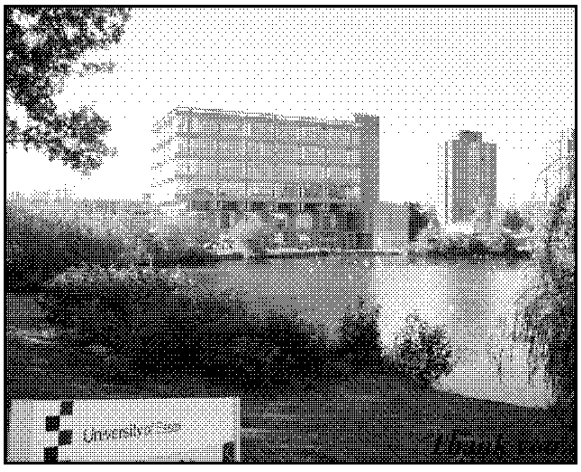
Useful feature of this study:

Eliminated a large number of gait and clinical parameters from 6MWT performance prediction.

Next step:

Revalidation of the results in bigger sample with a second set of simpler variables

[4] Pepera G., Peristeropoulos A., Taylor M, Sandercock G. (2010). Gait & Posture



APPENDIX E. POSTER PRESENTATIONS

Appendix E1. 7th Annual Graduate Forum (2008), University of Essex, Colchester, United Kingdom

University of Essex

Biological Sciences

Reliability of the Modified Shuttle Walk Test in Phase IV Cardiac Rehabilitation clients

Pepera Garyfallia, Sandercock Gavin

Department of Biological Sciences, University of Essex

Introduction

The British association for cardiac rehabilitation recommends the use of modified shuttle walk test (MSWT) to assess and monitor functional capacity in cardiac rehabilitation clients[3]. Although there is plenty of evidence that the MSWT is a valid, reliable, sensitive and useful tool for detecting cardiorespiratory fitness, the most of the scientific sources refers in short-term tested[1, 2]. Based on the above, the purpose of this study was to examine in a longer-term the reliability of the modified shuttle walk test in adults with cardiac disorders.

Methods

A convenience sample of 19 phase IV CR clients aged 55 to 80, participated in this study. Ethical approval was obtained from the Ethical Committee of the University of Essex. To determine reliability of SWT participants were assessed twice, with a minimum of 8 weeks between assessments. During this period, clients attended phase IV cardiac rehabilitation 1–2 times per week. Using the 15 level MSWT participants were required to walk up and down a 10-m course at increasing speeds, indicated by an audible signal.

At the end of each level, subjects were advised to go a little faster and they were allowed to run at any time.

Heart rate was monitored and recorded during the test and recorded at the end of each level (Polar Electro Sports Tester S810 I). Rating of Perceived Exertion (RPE) was used to determine perceived exercise intensity at the end of each level.

Test termination criteria were: breathlessness or other symptoms, voluntary withdrawal, failing to maintain pace, the achievement of the 85% of the predicted maximal heart rate, determined as :210-(0.65×age) or test completion.

Data were analyzed in SPSS 16.0. Reliability of SWT assessments was assessed by using intraclass correlation (ICC) and Cronbach's alpha. Pearson correlation and linear plots were used to evaluate the relationship between the variables of the 2 tests, while T-test examined the differences between them.

Results

Three variables were used to determine SWT reliability; Distance covered, Peak heart rate and RPE. There weren't any significant difference between the 2 assessments in any of the variables ($p<0.005$) (Table 1). However, there were significant relationships both between the distance walked (.79, $p<0.005$) and between the peak heart rate in the 2 tests ($r=.65$, $p<0.005$) (Table 3, Fig.1, Fig 2).

There was a decrease in the distance from the first test to the second from 514 m (S.D. 174) to 501m (S.D. 139), difference 13m. The peak heart increased from 130bpm (S.D. 17) in the first test to 132bpm (S.D. 13) in the second test. The mean Borg exertion score (RPE) (range 6-20) rose from 14.4 (S.D. 1.6) to 13.7 (S.D. 1.6.) from the first to the second assessment. Test-retest reliability in terms of the intraclass correlation coefficient (ICC) was high for the distance walked, moderate for the peak heart rate and low for the peak RPE value (table 2). Cronbach alpha was 0.87 for distance covered, 0.77 for peak heart rate and 0.19 for peak RPE (table 2).

