
Generic exercise rehabilitation
for patients with
Chronic Obstructive Pulmonary Disease
and Chronic Heart Failure

Rachael Andrea Evans

MRCP

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Abstract

Generic exercise rehabilitation for COPD and CHF

Rachael Andrea Evans

Background

Exertional breathlessness and fatigue are common disabling symptoms of patients with Chronic Obstructive Pulmonary Disease (COPD) and Chronic Heart Failure (CHF). The mechanisms behind these symptoms are similar including skeletal muscle dysfunction. Exercise training at least partially reverses the skeletal muscle abnormalities and improves exercise performance and health related quality of life in both conditions.

Pulmonary rehabilitation, with exercise training as a core component, is an integral part of the management of COPD, but a service for CHF has not developed in the same way. The hypothesis, for the main studies described in this thesis, was that the successful model of pulmonary rehabilitation could be applied to patients with CHF and patients with COPD and CHF could be beneficially trained together.

Methods

Two main studies were undertaken;

- 1) a randomised controlled trial of pulmonary rehabilitation (PR) vs. normal care (NC) in patients with CHF
- 2) a comparative observational study of PR between COPD and CHF.

Alongside these studies, the outcome measures commonly used for COPD were applied to patients with CHF. Two pilot studies were performed investigating the effect of exercise training on other systemic manifestations of COPD and CHF.

Results

Patients with CHF made significant improvements in exercise performance and health status with PR compared to NC. The improvements were similar to those seen in the patients with COPD. Measures of exercise performance and health status were applied successfully to patients with CHF.

Conclusions

Patients with COPD and CHF can be successfully trained together demonstrating the feasibility of generic exercise rehabilitation for exertional breathlessness. Further work would need to investigate whether combined exercise programmes for COPD and CHF provides economies of scale for both populations.

The work in this thesis highlights the possibility of organising services for chronic disease around a disability rather than an individual disease.

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Contents	
ABSTRACT	2
ACKNOWLEDGEMENTS	3
CONTENTS	4
INDEX OF TABLES	7
INDEX OF FIGURES	9
ABBREVIATIONS	11
DECLARATIONS	13
PAPERS AND ABSTRACTS	14
CHAPTER ONE	16
INTRODUCTION.....	16
<i>Epidemiology of Chronic Obstructive Pulmonary Disease and Chronic Heart Failure</i>	16
<i>The similar disability of COPD and CHF</i>	17
<i>Symptomatology and the associated disability of COPD and CHF</i>	18
<i>Comparison of the mechanisms of disability between COPD and CHF</i>	19
<i>Evidence of skeletal muscle dysfunction in COPD and CHF</i>	20
<i>Relevance of skeletal muscle dysfunction in COPD and CHF</i>	25
<i>Contributing factors to skeletal muscle dysfunction</i>	28
<i>Other systemic manifestations of both diseases</i>	47
<i>Effect of medication on exercise capacity</i>	48
STRATEGIES TO IMPROVE THE DISABILITY IN COPD AND CHF.....	51
<i>History of exercise training in CHF and COPD</i>	51
<i>A comparison of the effects of exercise training in COPD and CHF.</i>	59
<i>Mechanisms of improvement of exercise training in COPD and CHF</i>	60
<i>Content of an exercise training programme</i>	65
<i>Exercise training as part of a rehabilitation programme</i>	73
<i>Guidelines for exercise therapy in COPD and CHF</i>	76
<i>Coexistent disease</i>	77
<i>Growing interest in the similarity between COPD and CHF</i>	78
<i>Pulmonary rehabilitation for ‘non COPD patients’</i>	79
<i>Access to rehabilitation</i>	80
<i>Hypothesis</i>	81
CHAPTER TWO	83
METHODS.....	83
<i>Content</i>	83
<i>Background</i>	84
<i>Study design</i>	85
<i>Study design of both trials</i>	85
<i>Subjects</i>	85
<i>Recruitment</i>	87
<i>Trial progression</i>	87
<i>Randomisation</i>	90
<i>Intervention</i>	90
<i>Power Calculation</i>	92
<i>Outcome Measures</i>	93
<i>Description of how the outcome measures were performed</i>	96
<i>Background of the outcome measures used</i>	106

CHAPTER THREE	128
REPRODUCIBILITY OF EXERCISE AND STRENGTH TESTS IN COPD AND CHF	128
<i>Background</i>	129
<i>Methods</i>	133
<i>Statistical analysis</i>	135
<i>Results</i>	135
<i>Discussion</i>	146
CHAPTER FOUR.....	151
A RANDOMISED CONTROLLED TRIAL OF PULMONARY REHABILITATION COMPARED TO NORMAL CARE IN PATIENTS WITH CHRONIC HEART FAILURE	151
<i>Background</i>	151
<i>Methods</i>	152
<i>Statistical Analysis</i>	152
<i>Results</i>	153
<i>Discussion</i>	165
CHAPTER FIVE.....	171
A COMPARATIVE OBSERVATIONAL STUDY BETWEEN PATIENTS WITH COPD AND CHF UNDERGOING AN EXISTING PULMONARY REHABILITATION PROGRAMME.....	171
<i>Background</i>	171
<i>Methods</i>	172
<i>Statistical Analysis</i>	172
<i>Results</i>	173
<i>Discussion</i>	189
CHAPTER SIX.....	198
DEVELOPING GENERIC TOOLS TO ASSESS HEALTH RELATED QUALITY OF LIFE	198
FOR BOTH COPD AND CHF.....	198
<i>Introduction</i>	199
I) THE DEVELOPMENT OF A SELF REPORTED VERSION OF THE CHRONIC HEART QUESTIONNAIRE (CHQ-SR).....	200
<i>Background</i>	200
<i>Methods</i>	203
<i>Statistical Analysis</i>	204
<i>Results</i>	206
<i>Discussion</i>	212
II) ADAPTING THE USE OF THE PULMONARY FUNCTIONAL STATUS AND DYSPNOEA QUESTIONNAIRE – MODIFIED VERSION (PFSDQ-M) FOR PATIENTS WITH CHF.....	216
<i>Background</i>	216
<i>Methods</i>	217
<i>Statistical analysis</i>	218
<i>Results</i>	219
<i>Discussion</i>	223
III) APPLYING THE PFSDQ-M TO THE COMPARATIVE OBSERVATIONAL STUDY OF COPD AND CHF	227
<i>Background</i>	227
<i>Methods</i>	227
<i>Results</i>	228
<i>Discussion</i>	230
VI) ADAPTING THE USE OF THE MRC DYSPNOEA SCALE TO INCLUDE PATIENTS WITH CHF.....	231
<i>Background</i>	231
<i>Methods</i>	233
<i>Results</i>	234
<i>Discussion</i>	240

CHAPTER SEVEN	243
A COMPARISON OF THE EFFECT OF EXERCISE TRAINING ON SKELETAL MUSCLE FIBRE TYPE AND PPAR EXPRESSION BETWEEN COPD AND CHF	243
<i>Background</i>	243
<i>Methods</i>	246
<i>Statistical analysis</i>	247
<i>Results</i>	249
<i>Discussion</i>	264
CHAPTER EIGHT	272
A COMPARISON OF THE EFFECTS OF EXERCISE TRAINING ON PLASMA N-TERMINAL BRAIN NATRIURETIC PEPTIDE (NTBNP) AND C-REACTIVE PROTEIN (CRP) BETWEEN COPD AND CHF.	272
<i>Background</i>	272
<i>Methods</i>	277
<i>Statistical analysis</i>	278
<i>Results</i>	279
<i>Discussion</i>	293
CHAPTER NINE	302
DISCUSSION	302
<i>Main findings</i>	303
<i>Future work</i>	307
APPENDIX I	311
DEFINITIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND CHRONIC HEART FAILURE (CHF)	311
APPENDIX II	314
PATIENT INFORMATION LEAFLET AND CONSENT FORM.....	314
APPENDIX III	315
HOME WALKING DIARY AND DESCRIPTION OF THE PERIPHERAL MUSCLE EXERCISES	315
APPENDIX IV	316
QUESTIONNAIRES	316
APPENDIX V	317
REPORTING THE PEAK OXYGEN CONSUMPTION (PEAK VO ₂)	318
COMPARISON OF THE TWO DIFFERENT CPX SYSTEMS USED FOR THE MAIN STUDIES	325
APPENDIX VI	327
DOES BODY MASS INDEX INFLUENCE THE OUTCOME OF PULMONARY REHABILITATION IN PATIENTS WITH COPD?	328
APPENDIX VII	330
LABORATORY ANALYSIS OF NTBNP AND CRP	331
APPENDIX VIII	332
DEFINITIONS OF POLYMERASE CHAIN REACTIONS AND OTHER LABORATORY METHODOLOGY FOR CHAPTER SEVEN	333
LABORATORY ANALYSIS OF THE MUSCLE BIOPSIES	335
REFERENCES	ERROR! BOOKMARK NOT DEFINED.

Index of tables

TABLE 1.1.	SUMMARY OF SOME OF THE STUDIES INVESTIGATING SYSTEMIC INFLAMMATION IN COPD.....	33
TABLE 2.1.	SUMMARY OF PREVIOUS STUDIES INVESTIGATING THE REPRODUCIBILITY OF CARDIOPULMONARY EXERCISE TESTS ON A CYCLE ERGOMETER IN COPD AND CHF; PROTOCOL AND GAS ANALYSIS.....	115
TABLE 2.2.	SUMMARY OF PREVIOUS STUDIES INVESTIGATING THE REPRODUCIBILITY OF CARDIOPULMONARY EXERCISE TESTS ON A CYCLE ERGOMETER IN COPD AND CHF; REPRODUCIBILITY AND COEFFICIENT OF VARIATION OF THE INDIVIDUAL MEASUREMENTS	116
TABLE 3.2.	REPRODUCIBILITY OF CPX IN PATIENTS WITH COPD	136
TABLE 3.3.	REPRODUCIBILITY OF THE PEAK AUXILLARY PARAMETERS FROM THE CPX IN PATIENTS WITH CHF.....	138
TABLE 3.4.	REPRODUCIBILITY OF CPX IN PATIENTS WITH CHF USING THE MSX SYSTEM.....	139
TABLE 3.5.	REPRODUCIBILITY OF CPX IN PATIENTS WITH CHF USING THE ZAN SYSTEM	139
TABLE 3.6.	RESULTS OF THREE ISWTs IN PATIENTS WITH CHF.....	141
TABLE 3.7.	RESULTS OF TEST ONE AND TWO OF THE ESWT IN PATIENTS WITH CHF	142
TABLE 3.8.	MEASUREMENTS OF ESWT, ISWT AND CHQ OVER SEVEN WEEKS	143
TABLE 4.1.	COMPARISON OF THE BASELINE DEMOGRAPHICS, EXERCISE PERFORMANCE AND HEALTH STATUS BETWEEN THE TWO GROUPS	156
TABLE 4.2.	RESULTS OF EXERCISE PERFORMANCE FOR THE RCT	159
TABLE 4.3.	SERIAL ISWT AND ESWT THROUGHOUT PULMONARY REHABILITATION	160
TABLE 4.4.	RESULTS OF THE CHQ FOR THE RCT	162
TABLE 4.5.	RESULTS OF THE SF36 FOR THE RCT	163
TABLE 4.6.	CORRELATION BETWEEN CHANGES IN EXERCISE PERFORMANCE AND HEALTH STATUS WITH PULMONARY REHABILITATION	163
TABLE 5.1.	COMPARISON OF THE BASELINE DEMOGRAPHICS AND EXERCISE PERFORMANCE FOR PATIENTS WITH COPD AND CHF	176
TABLE 5.2.	FREQUENCY OF MRC DYSPNOEA SCALE GRADE BETWEEN COPD AND CHF.....	179
TABLE 5.3.	COMPARISON OF THE CRQ AND CHQ BASELINE RESULTS BETWEEN COPD AND CHF.....	180
TABLE 5.4.	COMPARISON OF THE SF36 BASELINE RESULTS BETWEEN COPD AND CHF	180
TABLE 5.5.	COMPARISON OF THE RESULTS OF PHYSICAL PERFORMANCE FROM PULMONARY REHABILITATION BETWEEN COPD AND CHF	186
TABLE 5.6.	A COMPARISON OF THE CRQ-SR OR CHQ-IL RESULTS WITH REHABILITATION BETWEEN COPD AND CHF	186
TABLE 5.7.	A COMPARISON OF THE CHANGE IN SF36 SCORES WITH PULMONARY REHABILITATION BETWEEN COPD AND CHF	187
TABLE 5.8.	CORRELATION BETWEEN THE CHANGE IN ISWT AND THE CHANGE IN THE CRQ OR CHQ DOMAINS WITH PR	188
TABLE 6.1.	COMPARISON OF MEAN SCORES FOR EACH DOMAIN BETWEEN THE IL AND SR VERSIONS OF THE CHQ	206
TABLE 6.2.	REPRODUCIBILITY OF THE CHQ-SR.....	208
TABLE 6.3.	RESULTS OF THE CHQ FOR THE RCT OF PR VS NC	209
TABLE 6.4.	COMPARISON OF THE RESULTS OF PULMONARY REHABILITATION FOR THE CHQ-IL AND CHQ-SR	209
TABLE 6.5.	COMPARISON OF THE CORRELATIONS OF THE CHQ-IL AND CHQ-SR WITH THE RELEVANT COMPONENTS OF THE SF36	210
TABLE 6.6.	SHORT TERM REPRODUCIBILITY OF THE PFSDQ-M IN PATIENTS WITH CHF.....	220
TABLE 6.7.	CORRELATIONS OF THE THREE MAIN COMPONENTS OF THE PFSDQ-M AND MEASURES OF HEALTH STATUS AND EXERCISE PERFORMANCE IN PATIENTS WITH CHF.....	221
TABLE 6.8.	COMPARING THE VALIDITY OF THE PFSDQ-M BETWEEN CHF AND COPD.....	222
TABLE 6.9.	RESULTS OF THE PFSDQ-M FOR PR VS NC IN CHF	223
TABLE 6.10.	RESULTS OF THE PFSDQ-M IN PATIENTS WITH COPD AND CHF	228
TABLE 6.11.	RESULTS OF PULMONARY REHABILITATION ASSESSED BY THE PFSDQ-M IN COPD AND CHF	229

TABLE 6.12.	FREQUENCY OF MRC SCALE GRADE FOR COPD AND CHF.....	234
TABLE 6.13.	RESULTS OF EXERCISE PERFORMANCE AND HEALTH STATUS PER MRC GRADE FOR BOTH COPD AND CHF.....	237
TABLE 6.14.	CORRELATION BETWEEN EITHER THE MRC SCALE OR NYHA CLASSIFICATION AND MEASURES OF EXERCISE PERFORMANCE AND HEALTH STATUS.....	239
TABLE 7.1.	COMPARISON OF THE BASELINE DEMOGRAPHICS BETWEEN COPD AND CHF.....	249
TABLE 7.2.	COMPARISON OF mRNA EXPRESSION OF PPARS AND PGC-1 IN SKELETAL MUSCLE BETWEEN COPD AND CHF.....	250
TABLE 7.3.	CORRELATIONS BETWEEN THE CHANGE IN mRNA EXPRESSION OF THE PPARS AND PGC-1 CO-ACTIVATOR AND THE CHANGE IN MHC ISOFORMS WITH EXERCISE TRAINING IN PATIENTS WITH COPD.....	262
TABLE 8.1.	COMPARISON OF THE BASELINE DEMOGRAPHICS AND PHYSICAL PERFORMANCE BETWEEN PATIENTS WITH COPD AND CHF.....	280
TABLE 8.2.	CORRELATION COEFFICIENTS BETWEEN PLASMA NTBNP AND BASELINE DEMOGRAPHICS, DISEASE SEVERITY, PHYSICAL PERFORMANCE AND FUNCTIONAL STATUS FOR COPD AND CHF.....	282
TABLE 8.3.	CORRELATION COEFFICIENTS BETWEEN PLASMA CRP AND BASELINE DEMOGRAPHICS, DISEASE SEVERITY, PHYSICAL PERFORMANCE AND FUNCTIONAL STATUS FOR COPD AND CHF.....	285
TABLE 8.4.	COMPARISON OF THE BASELINE DEMOGRAPHICS AND EXERCISE PERFORMANCE BETWEEN PATIENTS WITH COPD COMPLETING PR OR NC.....	291
TABLE AI.	PEAK VO ₂ MEASUREMENTS DERIVED BY SIX METHODS.....	321
TABLE AII.	EFFECT OF THE DIFFERENT METHODS OF REPORTING PEAK VO ₂ ON THE CHANGE IN PEAK VO ₂ BETWEEN TWO BASELINE EXERCISE TESTS.....	322
TABLE AIII.	EFFECT OF THE DIFFERENT METHODS OF REPORTING PEAK VO ₂ ON THE CHANGE IN PEAK VO ₂ BEFORE AND AFTER EXERCISE TRAINING.....	322
TABLE AIV.	COMPARISON OF THE RESULTS OF CPX BETWEEN THE TWO SYSTEMS.....	326

Index of figures

FIGURE 1.1	POTENTIAL MECHANISMS OF INFLAMMATION INDUCED SKELETAL MUSCLE DYSFUNCTION TAKEN FROM SUPINSKI'S REVIEW (123).....	35
FIGURE 1.2.	MECHANISMS OF CACHEXIA IN COPD FROM DEBIGERE'S REVIEW	38
FIGURE 2.1.	STUDY PROTOCOL FOR THE PATIENTS WITH CHF.....	88
FIGURE 2.2.	STUDY FLOW DIAGRAM FOR PATIENTS WITH COPD.....	89
FIGURE 3.1.	STUDY FLOW DIAGRAM FOR THE EXERCISE TESTS DURING THE TWO WEEK RUN IN PERIOD	133
FIGURE 3.2.	BLAND ALTMAN PLOT FOR THE PEAK VO ₂ FROM TWO CPX TESTS FOR COPD.....	137
FIGURE 3.3.	BLAND ALTMAN PLOT OF THE LIMITS OF AGREEMENT OF THE ISWT.....	141
FIGURE 3.4.	LIMITS OF AGREEMENT OF ISOMETRIC QUADRICEPS STRENGTH IN CHF.....	144
FIGURE 3.5.	LIMITS OF AGREEMENT OF ISOMETRIC QUADRICEPS STRENGTH IN COPD.....	145
FIGURE 4.1.	FLOW DIAGRAM OF THE RCT	154
FIGURE 4.2.	RELATIONSHIP BETWEEN ISWT DISTANCE AND NYHA CLASS	155
FIGURE 4.3.	RESULTS OF THE ISWT AND ESWT FOR THE RCT	158
FIGURE 4.4.	TRAINING PROFILE OF MAXIMAL AND SUBMAXIMAL EXERCISE CAPACITY.	160
FIGURE 5.1.	BASELINE [NTBNP] LEVELS BETWEEN COPD AND CHF	174
FIGURE 5.3.	STUDY PATIENT FLOW DIAGRAM.....	181
FIGURE 5.4.	COMPARISON OF THE CHANGE IN ISWT AND ESWT PERFORMANCE BETWEEN COPD AND CHF.....	183
FIGURE 5.5.	TRAINING PROFILE FOR COPD AND CHF.....	184
FIGURE 6.1.	LIMITS OF AGREEMENT BETWEEN THE IL AND SR VERSIONS OF THE CHQ FOR EACH OF THE FOUR DOMAINS.....	207
FIGURE 6.2.	THE MRC DYSPNOEA SCALE.....	231
FIGURE 6.3.	THE NYHA CLASSIFICATION OF FUNCTIONAL CAPACITY	232
FIGURE 6.4.	DEGREE OF ORGAN IMPAIRMENT PER MRC SCALE GRADE FOR COPD AND CHF	235
FIGURE 6.5.	ISWT DISTANCE PER MRC GRADE FOR CHF	236
FIGURE 6.6.	ISWT DISTANCE PER MRC DYSPNOEA GRADE FOR COPD AND CHF	237
FIGURE 7.1.	BASELINE RESULTS OF PPAR AND PGC-1 MRNA EXPRESSION IN SKELETAL MUSCLE IN COPD AND CHF.....	251
FIGURE 7.2.	COMPARISON BETWEEN THE MUSCLE FIBRE TYPE DISTRIBUTION IN SKELETAL MUSCLE IN COPD AND CHF.....	252
FIGURE 7.3.	CORRELATIONS BETWEEN PGC-1 MRNA AND PPAR DELTA MRNA EXPRESSION AND MHC ISOFORM PERCENTAGE.	254
FIGURE 7.6.	INDIVIDUAL RESPONSE TO PR IN MUSCLE FIBRE TYPE PROPORTION IN COPD.....	256
FIGURE 7.4.	CHANGE IN FIBRE TYPE PROPORTION WITH EXERCISE TRAINING IN COPD.....	257
FIGURE 7.5.	CHANGE IN FIBRE TYPE PROPORTION WITH EXERCISE TRAINING IN CHF.....	257
FIGURE 7.7.	THE RESULTS OF GEL ELECTROPHORESIS FOR THE MHC ISOFORMS	258
FIGURE 7.8.	GRAPHS OF THE CHANGE IN PPAR AND PGC-1 EXPRESSION WITH EXERCISE TRAINING IN PATIENTS WITH COPD	259
FIGURE 7.9.	GRAPHS OF THE CHANGE IN PPAR AND PGC-1 EXPRESSION WITH EXERCISE TRAINING IN PATIENTS WITH CHF	261
FIGURE 7.10.	GRAPHS TO SHOW THE RELATIONSHIP BETWEEN THE CHANGE IN MHC TYPE I PROPORTION AND THE CHANGE IN PPARS MRNA EXPRESSION WITH PR IN COPD	263
FIGURE 8.1.	COMPARISON OF THE BASELINE PLASMA NTBNP LEVEL BETWEEN COPD AND CHF.....	281
FIGURE 8.4.	GRAPH TO SHOW THE RANGE OF PLASMA CRP LEVELS FOR COPD AND CHF	284
FIGURE 8.5.	INDIVIDUAL VARIABILITY OF PLASMA NTBNP LEVELS BEFORE AND AFTER EXERCISE IN COPD AND CHF, BEFORE AND AFTER PULMONARY REHABILITATION	287
FIGURE 8.6.	GRAPH TO SHOW THE INDIVIDUAL VARIABILITY OF PLASMA NTBNP LEVELS BEFORE AND AFTER PULMONARY REHABILITATION (PR) AND NORMAL CARE (NC).....	288
FIGURE 8.7.	GRAPH TO SHOW THE INDIVIDUAL VARIABILITY OF PLASMA CRP LEVELS BEFORE AND AFTER PULMONARY REHABILITATION (PR) AND NORMAL CARE (NC).....	289
FIGURE 8.8.	GRAPH TO SHOW THE INDIVIDUAL VARIABILITY OF THE CHANGE IN PLASMA NTBNP WITH PULMONARY REHABILITATION AND NORMAL CARE.....	291

FIGURE 8.9. GRAPH TO SHOW THE INDIVIDUAL VARIABILITY OF PLASMA CRP LEVEL BEFORE AND AFTER PULMONARY REHABILITATION IN COPD..... 292

Abbreviations

ACCP	American College of Chest Physicians
ACE	Angiotensin converting enzyme
ATII	Angiotensin II antagonist
ATP	Adenosine Triphosphate
ATS	American Thoracic Society
BMI	Body mass index
BS	Borg Scale for breathlessness
CHF	Chronic Heart Failure
CHQ	Chronic Heart Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
CPX	Cardiopulmonary exercise test
CRP	C-reactive protein
CRQ	Chronic Respiratory Questionnaire
CSA	Cross sectional area
ECG	Electrocardiogram
ECHO	Echocardiography
ESWT	Endurance shuttle walk test
FEV1	Forced Expiratory Volume in 1 second
FFM	Fat free mass
Hb	Haemoglobin
HR	Heart rate
HRQOL	Health related quality of life
IL	Interleukin
ISWT	Incremental shuttle walk test
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MCID	Minimum clinically important difference
MHC	Myosin heavy chain
MI	Myocardial Infarction
MRC	Medical Research Council
NC	Normal care
NF-KB	Nuclear factor kappa B
NTBNP	N-terminal Brain Natriuretic Peptide
NYHA	New York Heart Association
PaO ₂	Arterial oxygen partial pressure
PCr	Phosphocreatine
PE	Borg Scale for perceived exertion
Peak VO ₂	Peak oxygen uptake
PFSQ-M	Pulmonary Functional Status Dyspnoea Questionnaire – modified version
PGC-1	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha
PMRS	Phosphorus magnetic resonance spectroscopy
PPAR	Peroxisome proliferator-activated receptor
PR	Pulmonary rehabilitation
RCT	Randomised controlled trial
6MWT	Six minute walk test
SD	Standard deviation
SF36	Short form 36

TCA	the citric acid cycle or Kreb's cycle
TNFalpha	Tumour necrosis factor alpha
WHO	World Health Organisation

Declarations

I hereby declare that this thesis has been composed by myself and the work has been performed by myself except where assistance has been acknowledged. The experimental work was all completed during my research time registered with the University of Leicester.

I received assistance in performing the shuttle walk tests. The laboratory muscle biopsy analysis was performed by Despina Constantin and the laboratory NTBNP/CRP analysis was performed by Pauline Quinn.

No part of this thesis has been submitted in any previous application for a higher degree.

I hereby give permission for this thesis to be made available for consultation, photocopying and use by other libraries directly or via the British Library.

Rachael Andrea Evans

Papers and abstracts

Papers

Submitted.

RA Evans, S Singh, R Collier, MC Steiner, MDL Morgan.

Generic exercise rehabilitation for patients with COPD and CHF: a randomised controlled trial.

Published.

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Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. *Respir Med.* 2009 Feb 12. [Epub ahead of print]

Abstracts

Oral presentations

Evans RA, Collier R, Singh SJ, Morgan MDL

Does the addition of strength training lead to increased activity measured by the PFSDQ-M in patients with COPD?

Thorax 2008; 63: suppl VII S32

Evans RA, Collier R, Singh SJ, Morgan MDL

Expanding the use of the MRC scale for patients with CHF.

ERJ 2008; 32: suppl 52 1328

Evans RA, Collier R, Singh SJ, Steiner MC, Morgan MDL

Combined training programmes for patients with COPD and CHF.

AJRCCM 2007; 175: A566

Evans RA, Ng LL, Singh SJ, Steiner MC, Morgan MDL

Pulmonary Rehabilitation modulates neurohumoral activation in patients with COPD.

ERJ 2006; 28: suppl 50 3572

Evans RA, Singh SJ, MDL Morgan

The functional assessment of Chronic Heart Failure is reliably achieved by the Incremental Shuttle Walk Test.

Heart 2006; 92: suppl II 134

Posters

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Developing the use of the PFSDQ-M in patients with CHF.
ERJ 2008; 32: suppl 52 P3381

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Proceedings of the ATS 2006; 3: A209

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Thorax 2005 Dec; 60 Supp II P40

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ERJ 2005; 26 Suppl 49 P4601

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ERJ 2005; 26 Suppl 49 P4590

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Is there supporting evidence for a competency based training programme?
Proceedings of the ATS 2005; 2: A51

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Proceedings of the ATS 2005; 2: A316

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Does oxygen supplementation reduce exercise induced metabolic stress of skeletal muscle in COPD?
AJRCCM 2004; 169 (7): A901

Evans RA, Collier R, Singh SJ, Morgan MD.
Are the results of exercise training in COPD influenced by starting disability?
Thorax 2003; 58: suppl III P125

Chapter one

Introduction

Epidemiology of Chronic Obstructive Pulmonary Disease and Chronic Heart Failure

Chronic diseases are the leading cause of death worldwide representing 60% of all deaths (1). Their prevalence is increasing across all regions and all socioeconomic classes. The World Health Organisation (WHO) has designed an 'Integrated Chronic Disease Prevention and Control Programme' where together with prevention the aims are to reduce premature mortality and morbidity, and to improve quality of life. Cardiovascular disease and chronic respiratory disease are two of the WHO's four priority noncommunicable diseases. Chronic Obstructive Pulmonary Disease (COPD) is the 5th leading cause of death (projected to become the 3rd in 2030) and affects approximately 210 million sufferers worldwide (2). Chronic Heart Failure (CHF) affects between 5-10% of the population over the age of 65 with the five year mortality similar to some common cancers (3;4). Both ischaemic heart disease and COPD were in the ten leading causes of burden of disease for all countries (3rd and 9th respectively) assessed by disability-adjusted life years (DALYs) in 2001 (5).

The true prevalence of COPD is unknown due to under detection. It is likely to be increasing worldwide (2;6) through increasing smoking rates in less developed countries. Until recently less was known about the epidemiology of heart failure than for coronary heart disease. This was for a variety of reasons including a lack of both a standardised definition and a gold standard for the detection of heart failure. Consensus

guidelines for the definition and diagnosis for heart failure are now available (7). The incidence of CHF is predicted to increase with the improved treatments for coronary heart disease and myocardial infarctions (8;9).

Both COPD and CHF exert a large and similar burden on health care resources. In England alone, COPD accounts for more than one million hospital bed days a year. In the US heart failure is the most common cause of hospitalisation in patients over the age of sixty and the hospitalisation rate is increasing in western countries (3) . COPD and heart failure are also responsible for a significant part of physician visits and emergency department visits. 1-2% of all healthcare expenditures is on heart failure in western countries (10). There is limited data on the true financial burden of COPD (11;12), but a recent study demonstrated a high use of healthcare utilization and expenditure for patients with COPD enrolled in U.S. Medicare managed care plans (13).

In summary, both COPD and CHF are common diseases with a high associated mortality, morbidity and socioeconomic burden along with a predicted increase in incidence. Both diseases are therefore an important target for any health care provider.

The similar disability of COPD and CHF

The definitions of these diseases are included in appendix I. There is a large individual burden to the sufferer from these diseases. Although the organ impairment for each disease is obviously different the symptoms they present with are very similar. In respective guidelines on how to diagnose the conditions, COPD is characterised by symptoms of breathlessness, cough and sputum production and CHF is characterised by symptoms of breathlessness and fatigue (6;7). Exertional breathlessness and fatigue are common for both COPD and CHF and result in activity limitation (disability). The

symptoms and subsequent limitation frequently leads to a number of negative effects; reduced health status, loss of work and financial losses, social isolation and anxiety and depression. Reduced exercise capacity is associated with an increased mortality in both COPD and CHF (14;15). The BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) system is a multidimensional severity scoring system for COPD and exercise capacity (assessed by the six minute walk test) was an independent prognostic indicator (16).

Symptomatology and the associated disability of COPD and CHF

Exertional dyspnoea and fatigue resulting in activity limitation are characteristic symptoms of both COPD and CHF and the various methods for assessing these symptoms are described in chapter two. The mechanisms generating these symptoms are subsequently described in this chapter. Dyspnoea is a well recognised symptom of COPD and affects health status¹ more than parameters of lung function (17). Hamilton and colleagues demonstrated that fatigue was a common limiting symptom to exercise for cardiorespiratory disorders, as well as breathlessness (18). The symptom of fatigue is heterogeneous and can relate to general lethargy or specific leg fatigue. A five subscale measurement of fatigue showed that all descriptions of fatigue were related to health status in COPD (19). In CHF the symptom of fatigue correlates with clinical and psychological parameters (20) and both the symptoms of breathlessness and fatigue are good predictors of health status (21). The symptoms of breathlessness and fatigue in CHF, not just functional status, are associated with a poorer prognosis (22). In COPD

¹ health related quality of life

the impact of dyspnoea on functional status assessed by the MRC scale is a prognostic indicator (16).

There are common mechanisms behind the disability of activity limitation between COPD and CHF described below.

Comparison of the mechanisms of disability between COPD and CHF

Originally the symptomatology of these diseases was thought to relate primarily to the severity of the underlying organ impairment. Subsequent studies have shown in both conditions that the degree of primary organ impairment, assessed by either left ventricular ejection fraction impairment or FEV₁, correlate poorly with exercise capacity (23;24). This phenomenon is particularly evident in severe disease with COPD, but is present across the range of severity with CHF. Invasive studies have shown that peak pulmonary artery wedge pressure is not responsible for the increased ventilation seen with exercise in patients with CHF (25).

Killian and colleagues demonstrated that fatigue was a common limiting symptom to exercise in both chronic lung disease and in a large cohort of patients with a variety of cardiorespiratory disorders (26;27) . Respiratory muscle and quadriceps strength were also reduced. After heart transplantation for heart failure, exercise capacity improves but remains significantly impaired (28) and after a single or double lung transplant exercise capacity is equally impaired despite greater improvements in pulmonary function after a double lung transplant (29). This data points towards the presence of other contributing factors to exercise capacity other than the primary organ impairment. Interest developed, almost simultaneously, into the recognition and effect of

the peripheral skeletal abnormality in COPD and CHF. However research involving the two disease groups occurred separately for almost two decades.

Evidence of skeletal muscle dysfunction in COPD and CHF

Skeletal muscle metabolism during exercise in COPD and CHF

Patients with COPD have an early lactate rise and at lower workloads during exercise compared to healthy controls (30;31). Belardinelli et al showed similarly that patients with CHF had an earlier onset of anaerobic metabolism compared to healthy sedentary controls using infrared spectroscopy to assess muscle deoxygenation (32). Muscle lactate accumulation is similar at peak exercise compared to healthy inactive subjects although at lower absolute peak work loads in both conditions (33;34). The metabolic response to exercise has been assessed with at least two different methods; skeletal muscle biopsy sampling before and after exercise and with ³¹P-phosphorus magnetic resonance spectroscopy (³¹P-MRS). The disadvantages of muscle sampling are the invasive procedure and the time consuming specialist analysis, but ³¹P-MRS can not easily assess whole body exercise and relies on correct quantification and calibration (35). In CHF initial studies used ³¹P-MRS and forearm and calf exercises. These showed that phosphocreatine was depleted with exercise quicker and at lower workloads than healthy subjects (36-38). These results were confirmed in subsequent studies using skeletal muscle biopsies. Naveri et al confirmed depletion of PCr, but at a third of the workload of the healthy subjects at peak exercise and ATP was reduced (34). A similar study was undertaken nearly a decade later in COPD, but the results were similar confirming a reduction of PCr, ATP and metabolites at peak exercise similar to healthy

controls but at a much lower workload (39). One of few studies directly comparing the skeletal muscles in COPD and CHF was in 1992 investigating skeletal muscle metabolism with ^{31}P -MRS (40). Both diseases showed similar abnormal muscle metabolism with increase depletion of PCr with exercise. The results of all these studies demonstrate that the skeletal muscles are under stress at the end of exercise in COPD and CHF.

Skeletal muscle mass and strength in COPD and CHF

In COPD the quadriceps muscles have a reduced muscle mass (measured by CT^2) and strength compared to age matched controls (41). In CHF a similar study using MRI^3 showed that the ‘thigh’ muscle mass was lower than in healthy sedentary controls (42). The muscle endurance was significantly reduced in CHF, but isometric muscle strength was not significantly different between the two groups. Isometric quadriceps strength has been shown in other studies to be reduced in CHF (43;44). In COPD isometric quadriceps strength and endurance are reduced compared to healthy controls (41;45-47). These studies were mainly on patients with moderate to severe COPD and the activity levels of the control group were not always specified.

Skeletal muscle fibre type and size in COPD and CHF

Skeletal muscle contains different myosin heavy chain isoforms types; type I, IIa and IIb(x). Type I are red, slow twitch fibres, which predominantly use oxidative metabolism and are fatigue resistant and Type II b/x are white, fast twitch fibres, which predominantly use glycolytic metabolism. Type IIa fibres have mixed features. They are red and fast twitch, but can use oxidative and glycolytic metabolism. Histochemical

² Computed tomography

³ Magnetic resonance imaging

studies have confirmed that there is a change in the fibre type proportion, with a shift from type I to type IIb fibres, in patients with COPD and CHF compared to age matched healthy controls (48-51). The initial studies were published at a similar time; 1990 for COPD (50) and 1988 for CHF (52). Further discussion on the various methods used to assess muscle fibre type, number and cross sectional area are discussed in chapter two.

Oxidative and glycolytic enzyme activity

There are lower levels of oxidative enzymes in the skeletal muscle in CHF and COPD compared to controls. Citrate synthase (53-56), alpha-ketoglutarate dehydrogenase (34), hexokinase (54), succinate dehydrogenase (53;54) and 3-hydroxyacyl CoA dehydrogenase have all been shown to be present in lower levels in CHF than in healthy controls. These are all enzymes involved in the TCA⁴ cycle in the mitochondria. 3- hydroxyacyl-CoA dehydrogenase (54;55) has also been shown to be lower in CHF. This enzyme is the rate limiting step in beta oxidation (converting fatty acids to acetyl CoA to enter the TCA cycle). All these enzymes are markers of oxidative capacity. In COPD citrate synthase (31;57), 3-hydroxyacyl-CoA dehydrogenase (31;57) succinate dehydrogenase (57;58) are all reduced compared to healthy controls. The activity of the glycolytic enzymes; lactate dehydrogenase (LDH), hexokinase and phosphofructokinase (PFK) were similar between COPD and healthy controls in the study by Maltais et al (31), but Jakobsson et al showed that PFK and LDH activity levels were significantly higher in COPD than healthy controls. In CHF the activity of PFK was similar to healthy controls (34) and only a trend towards an increase in LDH (55). Overall there is at least a trend towards a higher level of glycolytic enzyme activity in skeletal muscle of patients with COPD and CHF.

⁴ the citric acid cycle

Mitochondrial density

Two studies have reported that abnormalities of the mitochondria in the skeletal muscle of patients with COPD and CHF. Drexler et al in 1992 showed that the mitochondria volume density was reduced by about 20% in CHF (59). In COPD it was not until 2007 that a lower mitochondrial number and area was shown (60).

There does not appear to be a specific mitochondrial abnormality in COPD as P-MRS studies have shown a normal recovery time post exercise (61). Studies on rat models of deconditioning by using hind limb immobilisation showed a muscle fibre type shift towards type II fibres but no mitochondrial abnormality (62)

Peroxisome proliferator-activated receptors (PPARs) and skeletal muscle

Over the last decade there has been much research regarding a group of transcription factors named the peroxisome proliferator-activated receptors. They have been shown to have a key role in lipid homeostasis. PPARs are regulators of fatty acid oxidation and mitochondrial biogenesis and of oxidative capacity in skeletal muscle (63). The PPARs, in relation to skeletal muscle, are discussed in more detail in chapter seven.

Respiratory muscle strength in COPD and CHF

So far only the limb skeletal muscles have been discussed. The respiratory muscles have also been extensively investigated in COPD and CHF because of their contribution to the mechanics of breathing. The most common method used for assessing inspiratory and expiratory muscle strength is by the maximum inspiratory or expiratory pressure (P_Imax or MIP and P_Emax or MEP respectively). The main problem with these tests is the voluntary nature and considerable learning effect, but they are easy

to apply (64). More accurate testing of the diaphragm strength can be achieved by assessing the pressure from the diaphragm alone (Pdi) (65). This is achieved by an invasive test using an oesophageal and gastric balloon. The Pdi is calculated by the abdominal pressure (Pab) – the pleural pressure (Pes).

Inspiratory muscle strength measured by PImax is reduced in COPD, but the expiratory muscle strength can be preserved or reduced (66). Inspiratory muscle strength is inversely correlated to disease severity in COPD (67). The PImax is also reduced in CHF demonstrated in a large cohort of patients compared with age matched healthy controls (68). The PEmax was the same in both groups. In a much smaller study both the PImax and PEmax were reduced in patients with CHF compared to age matched controls (69).

Isolated diaphragmatic strength is reduced in COPD assessed by twitch transdiaphragmatic pressure (Tw Pdi) elicited by cervical magnetic stimulation (CMS) of the phrenic nerve (70). The same research group assessed diaphragmatic strength in CHF and showed a TwPdi of 21.4 cm H₂O compared to 28.5 cmH₂O in health subjects. The results for TwPdi for COPD were 18.5 cm H₂O compared to 25.4 cm H₂O in the healthy subjects, so the diaphragmatic strength was similar for the two disease groups.

The opposite phenomenon is seen in the diaphragm muscle fibres compared to the quadriceps fibres, in both COPD and CHF. There is an increased number of type one fibres compared to healthy controls (71-73). There has been one study directly comparing inspiratory muscle strength in COPD and CHF (74). Instead of measuring PImax, the inspiratory muscle power output was measured which includes both strength

and velocity of shortening. A similar reduction in power output was seen in both COPD and CHF.

The alteration of skeletal mass, strength, fibre type and oxidative capacity is often referred to as skeletal muscle dysfunction and is predominantly present in the locomotor muscles in both COPD and CHF. Most of the data for skeletal muscle dysfunction is for severe disease in COPD and a recent meta- analysis highlighted the paucity of data for mild disease (75).

Relevance of skeletal muscle dysfunction in COPD and CHF

Skeletal muscle dysfunction is a major and similar contributing factor to exercise intolerance in both CHF and COPD. Quadriceps muscle strength has been shown to be a contributing factor to exercise capacity in both diseases. Hamilton et al in 1995, described that peripheral muscle strength was lower in a large cohort (>3000) of patients with cardiorespiratory disorders compared to controls. A 'two fold increase in muscle strength led to a 1.4 to 1.6 fold increase in work capacity. Almost all subsequent studies were performed separately in CHF and COPD. However the questions raised were very similar; was the reduced quadriceps strength purely because of reduced muscle mass and how did this contribute to exercise capacity?

Harrington et al confirmed in 100 patients with moderate to severe CHF (mean LVEF 26 (2) %) that isometric quadriceps strength was reduced compared to controls (activity levels unmentioned). Quadriceps strength was still reduced after correction for quadriceps CSA⁵ and was an independent predictor of absolute peak VO₂ (76). Other

⁵ Cross-sectional area

studies have confirmed that quadriceps strength is one of the main contributing factors to exercise capacity in CHF (77-80). Harrington et al confirmed the other end of the spectrum that preserved exercise capacity, in asymptomatic patients with severe left ventricular ejection fraction, was associated with a lack of peripheral changes (81). The majority of the above studies demonstrated little relationship between the degree of LV impairment and exercise capacity. One small study (n=11) concluded that 'pump' capacity limited exercise capacity more than quadriceps muscle strength (56), but this relationship has never subsequently been shown.

Gosselink et al showed that quadriceps force was an important determinant of peak exercise capacity (peak VO_2) and the six minute walk test distance (6MWT) in COPD (82). FEV_1 was still a contributing factor to peak VO_2 , but not towards 6MWT distance. Steiner et al showed that quadriceps strength independently contributed to peak exercise capacity measured by the Incremental Shuttle Walking Test distance (ISWT), but not to submaximal capacity measured by the Endurance Shuttle Walk Test time (ESWT) (83). FEV_1 contributed to both in the regression analysis. The majority of both populations had severe disease defined by spirometry. These studies have involved volitional measurements. The quadriceps twitch force is a non volitional measurement and can be assessed before and at the end of exercise. Fatigue has been defined as a postexercise fall in quadriceps twitch force greater than 15% of resting values (). Patients with COPD have been shown to have contractile fatigue at the end of cycle exercise (84), but this is seen less after walking (in a small study n=12) (85). Saey et al demonstrated that patients who showed contractile fatigue at the end of cycle exercise had an increase in LDH (representing glycolytic metabolism) compared to 'non-

fatiguers', but there was no difference between fibre type proportion or oxidative capacity between the two groups (86). Inducing quadriceps fatigue prior to exercise has also been shown to decrease exercise tolerance in COPD (87). There are no similar studies in CHF.

Although diaphragmatic strength is reduced in COPD, it is not fatigued by either endurance exercise to symptom limitation or hyperventilation suggesting that it is not the limiting factor to exercise capacity (88-90). A similar study has shown that the diaphragm is not fatigued after exercise in CHF, but is related to the sensation of dyspnea (91). P_{Imax} and P_{E_{max}} have also been shown to have no correlation with either peak VO₂ or 6MWT distance in COPD (92). In CHF the reduction in endurance capacity was caused more by an abnormal breathing pattern rather than inspiratory muscle weakness per se (93). In COPD the respiratory muscles do not contribute to the lactate rise at peak exercise (94). In summary in both COPD and CHF there is evidence of respiratory muscle weakness, but this does not appear to have a major impact on exercise limitation in either group.

So far most of the current discussion, of the similarities in skeletal muscle dysfunction between COPD and CHF, has been extrapolated from separate studies. There has been one prospective study comparing the systemic factors contributing to reduced exercise capacity in CHF and COPD (95). 25 patients with CHF, 25 patients with COPD and 36 age matched controls were compared. The quadriceps and biceps strength were similarly reduced for the two diseases. Quadriceps strength and fat free mass both positively correlated with peak VO₂ in COPD and CHF. This study confirmed there was no correlation between the degree of organ impairment and peak exercise

capacity. Interestingly there was little correlation between the quadriceps strength and physical activity measure by a questionnaire⁶.

There is evidence that as well as the functional importance of quadriceps weakness in COPD and CHF, it is also associated with a worse prognosis. Quadriceps cross sectional area and strength (quadriceps maximum voluntary contraction: QMVC) are predictors of mortality in patients with COPD (96;97) and isokinetic quadriceps strength predicts mortality in patients with CHF (98). Inspiratory muscle strength has been shown to be an independent predictor of prognosis in CHF (68).

Quadriceps force is a significant determinant of health care resources in COPD (99). In the same study neither walking distance nor pulmonary function were related to increased use of health care services.

The recognition of skeletal muscle dysfunction led to the realisation that both diseases had important systemic manifestations and that concentrating potential therapies only towards the organ impairment was inadequate. In order to try and improve the skeletal muscle abnormalities it is necessary to understand the potential causes.

Contributing factors to skeletal muscle dysfunction

Much work has been conducted into the cause of the skeletal muscle dysfunction in COPD and CHF. Almost all of this work has been conducted separately for the two diseases yet the contributing factors are paralleled. Several different factors contribute to

⁶ PASE

these abnormalities, but the importance of each is still debated. The causes implicated in both diseases are deconditioning, systemic inflammation, oxidative stress, and nutritional status. The cause is likely to be multi-factorial and each factor is possibly present to a varied extent in any individual. There are also some causes that are disease specific e.g hypoxia in COPD, poor perfusion in CHF and there are implications in different medication e.g steroids in COPD and Angiotensin Converting Enzyme (ACE) inhibitors in CHF. Some of these factors contribute not only to skeletal muscle dysfunction, but to the other systemic features of the diseases. These other systemic features are discussed subsequently in this section (mechanisms of disability). The evidence for each of the contributing factors is now discussed for both diseases.

The predominant argument about the skeletal muscle dysfunction is whether it is due to deconditioning from inactivity or whether it is a separate myopathy (disease specific to the muscles).

Deconditioning due to inactivity

It is recognised that patients with COPD and CHF become less active to avoid their symptoms. The effect of deconditioning on skeletal muscle in healthy subjects is similar to the changes seen in COPD and CHF i.e a reduction in type 1 fibres (100). Disuse is known to be associated with muscle wasting in healthy subjects (from immobilization with the use of plaster casts (101) and prolonged bed rest (102)). Deconditioning is therefore a credible cause for the skeletal muscle dysfunction seen with these diseases.

The distribution of muscle weakness has been investigated in both COPD and CHF. As discussed the quadriceps muscle has been shown to be smaller, weaker and

with a shift in fibre type proportion towards more fatiguable fibres. Other muscle groups have been examined to establish whether there is a global myopathy i.e supporting a systemic cause or whether it is localised to the locomotor muscles i.e supporting inactivity and deconditioning

Most measurements of muscle strength are volitional and subject to the effect of motivation. Non-volitional assessment has been studied, using twitch forces generated by magnetic nerve stimulation, and confirmed quadriceps weakness in COPD (103). Man et al compared quadriceps, adductor pollicis and diaphragmatic strength and showed preservation of adductor pollicis and diaphragmatic strength (103). Adductor pollicis strength is also preserved in patients with CHF in the presence of quadriceps weakness (104). Man et al subsequently examined the abdominal muscle strength in patients with COPD. The abdominal muscles were chosen because systemic processes may affect different muscle fibre types. Abdominal muscles have a similar fibre type proportion to the quadriceps muscle. Although the adductor pollicis strength was preserved steroids affect proximal muscles more than distal and so could still be a factor. Abdominal muscle strength was preserved (assessed by cough gastric pressure) showing that predominantly locomotor muscles are affected in COPD suggesting that deconditioning is a major contributing factor to the muscle dysfunction.

Physical inactivity (assessed by a questionnaire) has been shown to correlate with quadriceps strength and endurance in COPD(105). However whether this was a cause, an effect or both was not investigated.

Muscle mass and function decline with age (106), but the studies quoted above have used age matched controls to exclude confounding of the ageing process.

Supporting evidence, for deconditioning as a major contributing factor to skeletal muscle dysfunction, is the abnormalities have been shown to be at least partially reversible in with exercise training in COPD and CHF. This will be discussed further in the section; the mechanisms of the beneficial effects of exercise training. Muscle fibre type is shifted towards an increase in type 1 fibres or an increase in CSA of type 1 fibres and the oxidative capacity of the skeletal muscle is improved in COPD (48;107) and CHF (108-110). Muscle strength can be improved with strength training in COPD and CHF (111;112).

In COPD muscle endurance has been shown to be both correlated with physical activity (105), but also to be impaired in the presence of normal activity levels (46). Both studies were in small numbers of patients with a control group and activity levels were assessed by different questionnaires.

The effect of disuse on muscle has been investigated in other scenarios. There is an associated critical illness neuropathy and myopathy with ventilated patients on intensive care units (113). The mechanisms of the 'ICU myopathy' are incompletely understood but are likely to be multifactorial; inflammatory, disuse, nutrition, drugs e.g steroids, paralysing agents. There is some evidence that activity via neuroelectrical stimulation can improve the 'myopathy' (114).

Systemic inflammation, oxidative stress and nutritionSystemic inflammation

COPD is characterized by airway inflammation secondary to noxious particles, but systemic inflammation is also present. Systemic inflammation has also been reported in CHF. There is evidence of circulatory inflammatory cells and increased plasma levels of proinflammatory cytokines (TNFalpha, IL6, IL8, CRP) in both conditions (115-118). The precise contribution of systemic inflammation to a myopathy is still underdebate. One hypothesis is that this occurs predominantly in patients with a cachectic phenotype (119). There is some evidence of inflammation in the skeletal muscles in COPD and CHF, but there is little evidence in exactly which phenotypes this occurs and the mechanisms are poorly understood. TNFalpha is considered one of the most relevant cytokines in cachexia.

The results of a selection of studies investigating plasma or muscle TNFalpha in COPD are summarized in table 1.1. Two studies described increased levels of TNF alpha and nitric oxide synthases in the skeletal muscle of patients with COPD compared to controls (120;121). Petersen et al showed no difference between TNF alpha in skeletal muscle between patients and controls (122) and Barreiro et al demonstrated the levels of TNFalpha were reduced in patients with COPD compared to controls and levels of TNFa positively correlated with increasing muscle strength (123).

<i>First Author</i>	<i>Subject no</i>	<i>Disease severity†</i>	<i>Comparative groups</i>	<i>Inflammatory markers</i>	<i>Where measured</i>
Montes de Oca	15 patients 14 controls	FEV ₁ 43% predicted	Patients vs. control Normal vs. low weight	↑ TNFα and NOS¶ ↔ TNFα and NOS	Skeletal muscle
Rabino-vich	11 patients 6 controls	FEV ₁ 40% predicted	Patients vs. control	↔ TNFα ↑ TNFα	Plasma Skeletal muscle
Peterson	20 patients 11 controls	FEV ₁ 32% predicted	Patients vs. controls	↔ TNFα and IL6	Plasma and skeletal muscle
Barreio	19 patients 7 controls	FEV ₁ 33% predicted	Patients vs. controls	↓ TNFα	Skeletal muscle
Crul	14 in-patients 11 out-patients 7 controls		Between all three groups	TNFα not detected in the muscle. IL6 and IL8 similar in all groups	Skeletal muscle

†Mean FEV1 percent predicted, ¶Nitric oxide synthase (NOS)

Table 1.1. Summary of some of the studies investigating systemic inflammation in COPD

A recent study of hospitalized patients sought to evaluate whether the muscle wasting that occurs during hospitalization is due to disuse or inflammation. Muscle levels of IL6 and IL8 were similar to controls and muscle TNF alpha was not detected and the authors concluded that disuse was a more likely contributing factor to muscle

wasting (124). Many other inflammatory markers have been studied, but a detailed review is out of the scope for this introduction.

All of the studies discussed were performed on small numbers of patients because of the invasive nature of muscle biopsies. It is likely that larger studies would enable separate study of the different phenotypes of COPD.

There is similar literature available for CHF although some is from animal models. Elevated levels of TNF alpha has been reported in skeletal muscle of rats with CHF (125). Levels of muscle IL6 and TNF alpha inversely correlated with muscle mass and strength in a small group of patients with CHF, despite no difference between serum TNFalpha between the patients and normal controls (126). This is opposite to the positive relationship Barreiro described in COPD. There is conflicting molecular evidence of the action of TNFalpha on skeletal muscle. There is evidence that supports TNF alpha associated with muscle atrophy, but there exist other reports that it is associated with skeletal muscle regeneration. Further understanding of the action of TNFalpha is needed and larger studies to understand the role in the generation of a 'myopathy' in COPD and CHF.

Couillard reviewed the data for fibre type proportion in healthy active subjects, healthy sedentary and COPD and found that the type 1 fibre proportion was much lower (23%) than for healthy sedentary (44%) and healthy active (60-67%) and therefore concluded disuse or deconditioning was unlikely to be the only answer. However it is difficult to control for exact levels of activity and direct evidence of the causal effect of systemic inflammation on skeletal muscle is still needed in COPD and CHF.

The diagram in figure 1.1 demonstrates the potential relationships between inflammation and muscle dysfunction by Supinski (127).

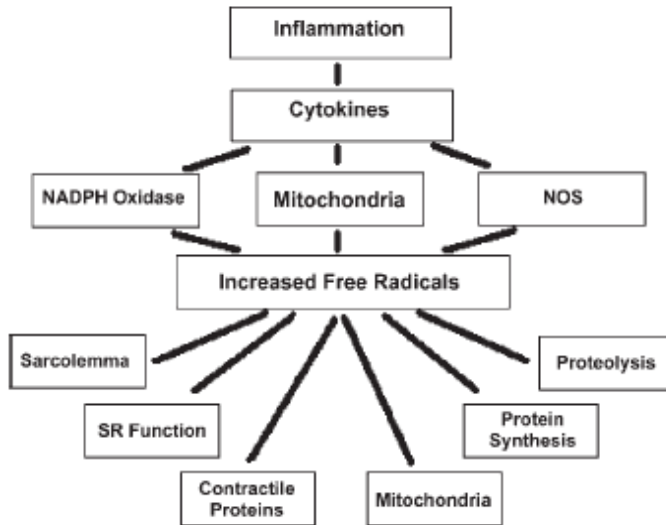


Fig. 1. Theoretical relationship by which inflammation induces muscle dysfunction. Inflammation is associated with cytokine release, and cytokines, in turn, activate free radical generation by skeletal muscle NADPH oxidase, mitochondria, and nitric oxide synthase (NOS). Potential downstream targets of free radicals include the sarcolemmal membrane, sarcoplasmic reticulum (SR), contractile proteins, mitochondria, protein synthesis, and proteolytic pathways.

Figure 1.1 Potential mechanisms of inflammation induced skeletal muscle dysfunction taken from Supinski's review (127).

The role of systemic inflammation on skeletal muscle is unlikely to be a single insult, but built into a complex chain of events which are described below.

Oxidative stress

The balance of oxidants and antioxidants is abnormal in both COPD and CHF and is associated with disease progression (128;129). Couillard reviewed the literature reporting the presence of oxidative stress in the skeletal muscle of patients with COPD (130). The levels of oxidative stress induced by exercise have been shown to be

inversely correlated with muscle endurance capacity (130). Three potential mechanisms were postulated; increase in myocyte apoptosis, reduced oxidative capacity and increased contractile fatigue. Systemic inflammation and hypoxaemia are potential mechanisms behind oxidative stress. In animal studies a measure of physical inactivity (hind limb holding) increases oxidative stress in skeletal muscle (131). In patients with COPD oral administration of N-acetylcysteine an antioxidant, improved both endurance time and exercise induced quadriceps oxidative stress above placebo (132) supporting a negative role of oxidative stress on exercise capacity in COPD. The mechanisms of systemic inflammation, oxidative stress and disuse may be inter-related.

In CHF, there has been much work examining the presence and effect of systemic oxidative stress, but very little about the effect on skeletal muscle. An animal model study of CHF examined the effect of oxidative stress on the diaphragm and soleus muscle and described weakness in both muscles compared to control (133). There was evidence of oxidative damage in the muscles and the MHC protein that was the most affected. The potential presence and effect of oxidative stress in the skeletal muscles of patients with CHF warrants further investigation.

Nutrition and protein synthesis and degradation

The nutritional state of patients with COPD and CHF is heterogenous. Both conditions can be associated with cachexia which is associated with a poorer prognosis (134-136). The definition and characteristics of cachexia are still not universal (137). The cachexia of COPD and CHF ('cardiac cachexia') is not ubiquitous and the causes are multifactorial.

Nutritional depletion occurs in about 20% of patients COPD and CHF (138;139). Calorie intake can be reduced because of breathlessness and early satiety in COPD and dietary problems correlate with a lower fat free mass index (140;141). In CHF there maybe deficiency in bowel absorption caused by reduced blood flow and oedema. Skeletal muscle dysfunction can be caused by malnutrition as evidenced by the literature in anorexia nervosa which was summarised in a review article (141). In anorexia nervosa there is muscle fibre atrophy, but the relative proportions of fibre type are normal. In contrast with the muscle dysfunction characterised in COPD and CHF, the glycolytic enzymes in the muscle were less active in anorexia nervosa. Tada et al reported that the abnormalities seen in skeletal muscle metabolism were not related to nutritional abnormalities in CHF and chronic lung disease, the subject numbers were small (142).

There is an association between cachexia and evidence of systemic inflammation in COPD and CHF. A subset of patients with COPD, with an increased resting energy expenditure and lower FFMI, have increased CRP levels and levels of circulatory cytokines (117;143). Cachectic patients with CHF have increased levels of TNF alpha and IL 6 and the levels correlated significantly with reduced muscle, fat and bone content (144).

Other mechanisms causing cachexia include alterations in the catabolic and anabolic pathways, the ubiquitin – proteosome pathway, and NF- κ B pathway (which is activated by TNF alpha) (145). A full review of the increase in catabolic and reduction of anabolic hormones is out of the scope of this introduction and is a topic in its own right. The following concentrates on the increase in catabolic factors.

The schematic version of these pathways in COPD are shown in figure 1.2 which was from a review by Debigare (146). The same mechanisms have all been outlined in CHF in a recent review (147). This review also discussed the regulation of fibre type involving the ‘growth hormone/insulin-like growth factor 1/calcineurin/transcriptional coactivator PGC1 cascade’. The involvement of the PPAR system behind the skeletal muscle dysfunction has also been studied in COPD (148).

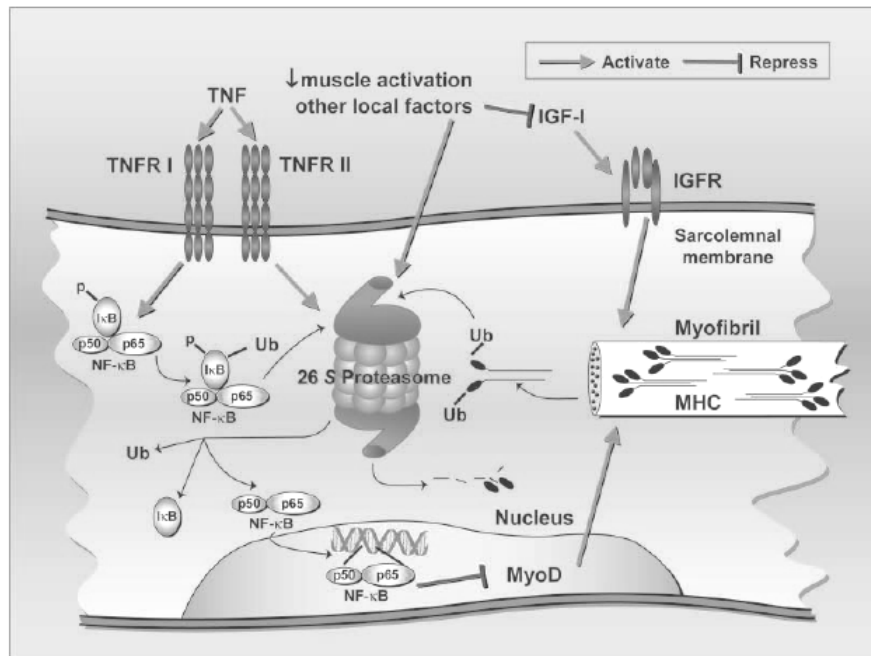


Figure 1. Schematic representation of the possible mechanisms of cachexia in COPD. Growth factors such as insulin-like growth factor-I (IGF-I) and MyoD have their anabolic effects by activating myofibrillar synthesis. Myofibrillar proteins are marked for degradation by ubiquitin (Ub) and are then processed through the 26 S proteasome. This protein degradation pathway can be activated by muscle inactivity. Proinflammatory cytokines such as TNF (shown here), IL-1, and IL-6, for instance, exert their catabolic action by activating NF- κ B, which can enter the nucleus after dissociating from its inhibitor (I κ B). One catabolic action of NF- κ B is to repress the gene expression of MyoD. Proinflammatory cytokines may also activate the ubiquitin-proteasome pathway. A reasonable hypothesis is that systemic (TNF, growth factors) as well as local factors (inactivity, acidosis) interact in the development of cachexia. Ub = ubiquitin; NF- κ B = nuclear factor κ B; I κ B = NF- κ B natural inhibitor; MHC = myosin heavy chain; IGF = insulin-like growth factor; IGFR = insulin-like growth factor receptor; TNF = tumor necrosis factor; TNFR I and II = tumor necrosis factor receptor I and II.

Figure 1.2. Mechanisms of cachexia in COPD from Debigere’s review

In both CHF and COPD the balance of catabolic factors (IL6 and cortisol) and anabolic factors (ie, bioavailable testosterone [Tbio], dehydroepiandrosterone sulfate [DHEAS], and insulin-like growth factor [IGF]-I) has been investigated as a cause of

cachexia. This was first investigated in CHF with a negative relationship shown between both TNF alpha and cortisol/DHEAS and BMI (149). Plasma insulin, cortisol, TNF-alpha, and norepinephrine correlate independently with wasting in CHF (150). In COPD, patients with a lower muscle mass (assessed by CT CSA of the thigh) had an increase in ratio of catabolic to anabolic factors (151). Testosterone in males is lower in CHF and COPD than in healthy men and is associated with quadriceps weakness in COPD (152;153). Other hormones have been implicated in the pathogenesis of cachexia in CHF e.g ghrelin, leptin, neuropeptide Y (154).

Koehler et al described an association between anorexia measured by a visual analogue scale and cachexia in COPD (155). The anorexia was directly correlated with a decrease in IGF-1 to GH ratio (anabolic hormones). There was supportive evidence of raised levels of inflammatory markers in cachectic patients. The paper raised the role of appetite stimulants which have been used in other conditions associated with cachexia.

There have been no direct comparative studies between COPD and CHF of muscle wasting and the presence of systemic inflammation or catabolic and anabolic factors. However, there are similarities between the causes of skeletal muscle dysfunction and cachexia in COPD and CHF and these include disuse, systemic inflammation, oxidative stress, an imbalance between anabolic and catabolic factors, and nutrition. These factors do appear to inter-relate.

Hypoxia

These are mechanisms behind the skeletal muscle dysfunction that are potentially different between COPD and CHF because of the different nature of the organ disease. Hypoxia at the muscle level may occur in both conditions, but by different mechanisms.

In CHF blood flow can be reduced to the peripheral muscles in CHF because of a reduced cardiac output and in COPD there can be reduced oxygen delivery to the skeletal muscle because of resting or exercise induced hypoxaemia.

Hypoxia induced by prolonged exposure to high altitude causes skeletal muscle wasting in healthy adults and loss of muscle oxidative capacity with a reduction in mitochondria [Reviewed in (156)]. In an experiment in healthy subjects, altitude was simulated with a hyperbaric chamber, reduced muscle mass was associated with a significant reduction in fibre type 1 by 25%, and a non significant reduction in type II fibres (157). An early study in COPD examined the effect of hypoxaemia on vastus lateralis muscle fibre type by causing haemodilution (158). The PaO₂ levels were increased with haemodilution (to normal Hb levels) and this was associated with a decrease in type II fibres. The proportion of type II fibres was also inversely related to PaO₂. In a study comparing patients with severe COPD with and without respiratory failure, both groups had a similar reduction in type 1 fibres (50). Studies demonstrating skeletal muscle dysfunction have shown abnormalities to be present in the absence of either chronic or intermittent hypoxaemia.

Around the similar time that it was shown that reduced cardiac output had little direct effect on exercise capacity in CHF, studies examining muscle metabolism using P-MRS investigated the effect of peripheral blood flow. The alterations in muscle metabolism were largely not related to impaired blood flow (159;160). Capillary density was reduced in skeletal muscle in CHF and was inversely related to exercise capacity (51;161). This has also been reported in COPD (162).

Overall hypoxia may play some part in the change in fibre type and oxidative capacity in COPD and CHF.

Age

Sarcopenia occurs with age [review (106)]. There is loss of muscle mass; a decrease of 20-40% between the ages of 20-60 yrs old and similarly a loss of muscle strength; a decrease of 20-40% by the 7th and 8th decade. Studies on skeletal muscle mass and function in disease states should ideally include age matched controls. MHC expression changes with age, with a reduction in type IIa and IIx fibres by about 10 and 14% per decade respectively, but no change in MHC type I fibres (163;164). The change in fibre type proportion seen with COPD and CHF cannot solely be explained as an age related phenomenon. The synthesis of the isoforms is reduced (165). In the same study myosin heavy-chain synthesis rate was correlated with measures of muscle strength, circulating insulin-like growth factor I, and dehydroepiandrosterone sulfate ($P < 0.05$) in men and women and free testosterone levels in men.

The loss of skeletal mass examined is largely the appendicular skeletal mass (approximately 75% of total body skeletal mass) and this can be measured by DEXA (166). Presumably this affects mechanistic studies as this is the muscle mass used for ambulation and activity. Interestingly, the contributing factors to sarcopenia in the elderly are similar to those postulated in CHF and COPD; physical inactivity, inflammation, poor nutrition, hormonal imbalance (106).

Medication

The pharmacological treatment of COPD and CHF is different, and some therapies for both can affect skeletal muscle. It is well recognized that steroids cause a

proximal myopathy. The muscle weakness in COPD is present in the absence of steroid therapy. Poux et al examined the tibialis anterior between 1) healthy controls, 2) patients with COPD taking long term steroids for over one year and 3) patients not on maintenance steroids and who had not been on short burst steroids for three months preceding the trial. There was no difference in energy metabolism or oxidative and glycolytic enzyme level between patients on long term steroids or not, but there was impairment of both energy metabolism and decreased oxidative and increased glycolytic enzymes compared to healthy controls (167).

ACE inhibitors and ATII antagonists are a common therapy for CHF and improve prognosis. ACE inhibitors have been shown to preserve peripheral muscle strength in patients receiving them for hypertension (168). ACE inhibitors have been shown to improve exercise capacity CHF. A recent study has shown that the muscle fibre type changes towards more type 1 fibres (169). Another study showed an increase in fibre type area of all muscle fibre types (170). These studies were over three and six months and exercise capacity was increased. Whether the fibre type change was as a result of increased activity or the other way around has not been established. Exercise capacity would not necessarily be expected to improve with ACE inhibition in patients with only hypertension and yet skeletal muscle function was relatively preserved in this group hinting at a direct effect on the muscle itself.

In healthy subjects a deletion polymorphism of the ACE gene is associated with higher circulating and tissue ACE activity. In health there is no difference in quadriceps strength between people with or without this polymorphism. However, in COPD the deletion polymorphism was associated with greater quadriceps strength (171).

Many patients with COPD are prescribed beta agonists, both short and long acting. In rats beta agonists appear to exert both potentially positive and negative effects on limb skeletal muscle. The MHC isoform is altered with increased levels of MHC type IIa fibre after four weeks administration of a β agonist pro drug (172). Similarly both unweighting (form of inactivity) and β agonist administration led to an increase in MHC type IIa in the soleus muscle of rats (173). Clenbuterol (β agonist) causes skeletal muscle hypertrophy and anti-atrophy in rats via the β_2 receptor. In healthy young adults three weeks of oral salbutamol improved quadriceps and respiratory muscle strength (174). One study in patients with CHF examined the effects of oral salbutamol on skeletal muscle by assessing quadriceps bulk by ultrasound and strength using MVC with the addition of a twitch response (175). No change was found on the quadriceps muscle after three weeks of salbutamol, but there were improvements in respiratory muscle strength. Although beta agonists are commonly prescribed in COPD there appears to be little in the literature assessing the effect on skeletal muscle in this group. Nava et al showed improved respiratory muscle strength in COPD after seven days of an oral β_2 agonist compared to placebo. The mechanism of improvement was not by improved pulmonary mechanics suggesting the involvement of peripheral muscle factors.

Cardiac and ventilatory limitations to exercise

There are some potential differences in exercise limitation between these diseases. The pulmonary component of exercise limitation involves lung function, ventilation and gas exchange. As airflow obstruction is the defining feature of COPD, and impairment of gas exchange is common these were thought to be the major limitation to exercise in COPD. Some patients with COPD have a ventilatory limit to exercise and one of the mechanisms behind this is dynamic hyperinflation (176). This occurs as a consequence of expiratory flow limitation. Dynamic hyperinflation is similar to air trapping or auto-PEEP seen in ventilated patients with acute asthma. The operational lung volumes are increased, increasing the work and weakness of the inspiratory respiratory muscles. Instead of being able to increase the volume of inspiration this plateau's and causes further increases in respiratory rate which worsens the hyperinflation. Pharmacological and surgical strategies can be employed to improve this. Dynamic hyperinflation is not a recognised feature of CHF.

Resting or exercise induced hypoxaemia is common in COPD and can result in inadequate tissue oxygenation as discussed under the mechanisms of skeletal muscle dysfunction. Patients with CHF rarely develop exercise induced hypoxaemia. However pulmonary abnormalities are recognized in CHF. Spirometric restrictive and obstructive deficits have been reported (177) with worsening deficits with increasing severity of heart disease. Cardiomegaly itself contributes to some of the restriction (178). However similarly to COPD spirometric measurements have little impact on exercise capacity (179). Several studies have demonstrated abnormalities in the diffusion capacity in CHF (180;181), but with conflicting results regarding the correlation with exercise capacity (182;183).

Patients with CHF have an early increase in ventilation during exercise with an increased VE/VCO_2 ratio, which is associated with a poor prognosis (184). This does not occur just because of an increase in lactate acid production (185), but is associated with an increased muscle ergoreflex (186;187). This is discussed in more detail in the subsequent section.

The associated co-existence of COPD and CHF is discussed later in the chapter, however left ventricular dysfunction per se is not a feature of COPD. Secondary pulmonary hypertension and right ventricular dysfunction are sequelae of COPD. The presence of pulmonary hypertension is associated with reduced ventilatory efficiency (188).

Neurohumoral activation

Neurohumoral activation is a pathological hallmark of chronic heart failure associated with chronic over activation of the sympathetic nervous system (SNS), but until recently had received little attention in COPD. Increased levels of adrenalin, noradrenalin, aldosterone, are all associated with a worse prognosis in CHF (189). In the 1980's the presence of Brain Natriuretic Peptides (BNP) were discovered (190). BNP is released from the left and right ventricles in response to stretch and is associated with a worse prognosis in CHF (191;192). They are potentially used to exclude heart failure in the community (193), assess responses to treatment and are involved in prognostic algorithms (194). BNP is also released from the right ventricle and is elevated in pulmonary hypertension and cor pulmonale (195-197).

BNP is absent in the blood of healthy humans. In athletes BNP is increased at the end of endurance events such as marathons. Plasma levels of BNP correlate with peak

oxygen consumption and exercise duration in CHF (198;199).

The skeletal muscle ergoreflex is affected as part of the overactivation of the SNS. The ergoreflex consists of the ergoreceptors which are the muscle afferents sensitive to exercise metabolites. The effect of the ergoreflex is assessed by performing two bouts of exercise, one with localised circulatory occlusion at the end of exercise (i.e. inactivating the reflex and also trapping the exercise metabolites in the muscle. This method has been shown to be reproducible (200). Overactivity of the muscle ergoreflex is associated with muscle wasting and reduced exercise tolerance in patients with CHF (201;202). The abnormality is present in both the upper and lower limbs suggesting a systemic effect.

The evidence described supports neurohumoral activation being associated with reduced exercise tolerance. However, plasma levels of catecholamines were not correlated with the degree of exercise capacity in CHF in one study (203).

A recent review summarised the evidence so far suggesting the presence of neurohumoral activation in COPD (204). Plasma noradrenalin is higher in patients with severe COPD compared to healthy controls (205). An elevated heart rate in patients with COPD has been demonstrated that can not be explained by medication alone (206). The muscle ergoreflex has had little investigation in COPD. A recent small study found no increase in ergoreflex activity in COPD compared to controls and therefore did not contribute to the ventilatory inefficiency seen (207). Although neurohumeral activation does not appear to be as dominant in COPD as for CHF, there is evidence of its presence.

There are other similar systemic manifestations of COPD and CHF are discussed

here for completeness although they do not directly affect the skeletal muscles.

Other systemic manifestations of both diseases

Anaemia of chronic disease

Both COPD and CHF have been associated with anaemia of chronic disease. In heart failure anaemia of chronic disease is associated with a poor prognosis independent of renal function and underlying ischaemic heart disease (208). A recent meta-analysis confirmed this; adjusted hazard ratios showed an increased adjusted risk for anemia (hazard ratio 1.46 [95% confidence interval: 1.26 to 1.69, $p < 0.001$]) (209;210). In COPD a prospective cohort study described 17% of patients as being anaemic (Hb<13d/L) (210). Anaemia was associated with a reduced median survival and was an independent predictor of functional capacity (assessed by the 6MWT).

The anaemia of chronic disease is thought to be mediated through inflammatory processes. In a cohort of 101 patients with COPD 13% were anaemic (Hb <13.5d/L) and these patients were associated with higher levels of CRP and IL6 and increased levels of EPO (EPO resistance) supporting an inflammatory process as the cause (211). A recent retrospective analysis has shown anaemia to be present in 33% of patients with COPD and this was associated with increased health care utilization (212)(Shorr AF).

The effect of therapies, aimed at the correction of anaemia, on exercise capacity are discussed under performance enhancement subsequently in the chapter.

Osteoporosis

Osteoporosis is associated with COPD and CHF (213-216). The nutritional, hormonal and inflammatory processes that affect the muscle potentially also affect the

bones of patients with COPD and CHF. Although this is unlikely to directly affect exercise capacity it is an important further systemic manifestation of these diseases. Evidence is also accumulating on the presence and importance of vitamin D deficiency in COPD (217). There is an association between systemic factors and vitamin D deficiency with associated worsening pulmonary function, inflammation and one study showed certain vitamin D genotypes influence quadriceps strength (218).

Anxiety and depression

Higher rates of anxiety and depression are documented in both conditions (219;220). This is often under-detected. Much of these symptoms are caused by the symptoms of breathlessness and the downward spiral of activity limitation and social isolation.

Effect of medication on exercise capacity

The pharmacological treatment of COPD and CHF is different and almost opposing in the case of beta agonists vs. beta blockers (albeit on different subsets of receptors). Some of the common medications used have an effect on exercise capacity.

ACE inhibitors and beta blockers are recommended prognostic treatments for CHF. Patients with COPD are not prescribed ACE inhibitors other than for co-morbid conditions. ACE inhibitors have been shown to improve exercise capacity and endurance in patients with heart failure (221;222). In healthy elderly patients 20 weeks of perindopril improved 6MWT by a mean of 31m compared to placebo (223). Proposed mechanisms for the improvement in exercise capacity range from peripheral vasodilation, neurohumeral modulation, endothelial modulation to the effects on skeletal

muscle described previously. At the time of writing no study had been published on the effects of ACE inhibitors of exercise capacity or skeletal muscle strength in COPD.

Beta blockers can make small improvements in exercise capacity in CHF (224), but this is not consistent (225;226). They do modulate the increased ventilation with exercise (227) so they may reduce the muscle ergoreflex. In one study the improvements with six months of carvedilol on LVEF and exercise tolerance were associated with reductions in BNP, but also TNF alpha and IL6 (228). This supports the 'notion' that neurohumeral activation and systemic inflammation are linked.

Tiotropium bromide is a long acting anticholinergic prescribed for COPD. It reduces resting and exercise hyperinflation, increases endurance capacity and reduces isotime fatigue and breathlessness scores (176).

In summary this part of the introduction has described the literature supporting the similar symptoms and disability of COPD and CHF.

- Both diseases are more like syndromes with similar systemic manifestations and common contributing factors
- The negative impact of these systemic consequences both on morbidity and mortality has been highlighted

The next section discusses and compares the development and effect of exercise training between COPD and CHF.

- The mechanisms (involving the systemic manifestations) of the improvements with exercise training are described and compared
- Finally the literature supporting the potential development of combined training programmes for COPD and CHF is explored

Strategies to improve the disability in COPD and CHF

History of exercise training in CHF and COPD

History of exercise training in chronic heart failure

In the 1970's several studies advocated bedrest for post partum, alcoholic, idiopathic and ischaemic cardiomyopathy (229-232). These were largely observational studies. 10 patients with ischaemic cardiomyopathy were hospitalised for bed rest (range 46 to 522 days) and their clinical course monitored (232). Four patients (4/9) had a decrease in heart size on a chest radiograph after six months of bed rest. It was thought that myocardial recovery occurred during bed rest based on the cardiac size reducing in four patients, but the mechanisms were not understood. The authors postulated that the reduced workload and myocardial tension, reduced myocardial oxygen requirements and improved hypoxia and that any improvement in survival would allow time for a collateral circulation to develop.

During the 1960's exercise training post myocardial infarction (MI) was investigated and early cardiac rehabilitation was developing (233). Exercise training was shown to be safe with a trend to improved left ventricular volumes, morbidity and cardiovascular mortality (234). An extension from exercise in patients post MI was to investigate the effect of exercise therapy on patients post MI that had LV dysfunction. There were fears regarding the safety of exercise in heart failure and early studies were performed on rats. Ten to twelve weeks of endurance training improved VO_2 max with a lower lactate response to submaximal exercise, compared to the sedentary group in rats (235). An early observational study on humans (n=10) demonstrated the feasibility of exercise training in patients with severe heart failure (236). Exercise capacity (expressed

by METS) and maximal oxygen pulse both improved with training. There was no exercise related morbidity and mortality. There were early reports of rehabilitation in 1960 before the studies of bed rest (237). Coats et al showed that home based training was feasible in stable patients with CHF in 1990 (238). The study included 11 patients that underwent eight weeks of home based cycling and then eight weeks of activity restriction as part of a cross over design. Patients improved their exercise duration by 2.6 mins and peak oxygen consumption by a mean 2.4 ml/min/kg. There were no adverse effects. Through the 1990's studies concentrated on the potential mechanisms of benefit from exercise training which will be discussed later in the chapter. There were far less studies involving practical physical training programmes.

Kavanagh et al performed a non-randomised, but controlled study of 52 weeks of aerobic training (moderate intensity 50-60% peak VO₂) on 21 patients mean age 65 yrs, 81% male and a mean LVEF of 21%. Patients undergoing training improved their exercise performance (assessed by the six minute walk test and peak VO₂ by a cardiopulmonary exercise test) whereas it was unchanged in the control group. No intergroup comparisons were made. Health status was assessed by the CHQ. Patients in the training group made statistically significant improvements in all four domains at 20 weeks, but the changes were not significant at one year. Over half of the improvement in 6MWT was made by week four and appeared to plateau by about 26 weeks. Subsequently two randomised controlled studies of long term training in CHF were performed have shown improvements in health related quality of life (HRQOL) (239) and exercise performance (239;240). The study by Belardinelli et al involved 110 patients randomised to moderate intensity training for one year or normal care. Both

peak VO_2 and quality of life improved in the training group and remained unchanged in the normal care group. This study was one of the first to show a reduced cardiovascular mortality with exercise training. All cause mortality was not significantly different between the two groups. The patients had a mean age of 55 yrs and were predominantly male.

The second randomised controlled study did not show any improvement in HRQOL after 3/12 of supervised training and 9/12 home based training (240). HRQOL was assessed by a responsive tool (Minnesota living with heart failure questionnaire). The patients in the exercise group improved the peak VO_2 at the end of both the 3/12 and 1year compared to the control group although the intergroup statistical significance was lost at one year. The training prescription was moderate intensity (60-70% max HR response) training (cycle, treadmill and arm ergometry) three times a week (two supervised) for 30 minutes. There was no education component. The study involved large numbers $n=180$. The patients were older than in the Belardenelli study with a mean age of approx 65 yrs and 80% were male.

In 2004 there was a Cochrane review of 29 RCT studies of physical training in heart failure and showed that exercise training improved VO_2 max by a mean of 2.16 ml/min/kg, exercise duration by 2.4 minutes and 6MWT distance by nearly 41m (241). Fewer studies (nine) had examined the effects of training on HRQOL and this was improved in seven of the studies. Another meta-analysis of 35 RCTs was published in 2006 and again reached the same conclusions regarding the beneficial effects of exercise training on exercise capacity and health related quality of life (based on the Minnesota living with heart failure questionnaire) (242).

The majority of these studies were conducted as primarily laboratory based training studies and the development of practical rehabilitation was slow to evolve. In part this may have been due to concerns over the safety of exercise training for patients with CHF, but recent studies have shown no adverse effects with training (241;243). In a prospective study of 80 patients NYHA II-III, with the primary aim to assess the safety of physical training, no adverse events were reported (243). In the Cochrane review of exercise rehabilitation for patients with CHF only 1/29 trials reported any adverse events associated with training.

There was a randomised controlled study involving practical rehabilitation vs. control in elderly patients with heart failure (244). Both groups received intensive medical therapy and visits during the trial so the medication was altered concurrently albeit in both groups. The rehabilitation group did make small improvements in walking distance and improved health status compared to normal care.

The way that exercise training and practical rehabilitation developed for patients with COPD was different and is outlined below.

History of exercise training and pulmonary rehabilitation in COPD

In COPD exercise training was incorporated and developed as the service of Pulmonary Rehabilitation much earlier and is currently a standard part of the management of COPD with international recommendations (grade A evidence) (245). However, there are still some guidelines with weaker recommendations (246). The investigations regarding the mechanisms of benefit occurred in parallel.

One of the earliest studies (1953) was based mainly on respiratory exercises for patients with emphysema (247) and one of the earliest references to rehabilitation for chronic lung disease was in 1958 (248). Clinical observations started to be made that exercise could benefit patients with chronic lung disease. In 1966 Ambrus et al performed an uncontrolled observational study of 43 inpatients with ‘chronic obstructive pulmonary emphysema’ undergoing a graded six week exercise programme. Walking time improved by approximately one minute and generally patients improved in the functional activities measured. Lung function also improved in just under half of the patients. It is not entirely clear whether the patients were already in hospital because of their disease or whether they were admitted for the exercises. If it were the former, without a control group the improvements may have just been the recovery from an exacerbation. No patient became acutely unwell during the exercises. As early as 1970 Thomas Petty published a report on an ‘ambulatory care system’ in 182 patients with ‘Chronic Airflow Limitation’⁷ (249). He wrote *‘the basic modalities of therapy are patient education, bronchial hygiene using simple home techniques, breathing retraining, physical reconditioning, oxygen and ancillary chemotherapeutic agents. The application of these principles in care provides great symptomatic benefit, improved exercise tolerance and a reduction in hospital needs’*. This was the beginning of the development of pulmonary rehabilitation programmes. By 1975 physical training was incorporated as part of a multi-disciplinary programme including education (250).

Alpert et al conducted one of the first mechanistic studies of physical training in COPD, but concentrated on the haemodynamic and pulmonary consequences (251). The study only included five patients with COPD, but involved invasive tests including a

⁷ Previous description for COPD

right heart catheter. The training lasted 18 weeks on a stationary bicycle that they took home for the duration of the study. Physiological improvements were demonstrated without any change in static lung function. Further discussion regarding the mechanisms behind exercise training occurs later in this chapter.

The importance of endurance training as a key component of pulmonary rehabilitation programme was highlighted in 1979 (252). Twenty patients with COPD underwent a programme of breathing exercises and were divided into two groups; with or without endurance cycle training. VO_2 max only improved in the group undergoing endurance training.

All the studies discussed so far were uncontrolled observational studies and one of the first controlled trials was published in 1980 (253). 33 patients with COPD were allocated to either exercise training or control. For convenience the allocation was selected by geography i.e those patients who lived in the city were allocated to exercise training (n=17). Patients in the exercise group improved their 12 minute walking distance with a reduced number of steps. The distance walked was unchanged in the control group. A crude assessment of dyspnoea, well being and physical activity was assessed by asking patients whether they had deteriorated, stayed the same or improved. No patients reported deteriorating in any of the three domains in the exercise group and all patients in the exercise group reported an improvement in dyspnoea. The subjective results were statistically significant between the exercise and control group.

The trials conducted progressed to a randomised controlled design. The earliest was in 1977 where patients with COPD were randomly allocated to exercises or normal care (254). The exercises were simple unsupervised stair climbing at home and a crude

individual prescription was made. The exercise group improved the 12MWT distance and cycling test after three months and these changes were not seen in the control group. One of the first studies conducted as inpatients was published in 1981 in Wales, UK (255). 39 patients with a mixture of coal workers pneumoconiosis and 'COAD' were randomised to six weeks supervised training, in a rehabilitation centre, and four months of home based training or to the control group. The exercise group improved their walking distance by 77m (12MWT) further than the control group $p < 0.05$. Ambrosino et al showed that medical therapy alone had no effect on exercise performance, but the addition of a short term rehabilitation programme improved exercise tolerance (256). As part of a review paper in 1989, Goldstein stated that pulmonary rehabilitation was popular in the USA and Europe (257). However, at this time there were only a few randomised controlled trials that had been conducted, all involving small numbers, but the service had already developed and was in progress. What constituted 'respiratory rehabilitation' was heterogenous and there were no definite guidelines or recommendations of what a programme should contain. One of the earliest reports on recommendations for pulmonary rehabilitation was published by the European Respiratory Society Rehabilitation and Chronic Care Scientific Group in 1992 (258).

One of the larger randomised controlled trials was published in 1994. Goldstein et al studied 89 patients with severe COPD that were randomised to either 'respiratory rehabilitation'; eight weeks of inpatient rehabilitation followed by 16 weeks outpatient rehabilitation, or normal care; conventional community care (259). The exercise group made significant improvements in exercise performance assessed by the 6MWT and quality of life assessed by the Chronic Respiratory Questionnaire. There were no

changes in exercise performance or quality of life in the control group. This was the beginning of evidence based support of the beneficial effects of exercise rehabilitation.

One of the first meta-analyses of pulmonary rehabilitation, or respiratory rehabilitation as it was then named, was in 1996. This was nearly a decade earlier than the first meta-analysis on exercise training for CHF was published. 14 RCTs were included and overall rehabilitation improved exercise tolerance assessed by the 6MWT (55.7m) and by an incremental cycle ergometer (ICE) test (8.3W) and health status; there were improvements over the MCID⁸ of the CRQ in two out of the four domains.

The first Cochrane review of pulmonary rehabilitation for COPD was published in 2002 (only two years earlier than for chronic heart failure) (260). 23 RCTs were reviewed (similar number to CHF – 29 RCTs). Similar results were found to the first meta-analysis. Patients undertaking pulmonary rehabilitation made significant improvements in walking distance and health status. However the mean improvement in 6MWT distance at 49m was just under the MCID (54m) (261). An update was reported in 2006 including 31 RCTs (262). The results on functional exercise capacity were similar (mean 6MWT - 48m) and the results were more positive for HRQOL with overall improvements being made in all four domains of the CRQ above the MCID of 0.5units.

In summary, exercise training improves exercise capacity and health status in patients with CHF and COPD, but exercise training was incorporated into a multidisciplinary programme of pulmonary rehabilitation for COPD at a much earlier stage.

So far only the benefits on exercise performance and health status of exercise

⁸ Minimum clinically important difference

therapy have been described. In the next section, the evidence of other benefits of exercise therapy and subsequently a comparison of the mechanisms behind exercise training between both conditions are discussed.

A comparison of the effects of exercise training in COPD and CHF.

The improvements in exercise performance and health status from exercise training have been described. The effect of a period of exercise training on broader outcome measures has also been investigated.

Improving physical performance is desirable, but it can not be assumed this directly translates to patients becoming more active. There is increasing recognition of the general importance of physical activity and health. Physical activity is associated with a marked decrease in cardiovascular and all-cause mortality (263). Patients with COPD and CHF have lower activity levels than healthy age matched controls (264;265). Lower activity levels in COPD are associated with increased risk of hospitalisation and a possible increase in mortality (266). In CHF lower activity levels are also associated with an increase in mortality (267).

Exercise training can improve physical activity in patients with COPD, but Pitta et al reported that this was only seen after longer term training (six months vs. three months) (268). The improvement in activity with PR was not related to improvements in walking distance or health status in another study (269). In CHF, three months of exercise training did not increase activity levels overall, but changes in activity were related to changes in peak VO_2 and quadriceps strength (270). It maybe that longer duration is needed to modify behaviour and increase physical activity.

In COPD, Griffiths et al described the effects of a short term training programme at one year (271). The improvements in exercise capacity and health status were reduced, but still present at one year. In the same study hospital admission rates were unchanged, but length of stay was reduced in the rehabilitation group and they required less GP home visits. A course of pulmonary rehabilitation has been shown to reduce the rate of exacerbations in COPD (272). Mortality as an outcome measure of pulmonary rehabilitation for COPD has received less attention than functional measures. There is a trend to improved survival in patients undergoing pulmonary rehabilitation (271-273). There appears to have been more studies with mortality as an outcome measure of exercise training in CHF. A meta-analysis of nine studies of exercise training in CHF showed a reduction overall in mortality (274). Hospital admission rates were also reduced with exercise training. A retrospective analysis of exercise training vs. normal care also showed less hospital events and days in the exercise training group (275). Duration of exercise training maybe important regarding mortality in CHF as one study showed greater improvements in mortality with long term (three years) vs. intermediate term (approx 18 months) training (276), although the two groups were allocated by the dropouts. More recently a large multi-centre study has reported a small reduction in mortality with short term training after risk stratification of patients (277).

Mechanisms of improvement of exercise training in COPD and CHF

Effect on organ impairment

The beneficial effects of exercise training in COPD are seen with little to no effect on FEV₁ (251;278) . Niederman et al showed that lung function also did not

correlate with the improvements in functional capacity, maximal exercise capacity and health status made with exercise training (279). Although resting lung function is unchanged with exercise, dynamic hyperinflation can be reduced leading to increased exercise endurance (280).

There have been several studies examining the effects of training on LVEF in CHF as there were concerns that training could worsen heart failure. Hambrecht et al examined the effect of six months home training on a cycle ergometer vs normal care in 73 patients with severe heart failure and found small a small improvement in LVEF and LV volumes with training (281). A multicentre study investigating the impact of exercise training on LV function found that long term training (6 months) attenuated abnormal remodelling and improved LV ejection fraction by 16% and which was unchanged in the control group ($p < 0.01$) (282). Another study confirmed a lack of any negative impact on LV function, but only a trend towards improvement after six months of training. However, there were statistically significant differences between LV function, volume and motion index between the trained group and the controls which may represent an anti-remodelling effect (283). All of these studies showed small but beneficial effects on LV volume and function.

Effect of exercise training on skeletal muscle

In COPD exercise training was incorporated early in the development of the PR service and the mechanisms elucidated subsequently. There was a view that the benefits were mainly psychological and that patients with COPD would not be able to exercise at the intensity for physiological adaptations to occur. In CHF careful mechanistic studies were conducted before practical rehabilitation developed. In both conditions similar true

physiological training has been shown. Physiological training is possible in both COPD and CHF. There are no published studies directly comparing the effects of exercise training between the two diseases.

In both conditions exercise training has been shown to delay the onset of an exercise induced lactate rise (107;284-286). The negative change in peripheral skeletal muscle fibre type distribution seen in both COPD and CHF is also at least partially reversed with exercise training. Hambrecht et al reported in 1997 a shift back towards type I muscle fibres after six months of training in CHF (287). There were also improvements in oxidative enzyme activity and an increase in mitochondrial density. These factors were unrelated to blood flow. Tyni-Lenne et al showed an improvement of skeletal muscle citrate synthase activity after only eight weeks of exercise training in CHF. Maltais et al demonstrated improvements in skeletal muscle oxidative enzymes with exercise training in COPD after twelve weeks (107). This was published in the same year as the similar study by Hambrecht in CHF. Whittom et al showed that fibre type cross sectional area was increased in type 1 and type IIa fibres, but the proportion of fibres were unchanged after exercise training (twelve weeks) in COPD (48). The skeletal muscle metabolism abnormalities are also partially reversed in both conditions. In COPD, PCr breakdown was reduced after eight weeks of training (288) and this has also been demonstrated after the same length of training in CHF (109). Both of these studies were published in 1999. In patients with CHF, Minnotti et al in 1990 reported improvements in the skeletal muscle metabolism after exercise training occurring without any change in cardiac function (289).

The beneficial effects of training on the skeletal muscle morphology and

metabolism support deconditioning as a major contributing factor to skeletal muscle dysfunction in both diseases.

Effect of exercise training on the other systemic manifestations of COPD and CHF

The effect of exercise training on the other systemic manifestations of the diseases has also been investigated.

There is some evidence of the presence of inflammation in the skeletal muscles in COPD and CHF and the effect of exercise training on both systemic and localised inflammation has been examined in both diseases. In CHF, twelve weeks of training lowered a number of peripheral inflammatory markers that have a role in endothelial function (290). In another study serum levels of TNF alpha, and IL 6 were unaffected by training, but the levels of expression for TNF alpha and IL6 in the skeletal muscle were significantly reduced (291). Similarly levels of serum inflammatory markers (TNF alpha and IL6) were not reduced after exercise training in COPD (292). Further work is needed to understand the effect of exercise training on systemic inflammation in both COPD and CHF.

There are only a few studies examining the effect of exercise training on oxidative stress either systemic or localised to skeletal muscle and they only involve a small number of patients. There is some evidence that exercise training leads to antioxidant effects in the skeletal muscle in CHF (293). In COPD, eight weeks of exercise training did not reduce resting systemic levels of oxidative stress, but did reduce exercise induced levels (294).

The effect of exercise training on neurohumoral activation has been studied in CHF. The literature regarding BNP and exercise training is discussed further in chapter

eight. Overall in CHF exercise training appears to have a beneficial effect demonstrated by a reduction in the levels of brain natriuretic peptide and a reduction in muscle sympathetic nerve activity (295-298). A beneficial effect of exercise training has been described on endothelial function in CHF (299;300). To date there are no published studies examining the effect of training on endothelial function in COPD.

Psychological

The improvement in exercise tolerance made with exercise training in COPD and CHF has a solid physiological basis as described above. Swerts et al showed that the improvement in exercise performance with training was not made by reducing a tolerance for dyspnoea in COPD (278).

The process of rehabilitation also has psychological benefits. Self efficacy for walking has been shown to improve with pulmonary rehabilitation, but not with patient education alone (301). Depression and anxiety are reduced in COPD after pulmonary rehabilitation assessed by formal psychiatric interviews using the Hamilton depression rating scale and the Hamilton anxiety rating scale (302). Significant reduction in anxiety and depression has also been shown in CHF after exercise training (303).

All the studies described in this section report an overall effect for the whole study population as, but in that population there is both a heterogenous effect of pulmonary rehabilitation and heterogeneity in the mechanism of benefit.

The majority of the studies discussed so far have used a variety of different exercise training regimens with the majority involving predominantly endurance based training, but the intensity, duration, situation, degree of supervision are all quite varied.

The next section discusses the evidence for what constitutes an optimal training programme.

Content of an exercise training programme

Modality

Different training modalities have been used, but cycling and walking are the commonest i.e a form of lower limb endurance training. Both modalities are effective at improving exercise performance in COPD (107;304) and CHF (305;306). Walking is an attractive modality because it directly translates to daily life. International guidelines for pulmonary rehabilitation advise lower limb training as an essential part of a programme supported by grade A evidence (307).

Intensity of training

The intensity of a training programme can mean either the frequency of training sessions or the intensity of the training prescription. Troosters performed a meta-analysis of training studies in COPD, examining the outcome of exercise performance by the 6MWT and found that the change in walking distance was related to the number of sessions undertaken (median 28 sessions; <28 sessions Δ 6MWT 34.5m compared to >28 sessions Δ 6MWT 50.3m) (308). Recently a retrospective analysis also shows a dose response benefit relating to physical activity and health related quality of life (309). The ATS statement on pulmonary rehabilitation states that three supervised sessions a week produces the 'optimal physiological benefits', but due to programme restraints two supervised and one unsupervised session a week may be acceptable (245). In CHF, few

studies have directly compared the training session frequency. The Cochrane review examined the effect of ‘dose’ of training on the change in exercise capacity, where the dose was a composite of the number of supervised sessions a week, the length of the training programme and the duration of the sessions (241). Overall the greater the dose the larger effect of peak VO_2 . The median dose was 30 units but the difference between <30 units and >30 units did not reach statistical significance.

There are various ways to calculate an individual training prescription e.g. percentage predicted peak or max VO_2 , percentage predicted peak HR, percentage of HRR⁹ etc. In COPD, high intensity endurance training programmes are feasible (310;311). One randomised controlled trial compared high and low intensity training (312). The high intensity group improved their peak VO_2 with training whereas the low intensity group did not, but the intergroup difference was not significant. The change in endurance capacity was significantly greater in the high intensity group than the lower. Maltais described high intensity training at 80% peak watts, but the duration of exercise was stipulated at 25-30 minutes. Only 5/42 patients achieved this. Other programmes have successfully used high intensity training from the onset, but allow the duration to increase (313).

For CHF there are few studies directly comparing intensity, but patients have managed high intensity training (85% predicted HR) (314). The Cochrane review states that the optimal training intensity is still unknown (241).

Interval versus continuous training

Some patients with COPD have a ventilatory limitation to exercise and groups have hypothesized that interval training may overall allow more work to be done than

⁹ Heart rate reserve

continuous training. In a cohort of patients with COPD, interval training and continuous training are just as efficacious in terms of peak exercise capacity (315). A recent study in CHF has shown aerobic interval training improves peak exercise capacity more than moderate continuous endurance training. For rehabilitating patients (i.e. inducing a behavioral change) conjecture could be that even the supervised sessions should involve walking and continuous exercise to encourage confidence with home training or activity. How daily activity is affected by the training modality and regimen is largely unknown.

Resistance and endurance training

As stated lower quadriceps muscle mass and strength is associated with a worse outcome in both populations. Improving muscle strength has therefore become an attractive target. In addition day to day activities also involve strength not just aerobic fitness e.g. sitting to standing, lifting etc. Resistance training has therefore been studied in both COPD and CHF with the aim of improving skeletal muscle function. Resistance training has been examined in COPD and CHF alone or in combination with endurance training, and the studies are described below.