Conclusions

It is concluded that modified shuttle walk test (MSWT):

- has moderate to good reliability for distance walked and peak heart rate in adults
- can be used as an endurance walking test for people with cardiac disorders
- may be used as an assessment tool in determining prognosis, evaluation, exercise prescription and show the react of new treatments in the area of cardiac rehabilitation.

Shuttle Walk Test: Comparison of the 2 trials (Test 1 vs Test 2)

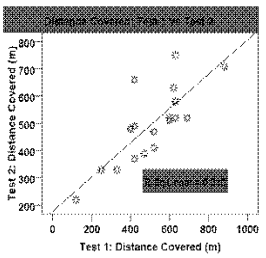
MEASURE OF EXERCISE PERFORMANCE (N=19)	TEST 1 Mean (SD)	TEST 2 Mean (SD)	MEAN DIFFERENCE 95%CI	T-test	Sig.(2-tailed)
Distance Completed (m)	514 (174)	501 (139)	13	0.54	0.6
Peak Heart Rate (bpm)	130 (17)	132 (13)	-2	-0.46	0.65
Peak Borg Rating of Perceived Exertion	14.4 (1.6)	13.7 (1.6)	0.7	1.29	0.22

Test-Retest Reliability

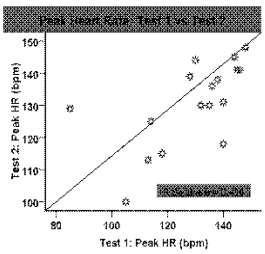
	ICC	95% CI	Cronbach Alpha
Distance Covered (Test 1-2)	.77	.49-.90	.87
Peak HR (Test 1-2)	.63	.24-.84	.77
RPE (Test 1-2)	.11	-.36 to .52	.19

Correlation between the 2 tests (test 1 vs test 2)

	Pearson r	P-Value
Distance Covered (Test 1-2)	0.79	0.000
Peak HR (Test 1-2)	0.65	0.004
RPE (Test 1-2)	0.11	0.67



Test-Retest Correlation: distance walked.



Test-Retest Correlation: peak heart rate.

References

1. *Campo L.A., Chilingaryan G., Berg K., Paradis B., Mazer B. (2006) Validity and reliability of the modified shuttle walk test in patients with chronic obstructive pulmonary disease. Archives of Physical Medicine and Rehabilitation, 87(7):918-22.*
2. *Fowler S.J., Singh S.J., Revill S. (2005) Reproducibility and validity of the incremental shuttle walking test in patients following coronary artery bypass surgery. Physiotherapy, 91:22-27.*
3. *Singh S.J., Morgan M.D., Scott S., Walters D., Hardman A.E. (1992) Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax, 47(12):1019-24.*

Appendix E2. BACR Annual Conference (2009), Birmingham, United Kingdom

University of Essex

Centre for Sports & Exercise Science

Long-term reliability of the modified shuttle walking test in clinical stable cardiovascular disease patients

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[2] North East Essex PCT Cardiac Rehabilitation Team, Independent Living Centre, Catalyst House, Severalls Business Park, Newcomen Way, Colchester, CO4 9YR

Introduction

The British association for cardiac rehabilitation recommends the use of modified shuttle walk test (MSWT) to assess and monitor functional capacity in cardiac rehabilitation clients [1]. Although there is plenty of evidence that the MSWT is a valid, reliable, sensitive and useful tool for detecting cardiorespiratory fitness, the most of the scientific sources refers in short-term tested [2, 3]. The purpose of this study was to examine long-term test-retest reliability of MSWT in clinically stable cardiac patients.

Methods

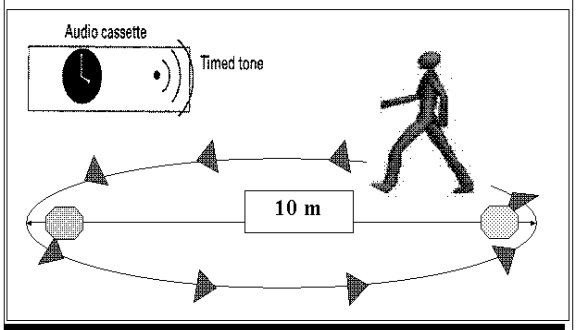
Design Test-retest reliability assessment.