In COPD resistance training alone has been shown to be feasible and well tolerated (111;316). In a randomised controlled trial of resistance training compared to endurance training alone, both training modalities led to similar improvements in exercise performance and health status (317). Quadriceps strength improved with both resistance and endurance training in a study by Spruit et al (317). In CHF, Pu et al showed there were no negative effects on resting cardiac indices with resistance training (112). Muscle strength improved and functional capacity improved assessed by the

6MWT. Hare et al showed an improvement in muscle strength with resistance training but no improvement in peak exercise capacity (318).

Randomised controlled trials have been performed in both diseases comparing combined resistance and endurance training compared to endurance alone. In COPD, patients undergoing combined training gained increased quadriceps strength compared to endurance training alone, but this did not translate into additional improvements in exercise performance or health status (319). A study of all three regimens; resistance vs. endurance vs. combined training, again showed only improvements in muscle strength in the regimens with resistance training (320). The resistance training group was the only group to significantly improve the ISWT distance. Endurance testing improved in all three groups, but was significantly higher in the endurance only group.

Similar randomised controlled trials have been undertaken in CHF with varied results. Beckers et al found that peak VO_2 improved similarly in the combined training group to endurance alone (321). Upper limb strength was improved in the combined training group and HRQOL improved more in the combined training group. Mortality and cardiovascular hospital admissions were similar between the groups. There have been two separate RCT's performed from the same research group from Luxembourg which drew slightly different conclusions regarding the effect on peak VO_2 . The first trial was comparing combined endurance and resistance training with endurance training alone (322). They concluded that combined training was superior to endurance alone regarding improvements in LV function, peak VO_2 and isokinetic extensor and flexor strength, however the intergroup differences were only significant for the improvement in LV function. Their second study published five years later was a RCT of combined

training vs. endurance alone vs. resistance alone vs. a control group (323). All training modalities improved peak VO_2 compared to control. QOL was not statistically improved for any training regime compared to control. Extensor muscle strength was not improved with endurance training alone, but was improved in both combined training and resistance training alone.

From the literature to date for both COPD and CHF, combined training improves peripheral muscle strength above that of endurance training alone. This does not appear to translate into additional improvement in exercise performance and health status compared to endurance training alone. Physical activity was not an outcome measure for these studies so whether the improvement in strength translates to increased physical activity is still unknown. There is evidence that weaker muscle strength is correlated with a worse prognosis, but it is not yet known if peripheral strength is improved whether this translates to a better prognosis. The sustainability of muscle strength after a course of resistance training is also largely unknown for both conditions.

Respiratory muscle training

Respiratory muscle training has received much attention for patients with COPD and some for CHF. A recent meta-analysis of RCTs of inspiratory muscle training in COPD was rigorously performed (324). Only a small number of trials were included fitting the set criteria. Overall inspiratory muscle training improved inspiratory muscle strength and endurance, and dyspnoea, but did not affect peak VO_2 . The mean 6MWT improved by 32.1m (MCID 54m). Quality of life assessed by the CRQ was significantly improved, but by a small amount. The ACCP guidelines for pulmonary rehabilitation in COPD do not support the routine use of inspiratory muscle training (307).

Similarly in CHF inspiratory muscle training (IMT) can improve respiratory muscle strength, improve dyspnoea and improve functional capacity (325). Studies have had varied results on peak exercise capacity with IMT in CHF showing both neutral (326) and positive (327). Inspiratory muscle training was not mentioned in the Cochrane review of exercise rehabilitation for CHF (241).

Performance enhancement

Performance enhancement for exercise training has been comparably investigated in both COPD and CHF. As discussed earlier the potential causes of exercise intolerance and skeletal muscle dysfunction are similar between the diseases and the studies involving performance enhancement have also been similar. The athletic literature is likely to have influenced study investigators for both conditions.

Nutrition

Nutritional supplementation has been investigated in COPD and CHF by increasing calorie, amino acid, fatty acid and creatine intake. This is a large topic so only the studies examining performance enhancement are discussed. Studies have been conducted based on the hypothesis that nutritional depletion is associated with reduced muscle mass and function and therefore enhancing nutrition may improve skeletal muscle function and physical performance. Endurance training can cause loss of weight which may not be desirable.

The effects of calorie and creatine supplementation as adjuncts to exercise training have been investigated separately in randomised controlled studies, but neither improved physical performance above exercise training alone in patients with COPD (328;329). Creatine supplementation appears to improve skeletal muscle metabolism and

performance in CHF (330;331), but has not been studied in addition to exercise training. A small study has shown an improvement in exercise capacity by amino acid supplementation (for only 30 days) in patients with CHF (332).

Although it could be hypothesised that the cachectic patients would be most likely to benefit from nutritional supplementation Steiner et al showed it was the non-depleted patients who had improved exercise tolerance with the combination of exercise training and carbohydrate supplementation.

Oxygen

Oxygen supplementation is advised for patients with COPD with either resting or exercising hypoxia (245). The original advice was for safety, based on the premise that cardiac arrhythmias were more likely to occur with hypoxaemia. The response to oxygen supplementation in patients with hypoxaemia is heterogenous. Garrod et al performed a randomised controlled trial of supplemental oxygen during exercise training versus air in patients with COPD with exercise induced hypoxaemia (resting mean PaO₂ 8.5 kPa) (333). The symptom of dyspnoea improved, but there was no overall effect on performance. Rooyackers et al conducted a similar study with similar results (334). A recent Cochrane review found similar results, but there are limited studies with a robust design and they only involve small subject numbers (335). The potential problems with oxygen supplementation are the weight of the oxygen cylinder and potentially not fully correcting exercise hypoxaemia.

The effects of hyperoxia on exercise capacity has been studied in COPD (submaximal exercise capacity) and CHF (both maximal and submaximal exercise capacity) and in both conditions exercise performance improved with hyperoxia

(336;337). Oxygen supplementation during exercise training in normoxic patients with COPD improved exercise endurance above training alone (338).

To date oxygen supplementation as an adjunct to exercise training has not been assessed in CHF. There is not the obvious role for oxygen supplementation because of neither exercise induced hypoxaemia or dynamic inflation. However the effect of oxygen on skeletal muscle metabolism is also not completely understood and this was not investigated in the papers by Somfay or Moore. The role of oxygen supplementation in CHF has the potential to be explored.

Testosterone

Lower testosterone levels in COPD are associated with reduced quadriceps weakness and therefore are a potential therapeutic target. Casaburi et al compared four groups; testosterone supplementation and placebo, with and without resistance training in male patients with COPD and low testosterone levels (339). The testosterone levels were significantly increased with supplementation and led to increases in weight. Peak VO_2 was increased compared to the non training group, but not more than the testosterone alone group. However, the peak VO_2 was not increased in the training alone group. A similar trial is in progress investigating the effects of testosterone therapy as an adjunct to exercise rehabilitation in hypogonadal males with CHF (340). The results have not been published yet.

Medication

ACE inhibitors and to a lesser extent beta blockers improve exercise capacity in CHF. The addition of ACE inhibition to exercise training in CHF did not lead to additional improvements in peak exercise capacity (341). There was some concern that

exercise training may not be as efficacious in the presence of beta blockade because of chronotropic incompetence. This concern has so far been unfounded (342;343), but cardioselective beta blockade does not appear to enhance the effects of training either. In COPD tiotropium¹⁰ has been assessed as an adjunct to pulmonary rehabilitation with additional improvements on exercise tolerance and health status (344).

Anaemia

Methods of correcting the anaemia of chronic disease and the impact on exercise capacity have been assessed. In CHF, intravenous iron was associated with improvements in relative peak VO_2 in patients with anaemia, but no change was seen in the non anaemic group. Six month treatment with darbepoetin alfa, an erythropoiesis-stimulating protein (ESP) increased haemoglobin levels in anaemic patients with CHF and improved HRQOL, but no change in exercise capacity or duration (345). In COPD only the effect of a blood transfusion has been investigated and this was described in a cohort of stable mechanically ventilated patients (346). The minute ventilation and work of breathing was reduced after transfusion.

Therapies aimed at the underlying inflammatory process maybe more beneficial rather than those aimed at improving the haemoglobin level.

Exercise training as part of a rehabilitation programme

The dictionary definition of the verb ‘to rehabilitate’ is the process of restoration of skills by a person who has had an illness or injury so as to regain maximum self-sufficiency and function in a normal or as near normal manner as possible.

¹⁰ a long acting anti-cholinergic

Rehabilitation medicine is *'a branch of medicine dealing with restoration of function despite physical disability. The development of a person to their fullest physical, psychological, social, vocational, and educational potential consistent with his physiological or anatomical impairment'*.

Exercise training was incorporated into a programme of pulmonary rehabilitation at an early stage for patients with COPD. Although the service has been termed pulmonary rehabilitation as exercise training is an essential component, the term exercise rehabilitation could be used. As stated before, this service has not developed in the same way for CHF. The next section describes what is already known about several features of a programme e.g. core components, duration, supervision, and the setting, but is predominantly describing the literature regarding COPD.

Duration of training programme

The optimum length of training programme is also unknown. Training programmes for COPD have ranged from four weeks to over one year. Physical training can lead to improvements in peak exercise capacity within a short period with high intensity training; there is evidence that this can occur within four weeks in both conditions (304;347;348). The process of rehabilitation may take longer, but health status improvements are seen within four weeks in COPD although these are less than after seven weeks of training (349). A further study with all the measurements made at seven weeks showed that after four weeks of supervised training improvements in health status continued and were similar at seven weeks compared to the seven week programme (304). The effects on the mastery component were less for the four week group. The ATS guidelines recommend at least seven weeks of training.

Studies comparing the duration of exercise training have been conducted in COPD and CHF. In COPD, 18 months of training improved self reported disability, but no measure of exercise performance significantly greater than three months of training (350). The trial was randomised. Tenenbaum et al observed patients with CHF undergoing exercise training for three years and compared a group that finished after 18 months with those that completed three years (276). The trial was neither randomised nor groups allocated a priori. The authors concluded that three years of training improved survival and exercise tolerance above intermediate training 18 months. The analysis was almost of completers vs. non completers and therefore there were many confounding variables other than just the duration of training.

There is evidence in COPD that the benefits from a short term programme are present at one year, but are reduced (271). The benefits of rehabilitation are not sustained long term and are no longer present after two years (301).

Maintenance programmes

In view of the lack of the long term sustainability of the improvements in exercise performance and health status the use of maintenance programmes have been reported. The timing and format is still being investigated. Ries et al evaluated weekly telephone calls and monthly supervised sessions after PR for one year compared to no maintenance (351). At the one year assessment exercise performance (maximal treadmill test and 6MWT) and health status were significantly higher in the maintenance group, but there was continued decline at two years. Repeating pulmonary rehabilitation at yearly intervals improved short-term outcomes, but these were not sustained at two years

(352). Although there were only small numbers, exacerbation frequency was less in the group who had yearly PR for two years.

Timing

Maintenance programmes try to adapt behaviour long term. Another strategy is to intervene after an exacerbation, the time where lung function, exercise capacity and health status declines. Man et al conducted a randomised controlled trial of community rehabilitation after hospitalisation for acute exacerbation of COPD (353). The ISWT distance and all four domains of the CRQ were statistically improved at three months compared to the normal care group. The study showed that early rehabilitation post exacerbation of COPD was feasible and safe.

Situation

Studies in COPD and CHF have shown that exercise rehabilitation can be conducted successfully in different environments; in patient, out-patient, in the community or as home based training (306;354). Multiple factors affect the efficacy of a programme; safety, quality of the programme, compliance. Practically different environments may suit different patients.

Guidelines for exercise therapy in COPD and CHF

There are international guidelines recommending PR in COPD (245). Although national guidelines recommend exercise for CHF they only suggest that ‘this may be more effective when part of an exercise programme’ (2003)(355). In contrast the same national body (2004) recommended PR for all appropriate patients with COPD with five statements of recommendations and a definition of PR. International guidelines for exercise and rehabilitation exist for CHF, but although detailed in the supporting

evidence for exercise training in CHF, how this translates into a pragmatic rehabilitation programme is only minimally covered (356;357;357).

It maybe assumed that patients with CHF will be incorporated into cardiac rehabilitation (CR) (357), but this is a service centred around secondary prevention. Patients with CHF have more in common with patients with COPD than the traditional CR population (358). A meta-analysis of exercise based CR for patients with coronary heart disease reported the benefits in terms of a reduction in mortality, total cholesterol, systolic blood pressure and smoking. Health related quality of life was not improved above normal care. The results of exercise performance were not mentioned supporting the priority of modifying risk factors. A recent study showed an improvement in exercise capacity from a CR programme in patients with CHF, but it was not clear if this was an existing CR programme for patients with CHD or whether it was solely for patients with CHF (303).

Coexistent disease

Co-existent COPD and CHF

So far the discussion has dealt with COPD and CHF as single disease entities, but these conditions often coexist and are under diagnosed. In a cohort of 405 patients with known COPD >65 yrs old from the Netherlands, 20.5% had undiagnosed CHF (359). The study highlighted the difficulty of not having a single reference test as a gold standard and a consensus expert panel determined the presence or absence of heart failure. Although used clinically, an echocardiogram is imperfect as a reference test (7) and there are technical problems in patients with COPD particularly if they are

hyperinflated . In one study 18/52 patients with COPD were excluded because of poor echocardiogram images (360). In a retrospective study of 186 patients with LVSD the prevalence of COPD was 39.2% (361). Concomitant severe COPD was associated with a worse prognosis. Another study evaluated the prognostic value of COPD in 5010 patients with CHF (362). They found that concomitant COPD was associated with worse symptoms, an increase in hospitalisations and an increase in non cardiovascular mortality. Similarly, patients hospitalised with heart failure had a worse short term prognosis if they also had COPD (363). In a cohort of patients with COPD undergoing pulmonary rehabilitation 14.7% had known CHF (364). The authors compared the results of PR depending on the particular co-morbidities. However, coronary disease and CHF were combined in the analysis so the results of the effect of CHF only with COPD are unknown. If exercise programmes are designed around different disease entities it would leave uncertainty which programmes patients with combined disease should be referred to.

Growing interest in the similarity between COPD and CHF

There have been reviews comparing the similarity of the muscle dysfunction between COPD and CHF (365;366) and one study directly compared the systemic manifestations on exercise capacity (95). After the studies described in this thesis were performed, one review has also highlighted that the management of these conditions could also be combined (367). To date there are no published studies directly comparing the responses to exercise training between COPD and CHF.

Pulmonary rehabilitation for ‘non COPD patients’

Although much of the literature for PR is for COPD there is an expanding group of other chronic respiratory patients who also gain benefit e.g. pulmonary fibrosis (368), bronchiectasis (369), cystic fibrosis (245) and also non respiratory e.g. obesity, pulmonary hypertension. One of the largest cohorts comparing the effects of pulmonary rehabilitation in patients with and without COPD showed that both groups benefited similarly in terms of functional capacity (6MWT) and health status (370). This was a retrospective analysis.

Skeletal muscle dysfunction has been shown to be present in other chronic pulmonary and non pulmonary conditions. Quadriceps weakness is present in pulmonary fibrosis and is an independent predictor of exercise capacity (371). Bauer et al described forearm weakness in patients with idiopathic pulmonary hypertension (372). Skeletal muscle weakness was present in patients with chronic kidney disease on haemodialysis and was associated with reduced exercise capacity (373). Nutritional status was the only predictor of loss of strength (374). In a comparison of patients with chronic renal failure and healthy sedentary controls ankle dorsiflexor muscles were weaker with atrophy of the contractile area in the patients and they were less active (375).

Exercise performance and health status can be improved from pulmonary rehabilitation in patients with pulmonary fibrosis (368). The Cochrane meta-analysis for patients with interstitial lung disease only included two RCT studies with a total of 43 patient undergoing training and 42 controls (376). Improvements in exercise

performance measured by the 6MWT (38.6m) and health status were seen with PR compared to the control group.

PR has been investigated in bronchiectasis. The Cochrane review published a negative conclusion, but it was only based on two studies in abstract form (377). Newall et al reported a RCT of PR vs. combined PR and inspiratory muscle training vs. normal care and showed significant improvements with PR in exercise performance and health status (369). There was no additional benefit in these parameters with IMT.

The ‘non COPD’ patients have been successfully incorporated into PR programmes. The success could be through targeting the common disability of activity limitation due to breathlessness.

Access to rehabilitation

There is at least in the UK still a shortage of rehabilitation programmes. A study by the BTS found that only 1.7% of patients with COPD had access to pulmonary rehabilitation (378). Keteyian highlighted in 1997 that despite the benefits of exercise training in CHF there were many patients who were not receiving this therapy (379). A recent national audit concluded that only a tiny fraction of patients with heart failure will receive rehabilitation (380) and recent American guidelines involving cardiac rehabilitation (CR) excluded CHF (381).

Chronic diseases are increasing in prevalence and there is an increasing number that may benefit from exercise rehabilitation. Strategies how to manage this are necessary. It may be that disability centred programmes maybe more cost effective than multiple disease centred programmes. However, the feasibility of this first needs investigating.

Hypothesis

There is clear supportive evidence that exercise training has multiple beneficial effects for patients with CHF, but there are fewer studies involving practical rehabilitation and patients may not have access to this service. In view of both the similar symptoms of exertional breathlessness and fatigue and the mechanisms of disability between COPD and CHF, the hypothesis was that the established model of pulmonary rehabilitation could be successfully applied to CHF and that both groups could be beneficially trained together. If successful this would provide a format of deliverable rehabilitation for patients with CHF, and if training both groups together provided similar benefits this would advance the concept of generic exercise rehabilitation for activity limitation due to exertional breathlessness.

This thesis describes;

- a randomised controlled trial of pulmonary rehabilitation compared to normal care in patients with CHF
- a comparative observational study of pulmonary rehabilitation between COPD and CHF

This required new, more generic outcome measures;

- the outcome measures used commonly in COPD were applied to CHF and those previously not used in CHF were assessed in CHF (ESWT, MRC, PFSDQ-M, CHQ-SR)
- As a subsidiary study the effect of exercise training in both CHF and COPD on biomarkers indicating neurohumoral activation (BNP) and systemic inflammation (CRP) were investigated.
- A direct comparison of the proportion of skeletal muscle fibre types and the effect of pulmonary rehabilitation was reported between COPD and CHF. The potential role of skeletal muscle PPAR gene expression in the adaptations to training was investigated.

Chapter two

Methods

Content

Design of the studies

Subjects

Recruitment

Randomisation

Intervention

Power calculation

Outcome measures

Background to the outcome measures

Physical performance

ISWT/ESWT, CPX and muscle strength

Health Status

CHQ/CRQ, SF36

Functional status

MRC dyspnoea scale, PFSDQ-M

Muscle biopsy

Fibre type proportion, Peroxisome proliferator activated receptors

Neurohumoral activation and systemic inflammation

Plasma NTBNP and CRP levels

Background

The **previous chapter** described the similarity between the systemic manifestations of COPD and CHF. Exercise training has been shown to improve exercise performance and modify some of the negative consequences of both diseases. Practical rehabilitation has not evolved the same way for CHF as it has for COPD.

In view of the similar symptoms and mechanisms behind the activity limitation the hypothesis for the main studies were

- the model of pulmonary rehabilitation could be successfully applied to patients with CHF
- patients with CHF and COPD could make similar improvements in exercise performance and health status from pulmonary rehabilitation and be beneficially trained together.

This chapter describes the methodology of the study designs and describes the outcome measures used

Study design

Two trials were designed in order to achieve the two main aims of this programme of work.

The first aim was to investigate whether patients with CHF could gain benefit in exercise performance and health status from a pulmonary rehabilitation programme compared to normal care. In order to establish this, a randomised controlled trial of pulmonary rehabilitation vs. normal care was conducted for patients with CHF in the context of an existing pulmonary rehabilitation (PR) programme.

The second aim was to establish whether patients with CHF could gain comparable benefits in exercise performance and health status from a PR programme to patients with COPD. An observational, comparative trial of the outcomes of PR between patients with COPD and CHF was therefore conducted. The two trials were conducted simultaneously.

Study design of both trials

- 1) A randomised controlled trial of pulmonary rehabilitation vs. normal care for patients with CHF**
- 2) An observational comparative trial of pulmonary rehabilitation between patients with COPD and CHF**

Subjects

Chronic Heart Failure

Patients with a clinical diagnosis of Chronic Heart Failure according to the European Society of Cardiology guidelines (212), New York Heart Association (NYHA)

class II-IV and evidence of left ventricular dysfunction on echocardiography¹¹ were eligible to participate. All patients had access to a community chronic heart failure nurse for at least three months prior to the trial and pharmacological treatment was optimised. No other intervention was to be performed during the study period and medication relating to CHF was unchanged. Patients with a major neurological, locomotor or peripheral vascular limitation to exercise were excluded. Other exclusion criteria were sustaining either a myocardial infarction or troponin positive acute coronary syndrome within three months, unstable angina, moderate to severe aortic stenosis, sustained ventricular tachycardia, and Chronic Obstructive Pulmonary Disease (COPD) or an obstructive ratio on spirometry (FEV_1/FVC of $<70\%$).

Chronic Obstructive Pulmonary Disease

Patients with COPD were eligible to participate if they had a clinical diagnosis and supporting spirometry of an FEV_1/FVC of $<70\%$ and an FEV_1 $<80\%$ predicted (Gold stage II or worse) (6). Patients were excluded if they met requirements to train with supplemental oxygen¹². Supplemental oxygen can improve dyspnoea and may affect other outcomes from exercise training (333;335). Exercise induced hypoxia was likely to be more common in patients with COPD than CHF and therefore the effects of training with supplemental oxygen could introduce bias to the outcome of rehabilitation when comparing the two groups.

¹¹ The echocardiograms had been performed as part of the patient's clinical care. They were re-reported by one operator at the end of the trial.

¹² In the local PR service any patient that has a peak desaturation of $<85\%$ has a repeat ISWT with supplemental oxygen. If they perceive an improvement they are offered supplemental oxygen during training.

The other exclusion criteria described for the patients with CHF were applied to COPD.

Recruitment

Patients with CHF were recruited from community chronic heart failure nurses and from cardiology outpatient clinics. All patients had originally been reviewed by a consultant cardiologist. Patients with COPD were recruited from the local Pulmonary Rehabilitation waiting list. They had been referred for PR primarily from the respiratory outpatients¹³.

Trial progression

The study was conducted from January 2003 until June 2006. The trial duration was ten weeks for both trials (figure 2.1). Patients attended four visits during the first two weeks to perform all the baseline outcome measures. On the first visit written consent was obtained and the hospital medical notes were reviewed. The patients' height and weight were recorded and a resting electrocardiogram (ECG) performed.

After they had completed all the baseline measures they were randomised to either seven weeks of rehabilitation or seven weeks of normal care. During the final week they attended two visits to complete the post trial measurements.

¹³ Patient information leaflets and consent form are in appendix II

	Week Number	Visit Number	Content
Two week control period	0	Visit One	Consent FFM CPX Muscle strength Questionnaires
	1	Visit Two	ISWT/ISWT/ESWT
		Visit Three	CPX Venous blood sampling Muscle strength Questionnaires
		Visit A Optional	Muscle biopsy
Start seven weeks of PR or NC	2	Visit Four	ISWT/ESWT
End of intervention	9	Visit Five	ISWT/SWT
Final week of measurements	10	Visit Six	FFM CPX Venous blood sampling Muscle strength Questionnaires
		Visit B Optional	Muscle biopsy
STUDY COMPLETED			

Figure 2.1. Study protocol for the patients with CHF

	Week Number	Visit Number	Content
Two week control period	0	PR assessment	ISWT/ISWT/ESWT
	1	Visit Two	Consent FFM CPX Muscle strength Questionnaires
		Visit Three	CPX Venous blood sampling Muscle strength Questionnaires
		Visit A Optional	Muscle biopsy
Start seven weeks of PR	2	Visit Four	ISWT/ESWT
End of intervention	9	Visit Five	ISWT/SWT
Final week of measurements	10	Visit Six	FFM CPX Venous blood sampling Muscle strength Questionnaires
		Visit B Optional	Muscle biopsy

STUDY COMPLETED

Figure 2.2. Study flow diagram for patients with COPD

Randomisation

Patients with CHF were randomised to receive rehabilitation or normal care. The subjects in the rehabilitation group were also part of the second trial (the comparative trial of PR between COPD and CHF) which required larger numbers¹⁴ therefore patients were randomised 2:1 rehabilitation to normal care respectively. The randomisation was undertaken by the Trent Institute of Health Research and was performed in blocks of four. Treatment allocation was concealed by an outside researcher and revealed after all the baseline testing was complete.

Intervention

Pulmonary Rehabilitation

An existing outpatient pulmonary rehabilitation programme for patients with chronic lung disease was used. The seven week programme involved two hospital visits a week for two hours (one hour of exercise and one hour of multidisciplinary education) and daily home training. The training was predominantly endurance with walking as the main modality. The walking speed was individually prescribed at high intensity; 85% VO₂ peak derived from the Incremental Shuttle Walk Test (ISWT) performance. The duration of the walk was assessed by the Endurance Shuttle Walk Test (ESWT) and was increased daily throughout the seven weeks at a constant speed constant. Patients kept a home diary to assess progress and compliance. Peripheral muscle exercises using free weights were recommended three times a week, once at hospital and twice at home.

The hour of exercise at the hospital began with a warm up. Patients subsequently performed the exercises using free weights (appendix III) recording the weight used and

¹⁴ See power calculation for further explanation

their perceived breathlessness (BS) and exertion (PE) using the Borg Scale (382;383). This was followed by their timed walk. Patients were encouraged to have their own stop watch to record the duration of their walk at home. For the second hospital session instead of using the free weights patients performed five minutes of cycling. The intensity of the cycling was increased, but not the duration because of the time pressures in the class.

The education component was a one hour lecture for both hospital sessions delivered by a member of the multidisciplinary team. The topics included a combination of pulmonary specific; disease education, inhaler use, pulmonary physiology and generic talks; exercise, energy conservation, nutrition, benefits advice. The talk order continued on a rolling basis. Patients were recruited to PR on a rolling basis i.e. new participants were enrolled each week.

Normal Care

The control group received their normal care for seven weeks with no extra visits.

Power Calculation

Advice for the statistical power for both the studies was sought from the Trent Institute for Health Research.

1. Randomised controlled trial of physical training versus normal care in patients with Chronic Heart Failure

Patients with CHF were randomised to two groups; either seven weeks of exercise training or normal care. The difference in the change in ISWT distance between the rehabilitation group and the normal care group was set at 50m. This was based on the minimum clinically important difference of the change in ISWT being 47.5m in patients with COPD (384). From local experience of the Pulmonary Rehabilitation programme in patients with COPD the standard deviation of the change in incremental shuttle walk test performance was estimated at 50m. To detect a difference in the change in ISWT of 50m between the two groups and assuming a standard deviation of the change in ISWT of 50m, with 80% power at the 5% level of significance 17 patients would be needed in each group.

2. A comparison of the physical training responses between Chronic Obstructive Pulmonary Disease (COPD) and Chronic Heart Failure (CHF) in the context of a Pulmonary Rehabilitation programme

The acceptable difference between the mean change in the ISWT to assume equivalence (non-inferiority) between CHF and COPD was decided clinically to be <30m. This was based on the SD of the change in ISWT between two tests after familiarisation being 20m (385) and the difference between patients detecting their

exercise tolerance as better or much better was 31m (384). Assuming a standard deviation of the change in ISWT distance to be 50m and with 80% power at the 5% level of statistical significance 44 patients would be needed in each group.

A total of 61 patients with CHF and 44 patients with COPD were needed to complete both the trials. Allowing for a 15 % dropout rate, 75 CHF patients and 50 COPD patients were to be recruited.

Outcome Measures

The outcome measures used are listed next. The detail of how they were performed and the background for why they were chosen follows.

Primary outcome measure

See study flow diagram for details of when the tests were performed (figure 2.1 and 2.2)

Incremental Shuttle Walk Test (ISWT)

The primary outcome measure was the Incremental Shuttle Walk Test (ISWT). The assessor of the ISWT was blinded to the intervention for the first trial and to the underlying disease for the second trial.

Secondary outcome measures

Endurance Shuttle Walk Test (ESWT)

The assessor of the Endurance Shuttle Walk Test (ESWT) was blinded as per the ISWT.

All the other outcome measures were assessed by the lead investigator and were not blinded.

Laboratory exercise testing

Patients performed a full cardiopulmonary exercise test (CPX) on a cycle ergometer. Both an MSX (MSX 671; Morgan Medical) system and a Zan system (Zan-680 Ergo Test; Zan Messgeraete GmbH, Oberthulba, Germany) were used.

Quadriceps strength

Quadriceps isometric strength was measured by a Cybex II Norm dynamometer (Cybex Norm™ Testing and Rehabilitation System, Cybex International, Inc, Ronkonkoma, NY).

Body composition

BMI was calculated by weight (kg) / height (m)². Weight was measured in light clothing only using digital scales (Seca, UK) and height by a wall mounted scale to the nearest 0.5cm. Body composition measured using bioelectrical impedance (Bodystat 1500; Bodystat Ltd, Douglas, Isle of Man). Fat free mass (FFM) kg was calculated using the disease specific regression equations for COPD described later in the section (386).

Health Status

Patients completed a disease specific questionnaire; the interview led Chronic Heart Questionnaire (CHQ) (387) and the self reported Chronic Respiratory Questionnaire (CRQ) (388) and a generic questionnaire; the short form 36 (SF-36) (389). The modified version of the Pulmonary Functional Status Dyspnea Questionnaire (PFSDQ-M) was used to assess the impact on activities of daily living caused by breathlessness and fatigue (390).

Functional Status

The NYHA classification of functional activity was used for the patients with CHF (391) and the MRC dyspnoea scale grade was recorded for all patients (392). The NYHA classification was assigned by a member of the rehabilitation team prior to the patients selecting the appropriated MRC scale. The patients were blinded to the selected NYHA classification.

N-terminal pro Brain Natriuretic Peptide (NTproBNP)

Venous blood for the analysis of serum N-terminal pro Brain Natriuretic Peptide was sampled before and after the CPX, and before and after the intervention period.

C-reactive protein (CRP)

Highly sensitive C-reactive protein was analysed on the venous blood sampled before and after the intervention.

Percutaneous vastus lateralis muscle biopsy

This part of the study was not compulsory.

Lung function

Spirometry was measured according to the Association for Respiratory Technology and Physiology (ARTP)/British Thoracic Society (BTS) standards (Vitalograph Model R; Vitalograph, Ltd, Bucks, UK).

Description of how the outcome measures were performed

Performing the ISWT

Patients were given standardised instructions on how to complete the test via a CD player. The course was 10m set with two cones 9m apart giving a turning distance of 1m at either end. Patients were asked to walk along the course at a speed indicated by an audiosignal (beeps) by the CD player. The aim is to have walked around the cone by the time the audiosignal is given. The pace is very slow to begin with (0.5m/sec) and the speed increases every minute. Patients were advised to continue until they were too breathless or tired to continue or could no longer keep up with the required speed. The distance walked is then calculated. A shuttle was completed if the patient reached within 0.5 m of the cone. The operator gave no encouragement throughout the test. Auxillary measurements of heart rate and oxygen saturation level were monitored continuously throughout the test via pulse oximetry and non invasive blood pressure recorded before and upon completion of the test. The Borg Scale for peak breathlessness [inspiratory effort sensation, but more commonly denoted (BS)] and perceived exertion (PE) were measured at rest and at the end of test. If the patient desaturated to a level of <85%, the ISWT was repeated with 2L of supplemental oxygen via nasal cannulae. If the patient perceived benefit then supplemental oxygen was advised for the training programme and the patient was excluded from this study.

Performing the ESWT

The ESWT is an externally paced test of submaximal exercise capacity. The same course as the ISWT was used. Patients were given standardised instructions on how to complete the test and no encouragement was given. The speed is derived from

the maximal ISWT performance. The predicted peak VO_2 for each ISWT distance has been derived from Singh et al 1992, the 85% predicted VO_2 is calculated and the speed is determined using a graph of peak VO_2 vs speed (393). There are 16 speeds available ranging from 1.78 – 6.00 km/hr. Patients were asked to walk at the speed indicated by audiosignals from a CD player. The test began with a two minute warm up. Again it is a symptom limited test. The duration after the warm up is reported.

Performing the cardiopulmonary exercise test on a cycle ergometer

Patients performed two symptom limited, maximal, incremental CPX tests, on an electronically braked cycle ergometer, on separate days. The background supporting the inclusion of a familiarisation test and the results of the reproducibility of the baseline exercise tests are described at the end of this chapter.

An MSX (MSX 671; Morgan Medical) system with a mass spectrometer, providing breath by breath gas analysis was used initially. Unfortunately due to the breakdown of this system, a Zan system (Zan-680 Ergo Test; Zan Messgeraete GmbH, Oberthulba, Germany) with a fast response analyser was used for the rest of the study. The system used was kept the same before and after the trial for any individual patient. A comparison of the two systems using a healthy control is covered in appendix V. The MSX system allowed for the parameters to be calculated using a rolling breath average or a timed average. The data package with the Zan system allowed only for a timed average. All the CPX results presented in this thesis are calculated using a 30 second average sampling interval. The manufacture provided data regarding validation of the gas analysis and the system was calibrated prior to each test.

Patients were asked not to eat four hours before. The tests were performed at the same time of day each time and by the same operator. The cycle ergometer seat was set to the same height each time allowing the knees to be slightly flexed at the maximum length. Patients were asked to cycle between 40-80 revolutions/ minute. There was two minutes of unloaded cycling initially. The increments increased by 10W/min until patient exhaustion. ECG monitoring and pulse oximetry were continuously monitored. Non invasive blood pressure readings were taken before and after the test and at one minute intervals during the test. The Borg Scale was used for peak BS and PE scores. At the end of exercise patients described the limiting symptom. Thirty second summary data was used for the peak oxygen consumption (VO_2 peak), peak ventilation (VE), and respiratory exchange ratio (RER). Patients with significant arrhythmias or a systolic BP drop of $>10\text{mmHg}$ post exercise were excluded as per the ‘American College of Sports Medicine’ guidelines (394).

Quality control for the CPX was monitored using a healthy biological control (395) who performed a full CPX monthly. The gas sampler and volumes were checked against the calibration before every test.

Measurements derived from the cardiopulmonary test (CPX).

Peak oxygen consumption (peak VO_2)

For healthy adults or athletes the maximal oxygen consumption (VO_2 max) is achieved at the end of exercise. If the test is maximal then a plateau for VO_2 is reached. In disease this plateau is rarely achieved and therefore the peak oxygen consumption (peak VO_2) is quoted. The peak VO_2 can be described in absolute terms (L/min) or relative, traditionally by weight. The peak VO_2 can be derived in a number of ways

depending on how the gas samples are analysed. When a mixing chamber is used the results are generated by sampling the mixture at regular intervals. These can be summarised into further timed averages e.g 10, 20, 30 mins. Fast response analysers e.g mass spectrometers or infrared carbon dioxide analysers enable breath by breath analysis. These results can either be summarized at timed intervals as with a mixing chamber or by a rolling breath average e.g 1, 5, 9 breaths. The ATS/ACCP guidelines (396) advice quoting peak VO_2 as a 30 second summary, but there is little supporting evidence for the optimal method for reporting peak VO_2 . Whether it matters how the peak VO_2 is reported in COPD was investigated as part of this work and is described in appendix V.

Peak ventilation (Peak VE)

VE is minute ventilation (L/min). This is used to calculate ventilatory capacity which will be discussed later in the chapter.

Peak respiratory exchange ratio (RER)

The respiratory exchange ratio is the VCO_2/VO_2 . It is a non steady state measurement. End exercise RER is usually between 1.1 and 1.5 in healthy subjects for a maximal test. Although RER can be used to assess subject effort, hyperventilation can also increase the RER which is often seen at the beginning of exercise.

Peak O_2 pulse

The oxygen pulse is calculated by VO_2/fc where fc is the heart rate. It is a measure of cardiovascular efficiency and is an estimate of stroke volume. In healthy subjects a higher maximal oxygen pulse reflects cardiovascular fitness. The peak oxygen pulse can

be reduced in deconditioning, non cardiovascular limitation and cardiovascular limitation.

Interpreting the results of cardiopulmonary exercise testing

The peak VO_2 can be assessed as a percentage of the predicted VO_2 max. Several studies have been conducted to provide predictive equations for VO_2 max. Cooper CB has combined these to make composite equations for each gender that are adjusted for height and weight (397). These studies were performed in subjects aged 20-70 years. A significant proportion of the patients described in this thesis are older than 70 years, these equations therefore have not been used and the peak VO_2 is described both as an absolute (L/min) and relative (ml/min/kg).

Males:

$$\text{VO}_2 \text{ max} = [(0.0716 \times \text{height}) - 0.0518] \times [44.22 - (0.394 \times \text{age})] + (0.0058 \times \text{ABW})$$

Females:

$$\text{VO}_2 \text{ max} = [(0.0626 \times \text{height}) - 0.0455] \times [37.03 - (0.371 \times \text{age})] + (0.0058 \times \text{ABW})$$

height (m), age (years), ABW = actual body weight (kgs), VO_2 max (L/min)

If the peak VO_2 predicted is not achieved, effort can be assessed by peak symptom scores (there are a variety of methods available; Borg Scale, visual analogue scale and transitional dyspnoea index (TDI) are all commonly used) and by the operator. If there was a good effort then the type of limitation can be assessed e.g cardiovascular, ventilatory, deconditioning etc. Other factors such as hyperventilation can also be assessed. There are different methods for calculating ventilatory limitation. For this thesis a ventilatory limitation (V_{Ecap}) was calculated by $(\text{FEV}_1 \times 20) + 20$. This calculation has been shown to better fit regression lines of published studies than either

the commonly used $FEV_1 \times 35$ or $FEV_1 \times 40$ (397). However, it may overestimate VE_{cap} in severe COPD and underestimate in patients with mild disease.

A cardiovascular limitation is considered to occur when a subject achieves a value for f_{cmax} that is within 2 SD of the reference value. There are two commonly used equations for the predicted maximum heart rate is $f_{cmax} \text{ predicted} = 220 - \text{age}$ (398) and $f_{cmax} \text{ predicted} = 210 - (\text{age} \times 0.65)$. The SD of f_{cmax} is 10 min^{-1} so the predicted f_{cmax} for an individual is in a minimum range of 40 min^{-1} . The eldest subjects in the original studies were all less than 70 years old (397). The equation $f_{cmax} = 220 - \text{age}$ underestimates the predicted maximum heart rate in the elderly (396). If a plateau for f_{cmax} is achieved then this increases the likelihood that there is a true cardiovascular limitation. If subjects are taking negatively chronotropic medication such as beta blockers then this equation will underestimate the peak f_{cmax} as a percentage of predicted (399). Brawner et al derived an equation from 334 patients aged 40 -80 yrs old with preserved left ventricular function taking beta blockers (post myocardial infarction or coronary artery bypass grafting) and then tested it prospectively on 94 different patients. The equation derived was $f_{cmax} = 164 - 0.7 \times \text{age}$ ($r^2 = 0.13$), with a standard error of the estimate of 18 beats per minute (400).

Another consideration with predictive equations for either peak heart rate or peak oxygen consumption is the platform of exercise. Peak VO_2 or f_{cmax} tend to be lower for cycling exercise than walking therefore the regression equations should be matched for the exercise platform.

Quadriceps isometric strength

Isometric quadriceps strength was measured using a Cybex II dynamometer. Six maximal voluntary contractions were performed in two sets of three with a thirty second rest between each manoeuvre and a two minute rest between both sets. The peak torque was taken as the highest value of the six manoeuvres. Patients were seated with the backrest at 15° from the vertical and secured with straps over their chest, pelvis and mid thigh. Shoes were removed to avoid any extra weight. An adjustable lever arm was attached to the lower limb proximal to the lateral malleolus via a shin pad. The axis of rotation was aligned to the lateral femoral epicondyle. Patients kept their arms folded over their chest. The lever arm was fixed at 70°. Patients were asked to push as hard as they could against the lever for five seconds or until fatigued whichever was shortest. Although the monitor records the contractions patients were prevented from visualising this. The machine was calibrated before each use and was maintained according to the manufacturer's instructions.

Percutaneous Vastus Lateralis muscle biopsy

Resting samples were taken before and after the intervention. Samples were taken from the left Vastus Lateralis muscle midway between the patella and the greater trochanter using the Bergstrom technique (401). The procedure was carried out in aseptic conditions, using 10mls 1% lignocaine (or no more than 3mg/kg). Two 5mm incisions were made and two biopsies taken to help increase the muscle sample size. Suction was applied to the needle with a 50ml syringe while the biopsy was taken (402).

The muscle samples were frozen immediately in liquid nitrogen and stored at -80°C for future analysis. Steristrips were applied to the 0.5cm wound and a pressure bandage applied which patients were advised to remove after twelve hours. All patients were given a patient information leaflet with contact numbers and advice.

The biopsies were analysed for fibre type and peroxisome proliferator-activated receptor (PPAR) alpha, delta, gamma and PGC-1 coactivator mRNA expression. Details regarding analysis for skeletal muscle fibre typing are discussed at the end of this chapter and the methods for the analysis of mRNA expression are discussed in chapter seven and the appendix.

Body composition

The test was carried out in the supine position after at least five minutes rest. Electrodes were placed on the right hand (on the dorsal surface between the 2nd and 3rd finger) and right foot (on the dorsal surface between the greater and 2nd toe). The black and red leads were positioned as per the manufacturer's instructions. All the specified details were entered into the device and the readings recorded.

Venous blood sampling for N-terminal Brain Natriuretic Peptide and C-reactive protein analysis.

20mls venous blood was sampled at rest and immediately after exercise. It was drawn into prechilled tubes with 0.25mls aprotinin and 80 μ mls of 1M EDTA. After centrifugation at 3000rpm for 20 mins at 4°C , plasma was separated and stored at -80°C until analysis. Details regarding the analysis are given in full in chapter eight.

Health Status

Examples of all the questionnaires are in appendix IV.

Short Form 36 (SF36)

The SF36 is a 36 item questionnaire with eight multi-dimensions; physical functioning (PF) (10 items), role limitation due to physical problems (RP) (4 items), role limitations to emotional problems (RE) (3 items), social functioning (SF) (2 items), mental health (MH) (5 items), energy and vitality (EV) (4 items), pain (2 items), and general health perception (GHP) (5 items). There is a further item asking about change in health over the last year (CH). For each dimension items are summed and transformed to a scale of 0-100 where 0 is the worst health possible and 100 is the best health possible.

Chronic Respiratory Questionnaire (CRQ) and the Chronic Heart Questionnaire (CHQ)

There are twenty items divided into four domains; Dyspnoea (D) (5 items), Fatigue (F) (4 items), Emotional Function (EF) (7 items) and Mastery (M) (4 items). The items are summed and divided by the number of items to give a mean score

The Pulmonary Functional Status and Dyspnoea Questionnaire – modified version (PFSDQ-M)

The PFSDQ-M is a self administered questionnaire. It takes an estimated seven minutes to complete. It has 40 items and three main components (10 items each) which are the change in activity (CA), dyspnoea with activity (DA) and fatigue with activity (FA). Each activity (10) is scored from 0-10 with 0 representing ‘as active as I’ve ever been’ to 10 representing that the activity ‘has been omitted entirely’. A cross is marked if the activity ‘has never been an activity’. A total score is summed (range 0-100) and the mean score is calculated by dividing the total score by the number of activities

(range 0-10). The ten individual scores can be listed if further detail is needed. The other ten items are divided into two sections, dyspnoea and fatigue, with five items in each section. The first question for both the fatigue and dyspnoea sections are simply whether the subject suffers from dyspnoea/fatigue. These are not included in the scoring system. One item in both sections asks how many times a month the subject suffers from severe or very severe dyspnoea/fatigue. This is the frequency score. There is a general score in each section including three items; severity of dyspnoea or fatigue most days, today and with most day to day activities and the subject marks on a scale of 0-10 where their symptom lies. 0 is no shortness of breath and 10 is very severe shortness of breath.

Background of the outcome measures used

Incremental Shuttle Walk Test performance (ISWT)

Laboratory exercise testing is the gold standard of assessing maximal exercise capacity. However, specialist equipment is necessary and it is not widely available. The ISWT was developed to provide a surrogate field test. It was originally developed for patients with COPD in 1992 (385). It is a symptom limited, externally paced, progressive test. The protocol was developed by modifying a 20m shuttle running test used by athletes (403). The final ISWT has 12 levels with the speed progressing from 0.5 metres per second (m/s) (level one) to 2.37 m/s (level 12). The distances walked range from 0 to 1020 metres.

Validity of the ISWT in patients with CHF and COPD

The ISWT has been shown to have an incremental cardiovascular response and incremental increase in peak VO_2 in patients with COPD (385;404). The peak distance

achieved on the ISWT was highly correlated with the peak VO_2 achieved on a laboratory treadmill test $r=0.88$ in nineteen patients; 17 male, mean (SD) age 61 (7) and mean (SD) peak VO_2 14.2 (14.1), 66.2 % predicted, and a wide range of FEV_1 impairment (0.5-3.3L) (404). A regression equation was calculated to derive the predicted peak VO_2 from the shuttle distance; $\text{VO}_2 \text{ peak} = 4.19 (1.12 -7.17) + 0.025 (0.018 - 0.031) \text{ distance}$, where $\text{VO}_2 \text{ peak}$ is in ml/min/kg and distance is in metres, and the 95% confidence intervals shown in brackets.

The ISWT has since been validated in chronic heart failure. The methodology and populations that the regression equations were derived from has relevance for the use of the ESWT in patients with CHF and will therefore be compared in detail. Keell et al assessed fifty men, mean (SD) age 62.9 (9.1) yrs, mean ISWT 380 (190) and mean peak VO_2 17.9 (range 6.8 – 39.1) ml/kg/min (405). There was a good correlation between peak VO_2 on the treadmill test and peak SWT distance $r=0.84$ $p<0.0001$. The regression calculation for peak VO_2 was $7.77 (5.56 - 9.89) + 0.027 (0.022 \text{ to } 0.032) \text{ distance walked}$. This calculation would give a higher predicted peak VO_2 than the calculation for COPD.

It is difficult to directly compare the regression equations as the treadmill protocol in the study by Keell et al is not described and maybe different to the protocol Singh et al used. The mean age and gender of the patients are similar, but the CHF patients have a higher mean VO_2 peak compared to the COPD patients. Although the exact range of peak VO_2 for COPD patients is not described by Singh et al Fig 1 depicts the data ranging from around 8 to 25 ml/kg/min (404). It would appear the COPD population were more disabled than the CHF patients. Lewis et al have also calculated a

regression equation, from a CHF population with a mean peak VO_2 of 15.2 (4.4) ml/min/kg, where peak $\text{VO}_2 = 6.4 + (0.022 \times \text{distance})$. In the current studies described in this thesis the ISWT uses the regression equation from Singh et al for both patients with CHF and COPD.

Reproducibility of the ISWT in patients with COPD and CHF

The ISWT is reproducible in patients with COPD, after one practice test. Singh et al showed there was a significant increase in mean distance walked of 31m between the first two tests, but only 2m between test two and three (95% CI m -21.9 to 17.9) (385). Both Green et al and Lewis et al assessed the reproducibility of the ISWT in patients with CHF and found that a practice test was necessary (406;407). After the second test the ISWT was reproducible, the difference between test two and three for the two studies was -7.0m $p=0.33$ and 1.3m (no p value stated), respectively. The populations in these two studies had a mean age of 53 years old and were predominantly males (27/31). The ISWT is also reproducible in older patients (>70 yrs old) with COPD (408). The reproducibility in older patients with CHF has not been assessed.

Comparison of the ISWT with the six minute walk test (6MWT) in COPD and CHF

Other field tests are based on how far a patient can walk in a certain time; self paced. The most widely used currently for patients with CHF and COPD is the six minute walk test (6MWT). There are advantages and disadvantages compared with the ISWT. In CHF and COPD, the peak performance of the ISWT more accurately reflects peak VO_2 than the 6MWT distance (385;409). The ISWT is less prone to the effects of motivation as it is externally paced and no encouragement is given. Two practice walks for the

6MWT are recommended (87). This is rarely done in trials and therefore may overestimate the benefit of an intervention (410). In a review of the six minute walk test as an outcome measure of randomised controlled trials in chronic heart failure the conclusion was that the 6MWT was 'yet to be proven a robust test for pharmacological interventions'. A smaller study involving 57 patients with COPD assessed the reproducibility of the ISWT and the 6MWT and showed that both were reproducible after a practice test (411). Both tests have been shown to be sensitive to pulmonary rehabilitation in COPD (329;353;412;413). The ISWT had not been used as an outcome measure in CHF at the time this study was conducted. Subsequently it was shown to be a sensitive outcome measure in a randomised controlled trial of testosterone therapy in men with CHF (152).

Many interventions rely on a statistical increase in a given outcome measure to provide evidence of benefit. However a more useful measure is to understand the clinical relevance of any improvement. It is not known what increase in peak VO_2 is useful for a patient to gain e.g 0.5ml/min/kg or 2ml/min/kg? The 6MWT has a clinically important threshold of 54m in COPD (261). Singh et al have shown that patients can detect a change of 48m in the ISWT in COPD (384). Having clinically important thresholds provides both field tests with an advantage over laboratory testing when assessing response to an intervention. The MCID for both tests in patients with CHF is unknown.

The advantage of the 6MWT is the availability of normal reference values which were derived from healthy subjects aged 40-80 years old (414).

The paired tests of the ISWT and ESWT provide measurements of maximal and sub-maximal exercise capacity. As the 6MWT is self paced it is not known what exactly the end distance reflects in terms of exercise capacity. However it maybe that behaviour during the 6MWT reflects the day to day behaviour of a patient and therefore might be a better reflection of functional capacity than the ISWT or ESWT.

In patients with COPD the 6MWT is an independent predictor of mortality and is one of the four components of the BODE index; a prognostic scoring system for COPD (16). In CHF the ISWT better predicted event-free survival at one year than the 6MWT distance (415). There is currently no published work on the relationship between ISWT distance and prognosis in COPD. In one study the ISWT distance was a predictor of rehospitalisation in moderate severe COPD (416).

The six minute walk test is more commonly used, but the scope of the ISWT is increasing. It has been shown to be a valid measure of exercise capacity in patients with pacemakers (417), coronary heart disease (418), pulmonary fibrosis (419), and bronchiectasis (369).

In summary the ISWT has been validated and highly correlates with peak VO_2 derived from laboratory treadmill testing in both COPD and CHF. The ISWT performance has a stronger correlation with peak VO_2 derived from treadmill testing than the 6MWT. The ISWT with a graded response is more standardised than the 6MWT. Self paced field tests may be influenced by motivation and encouragement, but maybe a better measurement of functional capacity.

Endurance Shuttle Walk Test (ESWT)

The Endurance Shuttle Walk Test was developed to assess submaximal capacity in patients with COPD (393). It is externally paced and uses the same 10m course as the ISWT. The speeds were calculated to be at an intensity of 85% predicted peak VO_2 derived from the ISWT performance. The graph correlating predicted peak VO_2 to walking speed is shown in the paper by Revill et al. The test was shown to be reproducible after one practice test in 11 patients with severe COPD; mean (SD) FEV_1 35 (4)% predicted. The difference in the time walked between the first two tests was 59.5 (9.7 – 109.2) seconds, but only 15 seconds between tests two and three which was not statistically significant.

The ESWT has not been used before in patients with CHF or in other diseases except COPD. There is evidence that the ESWT maybe a more sensitive outcome measure than the six minute walk test in patients with COPD (420).

Cardiopulmonary exercise tests

Laboratory exercise testing with gas analysis is the gold standard measurement of exercise capacity. Cardiopulmonary exercise testing (CPX) can be performed on a variety of platforms e.g. cycle ergometer, treadmill, rowing machine etc. For the studies reported in this thesis a cycle ergometer was selected over a treadmill. The advantage of a cycle ergometer is it provides a stable platform which is safer for elderly, frail patients. There is less interference from movement i.e. less artifact, better quality results and is probably less influenced by weight. The current study involved venous blood sampling before and after exercise and the stable platform makes this more straightforward.

Ideally the duration of an exercise test should be around 10 minutes. Maltais et al demonstrated that different peak VO_2 levels are achieved depending on the protocol; a higher peak VO_2 was achieved for 5W/min than 20W/min (421). All patients therefore had to do the same protocol to standardise the test and 10W/min was selected.

The peak VO_2 derived from a CPX is an independent prognostic indicator in both conditions as described in the introduction. It has been used successfully as an outcome measure to assess exercise rehabilitation in both COPD and CHF (241;412).

Laboratory exercise testing provides additional information about the cause of the limitation to exercise compared to field testing and was therefore performed for this study. Field walk tests have the advantage of being a familiar activity to the patient. Field tests are easily applied to larger cohorts of patients and are therefore more convenient as an outcome measure for a service. Field tests were used as well as a CPX in this study so that walking performance was also assessed as walking was the main modality of the training programme and many pulmonary rehabilitation services use only field tests as an outcome measure.

Reproducibility of exercise tests and muscle strength

The statement of the ATS/ACCP on exercise testing discusses the reproducibility of cardiopulmonary exercise tests (396). The guidelines highlight the discrepancy between the results of various studies i.e. some have shown a significant increase in individual measurements with repeat testing, and others have shown no significant change. There are several studies examining the reliability of parameters from a cardiopulmonary exercise test with varying conclusions. Studies were reviewed if the exercise platform was a cycle ergometer and are summarised in table 1. Swinburn et al

performed three different exercise tests (cycling, walking and a step test) on the same day with one hours rest in-between, in patients with COPD (422). Patients repeated these four times over twelve days. The results showed that the performance of each test kept increasing. There was a greater than 10% change in peak VO_2 between the 2nd and 3rd cycling test. The authors discuss that the continued improvements are unlikely to be a training effect in such a short time. However, the frequency of the exercise tests had the potential to be a training stimulus. The authors felt the continued improvement was due to patient confidence. Cox et al showed that peak VO_2 from CPX was reproducible in 11 subjects with mild to moderate COPD (423). Although they were not familiar with the exercise test before, the study was performed in the Netherlands where cycling is a common activity and these results may not translate to other populations. Brown et al also showed that the peak VO_2 was reproducible when three incremental cycle ergometer (ICE) tests were performed; two on the same day and one the next day (424). The peak VO_2 was similar for all three tests. This shows that the measurement of peak VO_2 is stable, when all the patients were already familiar with cardiopulmonary exercise testing.

The data shows that the parameters from expired gas analysis were stable in the short term. All these studies were using mixing chambers for the gas analysis and were sampled at 20 or 30 seconds. Owens et al examined reproducibility of ICE (CPX) over one month and showed that there was no change in the mean of the peak VO_2 (425), but there was an improvements in the peak work load achieved on the second test (mean 8.5W). The largest cohort was described by Covey et al in 56 patients with COPD and 16 healthy subjects (426). A metabolic cart and breath by breath analysis was used. The

conclusions were similar that the mean peak VO_2 was stable on repeat testing. There was intra-subject variability which could not be predicted by disease severity or lung function variability. A practice test was therefore recommended. The exercise protocol involved a five minute warm up of cycling separate to the other two tests which potentially may have acted as familiarisation.

Similar small studies have been separately conducted for patients with CHF. One study used data from breath by breath analysis and an incremental protocol, 25W every three minutes until exhaustion (427). The coefficient of variation was 6.7% for peak VO_2 . However the patients had a familiarisation test and then performed the two study tests so any learning effect is not represented. Meyer et al examined the effect of a ramp protocol at submaximal workloads 25W, 50W and 75W in patients with severe disease (428). Peak VO_2 was reproducible, but again all the patients had undertaken at least two exercise tests prior to the study. A French group assessed the reproducibility of the parameters from expired gas analysis in patients with mild heart failure in patients who had not previously undertaken a CPX (429). They showed that the mean peak VO_2 was reproducible, but patients exercised for longer on the second test.

Author	Disease and no.	Severity	Age (yrs)	Protocol	Gas analysis	Sampling time
Brown	COPD n=11	FEV ₁ 1.5L	61 (SD 5)	15 W/min	Mixing chamber	30 secs
Swinburn	COPD n=17	FEV ₁ 0.8L	66 (49-73) †	10 W/min	Mixing chamber	20 secs
Cox	COPD n=11	FEV ₁ % predicted 49.6%	49	5 or 10 W/min	Mixing chamber	30 secs
Owens	COPD n=13	FEV ₁ 1.15L	63 (SD 3)	10 W/min	'breath by breath'	20 secs
Covey	COPD n=56	FEV ₁ % predicted 49 (16)	66 (SD 6)	30W for 2 mins then 10W/ 2 mins	'breath by breath'	U
Marburger	CHF n=9	LVEF 52.3%	71 (SD 4)	12.5W for 2mins then 25/ 2mins	'breath by breath'	Final 30 secs of exercise
Meyer	CHF n=11	LVEF 25 (2)%	56 (SD 4)	Ramp	'breath by breath'	U

Subject number (no.), mean (SD) age unless † mean (range), increment in watts per minute (W/min), seconds (secs), data unavailable U

Table 2.1. Summary of previous studies investigating the reproducibility of cardiopulmonary exercise tests on a cycle ergometer in COPD and CHF; protocol and gas analysis

Author	Prior familiarisation	No. of tests	Interval between tests	CV of peak VO ₂	CV of duration	CV of heart rate	CV of VE
Brown	Yes	3	Same day and 1 day	<10%	U	U	U
Swinburn	No	4	12 days	U	U	U	U
Cox	No	2	1 day	3.5%	U	3.7%	6.6%
Owens	Not stated	2	1 month	6-10%	U	3.5%	6.3
Covey	No	2	1-2 weeks	6-7%	U	U	6%
Marburger	Yes	2	1 week	6.1%	5.2%	4.4%	U
Meyer	Yes	2	1 week	3.9%	N/A	N/A	N/A

Data unavailable (U), not applicable (N/A), coefficient of variation (CV), peak oxygen consumption (peak VO₂), heart rate (HR), ventilation (VE)

Prior familiarisation means that the patients had already performed a full CPX and this was not included in the reported tests.

Table 2.2. Summary of previous studies investigating the reproducibility of cardiopulmonary exercise tests on a cycle ergometer in COPD and CHF; reproducibility and coefficient of variation of the individual measurements

A familiarisation test was performed for the cardiopulmonary tests in COPD and CHF for the main trials and the data is presented in chapter three.

Peripheral muscle strength

Isometric quadriceps strength was evaluated for the reported studies in this thesis. Strength training was not a significant part of the pulmonary rehabilitation

programme used and therefore sophisticated measures of isokinetic muscle function were unlikely to be necessary. The individual visits for the patients were already long and further visits were not desirable.

There are several different techniques to measure voluntary isometric quadriceps strength; hand held dynamometry, a strain gauge or with a hydraulic dynamometer. Most of these techniques have been used and validated in healthy subjects, athletes and a variety of chronic rheumatological and neurological diseases. Hand held dynamometry has been used to assess upper limb and lower limb strength in COPD and CHF (77;317). The main limitation with hand held dynamometry is the operator has to provide the limiting force and therefore inaccuracies can occur if the operator strength is less than the muscle strength being measured i.e upper limb of the operator vs. the lower limb of the subject. Both the strain gauge technique and hydraulic dynamometry have been used as outcome measures in patients with COPD and CHF (47;76;77;83;430). The Cybex II dynamometer was used for this study as it was available, but a strain gauge could have been used as an alternative.

There are non volitional techniques to measure muscle strength (103), but these were not used in the current studies. Normal reference values for isokinetic quadriceps strength have been derived using a population of healthy subjects aged 20-80 years old (431). There are predictive equations for quadriceps isometric extension accounting for age, gender and weight. These apply for isometric quadriceps extension with 90 degrees of hip flexion and 60 degrees of knee flexion. The isometric quadriceps strength was measured at 70 degrees of knee flexion in the current studies so these reference equations were not applied.

The measurements were all taken at the same time of day. There is some evidence that the time of day may influence muscle force (432).

Reproducibility of isometric muscle strength

The literature concerning the reproducibility of isometric muscle strength in COPD and CHF was reviewed to decide how many manoeuvres were needed and whether the results were reproducible. Murray et al investigated isometric strength in males aged 20-80 using a Cybex II dynamometer (433). Subjects performed two consecutive maximum isometric contractions at three angles: 30, 45 and 60° and repeated the same manoeuvres one week later. The results of the second week were not significantly higher for the knee extensors, but 64% of the observations had a higher peak torque in the second week. Symons et al examined the reliability of a single session of isometric protocols in healthy men (434). Tests were performed using a Biodex System 3 dynamometer and subjects (mean (SD) age 72 (5) yrs) completed five maximal contractions on two separate days. The CV% was between 8-17% for isometric and isokinetic peak torque. The authors conclude that single session testing is not recommended. Isometric knee extensor force was evaluated in 113 patients with knee osteoarthritis using a load cell (Xtran Model S1W) applied to a frame of a chair (435). There was wide individual variability particularly in the age group 70-79 where the SEM was twice the mean measurement. There is little reported in the literature for the reliability of isometric testing in COPD and CHF despite it being widely reported as an outcome measure. Often familiarization testing is not carried out (45;83). The protocol of two sets of three manoeuvres was used which is similar to that used in similar studies (328).

All patients performed a familiarisation test for all the outcome measures and the results are presented and discussed in chapter three.

Body composition

Body composition was assessed by bioelectrical impedance analysis. This is a simple bedside assessment. It measures the resistance of current through the body which gives a level of impedance. The basic principle is lean mass has a higher water content than fat and therefore a lower impedance. FFM was estimated from impedance measurements using gender-specific regression equations (386):

$$\text{FFM} = 8.383 + 0.465\text{ht}^2 / \text{R} + 0.213\text{wt} \text{ (males)}$$

$$\text{FFM} = 7.610 + 0.474\text{ht}^2 / \text{R} + 0.184\text{wt} \text{ (females)}$$

Where ht is height, R is resistance, wt is weight, and mass is given in kg, height in centimeters and resistance in ohms. The fat free mass index is calculated by $\text{FFM} / \text{height}^2$ (436).

The accuracy of BIA depends on hydration status and in CHF this can be affected by fluid retention and diuretic therapy. Obesity lessens the accuracy of BIA. However BIA has been used in COPD and CHF. In COPD, BIA underestimates FFM (kg) compared to DEXA by 0.72 kg; limits of agreement-5.68 to 7.20 kg) (386). It is reproducible in CHF, coefficient of variation 1.7 – 4.3% and has been shown to be a suitable clinical alternative for diagnostic purpose to DEXA (437). Nutritional depletion has been defined as a $\text{BMI} \leq 21 \text{ kg/m}^2$ and/or $\text{FFMI} \leq 15 \text{ kg/m}^2$ for females or $\leq 16 \text{ kg/m}^2$ (438).

Skeletal muscle fibre types

Different methodology exists for analysing skeletal muscle fibre types and the results between the methods can vary. It is therefore important to understand which method has been used. Histochemical techniques use staining of myosin adenosine triphosphatase (mATPase). There are now seven different classification of fibre types; I, IC, IIC, IIAC, IIA, IIAB, and IIB. The technique commonly uses over 100 muscle fibres (58), but can also be performed on a single muscle fibre (439). Multiple cross sections of the fibre are analysed. The cross sectional area (CSA) of a muscle fibre type can also be measured. A certain length of fibre is measured and techniques have to be used to minimise any stretching of the fibre type which could affect the CSA.

The other common technique used is analysis of the different myosin heavy chain (MHC) isoforms using gel electrophoresis. The principles behind this technique are discussed in appendix VIII and chapter 7. Usually three different fibre types are classified from this technique; MHC I, IIA and IIX. (There are no IIB human fibres; 2X). Essentially MHC isoform analysis can provide the difference in overall proportion of fibre types and is less time consuming than histological staining. However, histochemical analysis provides more detail as it can assess the fibre number and size.

Combinations of the two techniques can be used to give an overall classification. For the reported study in this thesis, gel electrophoresis was used to differentiate between MHC isoforms and allows the proportion of isoforms to be calculated.

Health status or health related quality of life

Quality of life is the degree of well being felt by an individual or group of people. There are many factors contributing to quality of life, but they can be broadly

categorised into physical and psychological. Health related quality of life or health status is a specific component of quality of life and it has become an important outcome measure in chronic disease (440). Health status measurements provide an objective assessment of how a particular disease affects a group of patients and is commonly assessed in the format of multi dimensional questionnaires. There are many questionnaires available and therefore careful selection is needed to ensure the questionnaire is suitable for the intended purpose.

The desirable properties of an individual questionnaire depend on the intended purpose. If the purpose is to describe differences in a group of people at a given period of time then the questionnaire needs to be 'discriminative'. If the purpose is to describe changes with time then the questionnaire needs to be 'evaluative'. The questionnaire also needs to be responsive if the purpose is to assess changes with an intervention. Generic questionnaires tend to be discriminative, but less responsive than disease specific questionnaires (441;442). The different questionnaires provide different information (443).

A combination of disease-specific and generic questionnaires was chosen to assess health status for the studies reported in this thesis because both discriminative and evaluative properties were desirable.

Short Form 36 (SF-36)

The short form 36 is a commonly used generic questionnaire to assess health status. It was developed from the Medical Outcomes Study (MOS) in 1989. The MOS Functioning and Well-Being (MOSFWB) profile included 35 scales and 149 items which took 30-37 minutes to complete. This was then modified to the SF20 to provide a

comprehensive questionnaire that was quicker to administer. There were several problems with this questionnaire; there were some domains that were single item measures for which internal reliability could not be assessed and there was a ‘floor’ effect i.e did not allow further differentiation when patients were seriously ill. The SF-36 was then designed as a compromise between the longer and shorter previous versions (389). The SF-36 has been validated for content, criterion and construct validity (444). It has been widely used for chronic disease and has been used in patients with COPD and CHF (445;446). It also has the benefit of normal values depending on age, gender and social class (447). Several aspects of the SF36 have been found to be sensitive to the effects of rehabilitation in COPD (271;353). An expert panel has now established what represents a small, medium and large change for each of the eight domains of the SF36 for patients with COPD (448) and patients with heart disease (449). The values are different for the two groups and tended to be lower for COPD (450).

Chronic Respiratory Questionnaire (CRQ) and Chronic Heart Questionnaire (CHQ)

There are several well validated disease specific questionnaires for COPD and CHF. The St Georges Respiratory questionnaire and CRQ are both commonly used to assess health status in COPD. They have both been used to assess responsiveness to pulmonary rehabilitation and were found to be similarly responsive in one study (451) and the CRQ being more responsive in another (452). ‘The Minnesota living with heart failure questionnaire’ and the CHQ-IL are both commonly used for patients with CHF and have been found to be responsive to the affects of exercise rehabilitation (241;305).

For the study reported in this thesis, the SF36 was chosen because of its discriminative properties and the CRQ and the CHQ were chosen because they are

almost the same questionnaire so have the benefit of being disease specific, but would allow comparison between the two diseases; COPD and CHF. The CRQ and CHQ were developed by the same research team.

The CRQ was developed first in 1987 (453) and then subsequently developed for heart patients as the CHQ in 1989 (454). There is one item out of twenty different between the CRQ and CHQ. Item nine of the CRQ is about the symptom of cough and this was felt not to be relevant in CHF so it was changed to a question to assess how much of a burden on others they think they are. This item is in the mastery domain. The CRQ was originally an interview led questionnaire, but as it became used as a tool for clinical purposes a self completed questionnaire became desirable to save clinician time. A self reported version was developed and found to be reproducible and comparable to the IL version and also responsive (388;455). A different group performed a RCT comparing the two methods of administration and compared their sensitivity to an intervention (PR) (456). Again the SR version was comparable to the IL version but interestingly the SR version was more sensitive to the effects of rehabilitation. In the current study a self reported version of the CHQ was developed and is described in chapter four. Both the CRQ and CHQ have a minimum clinical important threshold of 0.5 units for any domain (457).

There are also two versions of the dyspnoea section; a standardised and an individualised version. The individualised version allows the patient to choose the five activities which make them the most breathless whereas for the standardised version the five activities are always the same ones. The individualised version is more responsive, but correlates less well with other assessments of health status than the standardised

version (458). The individualised version was used for this study, and same five activities were chosen before and after the intervention.

Pulmonary Functional Status and Dyspnoea Questionnaire – modified version (PFSDQ-M)

Improvements in exercise performance and health status are important outcome measures for rehabilitation, but the improvements in each are often not strongly correlated indicating that there are other factors involved which have not been directly measured (452). Measurements of exercise capacity (maximal or submaximal) show the potential of what an individual can do, but do not equate to functional capacity or physical activity as there are multiple other determinants e.g. confidence, motivation, co-morbidity (459). Functional status forms part of overall health status but is specifically how activities of daily living are affected. Many tools designed to assess HRQOL do not specifically assess the activities of daily living. One of the most accurate ways of measuring daily activity is with accelerometers and these have become quite sophisticated enabling differentiation of different types of activity and different speeds of walking [Reviewed (460)]. Although easy to use for short periods and tolerated by patients the software and analysis is time consuming. Questionnaires designed to assess functional status directly are therefore desirable as they are easily applicable, particularly to larger populations.

The Pulmonary Functional Status and Dyspnoea Questionnaire – modified version (PFSDQ-M) was originally designed for patients with COPD (390). It was designed to assess the effect of dyspnoea and fatigue on various activities providing further information on functional status than other questionnaires (PFSDQ vs SGs). The

PFSDQ was designed first (461), but it was a more detailed questionnaire and time consuming to complete so it was shortened and named the modified version. The PFSDQ has been found to be a responsive tool in COPD in two trials; one in a trial of lung volume reduction surgery and another in pulmonary rehabilitation (462;463).

The use of the questionnaire in patients with CHF had not been described at the time of the current study and was therefore assessed as part of the programme of work and is described in chapter six. The aim would be to provide a common questionnaire for COPD and CHF that assessed the impact on functional status of the common symptoms generated by both conditions. The short term reproducibility, cross sectional validity and responsiveness are described. The validity and responsiveness of the questionnaire in CHF was directly compared with a population of patients with COPD. The study design is described in more detail in chapter six.

Functional Status: MRC scale and NYHA classification

Although health status measurements are useful they are time consuming to complete and score. Often this is not practical in a clinical setting. Functional status can also be assessed by simple tools. The Medical Research Council Dyspnoea scale is a five point self assessed scale that can differentiate exercise performance in patients with chronic lung disease. It was developed to detect how respiratory symptoms affected the working population (464). It has been validated (465) and is reproducible (466). The New York Heart Association classification is commonly used for CHF. There are four different classes (391) which are described in chapter six. The reproducibility is unknown (467). The main difference compared to the MRC dyspnoea scale is it is not self assessed. There are no standardised guidelines for a clinician to use to determine

which NYHA class to attribute to a patient. If combined training programmes are feasible then it would be convenient to be able to use the same functional status scale for both COPD and CHF. The MRC scale has been used in a small population with cardiovascular disease (n=8) and was found to be valid. The population of cardiovascular disease was described as having ischaemic heart disease and pulmonary oedema. The current study applied the MRC scale to patients with CHF and the results are described in chapter six.

Borg Scale

The Borg Scale was used to assess the level breathlessness and fatigue at the end of exercise. It uses a scale of 0 to 10 for breathlessness [(Borg score for breathlessness commonly assigned BS although it was originally described as the inspiratory effort sensation (IES)] and 6 to 20 for the perceived exertion (PE) score (382;383). These scales have been previously used for patients with COPD and CHF and are reproducible (468).

This chapter has described the study design and main methodology for the work described in the subsequent chapters including

- The outcome measures used and how they have been performed
- The background to the development and use of the outcome measurements in COPD and CHF
- Only specific methodology is described in the subsequent chapters
- Relevant statistical analysis is described in each chapter

The next chapter describes the reproducibility of the measures of physical performance in COPD and CHF which were performed within the two week run in period.

Chapter three

Reproducibility of exercise and strength tests in COPD and CHF

Content

Reproducibility of exercise and strength tests in COPD and CHF;

Cardiopulmonary exercise tests

Field tests

Isometric strength testing

Relevant appendices III;

Reporting the peak VO_2 – does it matter which method is used?

Comparison of the two different bike systems using a biological control

Reproducibility of exercise and strength tests in COPD and CHF

Background

Lower limb exercise training is a key component of pulmonary rehabilitation and improving exercise performance is a major goal (307). Sensitive and reliable outcome measurements of physical performance are therefore necessary. For the main work described in this thesis identical tests were needed for COPD and CHF.

- **The previous chapter** described the background to the development and use of laboratory and field exercise testing and quadriceps strength testing in patients with COPD and CHF.
- The literature of the reproducibility for tests of physical performance was also reported in chapter two.
- **This chapter** describes the results of the reproducibility of the measures of physical performance.

For the main studies described in this thesis the outcome measures of physical performance were a full cardiopulmonary exercise test (CPX) on a cycle ergometer, the incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT) and isometric quadriceps strength.

When designing the original study the literature was reviewed to determine

- 1) whether a familiarisation exercise test was necessary for laboratory and field exercise testing in patients with COPD and CHF and
- 2) to assess the reproducibility of isometric quadriceps strength in COPD and CHF.

Reproducibility of cardiopulmonary exercise testing

There are several factors which potentially affect the reproducibility of an exercise test; the exercise conditions such as the time of day and the operator, the exercise equipment including calibration, the disease variability, patient motivation and instructions and any learning effect. There were seven studies found examining the reproducibility of a cardiopulmonary exercise test on a cycle ergometer in COPD or CHF and these were all described in chapter two (422-424;426-428;469). In all the studies the conditions were standardised to a degree; time of day, food, advice re no strenuous exercise the day before. The equipment was calibrated. Few commented about using a biological control although this is recommended as a reliable method of ensuring quality control (395). Both mixing chambers and rapid response gas analysers have been used in the studies and the peak VO_2 was reproducible in both. There was no direct comparison of the two systems in a single study. A short interval between tests is less likely to be affected by disease variability. Day to day variability is recognised in COPD and CHF. The studies described included a range of disease severity, but tended to be in a younger population.

Peak VO_2 appeared to be a stable measurement after familiarisation. However in CHF although peak VO_2 is a reliable measurement in the reported studies whether there is a learning effect for patients with severe disease is unknown and in COPD all the studies either involved some form of familiarisation with the equipment first or patients used to cycling.

The patients recruited for the current study were going to represent the 'true' COPD and CHF population. They were likely to be older than patients from previous

studies (often patients referred for transplantation) with severe disease and were unlikely to be familiar with cycling or exercise testing. The exercise protocol for the current study was an incremental 10W/min protocol. It would be difficult to extrapolate from the studies described that a familiarisation test was unnecessary. A full familiarisation test was therefore included in the study design for patients with COPD and CHF. The aim was then to assess whether or not a familiarisation test was necessary in an older, disabled population of both diseases.

Reproducibility of the shuttle walking tests

The incremental shuttle walk test has been shown to be reproducible after one practice test in COPD (385) and chronic heart failure (470). The patients recruited for the heart failure study were predominantly male and young (52.4yrs). Dyer et al described the reproducibility of the ISWT in ten elderly (mean age 76 yrs) patients who performed three tests. The coefficient of variability was 35.1%. The reproducibility of the ISWT has not previously been assessed in an elderly disabled population in CHF.

This was the first time the Endurance Shuttle Walk Test (ESWT) was used in patients with Chronic Heart Failure. A familiarisation test is necessary for the ESWT for patients with COPD (393). The study protocol therefore included a familiarisation test for each walk test for both diseases. To investigate the reproducibility of the ISWT in an older population of CHF the ISWT was performed three times.

Reproducibility of isometric quadriceps strength testing

The background of isometric knee extensor testing is described in chapter two. A

Cybex II dynamometer was used for this study. While designing the study protocol the literature was reviewed to establish the most accurate approach to assess isometric strength and this was described in chapter two.

A protocol of two sets of three manoeuvres was used which is similar to that used in similar studies (328). There was little guidance from the literature whether the peak torque from the six maximal voluntary contractions (MVC) in one session was a true maximum or whether the values would increase further with subsequent testing. For the main study protocol a further set of six MVCs were performed one week apart. The aim of this was to examine whether the quadriceps peak torque was reproducible after a single session of six maximal voluntary contractions in COPD and CHF.

This chapter describes the

- Reproducibility of a full cardiopulmonary exercise test on a cycle ergometer using an incremental 10 watt/minute protocol in COPD and CHF
- Reproducibility of the ISWT and ESWT in CHF
- Reproducibility of the quadriceps peak torque from six maximal voluntary contractions in one session in COPD and CHF

Methods

Patients with COPD and CHF were recruited for the main study and the exercise tests were conducted as per the methods in chapter two. The tests were all conducted within the two week run in period (figure 3.1).

Week No.	Visit No.	Exercise tests CHF	Exercise tests COPD
PR Assessment		X	ISWT/ISWT/ESWT
1	1	CPX Muscle strength	CPX Muscle strength
	2	ISWT/ISWT/ESWT	
2	3	CPX Muscle strength	CPX Muscle strength
	4	ISWT/ESWT	ISWT/ESWT

Figure 3.1. Study flow diagram for the exercise tests during the two week run in period

The priority for the main study design was the results of pulmonary rehabilitation (PR) for the outcome measures between COPD and CHF. It was important that there were no significant differences in the run in period that might affect this and therefore the protocol had to be similar for each condition. The reproducibility of the exercise tests was a subsidiary study and designed within the main study. There was a difference in the process of recruitment for the two groups which meant there were some fixed features to the study design that were unavoidable.

The patients with COPD were recruited from patients referred for pulmonary rehabilitation. They were recruited on the assessment for PR where they had performed two ISWTs and one ESWT as per the PR protocol. Patients with CHF were recruited

mainly from the community nurses and the majority had never performed any exercise testing. The initial exercise test was conducted in the laboratory i.e CPX, for safety purposes while experience was gained rather than the first exercise test being performed in the corridor (ISWT with telemetry). There was therefore a difference in the order the exercise tests were performed between patients with COPD and CHF. The recruitment process for COPD made the operator different for the two sets of shuttle walk tests. The operator was the same for the second set of field tests for both COPD and CHF which were the baseline results used for the main studies. This unavoidable feature in the study design also meant that two ISWT were always performed on the first day and the third one to two weeks later. All exercise tests were performed between one to two weeks apart for each disease.

Cardiopulmonary exercise tests

During this study there was a technical problem with the MSX (MSX 671; Morgan Medical) bike system and it was replaced by a Zan system (Zan-680 Ergo Test; Zan Messgeraete GmbH). The MSX system used mass spectrometry generating breath by breath data, and the data was initially analysed using a five breath rolling average. The Zan system used a rapid response analyser, but the software only allowed data expressed using a timed interval; thirty second summary was chosen (396). Whether it matters how the peak VO_2 is reported was investigated and is reported in appendix V. The majority of patients with COPD undertook their exercise tests on the MSX system so the reproducibility of CPX is reported only in these patients. 25 patients with CHF used the MSX system and 29 patients used the Zan system. How the peak VO_2 is reported did affect the absolute value (appendix V) and so the results from the MSX and

Zan system were presented from thirty second summary data.

Statistical analysis

Paired t tests were used to compare the changes in parametric data and the wilcoxon test for non parametric data. Intraclass correlations (ICC) between the two tests were calculated. The coefficient of variation (CV%) was calculated to demonstrate the variability of a measurement. This was calculated by the within subject SD divided by the mean. The within subject SD of a measurement (repeatability coefficient) was calculated by the $\sqrt{\text{Sum of the squares}}$ for that measurement. The sum of the squares was calculated by an ANOVA (471).

Results

Reproducibility of the cardiopulmonary exercise tests on a cycle ergometer

Reproducibility of CPX in patients with COPD

43 patients with COPD completed two full cardiopulmonary exercise tests on the MSX. The demographics were 24 male (56%), mean (SD) age 68 (8.3) yrs, FEV1 % predicted 39.6 (13.0)% (i.e patients with severe disease), FEV₁/FVC 48.6 (8.0), BMI 26.6 (5.0). The results of the two tests are shown in table 3.2.

	Peak VO ₂ (ml/min/kg)	Peak VO ₂ (L/min)	Peak VE (L/min)	Work load (watts)	Duration (secs)	Peak RER	Heart rate (bpm)
Test One	11.8 (2.6)	0.86 (0.27)	30.9 (10.5)	46 (20)	270 (120)	0.95 (0.07)	114 (17)
Test Two	12.2 (2.4)	0.88 (0.25)	31.8 (10.1)	50 (20)	294 (116)	0.98 (0.08)	120 (20)
Change between two tests	0.3 (-0.1 to 0.8)		0.9 (-0.4 to 2.2)	4 (1 to 7)	24 (6 to 43)	0.03 (0.01 to 0.04)	6 (2 to 9)
p value	0.157	0.250	0.172	0.011*	0.009*	0.001*	0.006*
ICC	0.835†	0.907†	0.911†	0.874†	0.878†		0.788†
Within Subject SD	1.03	0.08	3.09				
CV%	8.6%	8.9%	9.9%				

Mean (SD) *p<0.05 †ICC p<0.0005

Peak oxygen consumption (peak VO₂), ventilation (VE), respiratory exchange ratio (RER), intraclass correlation (ICC), within subject SD (repeatability coefficient) coefficient of variation (CV)

Table 3.2. Reproducibility of CPX in patients with COPD

Patients worked significantly harder on the second test as evidenced by significantly greater peak workload, longer duration, and higher peak heart rate. There was also a slightly higher end respiratory exchange ratio (RER). Peak oxygen saturation was 88% for both tests p=0.938. The median (IQ range) peak Borg Score for breathlessness and perceived exertion score were the same; test one 4.0 (3.75 to 5.0) and 15.0 (15.0 to 17.0) p= 0.699 and test two 4.0 (4.0 to 5.0) and 15.0 (15.0 to 17.0) p=0.415. There was no significant difference in peak VO₂ and peak VE between the two tests. The intraclass correlations were high >0.8 for all parameters (p<0.0005). Figure 3.2 shows Bland-Altman plots for the peak VO₂. Although the mean peak VO₂ is similar

for the two tests there is individual variability. The coefficient of variation was 8.6% for the peak VO_2 . There was no difference in the percent variability of the absolute change in peak VO_2 for the two tests, between patients with and without a ventilatory limitation; 13.2 (15.7)% without a ventilatory limitation and 11.8 (9.7)% with a ventilatory limitation ($p=0.726$).

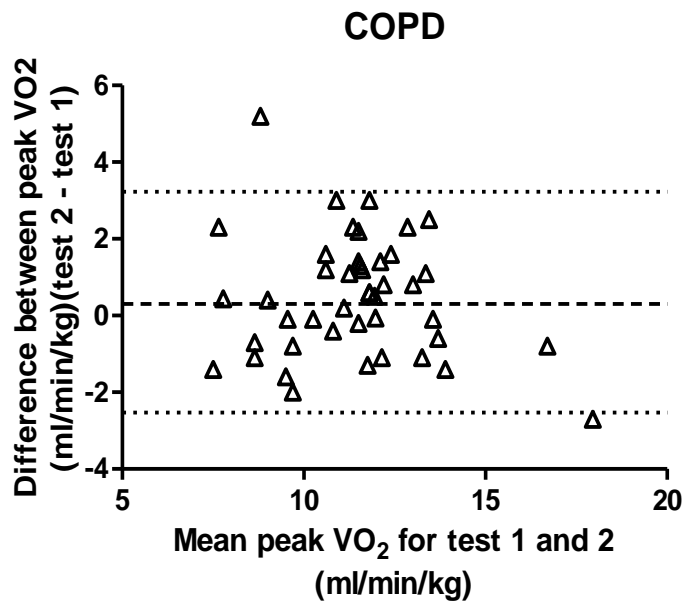


Figure 3.2. Bland Altman plot for the peak VO_2 from two CPX tests for COPD

Reproducibility of CPX for patients with CHF

48/57 patients performed two exercise test within two weeks. Two patients were unable to perform the cycle test due to hip problems. One patient declined a second test but was happy to continue with the rest of the main study. Three patients had performed the two tests on different systems and therefore were excluded (they were included in the main part of the study as the before and after intervention tests were on the same system). Three patients had already performed a full exercise test as part of their clinical

care so they were excluded from this part of the analysis.

The auxillary parameters and any data not generated by gas analysis were compared altogether. There was no significant difference between any of these parameters between the two tests (table 3.3).

	Peak HR (bpm)	Peak systolic BP (mmHg)	Peak diastolic BP (mmHg)	Peak SpO2 %	Peak watts (W)	Peak duration (secs)
Test one	106 (28)	139 (37)	75 (14)	94 (4)	49 (27)	293 (156)
Test two	104 (26)	137 (26)	73 (13)	95 (4)	49 (26)	289 (155)
Mean (95% CI) change	-2 (-7 to 3)	-2 (-13 to 8)	-2 (-7 to 3)	0.1 (-0.6 to 0.8)	-0.2 (-4.0 to 3.0)	-3 (-26 to 20)
p value	0.375	0.650	0.452	0.754	0.911	0.778

Mean (SD). Heart rate (HR), beats per minute (bpm), blood pressure (BP)

Table 3.3. Reproducibility of the peak auxillary parameters from the CPX in patients with CHF

The analysis was first performed for all the cycle ergometry tests n=48 and there was no significant difference in any of the parameters derived from expired gas analysis (data not shown). The patients were then divided into two groups by which equipment they had used. 24 used the MSX and 24 used the Zan system. The demographics of the patients were comparable between the two groups, but the group using the MSX system were heavier; 91.7 (24.4)kg vs 79.7 (16.0)kg (p<0.05). Table's 3.4 and 3.5 show the results of the two exercise tests for the MSX system and the Zan system.

	<i>Peak VO₂</i> (ml/min/kg)	<i>Peak VO₂</i> (L/min)	<i>Peak VE</i> (L/min)	<i>Peak O₂</i> <i>pulse</i>	<i>Peak RER</i>
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	<i>(ml/beat)</i>				
Test One	9.3 (3.3)	0.86 (0.38)	34.0 (14.0)	8.1 (3.1)	1.04 (0.11)
Test Two	9.8 (3.3)	0.89 (0.37)	34.9 (13.3)	8.8 (3.6)	1.05 (0.09)
p	0.107	0.201	0.518	0.031	0.763
ICC	0.911	0.939	0.893	0.930	0.747
Within subject SD	1.12	0.11	4.42	1.38	0.07
CV%	11.2%	12.1%	12.6%	15.2%	6.9%

Mean (SD). Abbreviations as for figure 3.2. Oxygen pulse (O_2 pulse)

Table 3.4. Reproducibility of CPX in patients with CHF using the MSX system

	<i>Peak VO_2</i> <i>(ml/min/kg)</i>	<i>Peak VO_2</i> <i>(L/min)</i>	<i>Peak VE</i> <i>(L/min)</i>	<i>Peak O_2</i> <i>pulse</i> <i>(ml/beat)</i>	<i>Peak</i> <i>RER</i>
Test One	11.6 (3.5)	0.91 (0.32)	34.3 (11.8)	9.2 (3.2)	0.98 (0.12)
Test Two	11.3 (3.5)	0.89 (0.32)	34.3 (11.7)	9.3 (2.9)	1.02 (0.11)
p	0.436	0.620	0.969	0.816	0.076
ICC	0.849	0.852	0.851	0.688	0.588
Within subject SD	1.34	0.12	4.44	1.66	0.08
CV%	11.5%	13.0%	12.4%	17%	8.3%

Mean (SD)

Table 3.5. Reproducibility of CPX in patients with CHF using the Zan system

There was no significant difference for any of the parameters derived from the gas analysis between the two tests for either system, except for an increase in the O₂ pulse on the MSX system for the second test. The coefficient of variation for the peak VO₂ was similar for both exercise systems, 11.2% using the MSX and 11.5% using the Zan. The peak O₂ pulse had the largest CV% of all the parameters derived from gas analysis.

Reproducibility of the ISWT

Reproducibility of the ISWT in CHF

45 of the 57 patients had three ISWTs within a two week period; mean (SD) age 72.9 (8.9) yrs, 64% male. Six patients had previously performed an ISWT test, so were excluded from this part of the analysis. There was missing data for one patient and longer than two weeks between the two sets of tests for five patients so they were excluded from this part of the analysis. There were no adverse events. One patient dropped their blood pressure by 10mmHg at the end of the test, but was asymptomatic and it did not recur on subsequent testing. There was a significant increase in mean (95% CI) distance walked between the first two tests; 26 (17-36) m $p < 0.0005$ but no further increase on test three; 0 (-8 to 10)m. There was no significant difference in the peak heart rate, oxygen saturation, change in systolic blood pressure, or the Borg Scale breathlessness (BS) score or perceived exertion (PE) score between any of the tests ($p > 0.05$).

The mean (SD) difference between test two and three was 0 (30)m. The individual variation is demonstrated by a Bland and Altman plot in figure 3.3. The

within subject SD was 21.2m. The coefficient of variation was 9.5% with an ICC for test two and three of 0.985.

	<i>Test One</i>	<i>Test Two</i>	<i>Test Three</i>
ISWT (m)	196 (121)	222 (128) *	222 (122)
Peak Heart Rate (bpm)	98 (24)	100 (19)	99 (21)
Peak O ₂ saturation (SpO ₂ %)	94 (5)	93 (5)	93 (5)
Change in Systolic BP	10 (-5 to 50)	10 (-10 to 50)	10 (-4 to 50)
BS	4 (2)	4 (3)	4(3)
PE	15 (4)	15 (4)	15 (4)

*p<0.05 between test one and two

Table 3.6. Results of three ISWTs in patients with CHF

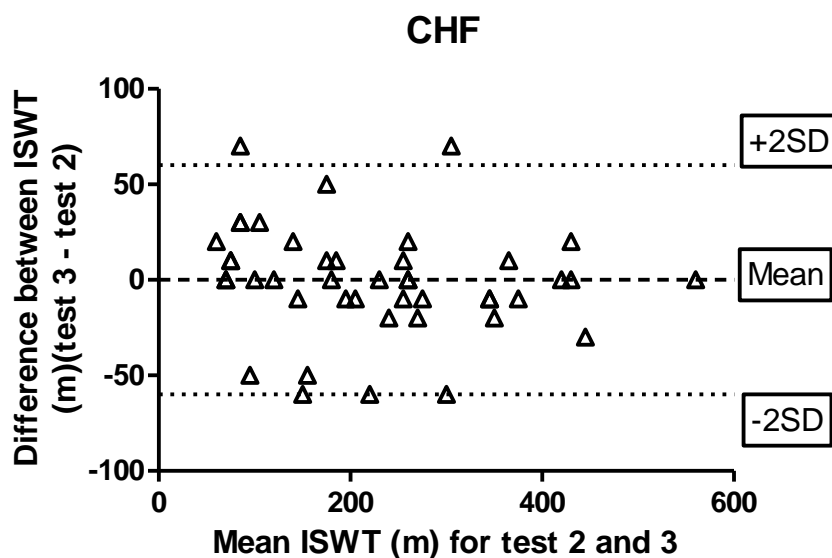


Figure 3.3. Bland Altman plot of the limits of agreement of the ISWT

Reproducibility of the ESWT in CHF

The ESWT had not been used before in patients with CHF therefore two tests were performed on separate days in case there was a learning effect. An ISWT was performed first on both occasions to prescribe the correct speed. Patients had a thirty minute rest between tests. The level of the ESWT was the same for 28 patients for both ESWTs. Patients were stable between the two sessions with no difference between resting HR, BP or BS shown in the table 3.7. The mean (95% CI) ESWT time between the two tests was 30 (1 to 60) secs $p=0.046$.

	<i>Test One</i>	<i>Test Two</i>	<i>p value</i>
Time (secs)	199 (95)	229 (88)	0.046*
Rest heart rate (bpm)	70 (11)	71 (12)	0.470
Rest BP (mmHg)	113 (22) / 62 (14)	111 (19) / 59 (11)	0.411
Rest SpO ₂ %	95 (4)	96 (1)	0.168
Rest Borg Score†	0.5 (0.0 -1.0)	0.5 (0.0 -1.0)	0.056
Peak heart rate (bpm)	100 (19)	102 (21)	0.494
Peak BP (mmHg)	127 (26) / 66 (13)	124 (24) / 65 (11)	0.638
Peak SpO ₂ %	94 (6)	95 (5)	0.373
Peak BS†	4.0 (4.0 – 5.8)	5.0 (4.0 – 6.8)	0.299
Peak PE†	15.0 (13.0 – 17.0)	15.5 (15.0 – 17.0)	0.151

* $p<0.05$, mean (SD) unless †median (IQ range), beats per min (bpm), blood pressure (BP), oxygen saturation (SpO₂%), Borg Score for breathlessness (BS), perceived exertion (PE)

Table 3.7. Results of test one and two of the ESWT in patients with CHF

Medium term reproducibility of ESWT (seven weeks)

17 patients randomised to the normal care (control) limb of the main study had a third ESWT seven weeks later. The ESWT level was the same for the first two tests in 12 of these patients i.e in total they had three ESWTs at the same speed (table 3.8). The ESWT remained unchanged over the seven weeks. Patients were stable over this 7/52 period (table 3.8).

	<i>Baseline (after familiarisation)</i>	<i>After seven weeks</i>	<i>p</i>
ESWT	246 (93)	219 (88)	0.253
Peak heart rate (bpm)	106 (16)	103 (12)	0.580
Peak BP (mmHg)	126 (20) / 66 (8)	130 (19) / 69 (10)	0.551
Peak SpO ₂ %	95 (2)	94 (2)	0.480
Peak BS†	4.5 (3.3 - 8.5)	4.5 (3.0 -6.8)	0.877
Peak PE†	16.5 (13.0 – 19.0)	15.0 (13.0 – 16.5)	0.176
ISWT	237 (106)	234 (117)	0.807
CHQ-Dyspnoea	3.58 (1.23)	3.68 (1.27)	0.754

Mean (SD) unless †median (IQ range)

Table 3.8. Measurements of ESWT, ISWT and CHQ over seven weeks

Quadriceps isometric strength testing

As described in chapter two, patients performed six knee extensor maximal voluntary contractions (MVC) in two sets of three with a thirty second rest between each contraction and a two minute rest between both sets. The peak torque was the highest of the six contractions.

Isometric strength testing in CHF

44 patients with CHF completed two sets of six isometric MVC. There was no statistical difference between the peak torque (PT) for set one 109.1 (38.1) Nm and test two 107.7 (37.4) Nm $p=0.519$ (mean [SD] difference -1.4 [15.1]). A Bland Altman plot of the peak torque from both tests is shown in figure 3.4. Although there was no difference in mean PT there was individual variability. The within subject SD was 10.6 Nm and the CV was 9.8%.

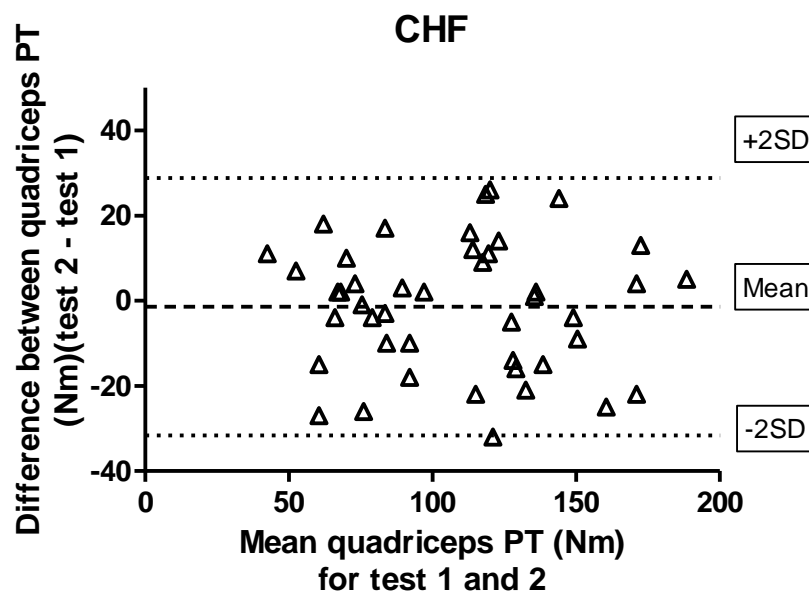


Figure 3.4. Limits of agreement of isometric quadriceps strength in CHF

Isometric strength testing in COPD

50 patients with COPD completed both sets of six isometric quadriceps manoeuvres. The mean peak torque did increase on the second test; 112.2 (44.5) Nm to 116.6 (43.7) Nm $p=0.029$ (mean [SD] difference 4.4 [13.9]). The within subject SD was 10.2 Nm and the CV was 8.9%. The individual individuality is demonstrated in figure 3.5.

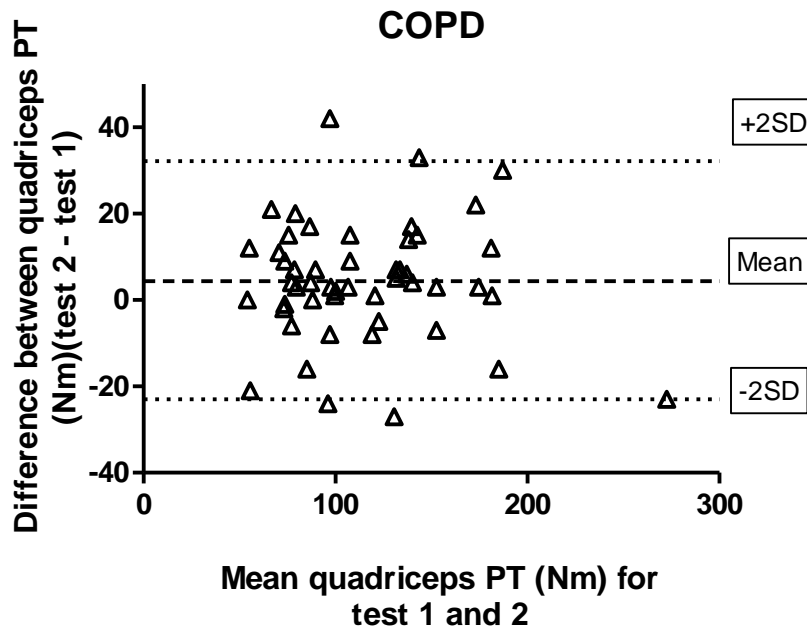


Figure 3.5. Limits of agreement of isometric quadriceps strength in COPD

Discussion

Studies to date have reported variable results of reproducibility of measurements derived from a CPX on a cycle ergometer (424;426). In COPD there is a learning effect for the ISWT and ESWT (385;393). There was little evidence regarding the reproducibility of the isometric quadriceps peak torque after one session of six maximal voluntary contractions in COPD and CHF. For the current study patients with COPD and CHF performed familiarisation tests for all the tests of physical performance within the two week run in period of the main trials. This chapter examines the results and investigates whether a practice or familiarisation test should be included in study designs.