Setting Continuous, **c**ommunity-based phase IV cardiac rehabilitation centre.

Participants Thirty cardiovascular disease (CVD) patients (15 males, 15 females; age 55 – 80 y) volunteered to participate in the study.

Interventions Participants undertook two modified shuttle walking tests (*Figure 1*), a minimum of 8 weeks apart.

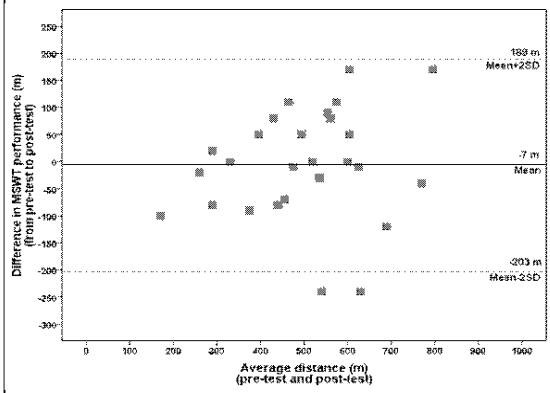
Main outcome measures MSWT performance in metres.



The 10-m Modified Shuttle Walking Test

Results

Distance walked during the MSWT ranged from 120 to 880 m. No significant change found in the mean distance from pre-test (502 ± 161 m) to post-test (509 ± 146 m). The ICC was (R= 0.80) indicating good test-retest reliability. Using the Bland and Altman method, there was a small mean test-retest difference (-7 m). The 95% limits of agreement (LoA) were large, ranging from -203 m to 189 m (*Figure 2*).



Limits of agreement plot.

Conclusions

Over long test-retest durations there appears to be no learning effect in the MSWT, negating the need for a practice walk. The long-term random variation in MSWT is larger than in previous studies. This is most probably due to greater physiological and psychological variation in the participants over 8 weeks compared with that seen in day-to-day testing. Factors (physiological and potential psychological) influencing long-term test-retest reliability of the MSWT require further elucidation.

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References
1. *Singh S.J., Morgan M.D., Scott S., Walters D., Hardman A.E. (1992) Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax, 47(12):1019-24.*
2. *Campo L.A., Chilingaryan G., Berg K., Paradis B., Mazer B. (2006) Validity and reliability of the modified shuttle walk test in patients with chronic obstructive pulmonary disease. Archives of Physical Medicine and Rehabilitation, 87(7):918-22.*
3. *Fowler S.J., Singh S.J., Revill S. (2005) Reproducibility and validity of the incremental shuttle walking test in patients following coronary artery bypass surgery. Physiotherapy, 91:22-27.*

Appendix E3. EuroPrevent (2010), Prague, Czech Republic

Biological Sciences

PREDICTORS OF SIX-MINUTE WALK TEST PERFORMANCE IN HEART FAILURE PATIENTS

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Introduction

The six-minute walk test (6MWT) is a simple, safe and inexpensive measure used to evaluate; functional limitations, the effects of interventions and aid prognosis in chronic heart failure (CHF) patients[1,2,3]. The purpose of this study was to identify simple, routinely-made measurements that were associated with 6MWT performance and establish a reference equation to predict 6MWT performance from them.

Methods

71 CHF patients (82% males; mean age 76 ± 9 years), enrolled in a chronic disease assessment programme completed the 6-MWT. Relationships between distance walked and potential predictors were assessed by multiple stepwise regression analysis. Multinomial logistic regression was performed to determine the factors associated with poor performance (≤300 m) in 6-MWT. Thresholds values identified for dependent (total distance 300 m) and independent variables (age >/<75; stature >/<1.72 m; BMI >/<25 kg·m^{-2}; LVEF >/<45 mm; step length >/<0.63 m). Odds ratios (ORs) with 95 % confidence intervals (CI) were calculated.