For patients with COPD this study shows that patients worked harder on the second (CPX) test. This could either be a learning effect or that patients felt more confident exercising on the second test. There was no significant difference between the peak VO_2 for both tests. The coefficient of variation was 8.6% for peak VO_2 which is comparable to other studies (426). The patients for the current study were older than for previous studies (423) and were unfamiliar with cycling prior to the test. The mean duration of the test was only four and a half minutes. A duration of around ten minutes is recommended for a maximal CPX (397). One limitation of an incremental protocol is that there is an abrupt increase in the workload at the end of each minute. A study comparing the peak response to exercise between a ramp and an incremental exercise test showed that patients with exertional dyspnoea achieved a higher workload on the ramp protocol, but there was no significant difference in peak VO_2 (472). The authors were careful to ensure that patients achieved a symptom limited maximum within

approximately 10 minutes by calculating the size of the work rate increment for each patient according to the equation of Wasserman et al (473). The 10W/min protocol may cause an abrupt termination of exercise that could potentially affect the reproducibility of the test.

The reproducibility of the CPX for patients with CHF was evaluated on two different systems; both using rapid response gas analysers, but one with mass spectrometry. There was no difference in the reproducibility of the parameters assessed by gas analysis between the two systems. The results of the two tests for patients with heart failure did not show any evidence of a learning effect. The mean peak VO_2 was similar between the two tests. The coefficient of variation was higher (11.2% and 11.5%) than for COPD (8.9%), despite patients with COPD working harder on the second test. There were less numbers for the patients with CHF because they were assessed on the two different systems. Overall the results showed that there is individual variability for the peak VO_2 over one to two weeks for CHF.

Subsequently a large, multicentre trial (83 sites) involving 401 patients evaluated the reproducibility of peak VO_2 in patients with CHF (474). 350 used a modified Naughton treadmill test and 48 used a 10W/min ICE protocol. The results from the different platforms were combined. There was no significant difference in mean peak VO_2 between the two tests. There was significant within subject variability of 1.3ml/min/kg between the two tests (mean peak VO_2 15 ml/min/kg) with a CV of 6.6%. The 90th percentile change was high at 3ml/min/kg. The authors conclude that a familiarisation test is not necessary. The trial was conducted as part of the HF-ACTION training trial. It would be interesting to see if the results of the change in peak VO_2 after

the intervention would be altered by using either the first test (as if familiarisation had not occurred), the second test or the average of both tests. Whether there was an effect on the change from an intervention would be more helpful to definitely conclude that only one baseline exercise test is necessary.

It is unclear why patients with COPD worked harder on the second test and why this was not observed with patients with CHF. The mean peak VO_2 , workload and duration was similar between the two groups. The mechanisms of limitation for COPD and CHF are discussed in chapter five. The main difference was that more patients with COPD than CHF, had a ventilatory limitation to exercise. However, there was no difference in the variability of peak VO_2 between the patients with or without a ventilatory limitation to exercise.

The reproducibility of the ISWT and ESWT were evaluated in this older population with severe heart failure than the studies by Green et al (470). There was a mean increase in the ISWT distance on the second test, but no further increase on the third test which is similar to the studies in younger patients with COPD and CHF (385;470). The CV% for the ISWT distance was 9.4% which was lower than Dyer et al described for elderly patients with COPD (408). A familiarisation test is therefore necessary for patients with CHF which has been previously recommended for patients with COPD (385). The within subject SD of 21m should be taken into consideration when interpreting the change in ISWT with an intervention for patients with CHF. The ESWT was reproducible after a familiarisation test in patients with CHF and therefore a practice test should be undertaken.

The reproducibility of isometric knee extensor strength measured on a Cybex II

dynamometer was evaluated in patients with COPD and CHF. The peak torque from six maximal contractions was similar between two sessions one to two weeks apart for patients with CHF, but improved on the second set of testing in patients with COPD. The CV% was 9.8% and 8.9% respectively so there was individual variability for both groups.

The main limitation to the results presented in this chapter is that the reproducibility of three different exercise tests was assessed in the same study involving the same patients. A training effect from performing so many exercise tests within two weeks can not be excluded (even though this was not seen overall it may have occurred in individual patients). There may be an effect from performing other exercise tests in-between the two exercise tests being examined.

From this data a practice ISWT and ESWT are recommended for patients with CHF, similar to the recommendations for patients with COPD. A practice CPX and two sets of six MVC for isometric strength testing are recommended for patients with COPD from this data. There was no learning effect demonstrated for the CPX for patients with CHF and also no learning effect for the peak torque after six contractions for isometric quadriceps strength for CHF. For studies involving only patients with CHF familiarisation testing is unnecessary for CPX or isometric strength measured by six MVC. However, whether an average of two baseline tests would be more accurate, in view of the wide individual variability, needs to be further investigated.

- For the measures of physical performance for the main studies described in this thesis, the results from the second visit were used as the baseline tests
- The next chapter describes the randomised controlled trial of pulmonary rehabilitation vs. normal care in patients with CHF.

Chapter four

A randomised controlled trial of pulmonary rehabilitation compared to normal care in patients with chronic heart failure

Background

The **previous chapter** described the need for a practice test for both the ISWT and the ESWT for patients with CHF and the baseline variability of a CPX. A familiarisation test was performed for all the tests of physical performance in this chapter. The tests performed on the second visit were used as the baseline measurements for the results described in this chapter.

The benefits of exercise training for patients with CHF were described in the introduction. The lack of both research and availability of practical exercise programmes for these patients was highlighted.

- The hypothesis for the main study was that patients with CHF and COPD could benefit similarly from pulmonary rehabilitation and be trained together
- Firstly, it needs to be established if the model of pulmonary rehabilitation could be successfully applied to patients with CHF
- A randomised controlled trial of an existing pulmonary rehabilitation programme compared to normal care in patients with CHF was therefore conducted and is described in **this chapter**

Methods

The description of the study design including the outcome measures are described in chapter two.

Statistical Analysis

Independent t-tests were used to compare normally distributed parameters between the PR and NC group and between the dropouts and completers. Gender and NYHA class distribution were compared using chi squared (χ^2) test and the median NYHA class compared with the Mann-Whitney U test. Analysis of variance (ANOVA) was used to assess the overall relationship between the ISWT distance and NYHA class and the interclass differences were assessed using post hoc analysis.

Paired t-tests were used to assess the intragroup differences with either intervention in normally distributed data. Mann-Whitney U test was used to assess the difference with the intervention in PE or BS scores. The intergroup differences in the change in normally distributed parameters were assessed by an independent t test and the Mann-Whitney U

test for non parametric data. Effect size was calculated by $\frac{\mu_1 - \mu_2}{\sigma}$ where μ_1 and μ_2 = mean of each group and σ = the SD of the mean of the two groups. Serial walk tests were assessed with repeated measures and Bonferonni's correction factor for multiple comparisons.

Results

Figure 4.1 demonstrates the patient flow through the trial. 57 patients were randomised; 37 to pulmonary rehabilitation (CHF-PR) and 20 to normal care (CHF-NC).

Demographics, baseline exercise performance and health status

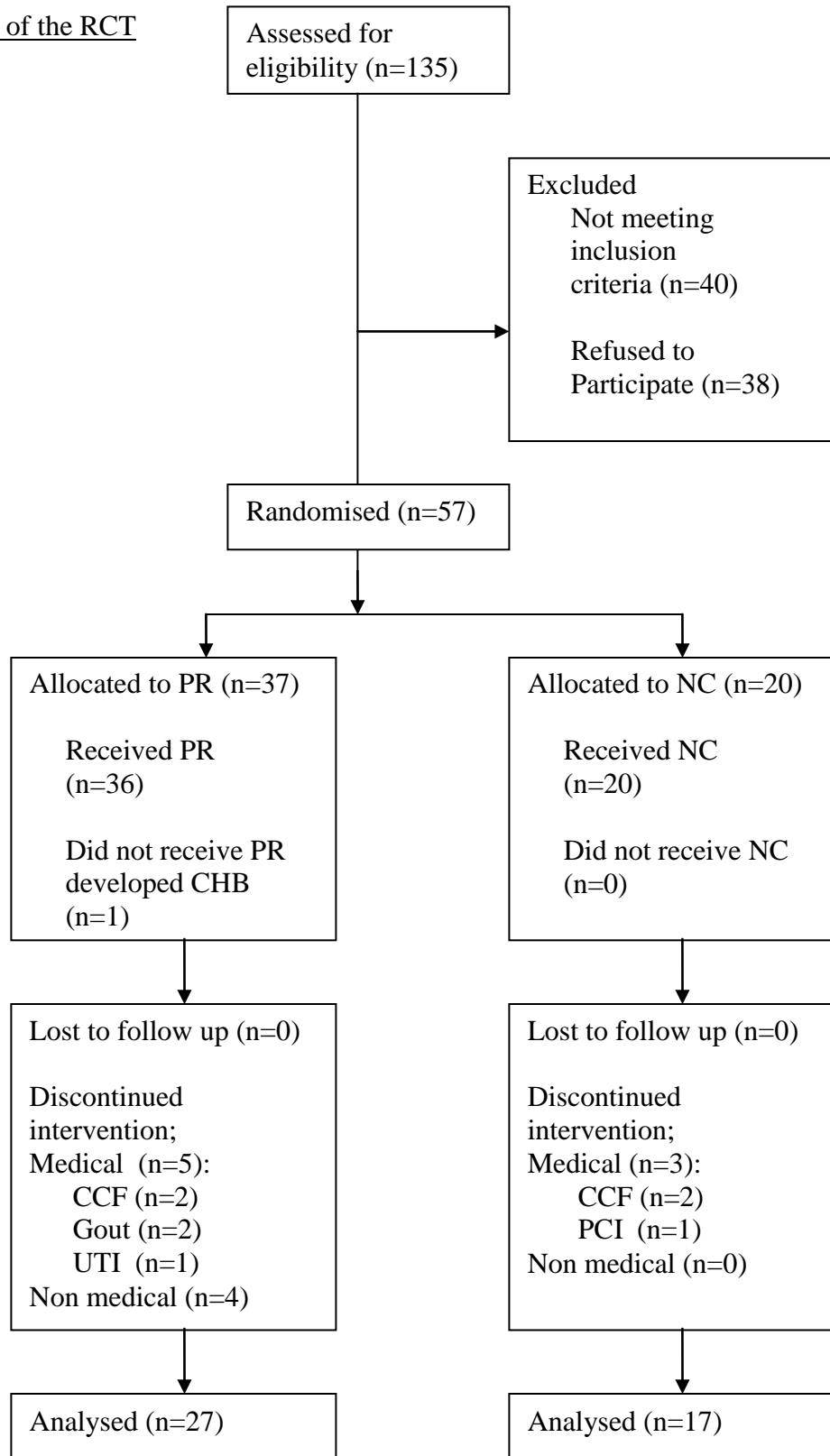
There were no significant differences in the baseline demographics between the CHF-PR and CHF-NC groups (table 4.1). Patients had a mean (SD) age of 71.0 (10.2) yrs, and just under a third were female. Median (IQ range) NYHA class was similar between the groups 3 (2-3) $p=0.145$. Both groups showed similar physical performance assessed by the ISWT distance (maximal exercise capacity), ESWT time (submaximal exercise capacity), peak VO_2 from the CPX and similar quadriceps isometric muscle strength. There were no significant adverse events during the exercise tests. The mean (SD) heart rate rose from 69 (13) bpm to 98 (22) bpm $p<0.0005$ at peak exercise with a mean (SD) rise in blood pressure from 109 (20) /63 (12) mmHg to 121 (24) /66 (12) mmHg $p<0.0005$. One patient had an asymptomatic 10mmHg drop in BP on their first ISWT, but on subsequent testing it remained constant and they were therefore not excluded. There was a small but significant decrease in mean (SD) oxygen saturation, with exercise, from 96 (3)% to 93 (5)% $p<0.0005$.

Relationship between ISWT distance and functional status assessed by the NYHA classification

There was a positive relationship between ISWT distance and NYHA class; NYHA 2 - 333 (276-390)m, NYHA 3 - 194 (158-230)m, NYHA 4 - 79 (62-95)m ANOVA $p<0.0005$ (figure 4.2).

Figure 4.1.

Flow diagram of the RCT



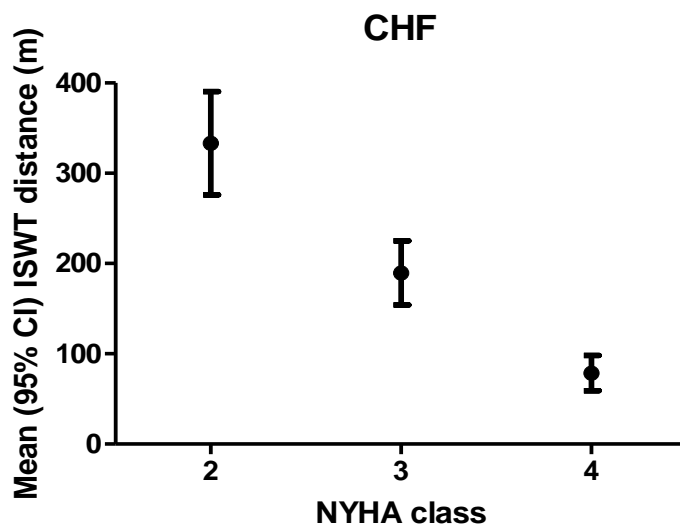


Figure 4.2. Relationship between ISWT distance and NYHA class

Description of medication and cause of heart failure

There were no differences in the medication between the two groups (see table 4.1). For one patient the medication was unknown so the data is for 56/57 patients. Overall 94.6% were prescribed either ACE inhibitors or ATII antagonists, 73.2% beta blockers, 32.1% spironolactone, 26.8% digoxin, 90.9% diuretics, 73.2% lipid lowering agents, 40.0% nitrates, 37.5% warfarin and 60.7% on antiplatelet therapy. Regarding the underlying cause of heart failure, 71.9% had ischaemic cardiomyopathy, 5.3% mixed valvular and ischaemic cardiomyopathy, 5.3% valvular cardiomyopathy and 17.5% other causes. There was no significant difference in the cause of heart failure between the PR and NC groups. 9.1% had biventricular pacemakers and 7.1% had an intracardiac defibrillator.

	<i>PR n=37</i>	<i>NC n=20</i>	<i>p</i>
Age (yrs)	69.8 (10.7)	73.2 (8.9)	0.236
Gender (% male)	67.6%	70.0%	0.852 ‡
LVEF %	31.2 (8.4)	30.7 (12.7)	0.540
NYHA Class	2 45.9%	2 25%	0.145 ‡
	3 37.8%	3 65%	
	4 16.3%	4 10%	
BMI	31.4 (6.4)	30.6 (6.5)	0.670
FFMI	19.9 (3.0)	19.0 (2.6)	0.636
ISWT (m)	242 (154)	213 (91)	0.441
ESWT (secs)	215 (83)	226 (93)	0.647
CPET PeakVO ₂ (ml/min/kg)	10.8 (3.8)	10.4 (2.5)	0.638
Quadriceps PT (Nm)	119 (53)	109 (39)	0.508
CHQ Dyspnea (CHQD)	3.57 (1.21)	3.73 (1.19)	0.654
CHQ Fatigue (CHQF)	3.40 (1.16)	3.25 (1.14)	0.636
CHQ Emotional Function (CHQEF)	4.73 (1.32)	4.17 (1.29)	0.135
CHQ Mastery (CHQM)	4.84 (1.17)	4.42 (1.18)	0.210
SF36			
Physical Function (PF)	29.2 (17.4)	34.7 (22.5)	0.347
Role –Physical (RP)	18.4 (31.0)	20.3 (31.9)	0.839
Role – Mental (RM)	56.2 (44.8)	60.4 (42.5)	0.752
Social Function (SF)	51.2 (24.7)	61.1 (31.7)	0.235
Pain (P)	59.9 (21.3)	52.8 (30.8)	0.347
Mental Health (MH)	72.5 (21.1)	67.0 (18.3)	0.379
Energy (E)	3.9 (17.8)	40.9 (19.1)	0.374
Health Perception (GHP)	32.7 (15.2)	37.2 (16.3)	0.347
Change in Health (CH)	37.5 (25-50)	37.5 (25-50)	0.493 †
Medication			
Beta Blocker	81 %	60 %	0.096
ACE inhibitor or ATII antagonist	97 %	90 %	0.250
Spirolactone	33 %	30 %	0.798
Diuretic	89 %	90 %	0.859
Digoxin	19 %	40 %	0.096
Warfarin	44 %	33 %	0.150
Antiplatelet agent	56 %	70 %	0.289
Lipid lowering agent	67 %	85 %	0.138
Nitrates	42 %	35 %	0.601

Mean (SD) $p < 0.05$ significant, value derived from an independent t test unless, † median (IQ range) Mann whitney U test, ‡ Chi squared test

Table 4.1. Comparison of the baseline demographics, exercise performance and health status between the two groups

Baseline Health Status

Baseline health status was similar between the two groups measured by the four domains of the CHQ and the nine domains of the SF36 (table 4.1).

Results of the RCT; pulmonary rehabilitation vs. normal care

27 patients completed the pulmonary rehabilitation course and 17 patients completed the normal care period achieving adequate power. The results of the walking tests are shown in table 4.2 and figure 4.3. The rehabilitation group (PR) made a significant mean (95% CI) improvement in ISWT performance of 62 (35 to 89)m p<0.0005 while the ISWT distance in the normal care group remained the same -6 (-11 to 23)m p=0.465. The intergroup mean (95% CI) difference in the change in the ISWT was also statistically significant; 68 (32-104)m p<0.0005 effect size 0.57 (greater than the between group difference of 50m for the power calculation). The ESWT improved by 351 (203 - 498) secs after rehabilitation p<0.0005 and there was a non-significant decrease in ESWT of -36 (-77 to 4) secs p=0.075 with normal care. The intergroup difference of 387 (201 – 573) secs [nearly six and a half minutes] was statistically significant p<0.0005 effect size 0.95. The ESWT appeared to be more sensitive to the effects of rehabilitation than the ISWT, 183 (230) % improvement in ESWT duration compared to 36 (47) % improvement in ISWT distance.

There was no statistically significant change in the heart rate, systolic blood pressure, oxygen saturation, or Perceived Exertion score at the end of the ISWT performance (before or after rehabilitation or before and after normal care) (table 2). There was no change in the end BS score for the ISWT performance before or after rehabilitation, but the end BS score for the ISWT was significantly lower after the

normal care period. The end parameters were not significantly different between the PR and NC group except for the BS score where the PR group reported a higher BS 4 (4-7) for the final ISWT performance than the control group 3 (3-4) $p < 0.005$ (there was no difference between the two groups in the baseline peak BS $p = 0.303$).

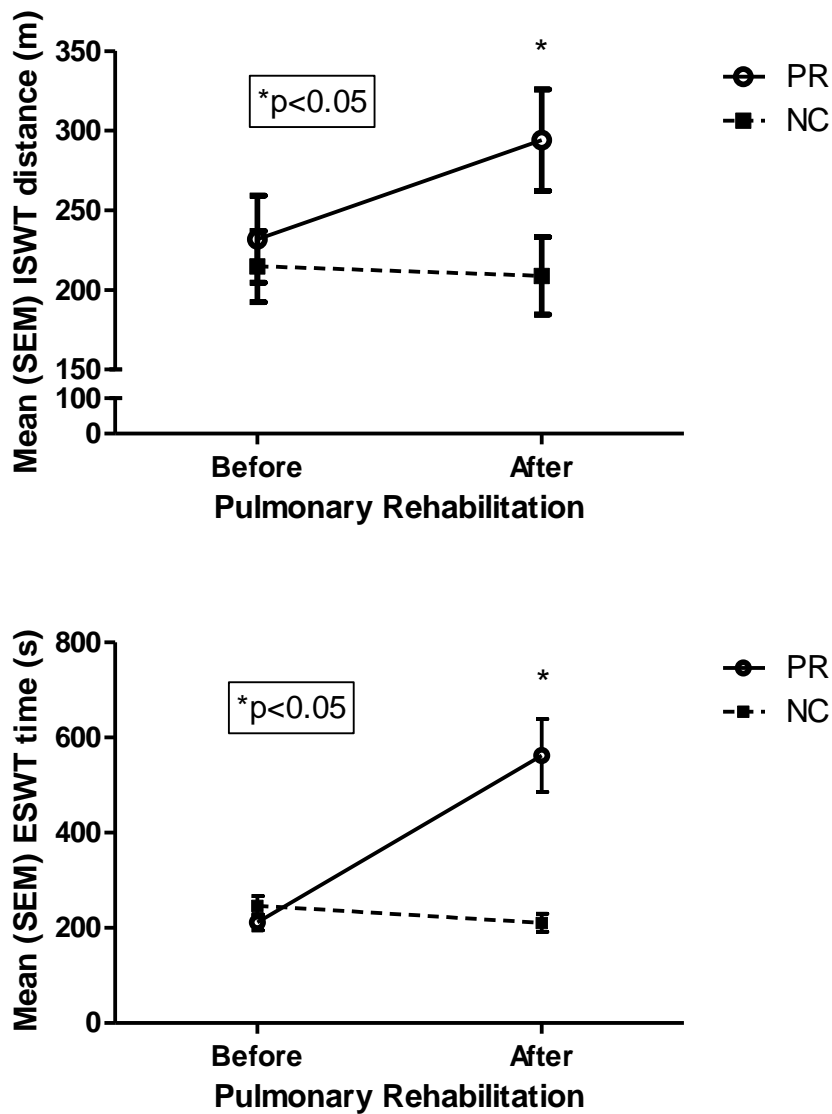


Figure 4.3. Results of the ISWT and ESWT for the RCT

	<i>Pulmonary Rehabilitation</i>			<i>Normal Care</i>		
	Before	After	p	Before	After	p
ISWT (m)	232 (141)	294 (166)	<0.0005*	215 (92)	209 (100)	0.465
ESWT (secs)	212 (87)	562 (399)	<0.0005*	247 (84)	210 (83)	0.075
Peak HR (bpm)	98 (23)	103 (26)	0.398	102 (20)	98 (19)	0.293
Peak SpO ₂ %	93 (6)	93 (6)	0.739	94 (3)	95 (2)	0.515
Peak BP (mmHg)	120 (19)/ 62 (12)	120 (24)/ 60 (9)	0.984	126 (20)/ 65 (8)	131 (21)/ 68 (10)	0.327
Peak BS†	5 (4-5)	4 (4-7)	0.464	4 (3-6)	3 (3-4)	0.046*
Peak PE†	15 (13-17)	16 (13-17)	0.309	15 (13-17)	15 (13-16)	0.329
CPET						
Peak VO ₂ (ml/kg/min)	11.2 (3.7)	11.8 (4.3)	0.199	10.3 (2.6)	10.2 (1.9)	0.829
Peak Work (W)	56.7 (29.1)	61.7 (26.2)	0.259	47.5 (17.7)	46.9 (20.2)	0.529
Duration (seconds)	339 (168)	368 (162)	0.130	266 (121)	283 (125)	0.849

mean (SD) †median (IQ range) *p<0.05, heart rate (HR), beats per minute (bpm)

Table 4.2. Results of exercise performance for the RCT

All patients had serial ISWT and ESWT every 3rd or 4th session throughout the seven weeks. 22/27 patients had complete data sets for all five time points. Patients made small non significant improvements in the first two weeks, but had made statistically significant changes in the ISWT distance and ESWT time by halfway (session seven) (table 4.3). The shape of the curves of the progression of the mean ISWT and ESWT appear to be different (figure 4.4). However, because the tests are measured in different units it is difficult to describe this in statistical terms.

<i>Session</i>	<i>Change in</i>	<i>%</i>	<i>p</i>	<i>Change in</i>	<i>% change</i>	<i>p</i>
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	<i>ISWT distance</i>	<i>change of total</i>		<i>ESWT time</i>	<i>of total</i>	
1-4	14 m	27	0.293	31 secs	9	0.237
1-7	20 m	39	0.045*	128 secs	36	0.003*
1-11	31 m	61	0.003*	167 secs	47	0.002*
1-14	51 m	100	<0.0005*	355 secs	100	0.001*

*p<0.05

Table 4.3. Serial ISWT and ESWT throughout pulmonary rehabilitation

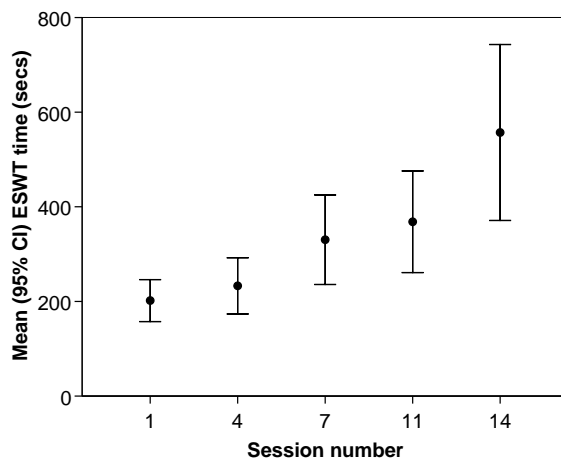
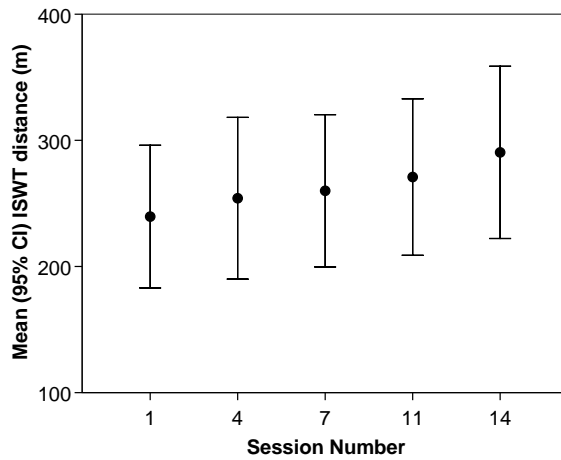


Figure 4.4. Training profile of maximal and submaximal exercise capacity.

Cardiopulmonary exercise test (CPX).

There was no statistical change in any of the peak parameters on the cycle ergometer with pulmonary rehabilitation or normal care (table 4.2).

Weight, FFM and quadriceps strength

Weight remained unchanged with pulmonary rehabilitation 0.35 (-0.50 to 1.19) kg $p=0.406$ and with normal care -0.25 (-1.52 to 1.02) kg $p=0.676$. However, total fat free mass was increased by 1.98 (0.04 to 3.93) kg with rehabilitation $p=0.046$ and remained the same -0.25 (-2.25 to 1.75) kg in the control group 0.759. The FFMI was not changed for either group; rehabilitation 0.43 (-0.10 to 0.96) $p=0.109$ vs. control -0.1 (-0.79 to 0.59) $p=0.759$. There was a non-significant small increase in muscle strength after rehabilitation from 111 (42) Nm to 118 (46) Nm $p=0.086$. The quadriceps muscle strength was unchanged with normal care 115 (43) Nm to 113 (47) Nm $p=0.747$.

Functional status

6/27 (22.2%) patients improved (decreased) their NYHA class with rehabilitation and no patients had a worse NYHA class. For the normal care group 16/17 NYHA classification stayed the same and 1/17 worsened. Overall there was a statistical improvement in the median (IQ range) NYHA class from 3 (2-3) to 2 (2-3) $p=0.014$ for the rehabilitation group which was not seen in the control group, NYHA 3 (2-3) to 3 (2-3) $p=0.317$.

Health Status

CHQ

Patients undergoing pulmonary rehabilitation made statistically significant improvements in all four domains of the CHQ (table 4.4). There was no significant change in any domain with normal care. The intergroup (PR vs NC) difference in the

change in score did not reach statistical significance in any domain (table 4.4).

	<i>Change with PR</i>	<i>p value</i>	<i>Change with NC</i>	<i>p value</i>	<i>Intergroup difference</i>	<i>p value</i>
CHQ-D	0.65 (0.21 to 1.09)	0.006*	0.14 (-0.34 to 0.62)	0.545	0.51 (-0.14 to 1.16)	0.120
CHQ-F	0.39 (0.06 to 0.72)	0.021*	0.16 (-0.27 to 0.59)	0.438	0.23 (-0.29 to 0.75)	0.371
CHQ-EF	0.38 (0.01 to 0.75)	0.049*	0.38 (-0.11 to 0.86)	0.118	0.00 (-0.59 to 0.59)	0.999
CHQ-M	0.36 (0.04 to 0.67)	0.028*	0.08 (-0.29 to 0.46)	0.638	0.27 (-0.21 to 0.75)	0.256

Mean (95% CI) units *p<0.05, dyspnoea (D), fatigue (F), emotional function (EF), mastery (M).

Table 4.4. Results of the CHQ for the RCT

SF36

Overall there was a trend in the rehabilitation group to improve the scores (table 4.5). Significant improvements were seen in social functioning (SF) 14.5 (4.3 to 24.7) p=0.007, energy and vitality (EV) 10.9 (2.6 to 19.2) p=0.012, and change in health score (CH) 15 p=0.006. There was a trend towards an improvement in general health perception (GHP) 7.9 (-0.6 to 16.3) p=0.066. The scores in the control group did not significantly change except for a decline in role limitation due to emotional problems (RE) -29.2 (-54.2 to -4.0) p=0.025.

Correlation between improvements in health status and exercise performance

There were no correlations between the improvement in ISWT distance (table 4.6) or ESWT duration (data not shown) and any of the four domains of the CHQ. Two patients improved the CHQ-D domain by over two units with PR but made no improvement in the ISWT performance. These data skewed the results towards the negative correlation between the change in ISWT distance and CHQ-D.

	<i>Change with PR</i>	<i>p value</i>	<i>Change with NC</i>	<i>p value</i>
Physical Function (PF)	0.52 (-7.5 to 8.6)	0.895	-5.0 (-17.7 to 7.7)	0.414
Role -Physical (RP)	6.3 (-11.2 to 23.7)	0.465	-8.3 (-34.3 to 17.6)	0.503
Role - Mental (RE)	16.7 (-3.7 to 37)	0.103	-29.2 (-54.2 to -4.0)	0.025*
Social Function (SF)	14.5 (4.3 to 24.7)	0.007*	-8.1 (-21.6 to 5.3)	0.215
Pain (P)	2.9 (-6.6 to 12.4)	0.534	-0.7 (-16.2 to 14.8)	0.920
Mental Health (MH)	6.7 (-0.6 to 13.4)	0.073	0.5 (-9.8 to 10.8)	0.913
Energy (EV)	10.9 (2.6 to 19.2)	0.012*	-5.3 (-12.2 to 1.6)	0.120
Health Perception (GHP)	7.9 (-0.6 to 16.3)	0.066	7.7 (-1.7 to 17.1)	0.102
Change in Health† (CH)	15	0.006*	12.5	1.00

Mean (95% CI), †change in median score *p<0.05

Table 4.5. Results of the SF36 for the RCT

	<i>Pearsons correlation coefficient</i>	<i>p</i>
ΔISWT with ΔCHQ-D	-0.178	0.394
ΔISWT with ΔCHQ-F	0.033	0.872
ΔISWT with ΔCHQ-EF	0.102	0.602
ΔISWT with ΔCHQ-M	0.092	0.655

Change in (Δ), dyspnoea (D), fatigue (F), emotional function (EF), mastery (M).

Table 4.6. Correlation between changes in exercise performance and health status with pulmonary rehabilitation

RCT dropouts vs. completers

There were a higher proportion of dropouts in the PR group than the NC group 27% vs 15% respectively, but this was not statistically significant $p=0.302$. The number of patients who dropped out of the trial because of decompensation of their heart failure was the same in each group $n=2$; 2/37 PR vs 2/20 for NC. There were more non-medical reasons for dropping out of the trial in the PR group. There was no significant difference in the mean age, LVEF, ISWT, or gender between the dropouts of rehabilitation and the dropouts out of the normal care. The subjects that dropped out from the whole trial were significantly younger 63.8 (11.9) yrs vs 73.1 (8.7) yrs $p=0.019$, had a significantly lower mean LVEF 22.5 (10.7)% vs 31.1 (6.2)% $p=0.006$, but had a similar gender mix 84.6% male vs 63.6 male $p=0.156$ and NYHA class $p=0.6$. They were similar in terms of exercise performance (ISWT distance 252 (170)m vs 225 (124)m $p=0.529$ and muscle strength 153 (50)Nm vs 129 (36)Nm $p=0.067$).

Patients in NYHA class 4

There were only small numbers of patients in NYHA class IV ($n=8$; 2 NC and 6 PR) but the data will be presented in more detail because there is little information about this class in the literature as historically they have been excluded from trials of exercise training (241). There was a 50% dropout rate in each group for NYHA IV. There were four patients in total that had an episode of decompensation of heart failure causing them to dropout of the trial, three of these were NYHA IV. 50% of the NYHA IV patients in the NC group and 33% of the PR group dropped out because of decompensation. Three of the six patients in the PR group completed the course and made a mean improvement of 20m (or 40% of baseline ISWT) in the ISWT (individual change in the ISWT was

60m, 20m and -20m). The other patient in the PR group dropped out for medical, but non cardiac reasons.

Discussion

The main aim of this programme of work was to investigate whether combined training programmes for COPD and CHF are feasible. The aim of the study discussed in this chapter was to investigate whether the model of pulmonary rehabilitation used successfully for patients with COPD, could be applied to patients with CHF. A randomised controlled trial of an existing pulmonary rehabilitation (PR) programme vs. normal care (NC) in patients with CHF was therefore conducted.

Patients with CHF undergoing pulmonary rehabilitation made highly statistically significant improvements in exercise tolerance assessed by the ISWT distance and the ESWT time compared to normal care. This study demonstrates that the individual exercise prescription derived from the ISWT, previously used in patients with COPD (328;475), is successful for patients with CHF. However, it should be noted that the patients in the PR group underwent three extra ISWTs during their seven weeks compared to the NC group.

The physical training was high intensity from the outset (85% peak VO_2). There is no consensus about the optimal intensity for training programmes in CHF (241) and there have been few well-conducted trials addressing this. Current guidelines suggest an intensity between 40-75% VO_2 max (476). Training has been shown to be feasible at 85% of the predicted heart rate in patients with impaired left ventricular function and coronary disease (314). In the current study improvements in walking performance

occurred in the first two weeks and became statistically significant by week four. The rate of increase in ISWT distance appeared linear and the rate of increase in ESWT time increased with time (see figure 4.4). The benefit in exercise performance, assessed by either test, did not appear to plateau by the end of the seven weeks. The optimal length of an exercise programme is unknown. The existing literature was discussed in the introduction; chapter one. This study only reports the short term outcomes. The benefit of short term programmes has been shown to be sustained for at least a year in COPD (271).

The safety of physical training has been a concern in CHF and may have had some impact on the slow development of practical programmes. However, recent studies have shown no adverse effects with training (243;477). In the current study, there were no adverse events due to training and the number of patients with de-compensation of CHF was similar in both the PR and NC groups. There were more non-medical reasons for dropping out of the PR group.

There were no changes in the peak parameters of the cardiopulmonary exercise test in either the PR or the NC group. This may in part be due to the platform of a cycle ergometer. This was chosen because it is more stable than a treadmill. However, the PR programme uses walking as the predominant mode of training and therefore a treadmill test may have been more sensitive. A fixed 10 watt/min incremental test was chosen rather than varying the W/min between patients as there is some evidence that the number of watts per minute alters the peak VO_2 achieved i.e a lower W/min is associated with a higher peak VO_2 for the same patient (421). The current study population was very disabled with a mean (SD) peak VO_2 of 10.6 (3.3) ml/min/kg and

mean (SD) peak workload of 51.5 (27.1) Watts. A fixed 5W/min incremental protocol may have provided a more desirable test duration for these disabled patients and therefore may have been a more sensitive test.

There are multiple mechanisms contributing to the improvements seen in exercise tolerance with pulmonary rehabilitation. The increase in ISWT distance and ESWT time occurred without an increase in peak heart rate or peak systolic blood pressure and the patients' reported peak breathlessness score and perceived exertion score were also similar suggests a physiological mechanism was involved rather than purely a psychological component. Serum lactate levels may have helped describe this in more detail. The contributing factors towards an improvement in exercise performance with PR are described in chapter five.

The peak BS decreased in the NC group over the seven weeks but there was not a corresponding reduction in peak heart rate or peak blood pressure. The operator for the ISWT was blinded to the intervention so should not be responsible for these differences.

The programme was predominantly endurance training and is probably why the isometric quadriceps strength was unchanged in both the PR group and the NC group. There was a small increase in total fat free mass (i.e muscle) in the PR group that was not seen in the NC group. This could mean that endurance training has a beneficial effect on body composition. There are some limitations with bioelectrical impedance which were discussed in chapter two. Firstly, it represents total body composition rather than specific compartments. Secondly, assumptions around intracellular water are used for the calculations and over 90% of these patients were prescribed diuretics. Bioelectrical impedance has been shown to be a suitable clinical alternative for diagnostic

purpose to DEXA scanning in CHF (437). The patients were clinically stable, the medication remained the same and overall weight was unchanged in both groups, so the trend in the results should represent true changes in body composition.

Patients undergoing pulmonary rehabilitation made significant improvements in all four domains of the CHQ whereas patients having normal care scores remained unchanged. Overall there was a trend to a small improvement in the nine domains of the SF36 with four reaching statistical significance. There was no correlation between the change in score of any of the domains of the CHQ and the change in either the ISWT or the ESWT with pulmonary rehabilitation. This highlights the discrepancy between improvements in exercise capacity and health status and demonstrates a heterogeneous response to rehabilitation within the population.

The education part of the Pulmonary Rehabilitation course was primarily designed for COPD. There were some generic lectures such as breathing control, exercise, energy conservation, nutrition but some were disease specific i.e pharmacology, physiology, and disease education around COPD. This could be modified further to incorporate patients with CHF and may enhance the effect on health status.

Medical trials can sometimes be criticised for not recruiting representative patients. The patients recruited for this trial were older (mean (SD) age 71 (10) years) and just under a third of the study patients were female compared to many studies involving CHF. Although cardiac cachexia is a recognised phenomenon in patients with CHF only 5/57 (<9%) of this group were cachectic¹⁵. Obesity was far more prevalent with nearly 30% of patients having a BMI of > 30. The high percentage of patients on ACE inhibitors and beta blockers reflects that the medication relating to heart failure had

¹⁵ (BMI <21 or FFMI <15kg/m₂ for females and <16kg/m₂ for males)

been optimised prior to the trial. This is an important difference to a study of exercise rehabilitation in CHF where the medication was optimised alongside the training regimen (244). This data adds to the literature supporting the efficacy of exercise training with patients on beta blockers.

This is the second reported study to use the ISWT as an outcome measure (152) and the first time the ESWT has been used in CHF. The ISWT distance has been validated in CHF as a reliable measure of peak exercise capacity (478). Data in chapter three showed that the ISWT is reproducible after a practise walk in this elderly, disabled population. The ISWT distance has a strong relationship with functional status assessed by the NYHA classification (figure 4.2) and is a sensitive outcome measure. The ESWT has not been used before in patients with CHF. Data described in chapter three demonstrates that it is reproducible in the medium term (seven weeks) after one practice test. The results of this study show that it is an even more sensitive outcome measure than the ISWT.

Recommendations for exercise rehabilitation do not include patients in NYHA 4 because of the lack of any studies including this group of patients (241). These patients were included in this study to match the disability of patients with COPD where patients with MRC grade 5 are included for PR. No definitive conclusions can be made from the current study because of the small number of patients in this group. The numbers of dropouts for decompensation of CCF were similar between the PR and NC groups.

There were limitations to the study. There was no sham training in the normal care group. However, no improvement in exercise performance is seen if exercise training is excluded from PR in COPD (301). The operator of the CPX and muscle

strength tests was not blinded to the intervention. However, the measurements were unchanged with both interventions so it is likely that no significant bias has been introduced. Although the patients improved their health status, with PR, the education programme had not been modified specifically for patients with CHF and there were sessions that were not directly relevant.

In conclusion **this chapter** described that;

- patients with CHF can make significant improvements in exercise performance and health status from an existing pulmonary rehabilitation programme
- The model of pulmonary rehabilitation can therefore be applied successfully to patients with chronic heart failure

The second part of the study was to investigate whether these benefits were of similar magnitude compared to patients with COPD and whether the two groups could be successfully trained together.

A comparative observational study was conducted of pulmonary rehabilitation between COPD and CHF. The results are described in the **next chapter**.

Chapter five

A comparative observational study between patients with COPD and CHF undergoing an existing pulmonary rehabilitation programme

Background

The **previous chapter** demonstrated that the format of pulmonary rehabilitation could be successfully applied to patients with Chronic Heart Failure. Patients undergoing PR made significant improvements in exercise performance and health status compared with normal care.

COPD and CHF can be thought of as syndromes with similar systemic manifestations as described in the introduction. There has been one study directly comparing the similar nature of these factors contributing to exercise intolerance between COPD and CHF, and between a healthy aged matched control group (95). Quadriceps and biceps isokinetic strength and peak exercise capacity were similarly reduced in both conditions. Quadriceps muscle strength and fat free mass both contributed similarly to peak exercise capacity in both conditions.

In view of the similar contributing factors to exercise intolerance between COPD and CHF and the similarities in the benefits from exercise training described in the introduction, the hypothesis for this study was that patients with CHF could achieve similar results from pulmonary rehabilitation as patients with COPD and that both groups could be trained together.

This chapter

- compares the disability (activity limitation) of patients with COPD and CHF
- describes a comparison of the responses to pulmonary rehabilitation between patients with COPD and CHF

Methods

The methodology of the study is described in chapter two. This chapter describes an observational comparative study of pulmonary rehabilitation between COPD and CHF.

Statistical Analysis

Appropriate parametric and non parametric tests were performed for baseline intergroup differences and for the intra and inter-group differences in the change with pulmonary rehabilitation. Gender and NYHA class distribution were compared using chi squared (χ^2) test. Analysis of covariance (ANCOVA) was performed to compare the change in ISWT and ESWT between COPD-PR and CHF-PR accounting for any difference in baseline variables. ANCOVA was also performed for the changes in the four domains of the CHQ or CRQ accounting for the baseline scores. Bonferonni's correction factor was applied for the main effects of the ANCOVA. A MANOVA with Pillai's trace was performed for a comparison between COPD-PR and CHF-PR for the serial ISWTs. Pearson's correlation coefficient was used when comparing parametric data and Spearman's correlation coefficient for non parametric data. Analyses were performed using SPSS version 14.0.

Results

55 patients with COPD were recruited and 44 patients with CHF. The baseline demographics were similar between the two groups (table 5.1) except for the BMI.

Severity of disease by degree of primary organ impairment

Mean (SD) left ventricular ejection fraction was 32.9 (9.6) % (moderate to severe heart failure). The mean (SD) FEV₁ % predicted for the patients with COPD was 42.9 (14.6) (GOLD stage I - 1.9%, II - 27.8%, III - 48.1%, 4 - 22.2%).

Exclusion of co-existent disease

Patients with known co-existent disease were excluded from the study. Baseline spirometry was significantly different between the two groups (table 5.1). Patients with COPD showed an obstructive deficit; mean (SD) FEV₁/FVC 50.0 (8.7)% whereas patients with CHF had an FEV₁/FVC ratio within normal limits 76.4 (5.2)%. 19/44 patients with CHF had a restrictive deficit on spirometry. Median (IQ range) NTBNP was also significantly different between the two groups; 97 (57-226) fmol/ml for COPD vs. 935 (350-1988) fmol/ml for CHF $p < 0.0005$, supporting the difference in disease between these two groups (figure 5.1).

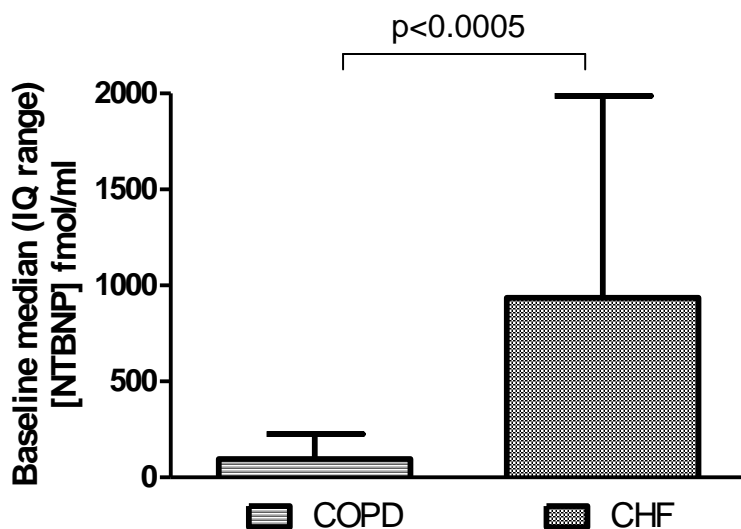


Figure 5.1. Baseline [NTBNP] levels between COPD and CHF

BMI and FFM

CHF patients had a significantly greater BMI than the patients with COPD 31.6 (6.2) vs 27.4 (5.2) $p < 0.0005$ respectively so the mean BMI for COPD was in the overweight category and for CHF was in the obese category by the WHO classification (479). One patient with COPD was in the underweight category, but no patients with CHF had a BMI < 21 . Patients with CHF also had a higher mean fat free mass compared to COPD (table 5.1 and figure 5.2). 16/55 (29.1%) of patients with COPD had a low FFMI kg/m^2 indicative for cachexia (defined in chapter two). The frequency of a reduced FFMI was much lower for patients with CHF 4/44 (9.1%) $p = 0.022$.

Exercise performance

The main results of the exercise tests are presented in table 5.1. The auxiliary parameters are shown for the ISWT, but a similar pattern was seen for the CPX and ESWT.

The baseline mean ISWT and ESWT (peak and submaximal exercise capacity respectively) were similar for the two conditions. The speed of the walk for the ESWT was also similar for the two conditions; 3.6 (1.3) km/hr for CHF vs 3.7 (1.3) for COPD $p=0.669$. Patients with CHF had a slightly reduced peak exercise capacity compared to COPD, measured by the cardiopulmonary exercise test on the cycle ergometer, when presented relative to body weight (ml/min/kg), but there was no difference in peak VO_2 when presented as an absolute value (L/min). There were some different features between the two groups of the auxiliary parameters. The patients with COPD had lower oxygen saturations at rest and at end exercise than the patients with CHF and the resting and heart rate at end exercise were significantly higher for the patients with COPD.

The mean FFMI was significantly higher in CHF than COPD, but despite this the quadriceps muscle strength was similar between the two groups (table 5.1 and figure 5.2).

	<i>COPD n=55</i>	<i>CHF n=44</i>	<i>p value</i>
Age (yrs)	69.1 (8.3)	70.6 (10.7)	0.423
Gender†	54.5 % male	65.9% male	0.255
Smoking history			
Current smoker	27.3	4.5	
Ex smoker	63.6	52.3	
Non smoker	9.1	43.2	
Pack year history	37.7 (19.7)	14.9 (19.3)	<0.0005*
BMI	27.4 (5.2)	31.6 (6.2)	<0.0005*
FFMI (kg/m ²)	17.1 (2.3)	19.5 (2.9)	<0.0005*
NTBNP†	97 (57-226)	935 (350-1988)	<0.0005*
FEV1/FVC	50.0 (8.7)	76.4 (5.2)	<0.0005*
FEV1 (L)	1.00 (0.34)	1.94 (0.63)	<0.0005*
FEV1 % pred	42.9 (14.6)	79.9 (21.1)	<0.0005*
FVC	2.00 (0.59)	2.51 (0.77)	<0.01*
Quad strength	114.6 (43.9)	117.7 (51.4)	0.753
ISWT (m)	225 (114)	234 (148)	0.767
Rest HR	84 (13)	68 (12)	<0.0005*
Rest sats	94 (3)	96 (4)	0.039*
Peak HR	107 (18)	97 (22)	0.017*
Peak sats	88 (8)	93 (5)	<0.0005*
Rest Borg†	1.0 (0.5-2.0)	0.5 (0.0-2.0)	0.148
Peak BS†	4.5 (4.0-7.0)	5.0 (4.0-6.0)	0.916
Peak PE†	15 (13-17)	15 (13-17)	0.765
ESWT (secs)	247 (154)	211 (81)	0.181
CPX			
peakVO ₂ (ml/min/kg)	12.1 (2.4)	10.9 (3.6)	0.049*
peak VO ₂ (L/min)	0.89 (0.29)	0.95 (0.44)	0.394
peak work rate (W)	51.5 (20.8)	52.3 (28.3)	0.866
peak duration (secs)	305 (118)	317 (167)	0.707
peak VE (L/min)	31.0 (9.2)	36.0 (13.0)	0.035*
peak RER	0.98 (0.07)	1.05 (0.10)	<0.0005*
peak O ₂ pulse	7.9 (2.5)	10.1 (3.9)	0.003*

Data expressed as mean (SD) with p derived from an independent t test except for † for median (IQ range) and p derived from Mann-Whitney U test, *p<0.05

Table 5.1. Comparison of the baseline demographics and exercise performance for patients with COPD and CHF

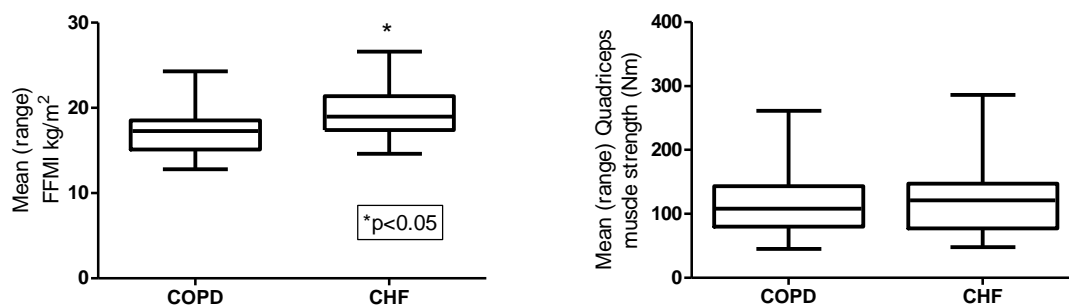


Figure 5.2. Comparison of FFMI and quadriceps strength between COPD and CHF

Comparison of the limitations to exercise

Comparison of the limiting symptom between walking and cycling

Dyspnoea was the most frequent limiting symptom when walking (ISWT) for both COPD 72.7% and CHF 63.6% $p=0.289$. In both groups more patients complained of leg fatigue when cycling compared to walking; COPD 22.2% vs 10.9% $p=0.022$ CHF 41.5% vs 11.6% $p=0.020$. Dyspnoea was still the most frequent limiting symptom when cycling for COPD 61.1% vs 22.2% (leg fatigue), but leg fatigue was the most frequent for CHF 41.5% vs 31.7% (dyspnoea).

There was no difference in the frequency of leg fatigue as the limiting symptom to either cycling or walking between COPD and CHF (both $p=1.0$).

Ventilatory Limitation

A ventilatory limitation was reached if the peak VE (L/min) was $>80\%$ predicted. The equation to calculate the predicted VE is shown in chapter two. Normal individuals use 50-75% of their ventilatory capacity at maximal exercise. 38.9% of patients with COPD had a ventilatory limitation to exercise and 12.5% of CHF patients $p=0.005$. Patients with CHF achieved a higher mean RER for the same absolute peak

VO₂ compared to patients with COPD (table 5.1) indicating that they achieved their anaerobic threshold earlier.

Cardiovascular Limitation

Patients with CHF had a lower peak heart rate than COPD. The peak O₂ pulse was higher for CHF than COPD indicating for a similar absolute peak VO₂ the stroke volume is higher for CHF patients than COPD. The predicted maximal heart rate was calculated using the calculations shown in chapter two for patients with and without beta blockade. The percentage of the predicted f_{cmax} achieved was calculated. A cardiovascular limitation was described if the percentage f_{cmax} achieved was >90%. Only one patient with COPD had a cardiovascular limitation compared to 48% of patients with CHF $p < 0.0005$. The patient with COPD with a cardiovascular limitation had also reached a ventilatory limitation.

Contributing factors to exercise performance

Quadriceps strength contributed to exercise performance in patients with COPD and CHF. Pearson's correlation coefficient between walking performance and muscle strength was 0.443 $p = 0.001$ for COPD and 0.612 $p < 0.0005$ for CHF. There was a lower correlation between cycle performance (ml/min/kg) and muscle strength (Nm) 0.274 $p = 0.047$ for COPD and 0.454 $p = 0.004$ for CHF.

There was no correlation between BMI and walking performance for either group COPD 0.076 $p = 0.584$ CHF 0.008 $p = 0.958$. There was no correlation between FFMI and walking performance for CHF 0.084 $p = 0.591$, but there was a moderate correlation for COPD 0.327 $p = 0.016$.

Baseline Health Status

Functional status

All patients demonstrated some disability by either the MRC dyspnoea scale for COPD or NYHA classification for CHF. The NYHA classification distribution for the patients with CHF was; class II - 43.2%, III - 43.2% and IV - 6.0%.

When the MRC dyspnoea scale was applied to patients with CHF¹⁶, there was no difference in the number of patients with each MRC grade between COPD and CHF; $p=0.302$ (table 5.2). There was no difference in median (IQ range) MRC grade between each group; COPD 3 (3-4) CHF 3 (3-4) $p=0.253$. Using the MRC grade for patients with CHF is described further in chapter seven.

<i>MRC grade</i>	<i>COPD</i>	<i>CHF</i>
2	11%	25%
3	48%	41%
4	26%	18%
5	15%	16%

Table 5.2. Frequency of MRC dyspnoea scale grade between COPD and CHF

Chronic Respiratory Questionnaire or Chronic Heart Questionnaire

Generally the scores measured on the CRQ-SR (self report) for patients with COPD were lower than those for CHF assessed by the CHQ-IL (interview led) (table 5.3). Patients with COPD described significantly more dyspnoea (lower score) and reduced mastery compared to patients with CHF.

¹⁶ Described fully in chapter six

	<i>COPD CRQ-SR</i>	<i>CHF CHQ-IL</i>	<i>Mean (95% CI) difference</i>	<i>p value</i>
Dyspnoea	2.43 (0.84)	3.48 (1.13)	-1.06 (-1.48 to 0.63)	<0.0005*
Fatigue	3.25 (1.25)	3.56 (1.21)	-0.35 (-0.81 to 0.11)	0.138
Emotional Function	4.28 (1.20)	4.69 (1.31)	-0.44 (-0.95 to 0.07)	0.091
Mastery	4.13 (1.18)	4.78 (1.24)	-0.67 (-1.16 to 0.18)	0.008*

Mean (SD) *p<0.05

Table 5.3. Comparison of the CRQ and CHQ baseline results between COPD and CHF

Short Form 36 (SF36) questionnaire

The majority of the dimensions of the SF36 were similar between COPD and CHF at baseline (table 5.4). The social functioning (SF) and the change in health scores were lower significantly lower for CHF compare to COPD.

	<i>COPD</i>	<i>CHF</i>	<i>p value</i>
PF	24.2 (16.8)	27.5 (17.6)	0.357
RP	15.7 (27.4)	16.4 (29.8)	0.901
RE	50.3 (44.4)	51.3 (45.1)	0.920
SF	62.1 (25.1)	50.9 (23.7)	0.038*
MH	66.0 (19.2)	72.6 (20.6)	0.126
EV	36.4 (19.9)	36.5 (17.7)	0.978
P	61.1 (27.9)	58.0 (22.4)	0.582
GHP	31.9 (18.1)	34.1 (15.1)	0.550
CH†	50 (50-75)	50 (25-75)	0.003*

Mean SD - independent t test †Median IQ range - Mann Whitney U test *p<0.05

Table 5.4. Comparison of the SF36 baseline results between COPD and CHF

Results of Pulmonary Rehabilitation

44 patients with COPD (80%) and 32 patients with CHF (73%) completed the rehabilitation course (figure 5.3). The proportion of dropouts were similar between the two groups $\chi^2 p= 0.475$. 8/11 patients with COPD and 7/12 patients with CHF dropped out because of medical reasons.

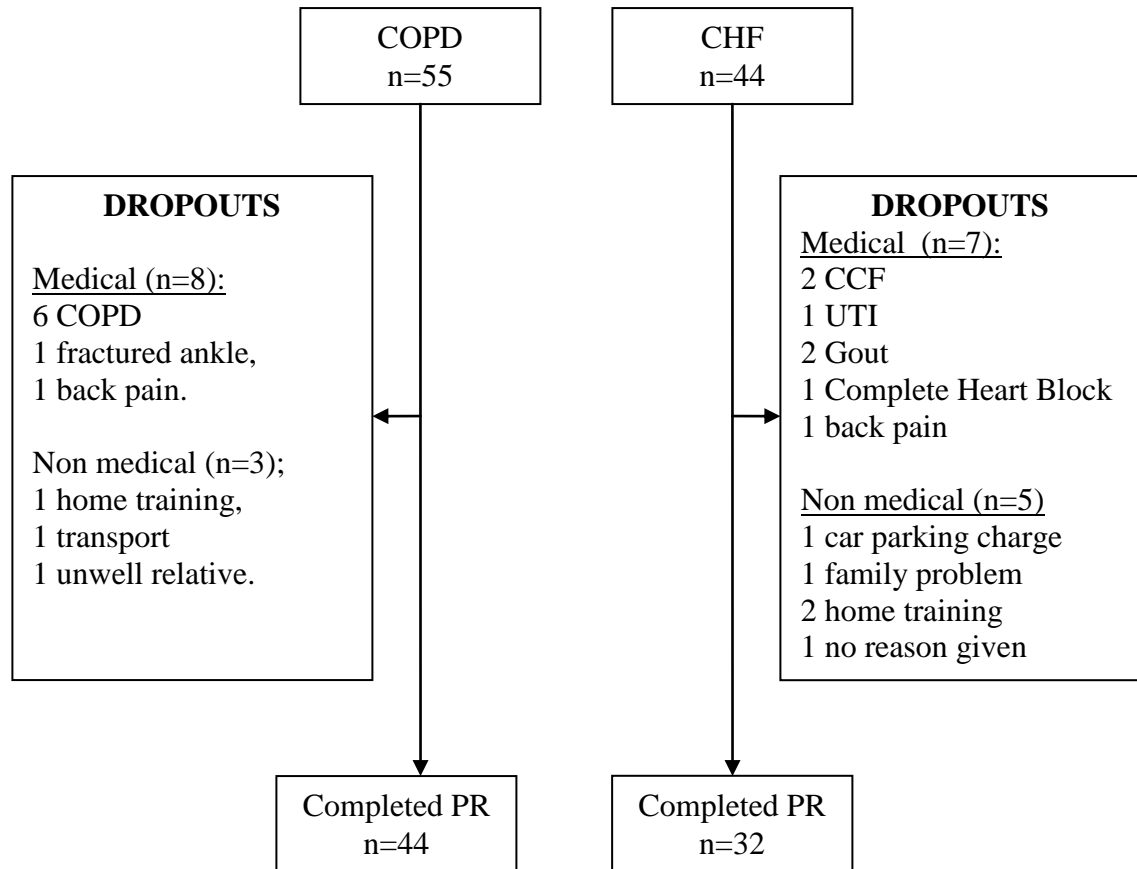


Figure 5.3. Study patient flow diagram

Exercise performance

Both groups made similar and significant mean improvements in ISWT distance with rehabilitation (figure 5.4); COPD 68 (50-85)m and CHF 63 (39-87)m. There was no significant difference between the two groups improvement with rehabilitation; mean (95% CI) difference 5 (-23 to 33)m $p=0.731$. An ANCOVA for the change in ISWT performance between COPD and CHF was performed including baseline ISWT performance, FEV₁ % predicted, BMI and age. There was still no difference between the two groups ($p=0.406$). The COPD group achieved a mean (SD) increase in ISWT distance of 34.3 (34.0)% compared to CHF 39.0 (48.5)% and the magnitude of increase was not statistically different between the groups $p=0.623$. The percentage of patients achieving the minimum clinically important difference for the ISWT (>48m) was 68.2% for patients with COPD and 59.4% for patients with CHF.

Both groups also made similar and significant changes in ESWT time; COPD 348 (249 – 447) [an increase of 5 minutes 48 secs] $p<0.0005$ and CHF 326 (199 – 454) $p<0.0005$ [an increase of 5 minutes 26 secs]. The intergroup difference in the mean (95% CI) change was 22 (-136 to 178) secs $p=0.783$. An ANCOVA for the change in ESWT performance between COPD and CHF was performed including baseline ESWT performance, FEV₁ % predicted, BMI and age. There was still no difference between the two groups ($p=0.246$). The COPD group improved their ESWT time by 147 (150)% and the CHF group improved by 179 (226)% ($p=0.490$).

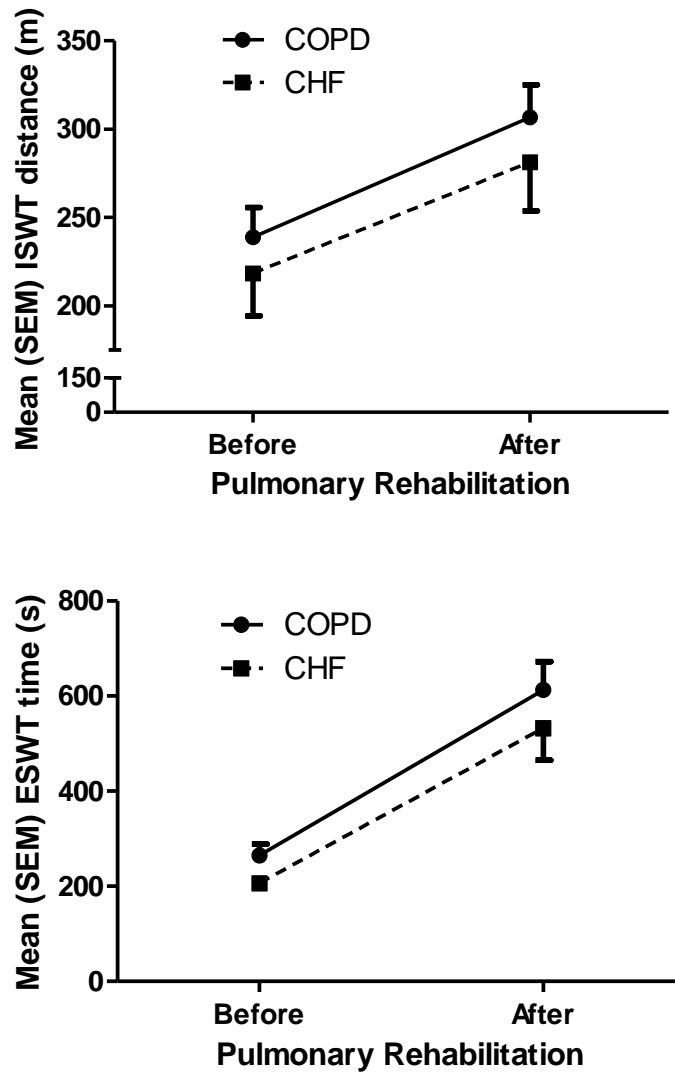


Figure 5.4. Comparison of the change in ISWT and ESWT performance between COPD and CHF

All patients had serial ISWT every 3rd or 4th session throughout the seven weeks. 25/32 CHF and 36/44 COPD had complete data sets for all five time points (figure 5.5). A MANOVA shows that there was no overall difference in the rate of improvement between the two groups ($p=0.084$). However, patients with COPD gained significant improvements by session four (33m $p<0.001$) whereas the CHF improvement was not significant (16m $p=0.185$) at that stage. There were no statistical differences in the ISWT performance between the two groups at any session number.

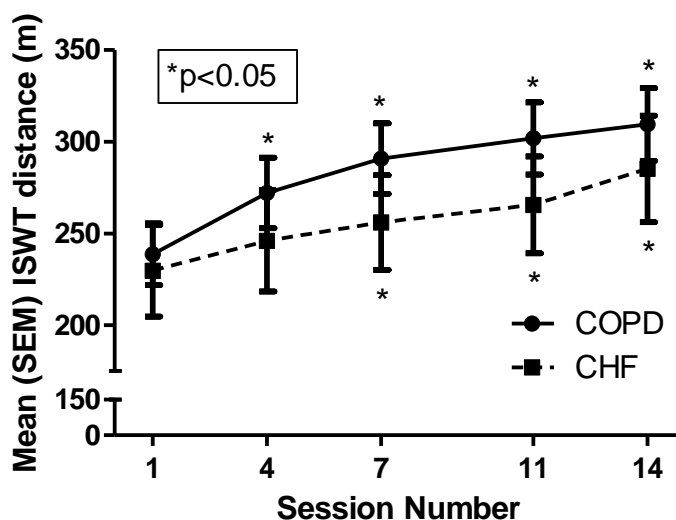


Figure 5.5. Training profile for COPD and CHF

For the patients with COPD there was no significant difference between the improvement in ISWT distance for the patients with a ventilatory limitation at baseline compared to those without $p=0.496$. Similarly for patients with CHF there was no difference in the change in ISWT with PR between the patients with or without a cardiovascular limitation $p=0.607$ or with and without a ventilatory limitation $p=0.741$. Univariate analysis was performed for the change in ISWT performance with PR for COPD and CHF (separately) using the variables of FEV₁ percent predicted, quadriceps

strength and either ventilatory limitation for COPD or cardiovascular limitation for CHF. All variables were non-significant.

There was no significant change in peak VO_2 assessed by the CPX after pulmonary rehabilitation in either of the groups (table 5.5). There was a small, but significant increase in peak watts and duration after PR with both groups.

Weight, fat free mass and muscle strength were all unchanged with PR in both groups (table 5.5).

Health Status

Disease specific questionnaire – CRQ and CHQ

Both groups of patients made statistically significant improvements in all four domains of the questionnaire after pulmonary rehabilitation (table 5.6). An ANCOVA was performed for each domain accounting for the baseline scores of that domain between the two groups. The dyspnoea domain was significantly and similarly improved in both groups of patients achieving a mean increase in the dyspnoea score above the clinically important difference of 0.5 units. After the ANCOVA was performed there was no difference between the changes in mastery or emotional function between the two groups, but there was still a greater improvement in the fatigue score for COPD.

	<i>COPD</i>			<i>CHF</i>		
	Before	After	p	Before	After	P
ISWT (m)	239 (111)	307 (122)	<0.0005*	218 (136)	281 (156)	<0.0005*
ESWT (secs)	265 (159)	613 (389)	<0.0005*	206 (84)	532 (378)	<0.0005*
<u>CPX</u>						
Peak VO ₂ (ml/min/kg)	12.3 (2.5)	12.5 (2.7)	0.354	10.9 (3.5)	11.5 (4.2)	0.119
Peak Watts (W)	53.7 (20.9)	57.0 (21.1)	0.015*	52.9 (27.0)	58.9 (24.4)	0.032*
Duration (secs)	321 (118)	349 (130)	0.003*	317 (157)	353 (151)	0.025*
RER						
Quadriceps Strength (Nm)	118 (46)	120 (54)	0.615	112 (42)	117 (46)	0.072
Weight (kg)	73.1 (17.3)	72.7 (16.7)	0.092	89.8 (26.5)	90.0 (27.3)	0.591
FFMI (kg/m ²)	17.2 (2.5)	17.2 (2.2)	0.881	19.3 (2.7)	19.6 (3.1)	0.196

Mean (SD), *p<0.05

Table 5.5. Comparison of the results of physical performance from pulmonary rehabilitation between COPD and CHF

	<i>COPD</i>	<i>p</i>	<i>CHF</i>	<i>p</i>	<i>Difference</i>	<i>p</i>
	<i>CRQ-SR</i>		<i>CHQ-IL</i>		<i>CvsC¶</i>	
Dyspnoea	0.94	<0.0005*	0.66	0.001	0.29	0.285
ANCOVA	0.72		0.94			0.428
Fatigue	1.24	<0.0005*	0.36	0.016	0.90	<0.0005*
ANCOVA	1.17		0.45			0.002*
Emotional Function	0.92	<0.0005*	0.35	0.035	0.57	0.028*
ANCOVA	0.82		0.50			0.172
Mastery	0.78	<0.0005*	0.36	0.014	0.39	0.09
ANCOVA	0.66		0.56			0.629

¶Difference in change in score with rehabilitation between COPD and CHF (intergroup difference) *p<0.05

Table 5.6. A comparison of the CRQ-SR or CHQ-IL results with rehabilitation between COPD and CHF.

Short form 36 questionnaire

Patients with COPD made statistical improvements in 6/9 domains whereas the CHF group made statistical improvements in 3/9 domains after PR (table 5.7). Patients with CHF did not report any improvement in their physical functioning. There were no intergroup differences between the change with rehabilitation for any of the domains.

	Δ with PR COPD	P value	Δ with PR CHF	P value	Δ with PR COPD vs CHF¶	P value
PF	7.1 (1.4 to 13.2)	0.016*	0.9 (-6.6 to 8.3)	0.81	6.5 (-2.8 to 15.7)	0.170
RP	17.3 (4.8 to 29.8)	0.008*	6.7 (-9.3 to 22.8)	0.39	11.5 (-8.2 to 31.2)	0.246
RE	13.2 (-2.7 to 29.0)	0.100	14.1 (-5 to 33.2)	0.14	-0.9 (-25.3 to 23.4)	0.938
SF	5.6 (-2.9 to 14.0)	0.190	12.9 (3.3 to 22.5)	0.01	-7.3 (-20.3 to 5.6)	0.263
MH	10.1 (4.6 to 15.7)	0.001*	4.5 (-2.9 to 11.9)	0.22	5.7 (-3.3 to 14.6)	0.211
EV	15.6 (10.3 to 20.9)	<0.0005*	9.0 (0.9 to 17.0)	0.02	6.6 (-2.4 to 15.7)	0.150
P	8.7 (1.5 to 15.8)	0.018*	2.2 (-7.1 to 11.6)	0.62	6.4 (-5.0 to 17.9)	0.265
GHP	3.5 (-1.4 to 8.3)	0.159	5.2 (-2.9 to 13.4)	0.19	-1.7 (-10.5 to 7.0)	0.690
CH†	0	<0.0005*	25	0.00	25	0.533

Mean (95% CI) change in SF36 scores per domain (units) †change in median score

*p<0.05 ¶ Difference between the change (Δ) in the score with PR between COPD and CHF

Table 5.7. A comparison of the change in SF36 scores with pulmonary rehabilitation between COPD and CHF

The change in health status assessed by either the CHQ or the CRQ score were correlated with the change in ISWT and ESWT with PR (table 5.8). Patients with COPD showed at least a moderate correlation between the domains of the CRQ and change in ISWT except in the dyspnoea domain. There was no association between the change in the CHQ and the change in the ISWT with PR in CHF. There was no correlation between the change in the ESWT with PR and any domain of the CRQ or CHQ in COPD and CHF.

	<i>COPD (n=44)</i>		<i>CHF (n=32)</i>	
	Correlation coefficient	p value	Correlation coefficient	p value
Δ ISWT distance and the Δ CHQ/CRQ				
Dyspnea	0.274	0.092	-0.136	0.481
Fatigue	0.383	0.015*	0.003	0.989
Emotional Function	0.562	<0.0005*	0.044	0.819
Mastery	0.382	0.015*	0.060	0.755

Pearson's correlation coefficients, *p<0.05

Table 5.8. Correlation between the change in ISWT and the change in the CRQ or CHQ domains with PR

Discussion

This study was performed to investigate whether combined, symptom-directed, exercise training programmes were feasible for the two common conditions, CHF and COPD. Patients with CHF underwent the PR programme alongside COPD subjects who were recruited consecutively as a comparator.

Both patients with COPD and CHF made similar and statistically significant improvements in ISWT distance and ESWT time with pulmonary rehabilitation. Combining the two different groups of patients did not adversely affect the improvements for COPD which were similar to that previously shown from the programme (mean [95% CI] 59 [54-65]m for 395 patients with COPD) (480).

The pulmonary rehabilitation programme was delivered identically and simultaneously to both groups. This included the assessment, outcome measures and the specific training programme. Currently there is no consensus on the optimal training programme for CHF (477). The PR programme adhered to the international recommendations for COPD (245). The physical training was individually prescribed and at high intensity from the outset (85% predicted peak VO_2) which the patients with CHF achieved. There were no significant differences in the training profile between COPD and CHF. Improvements in exercise performance occurred in the first two weeks and were statistically significant by session seven (halfway) in both groups. Although the improvement between the two groups at session four (two weeks) was not statistically significant, patients with COPD had a trend towards greater improvements. Theoretically patients with CHF are more likely to achieve an anaerobic threshold than patients with COPD because of the lack of a ventilatory limitation. This is supported by

this data with the CHF group achieving a higher mean peak RER for a similar mean peak VO_2 . It could have been expected that the CHF group would make greater initial improvements with training compared to COPD rather than a trend towards the opposite.

The programme was predominantly endurance training and this probably explains why quadriceps strength was unchanged in both groups. The evidence for combined resistance and endurance training for COPD and CHF is summarised in the introduction. At present combination training improves muscle strength above endurance alone, but in studies so far this has not translated into greater improvements in exercise performance or health status (307). Further work is needed to assess the impact of combined training on both physical activity and mortality in both conditions.

Neither group made a significant improvement in peak VO_2 assessed by the CPX. The reasoning here is similar to that described in the discussion in chapter four; the training was predominantly walking rather than cycling and the 10W/min incremental protocol may not have been sensitive enough. However, other groups have shown improvements in peak VO_2 with endurance exercise training in COPD (307). Neither group showed a plateau and a longer training programme may have been necessary. The cycling component of the training programme is limited by time in the class. Additional individually prescribed cycling at high intensity may have furthered physiological training. The addition of individually prescribed strength training was discussed above.

Both groups made significant improvements in all four domains of the CRQ or CHQ with PR. The improvements for CHF were comparable to COPD except in the fatigue domain, but there was a trend towards lower scores for CHF. There were no

significant differences overall between the change in the SF36 with PR between COPD and CHF, but patients with COPD made statistically significant improvements in more domains than patients with CHF. As discussed in chapter four the education part of the pulmonary rehabilitation course was primarily designed for COPD and was not adapted for the trial. At least half of the lectures were generic e.g. exercise, energy conservation, breathing techniques, relaxation but some were disease specific for COPD e.g. disease education, inhalers, pharmacology, respiratory physiology. This aspect of the programme could be modified further and may enhance the effect on health status. There may be an effect of the different administration of the two questionnaires. A recent study showed that a self-administered CRQ was more responsive to rehabilitation than an interview-led version (481).

The fatigue domain was the only domain where there was a significant difference in the change with PR between the two groups (COPD made greater improvements than CHF). The baseline scores for the fatigue domain was similar between the two groups and leg fatigue as a limiting symptom for walking and cycling was also similar for the two groups. Fatigue is a non specific term ranging from specific muscle fatigue to general lethargy. Potentially it may assess different symptomatology between the two groups accounting for the difference in outcome from PR.

The only adaption in the assessment for PR between COPD and CHF would be the assessment for exercise induced arrhythmias. All the patients with CHF recruited for this study had a laboratory exercise test with an exercise ECG prior to commencing training. No patients were excluded because of arrhythmias, but this is only in a small cohort of patients.

There is a growing appreciation of the similarity in the systemic manifestations and disability between CHF and COPD (366;367). The current study supports this as the two populations of COPD and CHF had similar exercise performance (peak and submaximal), health status and quadriceps strength.

The two populations of COPD and CHF were as pure as possible in the context of a pragmatic trial, but it is documented that the two conditions often coexist (20-39%) (359;361). COPD was excluded in the CHF group by spirometry, but CHF is harder to definitively exclude in COPD. Echocardiography is often technically difficult in COPD (360) and more invasive tests were not appropriate for this trial. There was a clear separation in the range of [NTBNP] between the two groups supporting different conditions.

Patients with CHF did have abnormalities of spirometry with 43% having a restrictive deficit. In the study by Gosker et al patients with CHF did not have a ventilatory limitation to exercise, however in the current study 12% of the CHF group met the criteria for a ventilatory limitation. In the COPD cohort only one patient had a cardiovascular limitation to exercise supporting that significant heart failure had largely been excluded. The individual described also reached a ventilatory limitation and had not achieved the peak VO_2 predicted when calculated. Overall the presence of a ventilatory limitation in COPD or cardiovascular limitation in CHF on the baseline CPX did not affect the outcome from rehabilitation. One study in COPD reported that patients with a ventilatory limitation at baseline achieved less improvement in peak VO_2 than patients either without a cardiopulmonary limitation to exercise or patients with a cardiovascular limitation (482). The changes in walking distance (6MWT) were the

same for all the groups in that study. Troosters et al tried to identify responders from non responders from PR via baseline measurements by performing regression analysis. The results supported that of Plankeel et al; patients with less ventilatory limitation were more likely to improve with training. Patients with reduced quadriceps and handgrip force were also more likely to improve exercise performance. Baseline muscle strength did not affect the outcome for PR on exercise performance in COPD or CHF in the current study.

Medication likely accounts for the lower resting heart rate seen in CHF compared to COPD. This could be affected by both the beta blockade therapy in CHF and the short and long acting beta agonist therapy in COPD.

This data supports the data of Gosker et al demonstrating a similar level of quadriceps strength between COPD and CHF (95). Gosker et al correlated quadriceps strength with peak VO_2 from a CPX on a cycle ergometer. The current data supports this data, but in addition shows that muscle strength also correlates to walking performance in both populations. This supports and extends the data previously described in COPD by Steiner et al (83).

At the time of this study there was little data on the effect of BMI on either exercise performance or the outcome of rehabilitation. The patients with CHF had a significantly higher BMI than the patients with COPD. As the main modality of training was walking (weight carrying exercise) there was a concern that this may reduce the improvement from exercise training in CHF. A retrospective analysis from 483 patients attending the local PR service was undertaken reporting the effect of BMI on the outcome of PR. An abstract of this work is in appendix VI. There was no correlation

between BMI and the change in ISWT distance overall, but patients with a BMI >40 appeared to do less well compared to the other categories¹⁷. For the current data an ANCOVA was performed for the change in ISWT and ESWT between COPD and CHF accounting for the differences in baseline BMI, but this did not alter the results.

Co-existent disease has implications for the current separate services of pulmonary and cardiac rehabilitation. A recent study showed that coexistent known heart failure was present in >10% of patients with COPD undergoing PR (483) and in a CABG cohort who would be referred for CR 18% had known coexistent COPD (484).

Although much of the literature for PR is for COPD there is an expanding group of other chronic respiratory patients who may also gain benefit e.g pulmonary fibrosis, bronchiectasis, cystic fibrosis, asthma, pulmonary hypertension (245). This was discussed in the introduction. It could be assumed that patients with CHF will be incorporated into cardiac rehabilitation (CR) but this is a very different service centred on secondary prevention not at targeting dyspnoea. The symptoms and disability of patients with CHF is much more similar to COPD than the traditional CR population (95;358) and currently many CR programmes exclude patients with CHF (380).

The PR population is becoming more heterogeneous and therefore a symptom based approach rather than a disease based approach might be more desirable. Already for COPD there are different strategies for PR that are preferred by different individuals; hospital, community, and home. Rather than designing different programmes for different diseases it maybe more beneficial to have a wider range of programmes and apply those to any specific disease. This is only a hypothesis and would need studies conducted to assess both cost and clinical effectiveness. Theoretically if a health

¹⁷ BMI was divided into 1; <20 2; 20-25 3; 25-30 4; 30-35 5; >40

provider had finances for three different rehabilitation programmes this could be divided into two strategies one disease based vs. one disability based i.e. three programmes per disease; COPD, cystic fibrosis and CHF all in one location vs. three different strategies; hospital based, community and home based for all of the three conditions.

There were limitations to the study. The number of patients with CHF completing the programme was 32 rather than the required 44 derived from the power calculation. The main difficulty was with recruitment. The community heart failure nurses were very supportive and the majority of patients were recruited through this route. There were very few patients suitable from the cardiology clinics at the local tertiary referral centre mainly because they were being assessed for devices. Recruitment was also tried from a specialist heart failure clinic at a different hospital site. However many of these patients were already recruited into different trials. Recruitment was not sought directly from primary care because of the diagnostic difficulties. There was some anecdotal negativity regarding exercise training from a few general practitioners and family members of potential subjects.

The power achieved was 72% at the 5% significance level from the initial power calculation. However if equivalence had been set at 35m rather than 30m only 33 patients would have been needed in each group for 80% power at the 5% significance level; the 95% CI of the intergroup difference in the change in shuttle walk test distance was -23m to 33m i.e below 35m.

The study was performed in a single centre, hospital outpatient setting, and the results may not be extrapolated to other situations. Only the short term effects are described, although these are likely to be sustained as in COPD (271). This study was

conducted to see if combined training was feasible and further studies would need to be done to investigate whether combined rehabilitation provides economies of scale for both populations.

In conclusion **this chapter** described that;

- patients with CHF made similar and significant improvements in exercise performance and health status from an existing pulmonary rehabilitation programme compared with COPD.
- combined training is feasible without any negative interaction between the groups.

The provision of rehabilitation needs to be increased for CHF and for an increasing number of other respiratory diseases therefore developing generic exercise rehabilitation could be a successful strategy. This study highlights the possibility of organising services for chronic diseases around a common disability rather than the primary organ disease.

The **next chapter** describes the development of health status measurements that could be used to assess both COPD and CHF. This includes developing a self reported version of the CHQ, the use of the Pulmonary Functional Status and Dyspnoea Questionnaire – modified version, and the MRC dyspnoea scale in CHF.

Chapter six

Developing generic tools to assess health related quality of life for both COPD and CHF

Contents

- i) Introduction
- ii) Developing a self reported version of the Chronic Heart Questionnaire (CHQ)
- iii) Developing the use of the Pulmonary Functional Status and Dyspnoea
Questionnaire – modified version (PFSDQ-M) for CHF
- iv) Applying the PFSDQ to the comparative trial of pulmonary rehabilitation
between COPD and CHF
 - a) comparing the baseline disability between COPD and CHF using the
PFSDQ-M
 - b) comparing the results of PR using the PFSDQ-M in COPD and CHF
- v) Applying the MRC dyspnoea scale to patients with CHF

Introduction

Developing common tools to assess health status

The **previous chapter** described the effects of pulmonary rehabilitation between COPD and CHF and showed that both groups of patients made significant and similar improvements in exercise performance and health status. Generic exercise rehabilitation for COPD and CHF is therefore feasible. Common tools to assess disability and health status are therefore desirable for assessment and outcome measures.

This chapter describes;

- 1) the development of a self reported version of the Chronic Heart Questionnaire (CHQ-SR)
- 2) adapting the use of the Pulmonary Functional Status Dyspnoea Questionnaire – modified version (PFSDQ-M) for patients with CHF
- 3) adapting the use of the MRC dyspnoea scale for patients with CHF

i) The development of a self reported version of the Chronic Heart Questionnaire (CHQ-SR)

Background

Some aspects of assessing health status were covered in chapter two. Health status is most commonly assessed by multi-dimensional questionnaires and there are many different tools available. As described in chapter two, although the Chronic Respiratory Questionnaire (CRQ) and the Chronic Heart Questionnaire (CHQ) are disease-specific questionnaires they are almost identical. They both have four main domains: dyspnoea, fatigue, emotional function and mastery. The CRQ is currently available in three formats; interviewer lead (IL), self reported (SR), and either a standardised or individualised dyspnoea section (described in chapter two). The original CRQ was developed using 123 items that were selected from a review of published studies and consultation with experts and then subsequently tested on 100 patients with COPD(453). The final selection of 20 items and four domains were the most commonly selected and deemed the most important by the patients. The original CHQ was developed two years later by the same research group (485).

Although the two final questionnaires are identical bar one question the CHQ was developed by a similar study design, rather than assuming the same items on the CRQ would be applicable to patients with CHF. 88 patients with heart failure were asked 123 items and ranked each item by importance on a five point Likert scale. The mastery section was not part of the original CHQ, but was added later. The CHQ was assessed via a randomised controlled trial of digoxin in patients with CHF and was

found to be valid, reproducible and responsive (485). Previous studies using the CHQ were described in chapter two.

The original CRQ was designed for patients with COPD for use in clinical trials and took about thirty minutes to complete. The importance of health status assessment for research trials became increasingly recognised and became applicable to certain clinical services. Measures of health status were used to evaluate pulmonary rehabilitation to ensure quality control. A self completed version of the CRQ was therefore designed to lessen the interviewer time (30 mins) and make administration of the questionnaire practical for clinical purposes (388).

Both the CHQ and CRQ have a minimum clinical important threshold of 0.5 units for each domain (457). This helps interpret changes which may be statistically significant, but the clinical relevance is often not intuitive.

The original CRQ and the CRQ-SR have the individualised version of the dyspnoea domain. The patient selects five frequent activities that make them the most breathless from either 20 prompts or one of their choice. There is a standardised version where the five activities are preselected. The five activities chosen were either the most frequently selected from other trials or 'captured important aspects of emotional or social functioning'. Schunemann et al compared the two versions (458). The individualised version showed lower (worse) results than the standardised version and was more responsive to the effects of rehabilitation. The standardised version showed superior discriminative validity.

The CHQ has already been successfully used as an outcome measure for exercise training in CHF (241). Exercise rehabilitation is likely to be an expanding service and a

self reported version of the CHQ would make the questionnaire more applicable to a clinical setting. For this purpose a more responsive questionnaire is desirable so the individualised dyspnoea domain was selected.

This study was designed to develop a self reported version of the CHQ. The aims were to assess 1) whether it was comparable to the IL version 2) the validity 3) the reproducibility and 4) the responsiveness

Methods

All 57 patients recruited for the randomised controlled trial of rehabilitation vs. normal care study were considered for this study. Recruitment criteria were the same as described in chapter two.

CHQ-SR

The design of the CRQ-SR was used for the CHQ-SR with the one question altered (described in chapter two) so the questions were identical to the CHQ-IL¹⁸.

Study design

The questionnaire format was administered in a different order to alternate patients i.e. SR version first and the IL version second and then the next patient would be allocated the IL version first etc. This was to exclude any systematic bias of the order in which the questionnaires were completed. Advice was sought from the Trent institute of health research regarding randomising the order allocation. The advice was administering the questionnaires in a different order to alternate patients was an acceptable study design and that randomising the order of administration was unnecessary.

The specific questions in the questionnaire concern a two week period. Both the IL and the SR version of the questionnaires therefore needed to be administered during this period. The duration between administering the IL and SR versions needed to be long enough to reduce the likelihood of patients recalling their previous responses. Seven days was considered reasonable. Administering a questionnaire only twice for reproducibility is acceptable (486). The SR version was therefore administered twice

¹⁸ All the questionnaires are in appendix six

within a two week period. In view of the order allocation it did mean that half of the patients would complete the two SR versions two weeks apart.

<u>Study design</u>	
Day 1	SR or IL version administered
Day 7	IL or SR version administered
Day 14	SR version administered

Patients were not shown their previous responses. The questionnaires were scored by calculating the mean score for each domain i.e the total score divided by the number of questions. Missing data was dealt with as per the guidelines for the CHQ.

The responsiveness of the SR version of the CHQ was tested and compared to the IL version by using it as an outcome measure for the RCT of PR vs NC described in chapter four. For this part of the study the order was not randomly allocated. The patients always completed the IL version first and the SR version second one week later.

The discriminative validity of the SR version was compared with the IL by comparing the correlations with the SF36.

Statistical Analysis

The results of the four domains of the CHQ are historically presented as mean (SD) despite the data being ordinal. The minimum clinically important difference is expressed as a change in mean units and so that is how this data is presented. Komogorov-Smirnov test for all four domains of the IL and SR versions showed the data was normally distributed $p > 0.05$. The mean differences between the IL and SR

versions for each domain were assessed by an independent t test. Bland and Altman have described the use of limits of agreement to assess two methods of measurement (487). Limits of agreement are the mean \pm 2SD and these were calculated for the means of the IL and SR versions. To determine cross sectional validity the SR domains were correlated to the SF36 and other functional measures and the correlations were compared to those for the IL version. Pearsons correlation coefficients were calculated¹⁹(488). The reproducibility of the self reported version was assessed by the mean differences between the two tests with a paired t test. Intraclass correlations were calculated and the coefficient of variation. The reliability coefficient was calculated by:

$$\frac{\text{Between subjects variability}}{\text{Between subjects variability} + \text{error}}$$

The coefficient of variation was calculated by the within subject SD divided by the mean. The within subject SD of a measurement (repeatability coefficient) was calculated by the $\sqrt{\text{Sum of the squares}}$ for that measurement. The sum of the squares was calculated by an ANOVA (489).

¹⁹ Cohen's categories were used; 0.1 - small correlation, 0.3 - moderate correlation, 0.5 - large correlation

Results

Fifty patients; 68% male, mean (SD) age 72.0 (9.6) years, LVEF 30.8 (10.7)%, peak VO₂ 10.9 (3.3) ml/min/kg, NYHA 2 38%, 3 52%, 4 10%, completed both the IL and SR versions of the CHQ. 26 subjects completed the IL version first and 24 completed the SR first. Three patients were not suitable for this study as the CHQ and CRQ were not validated in their language. Four patients failed to complete the second questionnaire within the necessary time frame and were therefore excluded²⁰.

Comparison between the self reported version and the interview led version of the CHQ.

All 50 IL versions were analysed compared to all 50 SR versions (table 6.1). There was no statistically significant change between the fatigue, emotional function and mastery domains between the two versions, but the CHQ dyspnoea domain was slightly lower (worse) for the SR version than the IL version.

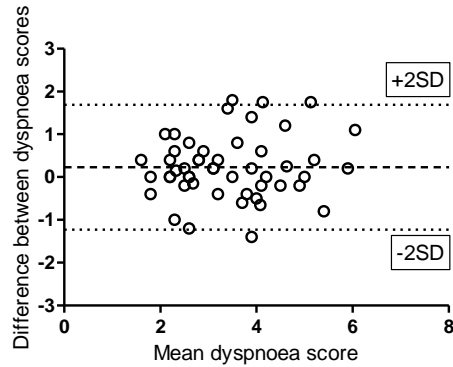
	<i>IL</i>	<i>SR</i>	<i>Mean (SD) difference</i>	<i>Limits of agreement</i>	<i>p</i>
Dyspnoea	3.54 (1.21)	3.31 (1.14)	0.23 (0.73)	-1.23 to 1.69	0.031*
Fatigue	3.28 (1.14)	3.33 (1.08)	-0.05 (0.71)	-1.38 to 1.47	0.655
Emotional Function	4.44 (1.32)	4.49 (1.33)	-0.06 (0.66)	-1.26 to 1.38	0.533
Mastery	4.67 (1.24)	4.68 (1.29)	-0.01 (0.87)	-1.74 to 1.74	0.977

*p<0.05, Mean (SD)

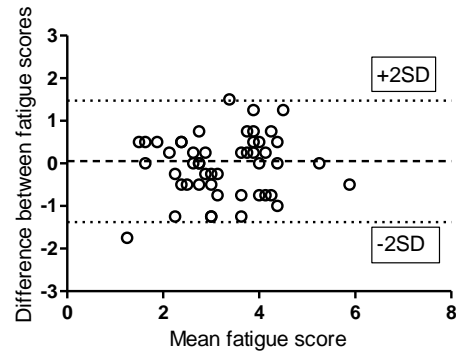
Table 6.1. Comparison of mean scores for each domain between the IL and SR versions of the CHQ

²⁰ allocation of administration order for these four dropouts - three SR first, one IL first.

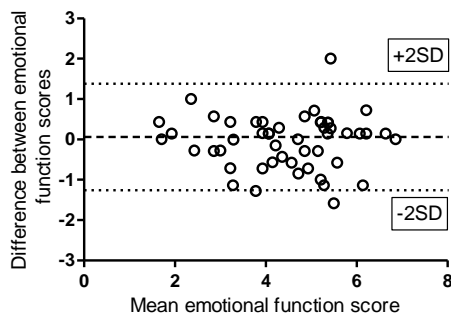
The limits of agreement between the CHQ-IL and CHQ-SR for each of the four domains are shown in figure 6.1.



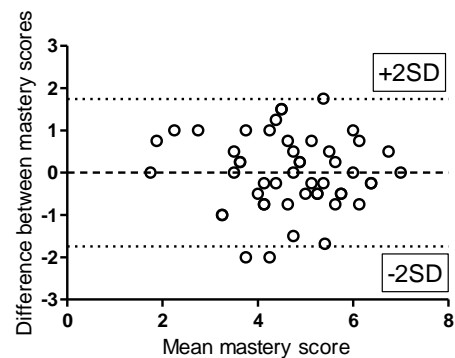
Limits of agreement between the CHQ IL and SR dyspnoea domain.



Limits of agreement between the CHQ IL and SR fatigue domain.



Limits of agreement between the CHQ IL and SR emotional function domain.



Limits of agreement between the CHQ IL and SR mastery domain.

Figure 6.1. Limits of agreement between the IL and SR versions of the CHQ for each of the four domains.

The reproducibility of the self reported version of the CHQ.

43 patients with CHF completed two self reported (SR) versions within a two week period. There was a trend towards a higher result on the second testing but this was only significant for the emotional function. All the intraclass correlation coefficients were >0.8 which is high and they were all statistically significant $p < 0.0005$. The coefficient of variation for each domain was; dyspnoea 15.7%, fatigue 16.0%, emotional function 9.2% and mastery 12.6%.

	<i>Test one</i>	<i>Test two</i>	<i>Mean (95% CI) difference</i>	<i>p value</i>	<i>Repeatability coefficient</i>	<i>ICC</i>
Dyspnoea	3.36 (1.15)	3.51 (1.21)	0.15 (-0.09 to 0.38)	0.211	0.54	0.89 (0.79-0.94)
Fatigue	3.34 (1.10)	3.56 (1.19)	0.21 (-0.02 to 0.45)	0.071	0.55	0.88 (0.77-0.93)
Emotional Function	4.58 (1.29)	4.78 (1.37)	0.19 (0.01 to 0.38)	0.036*	0.43	0.94 (0.90-0.97)
Mastery	4.70 (1.37)	4.94 (1.32)	0.25 (-0.01 to 0.50)	0.060	0.60	0.90 (0.81-0.95)

* $p < 0.05$, Mean (SD)

Table 6.2. Reproducibility of the CHQ-SR

Responsiveness of the self reported version of the CHQ

30 patients completed both the IL and the SR version before and after a randomised controlled trial of rehabilitation vs. normal care. 18 patients completed pulmonary rehabilitation (PR) and 12 patients completed the normal care (NC). The PR group made statistically significant improvements in the dyspnoea, fatigue and emotional function domain and there was a trend to improvement for the mastery domain for the CHQ-SR (table 6.3). There were only small changes for the NC group and they were non significant for all four domains.

	<i>Rehabilitation</i>		<i>Normal Care</i>	
	Mean (95% CI) change	p	Mean (95% CI) change	p
Dyspnoea	0.81 (0.29 to 1.33)	0.004	-0.20 (-0.59 to 0.20)	0.293
Fatigue	0.39 (0.08 to 0.69)	0.016	0.17 (-0.52 to 0.85)	0.601
Emotion	0.47 (0.13 to 0.81)	0.009	0.10 (-0.52 to 0.72)	0.779
Mastery	0.42 (-0.02 to 0.85)	0.06	0.08 (-0.36 to 0.53)	0.689

*P<0.05 for the between group difference

Table 6.3. Results of the CHQ for the RCT of PR vs NC

The results of the CHQ-SR were compared with the IL version (n=18) for the rehabilitation group. There were no statistical differences in the magnitude of change between the two types of administration (table 6.4).

	<i>Change in CHQ-IL</i>	<i>Change in CHQ-SR</i>	<i>Mean (95% CI) difference</i>	<i>p</i>
Dyspnoea	0.52	0.81	0.29 (-0.44 to 1.01)	0.418
Fatigue	0.42	0.39	0.03 (-0.53 to 0.47)	0.908
Emotional Function	0.42	0.47	0.05 (-0.62 to 0.72)	0.877
Mastery	0.28	0.42	0.24 (-0.37 to 0.84)	0.423

*p<0.05, Mean change.

Table 6.4. Comparison of the results of pulmonary rehabilitation for the CHQ-IL and CHQ-SR

Cross sectional validity (discriminative)

Table 6.5 shows the correlations between the domains of the CHQ (IL and SR) and the components of the SF36²¹. The energy and vitality component of the SF36 significantly correlated with all domains of the CHQ. The degree of correlation between the SF36 components and the CHQ were similar for the SR and IL versions. Only three out of the sixteen comparisons were different between the two versions. The SR version correlated significantly with the SF36 for all three whereas the IL version did not. The significant correlations were all at least moderate in size. Correlations for the CHQ domains and ISWT, LVEF, NYHA scale were also performed (data not included). All correlations were weak at best and very few were statistically significant.

		<i>CHQ-IL</i>	<i>p</i>	<i>CHQ-SR</i>	<i>p</i>
Physical Function	CHQ-D	0.519	0.0005*	0.446	0.002*
	CHQ-F	0.134	0.374	0.287	0.053
	CHQ-EF	0.083	0.583	0.120	0.426
	CHQ-M	0.282	0.057	0.313	0.034*
Social Functioning	CHQ-D	0.273	0.073	0.296	0.051
	CHQ-F	0.286	0.060	0.312	0.039*
	CHQ-EF	0.240	0.117	0.327	0.030*
	CHQ-M	0.323	0.032*	0.394	0.008*
Mental Health	CHQ-D	0.046	0.770	0.052	0.743
	CHQ-F	0.430	0.004*	0.354	0.020*
	CHQ-EF	0.680	0.0005*	0.649	0.0005*
	CHQ-M	0.510	0.0005*	0.431	0.004*
Energy and vitality	CHQ-D	0.343	0.024*	0.385	0.011*
	CHQ-F	0.714	0.0005*	0.718	0.0005*
	CHQ-EF	0.525	0.0005*	0.577	0.0005*
	CHQ-M	0.499	0.001*	0.403	0.007*

***p**<0.05, D – dyspnoea, F – fatigue, EF – emotional function, M - mastery

Table 6.5. Comparison of the correlations of the CHQ-IL and CHQ-SR with the relevant components of the SF36

²¹ Questionnaire in appendix 6

Longitudinal validity

The change in CHQ scores for the SR version with rehabilitation was compared to the change in SF36 scores and the change in ISWT and ESWT performance. There were no significant correlations between the change in any domain of the CHQ and any change in the SF36 components, except for a moderate correlation between the change in emotional function (EF) in the CHQ-SR and change in social function (SF) in the SF36; 0.607 $p=0.016$. There were no correlations between the change in any of the four CHQ-SR domains and the change in ISWT distance or ESWT time. These relationships were very similar for the IL version of the CHQ except for a moderate correlation between the change in dyspnoea score and the change in social function score; 0.561 $p=0.024$.

Discussion

The work in this chapter describes the development of a self reported version of the CHQ to increase the applicability of the questionnaire.

The self reported version of the CHQ was comparable to the interview led version, except for the dyspnoea domain where the mean score was significantly lower (worse) for the SR version. The magnitude of the limits of agreement for the two versions were wide, but are very similar to those found by Williams et al for the CRQ-SR (388). In that study the mean dyspnoea and emotional function domain scores were significantly lower (worse) for the CRQ-SR compared to the CRQ-IL version. The completion of the dyspnoea domain was divided into two groups; for one group the activities chosen for the first administration were transcribed for the second administration and for the other group they selected the five activities again. Also, for that paper the order of administration was always the same, the IL version first, which could have introduced bias. For the current study the order of administration was randomly allocated and the activities transcribed for the second administration, but the variability was still quite high between the two administrations. The CHQ-SR is comparable to the CHQ-IL, but the questionnaires are not interchangeable.