Results

Mean 6MWT distance was 305 ± 123 m. Age and stature were the only variables which correlated significantly with test performance. In regression analysis, 42% of variance in 6MWT performance was accounted for by age, but stature was no longer a significant predictor: 6MWT distance (m) = 762 – (6 × age), m.

Logistic regression to predict the likelihood of achieving less than 300 m in 6MWT

	Odds Ratio	95.0% C.I. for Odds Ratio Lower	Upper	*P* value
Gender (male vs female *)	0.82	0.15	4.64	0.822
Age (older vs younger *)	4.93	1.29	18.78	0.020
Stature (short vs. tall *)	1.23	0.31	4.84	0.770
BMI (overweight vs. normal weight *)	12.78	1.46	111.98	0.021
Stride length (short vs long step *)	0.71	0.22	2.35	0.575
Fatigue (fatigue vs. non-fatigue *)	2.97	0.19	46.37	0.44
LVEF (poor vs. normal LVEF *)	0.52	0.15	1.82	0.308

** The referent value (OR = 1) in each variable respectively is: female; younger; tall; normal weight; long step; non-fatigue; normal LVEF).*

Multinomial logistic regression analysis showed that independent predictors of poor performance were: BMI ≥ 25 kg·m^{-2} (OR = 12.8, 95% CI = 1.46 – 112) and age ≥ 75 years (OR = 4.9, 95% CI = 1.29 – 18.78).

Conclusions

Clinical variables such as ventricular function are unrelated to 6 minute walk test performance in heart failure patients. Old age and high BMI are, however, independent predictors of poor performance and should be accounted for when the test is used to categorise patients according to prognostic cut points.

Test performance may be better expressed as a percentage of normal population values which account for age and BMI.

Other non-clinical measures that might influence performance such as stature, should be investigated in a larger sample.

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Appendix E4. BACR Annual Conference (2010), Liverpool, United Kingdom

Influence of anthropometric and gait parameters on the modified shuttle walk test performance in patients with cardiovascular disorders

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Introduction

The shuttle walk test (SWT) is a reliable estimate of functional capacity in cardiac rehabilitation[1,2]. A number of anthropometric and biomechanical parameters associated with walking may influence test performance.

The purpose of this study was to evaluate the influences of anthropometric and biomechanical parameters on SWT performance in clinically stable CVD patients.

From these data we aimed to create a preliminary reference equation to correct for biomechanical (dis)advantage during shuttle walking.

Methods

After a practice trial, 16 (9 males) clinically stable CVD patients (69 ± 9 years) performed the SWT.

We collected anthropometric data (mass, stature, BMI, waist circumference, leg length) and gait characteristics (step length, cadence, turning strategy).

We used a Kistler force plate to collect ground reaction force data and to assess patient's static balance.

SWT performance was expressed in metres walked (m).

Correlation and linear regression analyses were used to identify predictors of SWT performance.

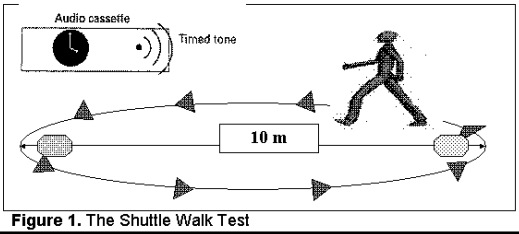

Figure 1. The Shuttle Walk Test

Results

Patients walked a mean distance of 499 (138 m). Distance walked correlated most strongly with stature (r=0.74; $p<0.05$) and step length (r=0.83; $p<0.005$). Stepwise regression revealed step length as the best independent predictor of performance.

Step length is not routinely assessed in clinical practice. We therefore entered stature, the second best-performing predictor of SWT performance, into a subsequent model which explained 55% of the variance in test performance.

Performance (m) = (10.7 × stature [cm]) – 1316

Conclusions

- Turning strategy, balance and ground reaction force data appear unrelated to SWT performance.
- Step length is the most important mediator of SWT performance, but stature acts as a suitable surrogate measure.
- An additional 1 cm of stature predicts that patients will complete an additional shuttle during the SWT.
- To reduce some of the advantage enjoyed by taller patients during the SWT, practitioners may wish to correct SWT performance for patient stature.

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