An evaluative questionnaire needs to be both reproducible and responsive i.e having a high ratio of signal to noise (490). The CHQ-SR was administered twice in two weeks and there was only a significant difference for the dyspnoea domain, but there was a trend to an improvement in all four domains on the second administration. The coefficient of variation was between 9-16% for all four domains. The original CHQ-IL was administered three times over four to six weeks (485). No raw data was presented in

this paper, but the authors stated that there was no time effect. The coefficient of variation for each domain was similar to the results in the current study; dyspnoea 14%, fatigue 18% and emotional function 18%. The original CRQ-IL was shown to be reproducible over six administrations in two weeks (n=25), with lower coefficient of variations; 6% for the dyspnoea domain, 9% for both fatigue and emotional function and 12% for the mastery domain (453). The raw mean data is not presented in the paper, but there were no statistically or clinically significant trends in improvement or deterioration. The results from the current study were similar to the reproducibility of the CRQ-SR which was administered twice in one week (388). There were no statistical differences seen between the mean results for any domain for the CRQ-SR, but there was a trend to higher scores on the second administration and the repeatability coefficients were higher (greater variability) for each domain for the CRQ-SR than for the CHQ-SR reported in this study. The CRQ-SR was developed in a smaller sample size (n=21) than the current study (n=43). Chinn S et al recognised the difficulty associated with administering a questionnaire three times for repeatability and although desirable accept that two administrations is more feasible (486). The authors of the CHQ recommend reminding patients of their previous responses when completing follow up questionnaires. This improved the validity of the questionnaire, but did not change the responsiveness (491;492). This was not performed for the current study and may have had an effect on the variability.

The results of this part of the study have implications for the use of the CHQ-SR particularly in an uncontrolled trial. It is usual practice to only administer a questionnaire once at baseline i.e no practice akin to a practice exercise test. In an

uncontrolled trial the effects of an intervention maybe exaggerated and study investigators should be aware of this.

The CHQ-SR was found to have cross sectional validity when the four domains were compared to the relevant domains of the SF36. There were no significant correlations with measures of exercise performance. This suggests that the CHQ-SR is not a discriminative questionnaire. The longitudinal validity was assessed by comparing the changes in the CHQ domains after exercise rehabilitation with the changes in the SF36 and exercise performance. There were very few correlations between the parameters. This is in contrast with the original CHQ-IL where the dyspnoea domain had a moderate correlation with the change in walk test, heart failure score and global rating of shortness of breath score (485). There were a similar number of patients; 20 for the original CHQ-IL compared to 18 in the current study. However, the results were compared with the total score for each domain rather than the mean score as in the current study.

The validity of the CRQ-SR was not reported, but the original CRQ-IL was found to have longitudinal validity by having moderate correlations between the changes in the domains with rehabilitation and changes in other indices such as walking performance. Further testing of the CRQ-IL showed that the fatigue, emotional function and mastery domains were all reliable and valid, but the dyspnoea (individualized version) was less reliable (493). In the current study the CHQ-IL also did not display longitudinal validity. The main difference between the current study and the original CHQ and CRQ studies is that the mean score for the domains were used instead of the total scores. Further assessment of the longitudinal validity of the CHQ-SR is needed.

The CHQ-SR was responsive. All domains improved with exercise rehabilitation and all domains remained unchanged with normal care. There were no statistical differences between the magnitude of the improvements measured on the CHQ-IL and CHQ-SR for each domain. These results are consistent with the CRQ-SR (388). However Schunammen et al found the self administered version of the CRQ more responsive in all domains than the IL version in a larger cohort n= 177 (494) compared to n=31 CRQ-SR and n= 18 for the current study. A consensus statement recommends a study number of n=50 to show relevant results for the CHQ-IL. The current data supports the use of the self reported version and shows that it is at least as responsive as the interview led version.

The limitations of the current study were the small numbers to assess the responsiveness of the CHQ-SR and the order of administration was not alternated for this part of the study which could have caused bias. A further study might be useful to ensure that there is not a time effect i.e administering the questionnaire three times, but no time effect was seen with the original CRQ or CHQ. The questionnaires may have shown greater validity if the total scores had been used rather than the mean scores which may have decreased the amplification of the change with an intervention.

In conclusion the CHQ-SR is comparable to IL version and is reproducible. It is has been shown to have cross-sectional validity and to be responsive.

ii) Adapting the use of the Pulmonary Functional Status and Dyspnoea Questionnaire – modified version (PFSDQ-M) for patients with CHF

Background

Improving health related quality of life or health status is an important aim for chronic disease therapies. Health status encompasses how symptoms, physical, psychological and social situations affect quality of life. Measures of health status have been developed usually in the format of multi-dimensional questionnaires²². Functional status forms a part of health status and specifically relates to how activities of daily life (ADLs) are affected (495). Functional status assessed by a questionnaire (Pulmonary Function Status Scale) has been shown to be a strong predictor of survival rate in chronic lung disease (496)

The PFSDQ-M was developed for patients with COPD to assess the impact of dyspnoea and fatigue on daily activity (390). It is a validated questionnaire which is reliable and responsive (390;497). It has been translated into several languages (498;499). Generic activity questionnaires are available that could be used for both COPD and CHF e.g Physical Activity Score for the elderly (PASE) (500) or International Physical Activity Questionnaire (IPAQ) (501). The predominant symptoms causing limitation in patients with CHF are also breathlessness and fatigue so the advantage of using the PFSDQ-M would be the assessment of the specific limiting symptoms on activities daily living.

²² described in chapter two

The aim of this study was to adapt the use of the PFSDQ-M to include patients with CHF. This part of the chapter describes the short term reproducibility of the PFSDQ-M in patients with CHF and evaluates the discriminative validity of the PFSDQ-M in CHF and compared with COPD. The responsiveness of the PFSDQ-M was assessed using the randomised controlled trial of pulmonary rehabilitation (PR) vs normal care (NC) in CHF (described in chapter four).

Methods

All the patients recruited for the randomised controlled trial of pulmonary rehabilitation vs normal care were recruited to this part of the study²³. The reproducibility of the PFSDQ-M was assessed in the two week run-in part of the study described in chapter two. The PFSDQ-M was administered twice within two weeks²⁴. The cross sectional (discriminative) validity of the PFSDQ-M was assessed by correlating the three main components of the questionnaire to measures of exercise performance (ISWT distance), quadriceps strength and health status (SF36 and the CHQ-IL). To avoid multiple correlations the physical function of the SF36 and the dyspnoea and fatigue components of the CHQ were chosen a priori. The exercise and strength tests were all performed as described in chapter two. The validity of the PFSDQ-M was compared to the validity in COPD and the patients with COPD recruited for the comparative observational study of PR were used, described in chapter two. The responsiveness of the questionnaire was assessed using the randomised controlled trial

²³ see chapter four

²⁴ questionnaire is in appendix six

of pulmonary rehabilitation vs. normal in patients with CHF (chapters two and four). All patients were asked to complete the PFSDQ-M before and after the seven week trial.

The content and scoring of the PFSDQ-M is described in appendix IV and chapter two. The questionnaire contains 40 items, the main three components (10 items each) are the change in activity (CA), dyspnoea with activity (DA) and fatigue with activity (FA). The other ten items are divided into two sections, dyspnoea and fatigue, with five items in each section; whether the patient suffers from breathlessness/fatigue (1 item), frequency score (1 item), general scores (3 items); intensity most days (GSMD), intensity today (GSTD), intensity day to day (GSDD).

Statistical analysis

All items of the PFSDQ-M were normally distributed (Kolmogorov-Smirnov test $p > 0.05$) except the general scores day to day. The data for the PFSDQ-M is ordinal, but was presented as mean data by the original authors of the questionnaires. The mean scores between the two administrations and the changes with either intervention were compared with paired t tests. The intra class correlations, between the two administrations for the three main components (CA, DA and FA), were calculated. Pearsons correlation coefficient was used to compare the components of the PFSDQ-M with measures of exercise performance and health status, except for the MRC scale where Spearman's correlation coefficient was used. Cohen's classification for the strength of correlations was used; 0.1 weak, 0.3 moderate 0.5 strong (488). Missing data was handled by analysing available data and no substitute was given for missing data.

Results

All 57 patients with CHF recruited for the RCT trial completed the PFSDQ-M; mean (SD) age 71.0 (10.2) yrs, 70.2% male, LVEF % predicted 30.9 (10.1), ISWT 231 (135)m and 41 patients completed the reproducibility part of the study.

Reproducibility of the PFSDQ-M in CHF

One patient was excluded from this part of the study because of short term memory loss and two were excluded because of language difficulties. Four patients dropped out of the study at the end of the two week run in and did not complete the second administration of the questionnaire. Eight patients did not complete the two administrations within two weeks and were therefore excluded from further analysis. The baseline demographics for the group that completed the two administrations of the questionnaire were similar to the dropouts except for age (the ‘dropouts’ were significantly younger, 7.0 (0.9 -13.0) yrs $p=0.025$). There was no significant difference between the scores of the three main components of the questionnaire between the completers and dropouts.

There was no significant difference between the two administrations for the mean data for any item (table 6.6,) but there was a trend for the results to be lower (better) on the second test.

	<i>Test one</i>	<i>Test two</i>	<i>Mean (95%CI)</i>	<i>P</i>
Activity				
Changes in Activity (CA)	2.25 (1.66)	1.94 (1.52)	-0.31 (-0.76 to 0.14)	0.175
Dyspnoea				
SOB with Activity (DA)	2.32 (1.63)	2.03 (1.75)	-0.29 (-0.69 to 0.12)	0.161
Experience	All Yes	All Yes		
Frequency	18.6 (23.1)	19.1 (34.7)	0.5 (-6.7 to 7.7)	0.888
GSMD(0-10)	4.6 (2.2)	4.6 (2.3)	-0.1 (-0.7 to 0.6)	0.861
GSTD (0-10)	4.3 (2.4)	3.7 (2.3)	-0.6 (-1.3 to 0.1)	0.101
GSDD (0-10)	4.6 (2.3)	4.5 (2.2)	-0.1 (-0.7 to 0.5)	0.643
Fatigue				
Fatigue with Activity (FA)	2.85 (1.96)	2.48 (1.92)	-0.37 (-0.82 to 0.08)	0.105
Experience	All Yes	All Yes		
Frequency	18.4 (16.0)	16.4 (16.6)	-2.0 (-5.6 to 1.5)	0.255
GSMD(0-10)	5.2 (2.6)	4.9 (2.6)	-0.3 (-1.0 to 0.3)	0.323
GSTD (0-10)	4.8 (2.2)	4.1 (2.3)	-0.6 (-1.2 to -0.01)	0.047*
GSDD (0-10)	5.4 (2.1)	4.8 (2.2)	-0.6 (-1.2 to -0.04)	0.035*

*p<0.05, general score - most days (GSMD), general score - today (GSTD), general score – day to day (GSDD)

Table 6.6. Short term reproducibility of the PFSDQ-M in patients with CHF

The intraclass correlation (ICC) between the two administrations was high for all three domains; CA 0.86 (0.71-0.92) p<0.0005, DA 0.78 (0.58-0.89) p<0.0005 and FA 0.83 (0.65-0.91) p<0.0005

Cross-sectional validity

There were moderate and statistically significant correlations between the three components of the PFSDQ and other measures of health status in patients with CHF (table 6.7). The ISWT distance also had a moderate correlation with all three components of the questionnaire. Quadriceps strength correlated significantly for the activity component, but not for the fatigue or dyspnoea components.

	<i>Activity (CA)</i>	<i>p</i>	<i>Dyspnoea (DA)</i>	<i>p</i>	<i>Fatigue (FA)</i>	<i>p</i>
MRC grade	0.416*	0.001	0.444*	<0.0005	0.376*	0.003
CHQ dyspnoea	-0.275*	0.044	-0.376*	0.004		
CHQ fatigue	-0.326*	0.015			-0.372*	0.005
SF36-physical function	-0.583*	<0.0005	-0.567*	<0.0005	-0.463*	<0.0005
Quadriceps Strength (Nm)	-0.308*	0.019	-0.237*	0.076	-0.232	0.077
ISWT (m)	-0.387*	0.002	-0.342*	0.008	-0.330*	0.009

* $p < 0.05$

Table 6.7. Correlations of the three main components of the PFSDQ-M and measures of health status and exercise performance in patients with CHF

The correlation between the components of the PFSDQ-M, health status and exercise performance are shown for COPD and CHF in table 6.8. The components of the PFSDQ-M had more significant correlations with measures of exercise performance and health status for patients with CHF than patients with COPD.

<i>Component of the PFSDQ-M</i>	<i>COPD correlation coefficient</i>	<i>p</i>	<i>CHF correlation coefficient</i>	<i>p</i>
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Dyspnoea (DA)				
DA and CHQ/CRQ-Dyspnoea	-0.181	0.292	-0.275*	0.044
DA and MRC scale grade	0.122	0.429	0.444 *	<0.0005
DA and SF36-PF	-0.362*	0.016	-0.576*	<0.0005
DA and ISWT (m)	-0.162	0.294	-0.342*	0.008
DA and quad. strength (Nm)	-0.22	0.885	-0.237	0.076
Fatigue (FA)				
FA and CHQ/CRQ-Fatigue	-0.345*	0.031	-0.372*	0.005
FA and MRC scale grade	0.196	0.192	0.376*	0.003
FA and SF36-PF	-0.375*	0.010	-0.463*	<0.0005
FA and ISWT	-0.258	0.083	-0.330*	0.009
FA and quad. strength	-0.090	0.553	-0.232	0.077
Activity (CA)				
CA and MRC scale	0.275	0.062	0.416*	0.001
CA and SF36-PF	-0.433*	0.020	-0.583*	<0.0005
CA and ISWT	-0.267	0.070	-0.387*	0.002
CA and quad. strength	-0.127	0.397	-0.308*	0.019

*p<0.05

Table 6.8. Comparing the validity of the PFSDQ-M between CHF and COPD

Responsiveness of the PFSDQ-M in patients with CHF

There were 27 patients with CHF who completed pulmonary rehabilitation and 17 who completed the normal care limb. All 27 patients completed the PFSDQ-M before and after rehabilitation, but one questionnaire was missing from the normal care group (n=16). All patients answered 'yes' to whether they suffered from SOB and fatigue. Only the fatigue (FA) component improved significantly after pulmonary rehabilitation from the three main components of the PDSQ-M (table 6.9). For the remaining eight items, two of the dyspnoea and two of the fatigue components improved. There were no improvements seen for the normal care group in any item except for the fatigue general score 'today' (GSTD). There were no between group differences for the three main components, and only one for the remaining eight items; the dyspnoea general score 'day to day' (GSDD) was significantly improved with PR compared to NC.

	<i>Pulmonary Rehabilitation (PR)</i>			<i>Normal Care (NC)</i>		
	Before	After	p	Before	After	p
Dyspnoea						
Freq	16.0 (13.1)	9.1 (11.3)	0.026*	20.2 (32.8)	21.3 (36.3)	0.667
GSMD	4.8 (1.9)	4.3 (2.1)	0.225	4.3 (2.7)	4.5 (2.8)	0.625
GSTD	4.4 (2.3)	3.6 (2.6)	0.035*	4.1 (2.7)	3.8 (2.4)	0.423
GSDD	5.0 (2.2)	4.4 (2.2)	0.075	4.4 (2.4)	5.2 (2.5)	0.148
DA	2.4 (1.7)	2.1 (1.5)	0.178	2.4 (2.1)	2.4 (2.0)	0.967
Fatigue						
Freq	15.0 (11.6)	12.2 (11.6)	0.215	17.8 (13.8)	14.3 (14.3)	0.478
GSMD	5.6 (2.3)	5.4 (2.2)	0.413	5.2 (2.9)	5.1 (2.3)	0.964
GSTD	4.9 (2.1)	4.3 (2.3)	0.037*	4.9 (2.3)	3.9 (2.0)	0.036*
GSDD	5.4 (2.0)	4.8 (2.3)	0.018*	5.6 (2.2)	4.9 (2.3)	0.061
FA	2.5 (1.6)	1.9 (1.4)	0.028*	2.5 (2.2)	2.1 (1.8)	0.410
Activity						
CA	2.7 (1.6)	2.7 (1.5)	0.918	3.3 (2.5)	2.6 (1.8)	0.288

*p<0.05, mean (SD), general score - most days (GSMD), general score - today (GSTD), general score - day to day (GSDD)

Table 6.9. Results of the PFSDQ-M for PR vs NC in CHF

There was a substantial amount of missing responses to the components of the questionnaire. The number completing each response ranged from n= 20-25 for the PR group and n= 11- 15 for NC so no single item was completed by all patients.

Discussion

This study was conducted to see if the PFSDQ-M could be used for patients with CHF. The short term reproducibility, discriminative validity and responsiveness were described. The PFSDQ-M was reproducible in the short term. The 40 items of the questionnaire are presented as 11 separate scores. Only one of these 11 was significantly different on the second administration. There was a trend to improvement on the second

administration which is a similar pattern to that described earlier for the reproducibility of the CHQ-SR. The test-retest reliability has been described in 30 patients with COPD also at two weeks apart (502). The mean data for both administrations was not presented in this paper only the 'inter-item correlations'; DA $r=0.83$, FA $r=0.79$ and CA $r=0.70$). The intraclass correlations for DA, FA and CA for CHF described in this chapter were similarly high. Only 41 out of a possible 57 completed the two administrations twice. It was difficult to conduct a power calculation for sample size as the questionnaire had not previously been used in CHF. Therefore the sample used was the same as for the RCT. The numbers are comparable ($n=41$) as describe originally for COPD ($n=30$).

The PFSDQ-M is reliable for patients with CHF, but there was a non significant trend to improvement on the second test. Study investigators should be aware of this when interpreting changes in the PFSDQ-M. A similar conclusion can be drawn to that made earlier in this chapter for the reproducibility of the CHQ-SR; that ideally they are better used in a randomised controlled design. In an uncontrolled setting an intervention may have an exaggerated effect size using the PFSDQ-M if there is only one administration at baseline (which is usual).

The reproducibility of both questionnaires (PFSDQ-M and CHQ-SR) were assessed during the run in part of the main study. During this time the patients underwent four separate sessions of exercise testing (twice a week). This small amount of exercise/visits/attention may have improved health status and be reflected in the second administration. However the results of the ISWT were stable for these two weeks (see chapter three) making this less likely. This is a limitation in conducting separate studies within one large study.

The three main components of the questionnaire correlated significantly and moderately with measures of exercise performance and health status in patients with CHF. The correlations between PFSDQ-M and the SF36 physical function score (SF36-PF) were higher than for the PFSDQ-M and the CHQ dyspnoea and fatigue domains. The SF36 physical function (SF36-PF) score comprises of ten activities and patients are asked to select whether they are limited a lot, limited a little or not limited at all (appendix IV). For the CHQ the subject selects the activities that makes them the most breathless. It is likely that the range of breathlessness will be smaller, as the amount of exertion an activity needs will vary e.g. two patients may both select that they get 'extremely short of breath', but the activity selected might be running vs. bending'. The CHQ dyspnoea section is probably not as discriminative as the SF36-PF score. Few of the correlations were strong (>0.5) between the PFSDQ-M and other measures of health status and exercise performance suggesting that the PFSDQ-M provides additional information about functional status in patients with CHF. Although the PFSDQ-M has been shown to have discriminative validity previously in COPD (390), for the cohort described in the current chapter the validity was better for CHF than COPD.

The PFSDQ-M demonstrated little responsiveness in the trial of PR vs. NC. This might be because of being underpowered as the study was powered for a significant difference in the ISWT distance not the PFSDQ-M. There were differences between the two interventions (PR vs. NC) detected by the ISWT and the CHQ (chapter four). Only a short course of rehabilitation was used and it maybe that functional status takes longer to be altered. One group reported using the PFSDQ-M before and after seven weeks of PR in 59 patients with COPD and showed that five of the ten activities were performed

better. The mean results for the DA, CA and FA were not given. Another study showed that three months of PR significantly improved all three main components of the questionnaire (497). The responsiveness of the questionnaire should be assessed in a study with an objective measure of physical activity to ensure that the intervention is improving activity.

The PFSDQ-M is supposed to be a self complete questionnaire, but anecdotally help was often needed to complete it. Whole sides were missed and the charts were particularly poorly completed. In the development of the PFSDQ-M in COPD <8% of data was missing, but it is unclear if help was needed or given to complete the questionnaire. Another limitation of the PFSDQ-M is the multiple components it contains. This makes the results more difficult to display and analysis tends to involve multiple t tests. There appears to be a floor effect with the PFSDQ-M in COPD and CHF. The study population by definition are symptomatic, but the questionnaire may have even less sensitivity when applied to a less severe population.

A major limitation of this work is that the PFSDQ-M has not been validated for patients with CHF. The tool was not prospectively developed for CHF so it is not known whether the items are relevant to CHF or whether other items would have had greater relevance.

In conclusion the PFSDQ-M demonstrates short term reproducibility and discriminative validity in patients with CHF. It was not particularly responsive when used in a randomised controlled trial of pulmonary rehabilitation vs. normal care in CHF and this should be tested again in larger numbers in an appropriately powered study.

iii) Applying the PFSDQ-M to the comparative observational study of COPD and CHF

Background

In chapter five, the health status between COPD and CHF was compared and was similar between the two groups assessed by the CRQ or CHQ and by the SF36. The PFSDQ-M was specifically designed to provide further and specific information about how dyspnoea and fatigue affect functional status in patients with COPD. The use of the PFSDQ-M for patients with CHF has just been described. It was reproducible and has discriminative validity. This part of the chapter compares, between COPD and CHF, 1) the components of the questionnaire and 2) the response to pulmonary rehabilitation using the PFSDQ-M. The aim was to investigate whether the PFSDQ-M provides additional information, to that gained from the CHQ/CRQ and SF36, regarding the baseline functional status and the response to pulmonary rehabilitation for both conditions.

Methods

Patients were recruited as per methods in chapter two. The PFSDQ-M was given to all patients before and after seven weeks of pulmonary rehabilitation²⁵. The ISWT distance and isometric quadriceps strength were assessed and all patients completed the CHQ or CRQ described in chapter two.

²⁵ described in chapter two

Results

49 patients with COPD and 57 patients with CHF completed the PFSDQ. The baseline demographics were similar and are described in chapter five. Table 6.10 shows the result of the questionnaire in both populations.

	<i>COPD</i>	<i>CHF</i>	<i>p value</i>
Activity			
CA Mean	3.2 (2.3)	3.2 (2.0)	0.980
Dyspnoea			
DA	2.9 (2.1)	2.7 (1.8)	0.627
Frequency	20.6 (17.0)	19.3 (25.5)	0.780
GSMD	5.9 (1.5)	4.7 (2.1)	0.001*
GSTD	5.1 (1.9)	4.2 (2.3)	0.300
GSDD	5.9 (1.4)	4.7 (2.1)	0.001*
Fatigue			
FA	2.9 (2.4)	2.6 (1.8)	0.587
Frequency	11.6 (11.7)	16.5 (14.1)	0.062
GSMD	5.3 (2.1)	5.3 (2.3)	0.990
GSTD	5.0 (2.2)	4.8 (2.2)	0.752
GSDD	5.2 (1.8)	5.3 (2.0)	0.713

Mean (SD), * $p < 0.05$, general score - most days (GSMD), general score - today (GSTD), general score – day to day (GSDD)

Table 6.10. Results of the PFSDQ-M in patients with COPD and CHF

There was no significant difference in the main three components of the PFSDQ-M (CA, DA, and FA) between COPD and CHF. The two groups suffered from dyspnoea for a similar number of days a month (frequency), but patients with COPD described a higher intensity of breathlessness (on most days and with most day to day activities). There was a trend for patients with CHF to have a higher frequency of fatigue, but the intensity was similar between the groups.

The results of pulmonary rehabilitation for patients with COPD and CHF are shown in table 6.11. There is a trend that all the results are lower (better) after rehabilitation for patients with COPD. The activity score (CA) was significantly lower for COPD but this wasn't seen in CHF. There were no significant between group differences, although the difference in the change in activity score approached significance 0.74 (-0.1 to 1.6) $p=0.075$.

	<i>COPD-PR</i>			<i>CHF-PR</i>		
	Before	After	p	Before	After	P
Activity						
CA Mean	2.8 (1.8)	2.2 (1.6)*	0.038	2.8 (1.7)	3.0 (1.6)	0.641
Dyspnoea						
DA	2.7 (1.9)	2.4 (1.7)	0.189	2.4 (1.6)	2.4 (1.8)	0.972
Frequency	21.0 (19.4)	14.0 (12.3)	0.075	15.8 (12.8)	10.4 (11.9)	0.065
GSMD	5.8 (1.4)	5.5 (1.7)	0.336	4.9 (1.9)	4.7 (2.3)	0.546
GSTD	4.9 (2.1)	4.3 (1.7)*	0.028	4.3 (2.3)	3.8 (2.7)	0.157
GSDD	5.7 (1.3)	5.1 (1.5)*	0.030	5.0 (2.1)	4.6 (2.4)	0.132
Fatigue						
FA	2.4 (2.1)	2.0 (1.6)	0.230	2.5 (1.7)	2.1 (1.5)	0.091
Frequency	12.6 (11.7)	10.3 (9.9)	0.301	14.9 (11.3)	13.0 (11.9)	0.441
GSMD	5.1 (2.2)	4.8 (2.2)	0.552	5.6 (2.3)	5.4 (2.4)	0.590
GSTD	4.8 (2.4)	3.8 (2.0)*	0.016	5.1 (2.3)	4.3 (2.3)*	0.012
GSDD	5.0 (1.9)	4.9 (1.9)	0.698	5.5 (2.0)	4.9 (2.5)	0.122

Mean (SD) * $p<0.05$ general score - most days (GSMD), general score - today (GSTD), general score - day to day (GSDD)

Table 6.11. Results of pulmonary rehabilitation assessed by the PFSDQ-M in COPD and CHF

Discussion

The PFSDQ-M was used for both COPD and CHF. The results were very similar for the majority of the components. There was only one subtle difference; patients with COPD suffering from a similar frequency of breathlessness but higher intensity than the patients with CHF.

The overall similarity of the degree of symptoms and the limitation on daily activity supports the hypothesis and results of chapter five that the disability between COPD and CHF is similar.

The PFSDQ-M was not particularly responsive to the effects of pulmonary rehabilitation in either group. A limitation of the current study is that it can not be differentiated whether activity was not improved with PR or whether the PFSDQ-M failed to detect a change. As stated in the previous part of the chapter this should be tested again, but against an objective measure of activity.

vi) Adapting the use of the MRC dyspnoea scale to include patients with CHF

Background

The Medical Research Council (MRC) dyspnoea scale is a simple to use, validated, reproducible, self assessed tool of breathlessness (392;466). It is comprised of five different grades (figure 6.2).

1	I get breathless only with strenuous exercise
2	I get breathless when hurrying or walking uphill
3	I walk slower than people of the same age on the level or I have to stop because of breathlessness on the level
4	I can only walk 100 yards before stopping because of breathlessness or after a few minutes on the level
5	I am breathless when dressing or undressing or I am too breathless to leave the house

Figure 6.2. The MRC dyspnoea scale

It was originally developed as part of an assessment of the prevalence of respiratory symptoms amongst a working class population (464). The different grades have been shown to have a strong relationship with objective measures of exercise performance in COPD (465). Currently it is used as a guide for referral for Pulmonary Rehabilitation for patients with COPD, a threshold of grades 3-5 is recommended (245). The NHYA

classification of activity restriction is the nearest comparison for patients with CHF. It was developed in 1928 and has several modifications the last one was in 1994 by the AHA (391) (see figure 6.3).

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Figure 6.3. The NYHA classification of functional capacity

Criteria for use of the terms ‘ordinary physical activity’, ‘slight limitation’ and ‘marked limitation’ are not defined precisely and the grading is based on the individual physician's judgment. This is a notable difference between the self assessed MRC dyspnoea scale and the NYHA classification. The inter-operator variability for assessing NYHA class showed only 54% concordance (503). However, despite there being no agreed way to assign an NYHA class to an individual, increasing (worse) NYHA

classification has been shown to be associated with a higher hospitalization rate and mortality (504) and also correlates with maximal exercise capacity (505).

If generic rehabilitation were feasible it would be useful to have a generic tool to assess and describe disability. The MRC dyspnoea scale was chosen to be developed to be a generic tool, rather than the NHYA classification, because it is self assessed and has less subjective descriptions for each grade. The use of the MRC dyspnoea scale was therefore investigated in patients with CHF.

Methods

55 patients with COPD and 57 patients with CHF were recruited according to the criteria stated in chapter two. All patients selected the MRC Dyspnoea Scale Grade that best described their symptoms. Prior to this a member of the rehabilitation team assigned an NHYA classification for the patients with CHF, which the patients were blinded to. Each patient performed an Incremental Shuttle Walk Test (ISWT), a cardiopulmonary exercise test on a cycle ergometer and completed the SF36. The patients with CHF had a higher BMI than patients with COPD²⁶ so the peak VO₂ was presented as L/min rather than ml/kg/min. The tests were performed as described in chapter two with a familiarisation test. The responsiveness of the MRC scale was assessed in CHF using the RCT of pulmonary rehabilitation (PR) and NC (NC) described in chapter four. The responsiveness of the MRC scale in CHF was compared with COPD using pulmonary rehabilitation as the intervention²⁷.

²⁶ see chapter five

²⁷ described in chapter six

Results

53 patients with COPD; mean (SD) age 68.8 (8.2)yrs, 52.8% male, FEV₁ % predicted 42.9 (14.9) and 57 patients with CHF; age 71.0 (10.2)yrs, 70.2% male, LVEF % predicted 30.9 (10.1) had complete data sets. The median (IQR) MRC grades for COPD 3(3-4) and CHF 3(2-4) were similar p=0.254. The frequency of each MRC grade for COPD and CHF were similar p=0.226 shown in table 6.12.

There was no relationship between MRC grade and degree of organ impairment assessed by LVEF% in patients with CHF (ANOVA p=0.915) (figure 6.4). There was a trend to a decrease in FEV₁ % predicted with increasing MRC scale grade for COPD p=0.083 (figure 6.4).

<i>MRC grade</i>	2	3	4	5
CHF	26%	37%	25%	12%
COPD	11%	49%	25%	15%

Table 6.12. Frequency of MRC scale grade for COPD and CHF

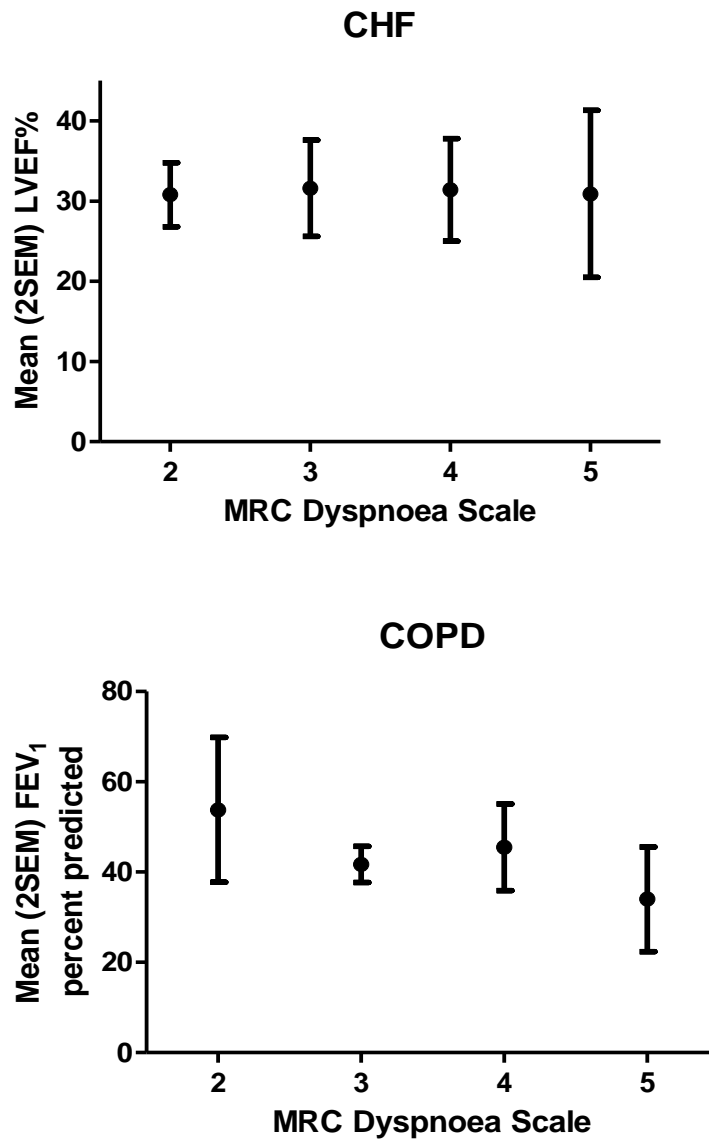


Figure 6.4. Degree of organ impairment per MRC scale grade for COPD and CHF

Results of the MRC grade in CHF

Exercise performance (ISWT distance, and peak VO_2 derived from the CPX) significantly decreased with increasing (worsening) MRC grade (figure 6.5). The SF36 physical function (PF) score increased (worsened) with increasing MRC grade for CHF. These relationships were paralleled for COPD (table 6.13).

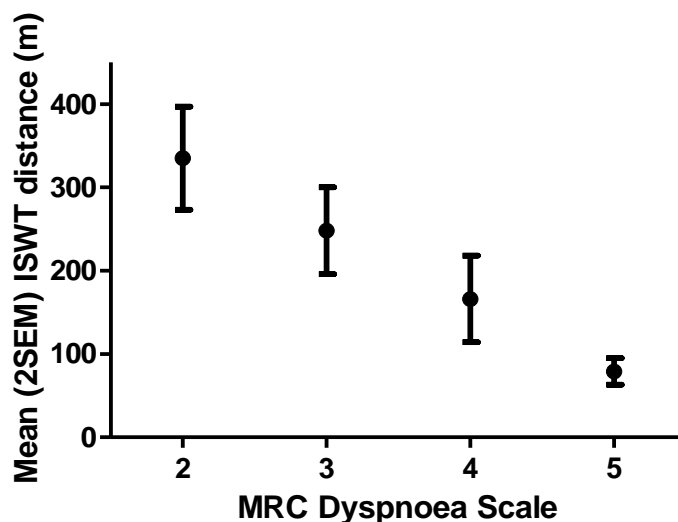


Figure 6.5. ISWT distance per MRC grade for CHF

Comparison of exercise performance and health status for MRC grade between COPD and CHF

The mean (SD) ISWT distance, peak VO_2 from CPX and SF36 physical function score were the same for both groups, COPD and CHF $p=0.793$, $p=0.390$, $p=0.106$ respectively as described in chapter six. There were no differences for each grade

between COPD and CHF for ISWT, ANCOVA $p=0.545$, peak VO_2 $p=0.408$ and SF36-PF $p=0.233$ (figure 6.6).

	<i>COPD</i>	<i>CHF</i>	<i>COPD</i>	<i>CHF</i>	<i>COPD</i>	<i>CHF</i>
MRC Grade	ISWT (m)	ISWT (m)	Peak VO_2 (L/min)	Peak VO_2 (L/min)	SF36-PF	SF36-PF
2	328 (56)	335 (126)	1.11 (0.32)	1.06 (0.44)	15.5 (4.5)	18.9 (3.5)
3	251 (119)	248 (115)	0.91 (0.27)	1.07 (0.41)	16.1 (2.9)	16.5 (3.3)
4	197 (68)	166 (98)	0.77 (0.16)	0.77 (0.18)	13.9 (3.1)	13.3 (2.5)
5	91 (56)	79 (21)	0.73 (0.16)	0.65 (0.20)	11.9 (1.8)	13.7 (3.0)
ANOVA	<0.0005	<0.0005	0.002	0.013	0.008	<0.0005

Table 6.13. Results of exercise performance and health status per MRC grade for both COPD and CHF.

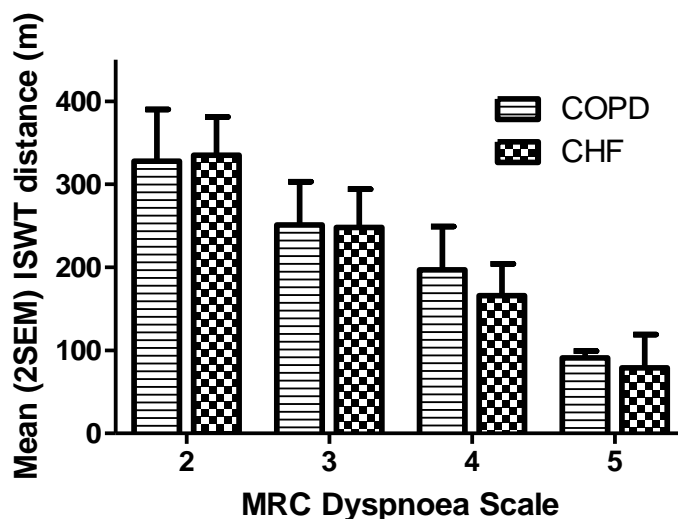


Figure 6.6. ISWT distance per MRC dyspnoea grade for COPD and CHF

Responsiveness of the MRC scale

The mean (SD) MRC scale improved from 3.1 (0.9) before rehab to 2.6 (1.0) after pulmonary rehabilitation in patients with CHF [mean (95%CI) change -0.5 (0.3 – 0.7) $p < 0.0005$]. In COPD, the mean MRC scale grade improved by -0.9 (0.6 – 1.1) $p < 0.0005$ after rehabilitation. There was no difference between the change in MRC grade between COPD and CHF ($p = 0.604$). MRC data is nominal and the same relationships hold when non parametric analysis is applied. The mean data is described as the data is more intuitive than the median change. The responsiveness of the MRC grade was also tested by the RCT of PR and NC. 27 patients completed rehab and 17 patients completed NC. The change in MRC for rehab was ‘-0.5 grades’ and ‘0.2’ grades for the NC group with a between group difference of -0.6 (-0.9 to -0.3) $p < 0.0005$.

Comparison between the MRC scale and NYHA classification for CHF

The correlations between both scales (MRC scale or NYHA classification) and measures of exercise performance and health status are shown in table 6.14. Spearman's correlation coefficient was at least moderate and statistically significant between exercise capacity and each scale. The NYHA classification and MRC scale also showed moderate and strong correlations with the SF36-PF. The poor correlations for both scales with the CHQ domains reflect the poor discriminative properties of the CHQ.

Responsiveness of the NYHA classification

The responsiveness of the NYHA classification was also tested by the RCT of pulmonary rehabilitation (PR) and normal care (NC). The NYHA classification decreased (improved) by -0.2 grades in the PR group and 0.1 in the NC group with a mean difference of 0.3 grades (0.1 -0.5) $p = 0.008$.

	Correlation for MRC scale	p value	Correlation for NHYA class	p value
LVEF	-0.068	0.665	-0.194	0.213
ISWT	-0.661*	<0.0005	-0.687*	<0.0005
Peak VO ₂ from CPX	-0.353*	0.01	-0.457*	<0.0005
SF36-PF	-0.584*	<0.0005	-0.421*	0.002
CHQ-D	-0.255	0.063	-0.160	0.249
CHQ-F	-0.312*	0.022	-0.103	0.458
CHQ-EF	-0.381*	0.004	-0.214	0.121
CHQ-M	-0.237	0.084	-0.154	0.267

*significance at $p < 0.05$

Table 6.14. Correlation between either the MRC scale or NYHA classification and measures of exercise performance and health status

Discussion

The purpose of this part of the study was to develop a simple classification of functional capacity that can be used for both COPD and CHF. The MRC dyspnoea scale was chosen for several reasons; it assesses the consequence of a common symptom for both conditions, it is self assessed and it was not specifically designed for a particular disease.

The MRC dyspnoea scale was found to be discriminative for disability (functional status) in patients with CHF, assessed by objective measures of exercise performance and health status. The degree of disability for each grade was similar between COPD and CHF. Potentially submaximal exercise capacity might have a stronger relationship between MRC grades than maximal capacity. The ESWT time was available for these patients, but it incorporates two variables; speed and duration and is derived directly from the ISWT so was unlikely to add any further information. The six minute walk test was not performed.

This data confirms previous findings that organ impairment does not predict disability. The lack of relationship was even more evident in CHF than for COPD.

For patients with CHF the MRC scale was responsive, it improved (decreased) after PR and was unchanged with NC, with a significant intergroup difference. The MRC scale was similarly responsive to the effects of rehabilitation between COPD and CHF. This data shows that the MRC scale is not superior to the NYHA classification for patients with CHF. Both are discriminative for disability and are responsive. However the self assessed nature of the MRC scale and the specific description for each grade makes it an attractive functional scale especially in the context of rehabilitation. In the current study,

the NYHA classification was designated by a member of the rehabilitation team experienced in assessing disability. A recent study compared both patient assigned and physician assigned NYHA classification for patients with heart failure. Classifications varied by at least 1 class in nearly 50% of cases. The doctor designated NYHA class correlated better with mortality and the authors conclude that 'for physicians the NYHA classification may have become a "heart failure severity score" and not as was intended, purely a measure of a patient's symptoms and functional status'. However, the physician designated NYHA class also correlated better for the six minute walk test than the patients designated score (34).

A limitation of this work was that the reproducibility of the MRC dyspnoea scale was not assessed for patients with CHF. The population studied were by definition symptomatic. The results may not be extrapolated to an asymptomatic population.

In conclusion the MRC dyspnoea scale is discriminative and responsive in patients with CHF and so can be applied successfully to this population. The MRC dyspnoea scale can therefore be used as generic tool to assess disability in patients with COPD and CHF.

Summary and conclusions for chapter six

1) A self reported version of the CHQ has been shown to be reproducible, valid and responsive

2) The PFSDQ-M is reproducible and valid for patients with CHF. Further assessment is necessary to determine its responsiveness ideally with objective measures of activity (activity monitors)

3) The MRC dyspnoea scale is valid and responsive in patients with CHF

- So far in this thesis it has been established that combined training programmes for COPD and CHF are feasible.
- **This chapter** has adapted three outcome measures of health status to be used for both COPD and CHF.
- **The next chapter** describes a potential mechanism behind the improvements in skeletal muscle with exercise training in COPD and CHF.

Chapter seven

A comparison of the effect of exercise training on skeletal muscle fibre type and PPAR expression between COPD and CHF

Background

Chapter five described the similarity in quadriceps muscle strength and exercise performance between COPD and CHF. Both groups of patients made similar, statistical and clinically important improvements in peak and submaximal exercise capacity after seven weeks of endurance training.

- The work in **this chapter** investigates a potential novel mechanism behind the beneficial skeletal muscle adaptations with exercise in COPD and CHF.

The importance of the systemic manifestations of COPD and CHF has been emphasised throughout this thesis. Quadriceps strength and mass is reduced in patients with COPD and CHF compared to age matched controls and is associated with a worse prognosis and increased morbidity (76;82;97;98;506). There are alterations in the skeletal muscle fibre type proportion in the vastus lateralis with an increase in the fatiguable type II fibres and a reduction in type I fibres (59;75). Similar contributing factors such as deconditioning, oxidative stress and systemic inflammation have all been implicated for both diseases (365). A review compared the separate studies in COPD and CHF and highlighted the similarity of the muscle fibre type changes and the effect

of exercise training (365). To date there have been no published direct comparative studies.

PPARs are nuclear receptor proteins and are ligand-inducible transcription factors (regulators of gene expression). Their key role is in lipid homeostasis. PPARs are key regulators of fatty acid oxidation and mitochondrial biogenesis and hence of skeletal muscle oxidative capacity (63). There are three different types of receptor; alpha, gamma and delta that are expressed in skeletal muscle but also the liver (predominantly PPAR alpha), kidney, heart and adipose tissue (predominantly gamma). PGC-1 is a coactivator of PPAR transcriptional activity. There is evidence in particular that PGC-1 promotes gene expression that favours oxidative metabolism (507). PGC-1 is expressed higher in slow twitch type I fibres than faster type IIb fibres in skeletal muscle.

Recently Remels et al described the peroxisome proliferator-activated receptor (PPAR) alpha, delta, gamma and PGC-1alpha mRNA expression and protein level in the skeletal muscle of patients with COPD compared to healthy controls (148). There were lower levels of PGC-1alpha mRNA expression in COPD and lower levels of PPAR delta protein compared to healthy controls.

PPAR expression maybe one of the regulatory mechanisms behind the alteration in fibre type distribution seen in COPD (508). The similar pattern of fibre type shift from type I towards the faster type IIx fibres in skeletal muscle seen in CHF and COPD may indicate PPAR expression in CHF maybe similar.

To date there are no published studies on the effect of exercise training on PPAR expression in the skeletal muscle in COPD or CHF. This chapter describes a pilot study to examine whether the expression of PPARs in skeletal muscle would be affected after

a period of exercise training in patients with COPD and CHF. The PPARs could be a potential therapeutic target.

This chapter describes

- a direct comparison of skeletal muscle fibre type distribution and the effects of exercise training between COPD and CHF
- a direct comparison of the mRNA expression of the peroxisome proliferator- activated receptors (PPARs) and the co-activator (PGC-1) in skeletal muscle in COPD and CHF
- the effects of exercise training on PPAR and PGC-1 mRNA expression in skeletal muscle in COPD and CHF

Methods

Patients were recruited from the comparative study of PR between COPD and CHF according to the criteria described in chapter two. This part of the study was optional. Patients prescribed warfarin or other anticoagulants were excluded.

Outcome measures

Vastus lateralis muscle biopsy

The procedure was undertaken using the Bergstrom technique as described in the methods in chapter two. Aspirin was temporarily stopped two days prior to the procedure and clopidogrel was stopped five days before.

Analysis for PPAR receptors and PGC-1 by quantitative RT-PCR

A description of the polymerase chain reaction (PCR), reverse transcription and real – time or quantitative PCR is outlined in appendix VIII with some of the terminology used in this chapter. All the muscle laboratory work was undertaken by a colleague; Despina Constantin, in the Centre for Integrated Systems Biology and Medicine, Department of Biomedical Sciences, University of Nottingham, UK. The methodology is described in appendix VIII.

In summary the PPAR mRNA expression was analysed using quantitative PCR and the myosin heavy chain (MHC) analysis were analysed with gel electrophoresis. The data analysis and interpretation was performed by myself.

Other outcome measures;

The ISWT, ESWT and isometric quadriceps strength were performed according to the protocols described in chapter two.

Intervention

The seven week pulmonary rehabilitation programme was predominantly endurance training described in chapter two.

Statistical analysis

The MHC isoforms expressed as a percentage were normally distributed according to KS tests $p > 0.05$. Paired t tests were therefore applied to assess the changes with PR and independent t tests for any between group comparisons. Pearsons correlation coefficients were reported for the correlations between exercise performance and MHC isoform data. Spearman's correlation coefficients were applied for the correlation between MHC isoforms and the MRC scale.

The mRNA expression for the PPARs and PGC-1 coactivator was analysed using quantitative PCR and performed in duplicate. The average Ct (cycle number) for each gene, including the house keeping gene, was calculated. For the baseline mRNA gene expression each Ct was divided by the house keeping gene Ct. The Ct was normally distributed for all the genes therefore parametric tests were applied.

The comparative Ct method was used to quantify the PPAR mRNA expression before and after seven weeks of exercise training. The Ct values after training were compared with the baseline samples as a control (calibrator). The Ct values for both the before (calibrator) and after training samples were normalised to an endogenous housekeeping gene –HMBS (hydroxymethylbilane synthase) which has previously been shown not to be affected by exercise in human subjects (509).

The comparative Ct method is also known as the $2^{-[\Delta][\Delta]Ct}$ method, where

$[\Delta][\Delta]Ct = [\Delta]Ct \text{ sample} - [\Delta]Ct \text{ reference}$. $[\Delta]Ct \text{ sample}$ is the Ct value for any sample normalised to the endogenous housekeeping gene and $[\Delta]Ct \text{ reference}$ is the Ct value for the calibrator also normalised to the house keeping gene. For this calculation to be valid the amplification efficiencies of the target and the endogenous reference must be approximately equal.

Spearman's correlation coefficients were calculated between the change in MHC isoform and the change in mRNA expression with exercise training.

This was a pilot study using the participants from the comparative training study described in chapter five so no power calculation was performed for this part of the study.

Results

22 patients with COPD and 6 patients with CHF were recruited and all had a resting muscle biopsy performed before pulmonary rehabilitation (table 7.1). Nearly 40% of the patients with CHF recruited to the main study were prescribed warfarin and were excluded from this sub-study. One patient with CHF was excluded because of the technical difficulties of muscle sampling associated with a BMI of 54.

	COPD n=22	CHF n=6	p
Age	66.5 (9.5)	67.8 (14.5)	0.794
Gender †	50%	17%	0.182
FEV ₁ % predicted	42.0 (13.8)	92.7 (30.1)	<0.0005*
FEV ₁ /FVC	50.3 (8.4)	78.3 (3.7)	<0.0005*
LVEF	NA	27.0 (10.4)%	NA
FFM m/kg ²	17.3 (2.6)	20.0 (2.7)	0.037*
BMI	27.1 (5.1)	31.2 (6.1)	0.073
MRC ‡	3.5 (3.0 to 4.0)	3.0 (2.75 to 3.25)	0.139
ISWT (m)	242 (148)	303 (166)	0.394
ESWT (secs)	267 (212)	231 (63)	0.693
Muscle strength	121 (51)	162 (89)	0.328

Mean (SD) †chi squared test ‡ median (IQ range) *p<0.05, not applicable (NA)

Table 7.1. Comparison of the baseline demographics between COPD and CHF

Results of the baseline PPAR expression between COPD and CHF

18 patients with COPD and 4 patients with CHF had adequate muscle sample for quantitative PCR. All four genes were expressed in the skeletal muscle of both patients with COPD and CHF. There was a significant overall difference in the mRNA expression of the PPARs and PGC-1 in patients with COPD; ANOVA p<0.0005 (figure 7.1). Subgroup analyses demonstrated that the expression of PPAR delta was significantly higher than PPAR alpha (p<0.0005), PPAR gamma (p<0.0005) and PGC-1 (p<0.0005). There were no other significant differences between the genes. There was a

similar significant difference between the baseline PPAR and PGC-1 expression for CHF (ANOVA $p=0.016$). The numbers were too small to perform subgroup analyses. Table 7.2 and figure 7.1 show a similar profile for the gene expression between COPD and CHF. Statistical analysis although shown in table 7.2 should be interpreted with caution because of both the low numbers of patients in the CHF group and difference in subject numbers between the two groups.

	COPD n=18	CHF n=4	p value
PPAR alpha	0.94 (0.2)	0.97 (0.01)	0.026*
PPAR delta	1.15 (0.05)	1.13 (0.09)	0.406
PPAR gamma	0.98 (0.08)	1.00 (0.08)	0.606
PGC-1	0.97 (0.04)	1.00 (0.03)	0.083

Mean (SD) * $p<0.05$

Table 7.2. Comparison of mRNA expression of PPARS and PGC-1 in skeletal muscle between COPD and CHF

Baseline MHC isoform distribution for COPD and CHF

14/18 patients with COPD and 4/6 patients with CHF completed the seven week pulmonary rehabilitation programme. MHC analysis was not performed on the patients who did not complete rehabilitation. The PCR analysis for PPARs and PGC-1 was performed prior to the MHC analysis. There was inadequate muscle sample remaining for the MHC analysis for 3/14 of the patients with COPD and 1/4 patients with CHF.

Before rehabilitation the mean (SD) percentage of MHC type IIX fibres was 41.0 (33.1)%, MHC type IIA fibres 49.5 (35.7)% and MHC I 9.4 (11.4)% for patients with COPD and in patients with CHF; MHC IIX fibres 53.7 (40.5)%, MHCIIA 20.7 (32.7)%

and MHC I 26.0 (26.5)%. There were no statistical differences in the fibre type proportion in skeletal muscle between COPD and CHF (figure 7.2).

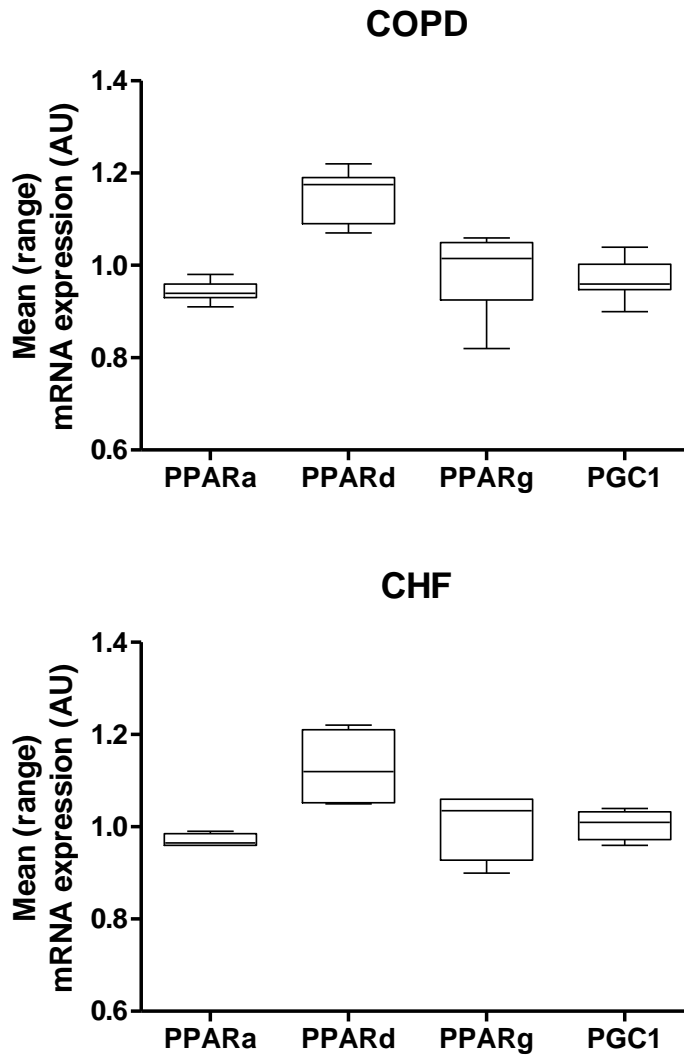


Figure 7.1. Baseline results of PPAR and PGC-1 mRNA expression in skeletal muscle in COPD and CHF

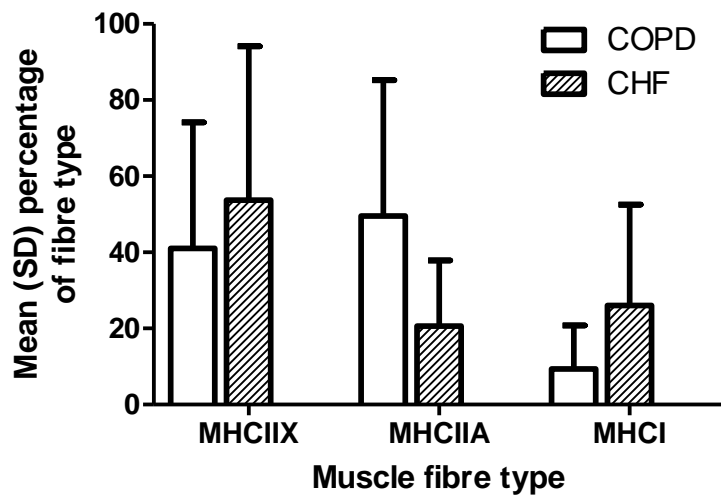


Figure 7.2. Comparison between the muscle fibre type distribution in skeletal muscle in COPD and CHF

Correlation between the MHC isoform distribution , PPAR expression and measures of exercise performance in COPD

Correlation coefficients were calculated between the MHC isoforms and measures of disease severity (FEV_1 percent predicted), exercise performance (ISWT, ESWT, peak VO_2 derived from the CPX), measures of health status (SF36 physical function score, CRQ dyspnoea and fatigue domains) and dyspnoea (MRC scale) for the COPD group. The only trend towards a positive correlation was between disease severity (FEV_1 percent predicted) and the percentage of MHC type I fibres; 0.548 $p=0.081$. There were no other relationships between the parameters. The same parameters were also correlated with the baseline PPARs and PGC-1 mRNA expression in patients with COPD. The only significant correlations were between both PPAR delta

and PPAR gamma and peak VO_2 measured by CPX on a cycle ergometer; 0.549 $p=0.042$ and 0.540 $p=0.046$ respectively. Greater than 20 correlations were performed so significance at $p<0.05$ may not be valid.

Correlation between MHC isoform distribution and PPAR expression in COPD

Correlations between the mRNA expression of PPARs and PGC-1 and the MHC isoforms were not performed for CHF because the numbers were too small to be meaningful. Figure 7.3 shows the correlation between the different MHC isoforms and PGC-1 coactivator and PPAR delta for patients with COPD. The PGC-1 coactivator mRNA expression was inversely significantly correlated with the percentage MHC IIX; -0.655 $p=0.029$, but positively correlated with the percentage of MHC IIA fibres; 0.631 $p=0.037$. There was no significant correlation between PGC-1 and MHC I fibre proportion; -0.093 $p=0.785$. There was a trend for PPAR delta to be inversely correlated to MHC I fibre proportion; -0.588 $p=0.057$. There were two data points where the MHC I proportion was $>20\%$ that appeared to skew the data. There was no relationship between PPAR delta and type 1 fibre type when they were removed from the analysis. There was no relationship between PPAR delta and the other MHC isoforms or between PPAR alpha or PPAR gamma and any of the MHC isoforms.

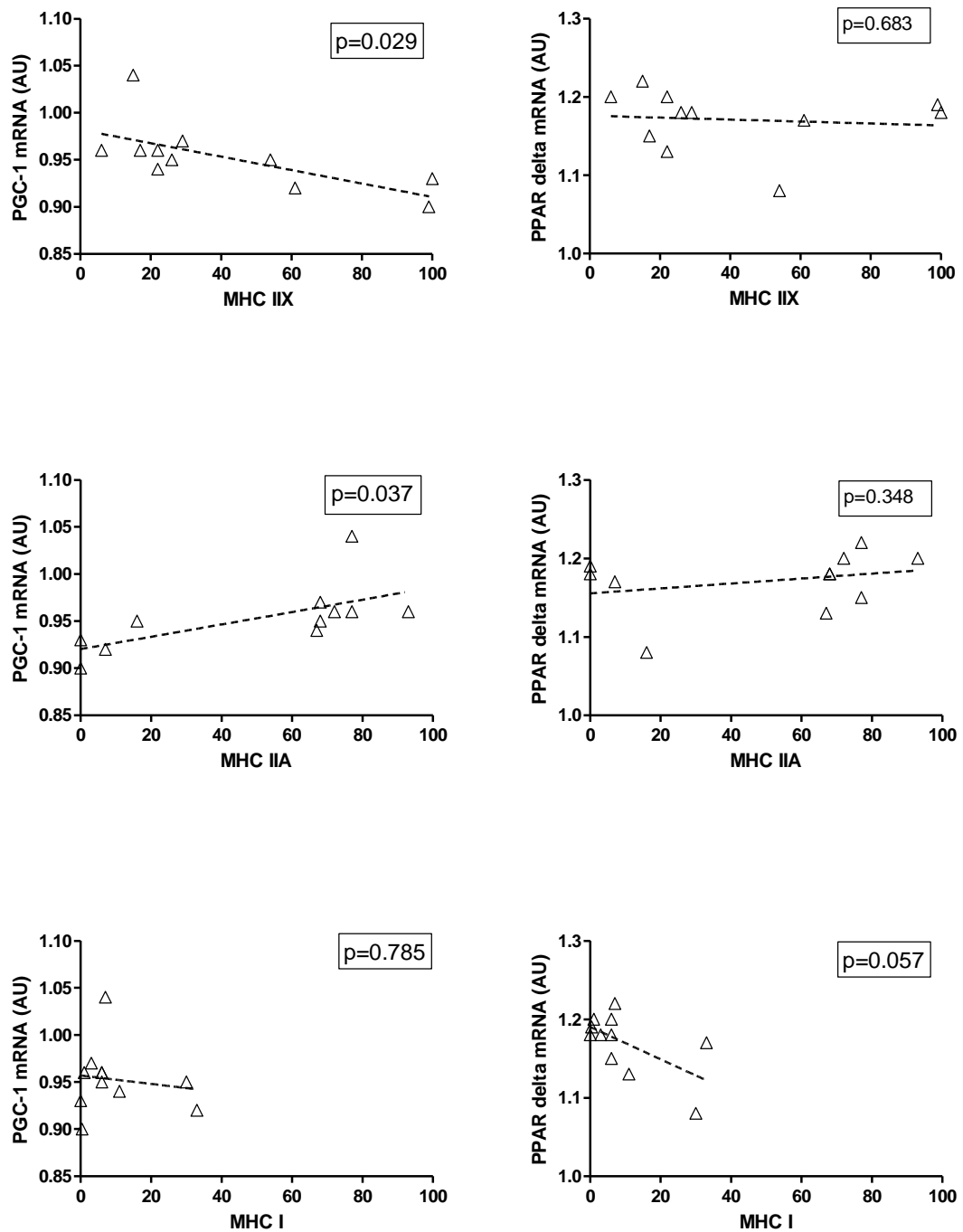


Figure 7.3. Correlations between PGC-1 mRNA and PPAR delta mRNA expression and MHC isoform percentage.

Correlation between the PPARs and PGC-1 in patients with COPD

There was a positive correlation between baseline PGC-1 mRNA expression and PPAR alpha mRNA; 0.633 $p=0.005$, and a negative correlation between PGC-1 mRNA and PPAR gamma mRNA; -0.596 $p=0.009$. The inverse relationship between PGC-1 and PPAR delta did not reach significance; -0.403 $p=0.097$. PPAR delta mRNA expression was positively correlated with PPAR gamma mRNA expression, but not PPAR alpha mRNA expression and there was no relationship between PPAR gamma and alpha.

Results of pulmonary rehabilitation**Exercise performance and strength with PR**

The mean (95% CI) ISWT distance improved by 86 (44 to 128)m $p=0.001$ for the 14 patients with COPD who completed rehabilitation and the mean (95% CI) ESWT time improved by 283 (161 to 405) seconds $p<0.0005$. 12/14 patients achieved the minimum clinically significant improvement in the ISWT (>48m). There was no change in the peak VO_2 by CPX with PR; mean (95% CI) 0.0 (-0.8 to 0.8) $p=0.987$. Quadriceps strength was unchanged before and after rehabilitation; mean (95% CI) 8 (-6 to 22) Nm $p=0.222$.

Four patients with CHF completed rehabilitation. The mean (95% CI) change in the ISWT was 55 (40 -66)m ($p<0.001$), in the ESWT was 270 (201 to 340) secs ($p<0.001$) and in the quadriceps strength was 12 (-11 to 35) Nm $p=0.183$.

Results of MHC isoform distribution with PR in COPD and CHF

For the 11 patients with COPD after the seven weeks of exercise training, type IIA fibres changed from 41.0 (33.1)% to 41.9 (23.5)% $p=0.923$, type IIX fibres from 49.5 (35.7)% to 40.1 (28.9)% $p=0.282$ and type I fibres from 9.4 (11.4)% to 18.9 (15.9)% $p=0.158$ (figure 7.4). The individual response with PR is shown in figure 7.6 to demonstrate the wide variability. Figure 7.7 shows the results of the gel electrophoresis. proportion change from 53.7 (40.5)% to 42.0 (39.8)% $p=0.598$, type IIa 20.7 (17.2) to 32.7 (26.0)% $p=0.303$ and type I 26.0 (26.5) to 25.7 (23.5) $p=0.981$ shown in figure 7.5.

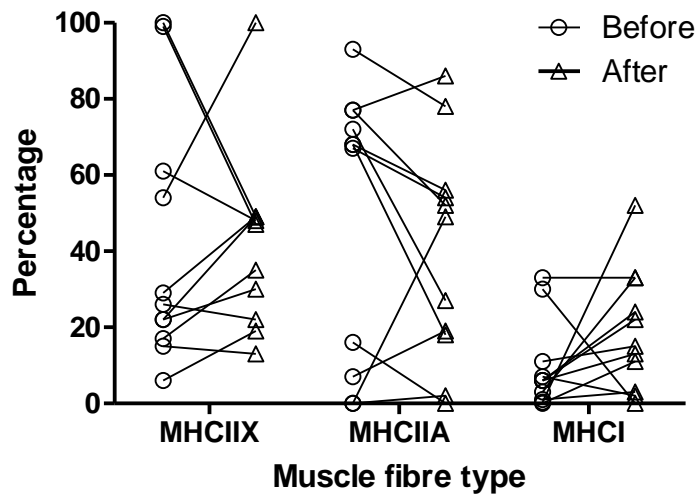


Figure 7.6. Individual response to PR in muscle fibre type proportion in COPD

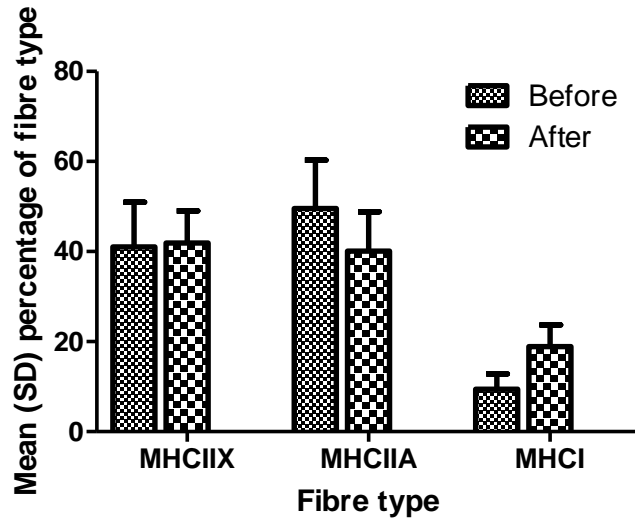


Figure 7.4. Change in fibre type proportion with exercise training in COPD

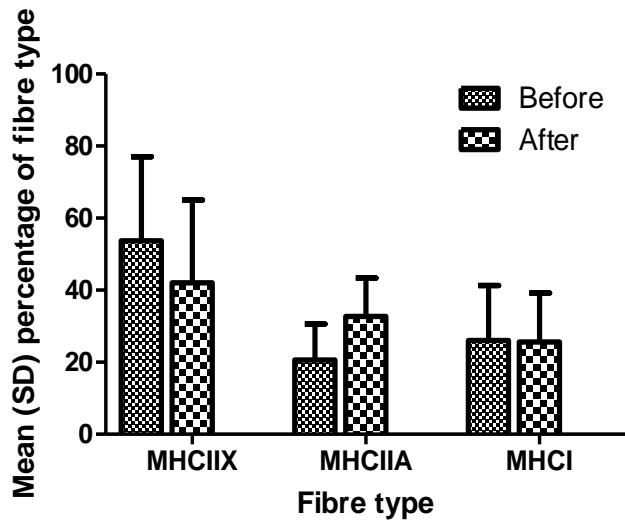
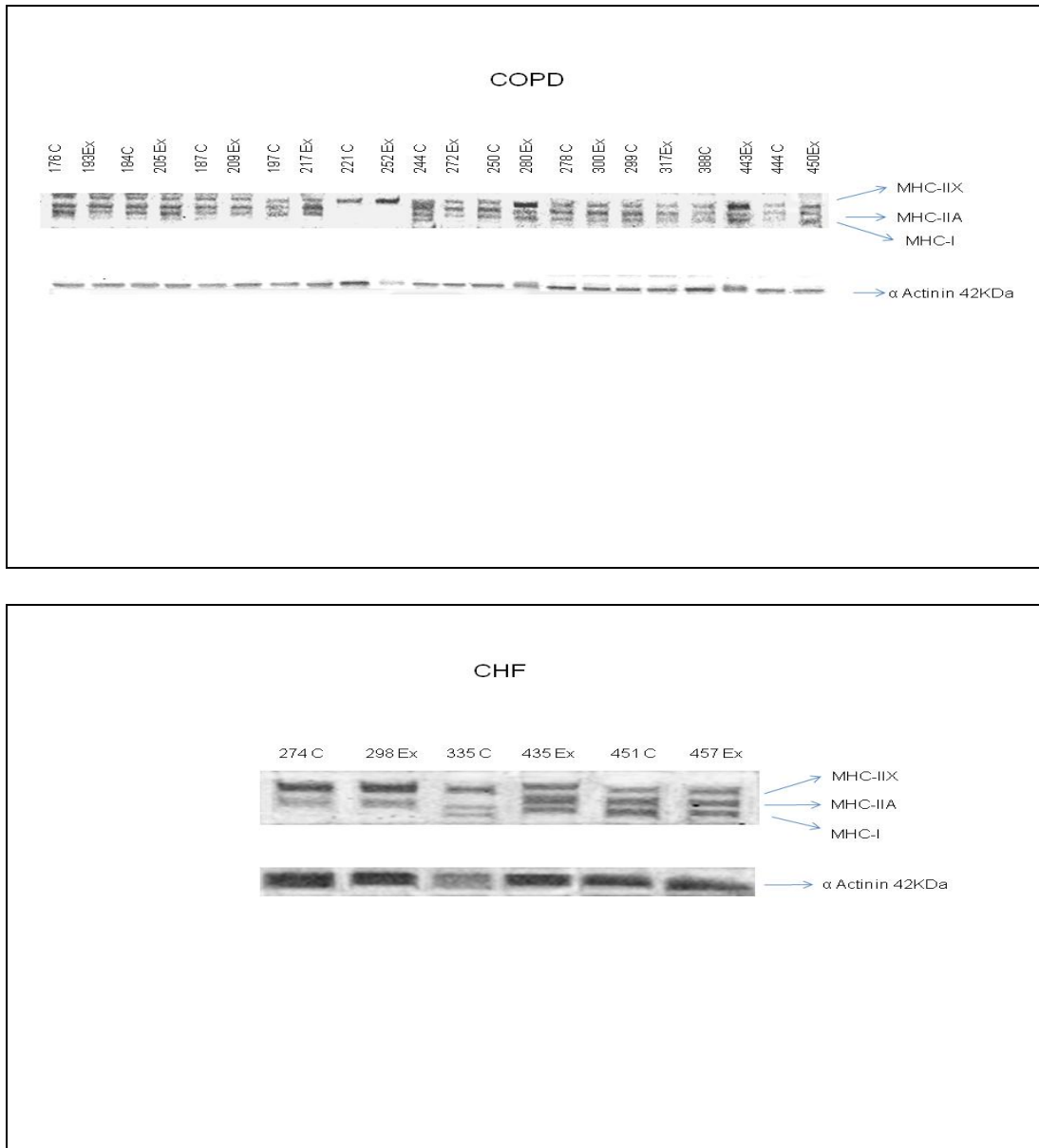


Figure 7.5. Change in fibre type proportion with exercise training in CHF.



C = before pulmonary rehabilitation E= after pulmonary rehabilitation
 The sequence is in order of each patients' paired samples

Figure 7.7. The results of gel electrophoresis for the MHC isoforms

Results of PPAR receptor and PGC-1 expression in quadriceps muscle with PR in COPD and CHF

Using the technique described in the methods all the baseline biopsies were manipulated to have a value equal to one. The gene expression after rehabilitation is reported relative to the baseline value of one. After seven weeks of pulmonary rehabilitation the median (IQ range) change for PPAR alpha was; 0.99 (0.77 - 1.34) $p=0.572$, PPAR delta; 1.56 (0.90 - 2.42) $p=0.019$, PPAR gamma; 1.22 (0.57 - 2.21) $p=0.221$ and PGC-1; 0.85 (0.45 - 2.54) $p=0.851$ (figure 7.8)²⁸.

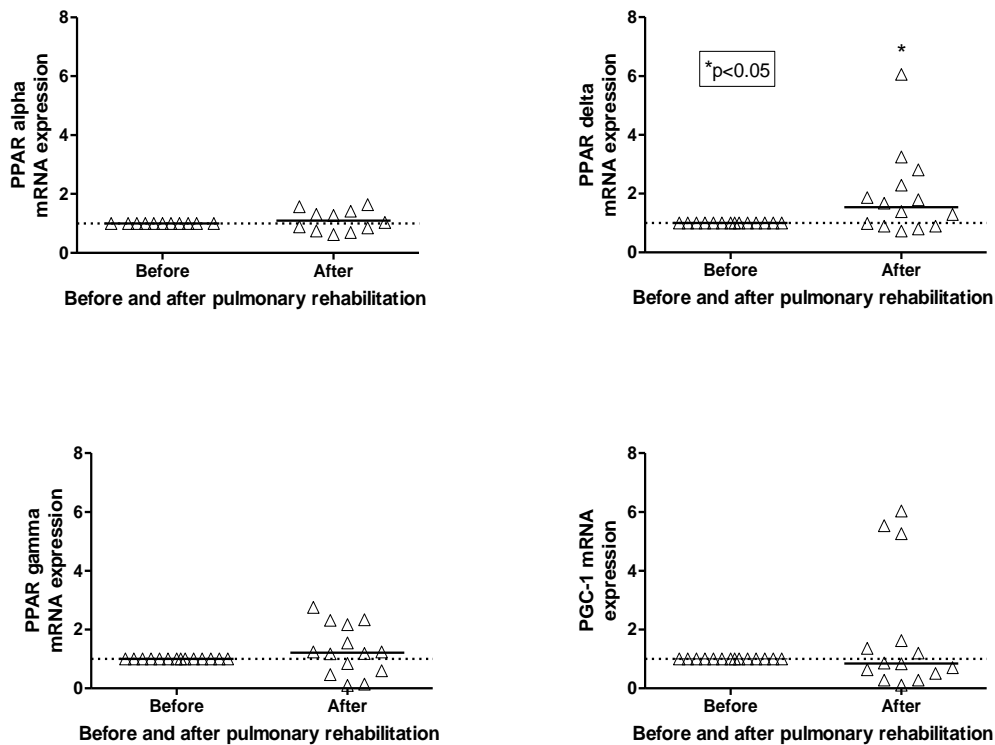


Figure 7.8. Graphs of the change in PPAR and PGC-1 expression with exercise training in patients with COPD

²⁸ The increase in PPAR delta expression after rehabilitation remains even when the one patient with a six fold increase was removed from the analysis ($p=0.033$).

The range of PPAR delta expression after rehab was 0.8 – 6.06 au.

Three patients had a large increase in PGC-1 expression. These were not the same patients that had a large increase in PPAR delta expression. There were no obvious differences in any demographic or exercise parameter between these three patients and the rest of the patients.

Subgroup analysis was performed by dividing the patients into two groups ‘responder’ or ‘non responder’ depending on whether they achieved the minimum clinically important difference on the ISWT of >48m with PR. There was no difference in the mean difference in PPAR alpha, delta, gamma or PGC-1 expression with rehabilitation between the two groups.

Change in skeletal muscle PPAR mRNA expression with training in patients with CHF

There were only four complete sets of muscle biopsy pairs before and after training in patients with CHF. The median (IQ range) change in PPAR alpha after rehabilitation was 1.76 (1.21 to 1.38) $p=0.068$, PPAR delta 0.67 (0.14 to 1.10) $p=0.461$, PPAR gamma 0.96 (0.59 to 1.06) $p=0.465$ and for PGC-1 2.95 (1.75 to 4.92) $p=0.068$ (figure 7.9).

In patients with CHF there appeared to be a trend towards an increase in PPAR alpha and PGC-1 expression after training which was not seen in COPD (between group difference in the change in PPAR alpha and PGC-1 after training $p=0.026$ and $p=0.089$ respectively). In patients with COPD the predominant effect with training was a significant increase in PPAR delta which was not seen in CHF (between group

difference in the change $p=0.056$). PPAR gamma appeared unaltered by training in both groups ($p=0.288$).

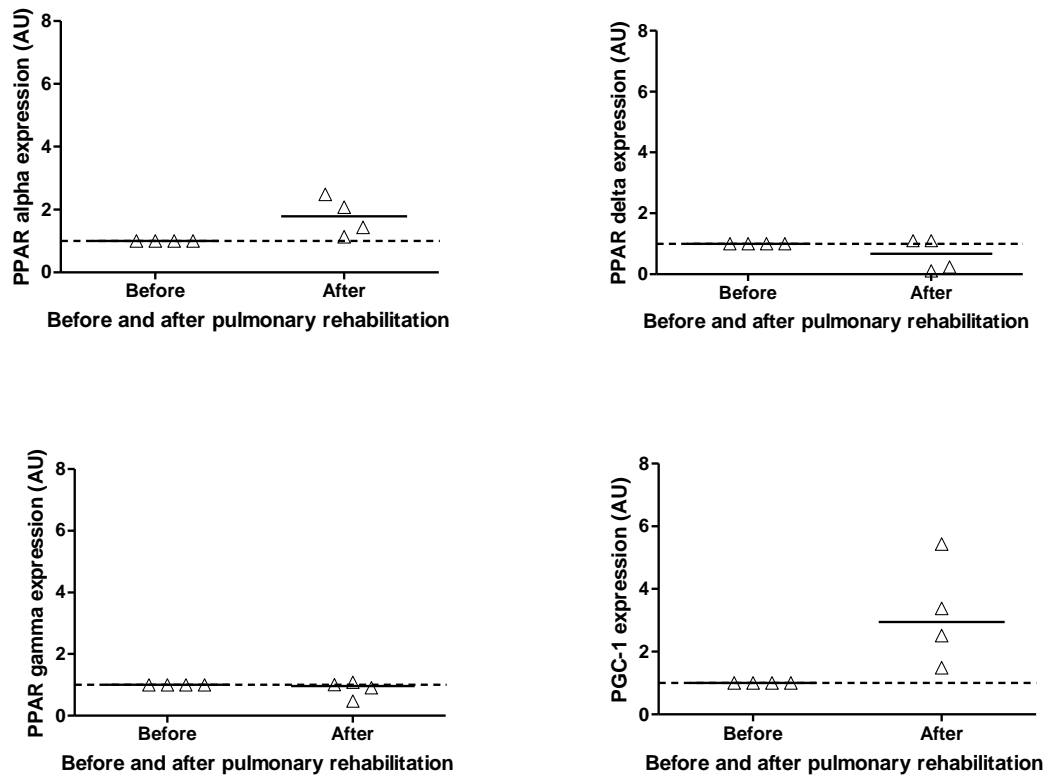


Figure 7.9. Graphs of the change in PPAR and PGC-1 expression with exercise training in patients with CHF

Correlation between the change in MHC isoform distribution and the change in PPAR expression in COPD

The correlations between the change in MHC isoform with exercise training and the change in mRNA expression for the PPARs and PGC-1 are shown in table 7.3. The only significant correlations were between both the change in PPAR alpha and PGC-1 mRNA expression and MHC type I. The graphs in figure 7.10 present the individual data points for clarity. There was a significant positive correlation between the change in PGC-1 and PPAR alpha; 0.807 p=0.003 and no relationship between PGC-1 and both PPAR delta; 0.475 p=0.139, and PPAR gamma; -0.379 p=0.250.

	Δ MHCIIIX		Δ MHCIIA		Δ MHCI	
Δ PPAR α	-0.469	0.145	-0.050	0.884	0.803	0.003*
Δ PPAR δ	0.050	0.885	-0.092	0.787	0.503	0.877
Δ PPAR γ	0.303	0.365	0.058	0.866	-0.472	0.142
Δ PGC-1	-0.451	0.164	-0.073	0.832	0.767	0.006*

*p<0.05, Δ Change with exercise training

Table 7.3. Correlations between the change in mRNA expression of the PPARs and PGC-1 co-activator and the change in MHC isoforms with exercise training in patients with COPD

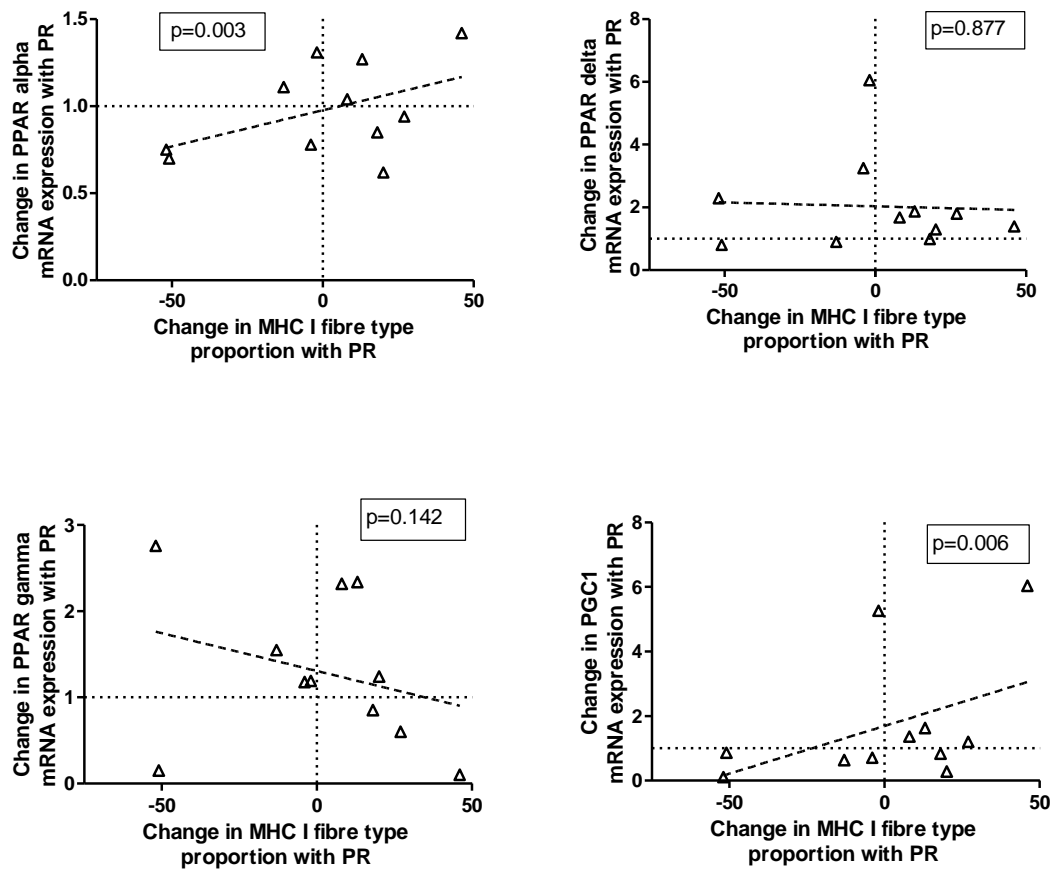


Figure 7.10. Graphs to show the relationship between the change in MHC type I proportion and the change in PPARs mRNA expression with PR in COPD

Discussion

Patients with COPD and CHF both gained clinically and statistically important improvements in exercise performance with seven weeks of exercise training. A detailed assessment was performed with a percutaneous muscle biopsy in a sub-study of patients undergoing the main trial. At least partial reversal of the muscle fibre shift, back towards the oxidative type I fibres has previously been shown with training in both COPD and CHF. The PPARs are transcription factors involved in the regulation of fatty acid metabolism and the oxidative capacity of skeletal muscle. The hypothesis for this pilot study was that the PPARs and PGC-1 maybe involved in the beneficial change in fibre type previously reported with exercise training in COPD and CHF.

All four receptor PPAR alpha, delta, gamma and PGC-1 mRNA were expressed in skeletal muscle in COPD and CHF. PPAR delta was expressed significantly higher than the others receptors in both conditions. This is similar to data for healthy humans (510). There was a significant and positive correlation between peak VO_2 and skeletal muscle PPAR delta and gamma mRNA expression in COPD, but no correlation between PGC-1 coactivator. A significant correlation between PGC-1 coactivator and peak VO_2 has been reported in sedentary controls (511). This study included a group of patients with CHF. The levels of PGC-1 coactivator were not significantly different between the patients with CHF and the sedentary controls. In COPD a lower level of PGC-1 compared to controls has been reported (148). Unfortunately there were no healthy controls in the current study.

The sample number for CHF in the current study was very small so the next part of the discussion will only be regarding COPD.

Remels et al reported no difference in baseline PPAR delta mRNA expression between COPD and healthy adults, but PPAR delta protein was significantly reduced (148). In the current study there was a trend towards a negative relationship between PPAR delta mRNA expression and the proportion of type I fibres, but there was no relationship between the other receptors and type I fibre proportion. Previous reports in healthy humans also showed a trend for mRNA expression of PPAR delta to be negatively related to the proportion of type I fibres in the triceps, vastus and soleus muscles (512). The negative correlation could suggest the presence of a feedback signalling pathway to increase PPAR delta expression in response to a reduced proportion of type I fibres. In healthy human skeletal muscle PPAR delta is expressed higher in the type I muscle fibres relative to type II (63). Without a feedback system a positive correlation between PPAR delta expression and type I fibres would be expected. The MHC isoforms in the study by Plomgaard and the current study were expressed as a proportion of total fibres not as the total number of fibres. Overall there was heterogeneity in the relationship between the PPAR mRNA expression and each of the fibre types within this group of patients with COPD.

The PPARs and PGC-1 mRNA expression were quantified before and after seven weeks of exercise training. The training programme was effective with 12/14 patients achieving the MCID of the ISWT of >48m. 6/11 patients had an increase in the proportion of MHC type 1 fibres i.e physiological training was demonstrable in over half of the patients. Overall there was a significant increase in the mRNA expression of PPAR delta, but no change in the other PPARs or PGC-1 co activator. The literature regarding PPAR delta and skeletal muscle will be discussed in more detail.

PPAR delta has been shown to regulate fatty acid oxidation in skeletal muscle. In mice models over expression of PPAR delta enhanced fatty acid oxidation (513). Luquet et al performed a similar study using an animal model with muscle-specific PPAR delta over expression (514). The model resulted 'in a change in fibre composition due to hyperplasia and/or shift to more oxidative fibre type and lead to increases of both enzymatic activities and genes implicated in oxidative metabolism'. There was an associated reduction in fat mass. The potential role of PPAR delta agonists in the management of obesity and the associated 'metabolic syndrome' has therefore been highlighted (515). If the increase in PPAR delta with exercise training in the current study had led to hyperplasia of type I fibres this may not have been detected by gel electrophoresis (particularly if there was an increase in number of all the fibre types).

The expression of PPAR delta has been shown to be increased where an increase in fatty acid utilisation occurs i.e fasting and exercise (516). The effect of exercise on the expression of PPAR delta has been studied in patients with diabetes mellitus type II (517). There was a non-significant trend towards an increase in mRNA expression after four months of increasing physical activity, and a significant increase in PPAR delta protein expression. This relationship was only seen in the 'exercise responders'. Exercise responders and non-responders were defined on the basis of changes in insulin sensitivity. This was not a randomised controlled trial. All patients were given the same advice to increase physical activity and those patients who failed were designated as the control group.

Wang et al reported the effects of a mouse model with PPAR delta over expression (transgenic) in the skeletal muscle, the null mouse and the use of a PPAR

delta agonist in the wild type ‘sibling’ (518). The transgenic mice ran twice the distance as the wild type mice and had an increase in skeletal muscle type I fibres. The wild type mice ran for significantly longer than the null mice. The PPAR delta agonist; GW501516, given for 10 days, upregulated genes for slow fibre contractile proteins, mitochondrial biogenesis, and beta-oxidation. They did not report the effect on endurance capacity. The same group reported the effects of four weeks of a PPAR delta agonist (GW1516) on sedentary mice (519). The expression of oxidative genes in skeletal muscle were again increased, but this did not lead to an increase in type I muscle fibres or any change in endurance capacity. However, the PPAR delta agonist appeared to be a performance enhancer, as it increased endurance capacity when given in combination to four weeks of training compared to training alone. The use of a PPAR delta agonist (GW501516) has been reported in a human study of obese men. The study was mainly reporting the beneficial effect of the PPAR delta agonist on the components of the metabolic syndrome. The carnitine acyltransferase (involved in beta oxidation in the mitochondria) was increased in the skeletal muscle, but there was no change in the PPAR delta mRNA expression. This does show that a PPAR delta agonist has the potential to improve oxidative capacity of skeletal muscle.

The current study showed wide variability for the change in the expression of the other genes with exercise training. Although only the increase in PPAR delta was significant, the upper limit of the IQ range was similar for PPAR delta (2.42), gamma (2.21) and PGC-1 (2.54). The varied response with PGC-1 expression was particularly marked. PGC-1alpha has been reported to have a transient increase in activation with a bout of exercise in human skeletal muscle, with a greater response after training (520).

However, another study showed no change in PGC-1 mRNA expression, PPAR alpha or gamma with either a single bout of exercise or nine days of training in human subjects (521). In 2001 when the study was conducted less was known regarding PPAR delta and it was not included in this study. In a mouse model it was also shown that PGC-1alpha was not mandatory for beneficial, training induced gene expression (522).

The relationship between the change in MHC fibre type proportion and the change in PPARs mRNA expression with exercise training in COPD was heterogenous. There was a positive correlation between the change in fibre type I and PGC-1 and PPAR alpha. However there was no consistent relationship between the change in fibre type I and the change in PPAR delta. This was mainly because two patients who had a 4 fold increase in PPAR delta after training did not alter the fibre type I proportion. The number of fibres rather than just the proportion may have been informative.

The next part of the discussion will concentrate on a comparison of the data between COPD and CHF appreciating the small number of CHF samples. The baseline fibre type proportion showed a reduced percentage of type I fibres in the vastus lateralis in CHF and COPD. In healthy untrained males about 58% of the muscle fibres are type 1 fibres (523). Couillard reviewed the data for fibre type proportion in healthy active subjects, healthy sedentary and COPD and concluded that the type 1 fibre proportion was much lower (23%) in COPD than for healthy sedentary (44%) and healthy active (60-67%) (130). Gosker published a meta-analysis on vastus lateralis muscle fibre type shifting and reported a mean of 51% type I fibres and 13% for type IIX in patients with COPD GOLD III-IV (75). A proportion of fibre type I <27% and type IIX were classified as pathologically abnormal. The COPD group in the current study had a very

low mean percentage of type I fibres <10% and a mean of >40% of type IIX. A similar distribution was seen in patients with CHF (type I fibres <26%) supporting the current literature that the histological changes in the skeletal muscle are similar for the two diseases.

There was no overall change in fibre type proportion for COPD or CHF with training, but there was a trend towards an increase in type I fibre proportion in COPD. The response was heterogeneous. As discussed in the methods chapter there are different laboratory techniques for muscle fibre typing. The MHC isoform analysis only provides the proportion of fibre type, but the number and size are also factors. It may be that using a combination of methods would provide more detailed and therefore accurate data.

The number of samples for CHF was small so it would be prudent not to draw too many conclusions from the data regarding the expression of the PPARs. However all four genes were detected in the skeletal muscle in a similar distribution to COPD i.e. PPAR delta was expressed the most. In a rat model of CHF, there was a decrease in skeletal muscle oxidative capacity and PGC-1 was down-regulated (524). There were also changes in mRNA expression with exercise training. PPAR delta did not increase with exercise training in the four patients with CHF, but both PPAR alpha and PGC-1 were increased in all four patients. A larger study would be need to confirm whether the PPARs and PGC-1 mRNA expression is expressed differently between COPD and CHF after exercise training.

There are some major limitations of this pilot study. There was no healthy control group so the relative mRNA expression of the genes of interest in COPD

compared to healthy subjects is not described. The method used to calculate the baseline gene expression in COPD and CHF is not as accurate as the $2^{-[\text{delta}][\text{delta}] \text{Ct}}$ method which could have been used if a control group was available. Only the mRNA expression is described and not the proteins of the genes of interest. This means only the frequency and not the activity of the genes is described.

There are only small numbers of samples involved. A percutaneous muscle biopsy is an invasive procedure and less than half of potential patients volunteered for this sub-study. Despite two samples being taken there was still insufficient sample in a few cases. The heterogenous response to pulmonary rehabilitation means larger studies are necessary to further understand the effect of training on these genes.

In summary for **this chapter** the regulatory role of PPARs and PGC-1 co-activator on the oxidative capacity in skeletal muscle is an area of relevance to both COPD and CHF.

- There is a potential positive feedback system from a reduction in type 1 fibres to an increase in PPAR delta expression
- PPAR delta appears to be upregulated with a short period of exercise training in COPD
- The changes in PPAR alpha and PGC-1 coactivator mRNA expression were positively correlated with an increase in type I fibre type proportion in COPD.

These findings would need confirming in a larger randomised controlled study with a comparative healthy sedentary age matched population. The activity of the genes should be assessed by the addition of the protein measurements. The existence of a PPAR delta agonist and positive animal studies of performance enhancement make this an interesting area to pursue.

The similar skeletal muscle PPAR and PGC-1mRNA expression between COPD and CHF is further supportive evidence of the similarity of skeletal muscle in COPD and CHF.

The next chapter continues the theme of comparing the systemic manifestations of COPD and CHF.

- Neurohumoral activation is a pathological hallmark of CHF. A biomarker is used to compare neuroendocrine activation between COPD and CHF and the effect of exercise training on this biomarker is described in both diseases
- Systemic inflammation is associated with COPD and CHF and a different biomarker is used to assess the effect of exercise training in both conditions

Chapter Eight

A comparison of the effects of exercise training on plasma N-terminal Brain Natriuretic Peptide (NTBNP) and C-reactive protein (CRP) between COPD and CHF.

Background

- The work described in chapter five demonstrated that combined training programmes for COPD and CHF are feasible and effective
- **The previous chapter** investigated a potential mechanism behind the improvements in skeletal muscle dysfunction seen with exercise training in COPD and CHF
- **This chapter** continues the theme of comparing the systemic manifestations of COPD and CHF.

Neurohumoral activation is a pathological hallmark of CHF and is associated with a worse prognosis (189). There is evidence suggesting that patients with COPD may also have increased neurohumoral activation (review)(204).

Patients with COPD have an increased cardiovascular mortality after adjustment for smoking (525). Cardiovascular mortality is slightly higher than mortality due to pulmonary causes (526). The risk increases with worsening lung function assessed by FEV₁. The contributory mechanisms were reviewed by Macnee et al included systemic inflammation, oxidative stress, hypoxia, increases SNS activity, vascular dysfunction,

connective tissue dysfunction and accelerated ageing and atherosclerosis (128). Recently increased arterial stiffness and high blood pressure has been reported in COPD compared to age matched controls (527). There is good evidence that patients with COPD have an associated cardiovascular mortality. Macnee raised the evidence supporting increased SNS activity in COPD. The biomarker plasma brain natriuretic peptide is discussed in more detail subsequently, it is associated with a worse prognosis in both CHF and COPD (192;528). The relevant biochemistry and physiological mechanisms are discussed next.

Brain natriuretic peptide (BNP) was first isolated from porcine brain in 1988 which is where the name originated (190). The BNP gene is on chromosome one and encodes for a 108 amino acid prohormone; proBNP (191). It is cleaved by Furin, a proteolytic enzyme to N-terminal pro-brain natriuretic peptide (NTBNP) and biologically active BNP (32AA). BNP is secreted from the cardiac myocytes in response to stress and stretch. Only a small amount of BNP is stored in granules, but an increase in gene expression increases production quickly in response to stretch. In a normal heart the atria are the main source of both atrial natriuretic peptide (ANP) and BNP. In chronic myocyte stretch there is upregulation of ventricular natriuretic peptide and this occurs in both left and right ventricular dysfunction. NTBNP has a longer half life and is probably more sensitive than BNP as it is present at higher levels (191;529). NTBNP is predominantly excreted by the kidneys. The biological effects of the BNP are diuresis, vasodilatation, inhibition of renin and aldosterone production and of cardiac and vascular myocyte growth (191).

Both BNP and NTBNP are independent prognostic indicators in CHF (192;194), but NTBNP maybe superior to BNP (530). The use of the BNP's as a diagnostic tool for CHF has been extensively investigated. Their main utility is in a 'rule out' approach for CHF rather than a 'rule in'(531). Although both can be used NTBNP is probably more sensitive in detecting mild disease (529;532;533). Both BNP and NTBNP are affected by gender, age, and creatine clearance (530).

In the study by Tsutamota et al, there was a positive correlation between levels of noradrenalin and BNP ($r=0.67$, $P<0.0001$) indicating that sympathetic nervous system activation increases the levels of BNP either directly or indirectly in CHF (192). Therefore measuring BNP is either a direct or indirect assessment of neurohumoral activation.

Although the majority of research using BNP's as biomarkers has involved patients with left ventricular dysfunction there have been a few studies investigating their role in patients with right ventricular failure. A small study reported higher levels of BNP in patients with chronic respiratory failure with cor pulmonale compared to those without and higher than patient controls with lung cancer and healthy controls (195). More recently BNP has been shown to be able to identify pulmonary hypertension in a variety of chronic lung diseases (both obstructive and restrictive) with a sensitivity of 0.85 and specificity of 0.88 (528). A higher BNP level ($>0.33\text{pg/ml}$) was associated with a worse prognosis in patients with chronic lung disease. All patients had a left and right cardiac catheter so left ventricular disease had been excluded.

Patients with a larger reduction in BNP had a better prognosis in the 'Valsartan and heart failure trial' (534) and a subsequent study suggested that serial measurements

may better reflect mortality than a single reading (535). This was not confirmed though in a larger trial of pharmacological therapy titrated against symptoms vs. BNP(536).

There is some evidence that exercise training in CHF is associated with a reduction in left ventricular remodelling ((281;281;282;537;538). Exercise training is associated with a favourable prognosis reported from a meta-analysis (274), although this needs confirming in a large randomised controlled trial. One hypothesis for the study described in this chapter was that exercise training may reduce NTBNP levels in CHF. Data suggests a trend towards an improved prognosis with exercise training in COPD (271;272).

Prognosis is negatively affected by the presence of systemic inflammation in COPD and CHF. Plasma C-reactive protein is (CRP) has been shown to be associated with a worse prognosis in CHF and mild to moderate COPD (539;540). However this was not confirmed in a prospective study of patients with moderate to severe COPD (541). CRP is an acute phase protein and is a sensitive marker of inflammation. It is produced by hepatocytes under the control of IL6. Levels increase by six hours after a stimulus, with a peak at 48hrs and the half life is 19hrs. It is a calcium dependent ligand-binding protein. Plasma levels of CRP are associated with coronary events in the normal population (537).

This chapter describes pilot work investigating whether the biomarkers 1) NTBNP and 2) CRP were affected by exercise training in COPD or CHF reflecting 1) either anti- left or right ventricular remodelling or a reduction in neurohumoral activation and 2) modulation of systemic inflammation. If they were reduced this may reflect an improved prognosis. Baseline NTBNP values were desirable to further

characterise the two populations; COPD and CHF studied in chapter five. The response of NTBNP with exercise was assessed to inform about the stability of the measurement.

This chapter describes

- Plasma levels of NTBNP and CRP in COPD and CHF and the relationship with disease severity and physical performance
- Response of NTBNP to a short bout of exercise in COPD and CHF before and after exercise training
- The effect of exercise training on NTBNP and CRP in patients with CHF – a RCT of exercise rehabilitation vs. normal care
- The effect of exercise training on NTBNP and CRP in patients with COPD – a prospective study of exercise rehabilitation vs. normal care

Methods

The patients with CHF were the same patients recruited for the randomised controlled trial of pulmonary rehabilitation vs. normal care described in chapter four. The patients with COPD were the same recruited for the comparative study of pulmonary rehabilitation between COPD vs. CHF. Another group of patients with COPD were recruited as per the criteria described in chapter two, for seven weeks of normal care. The patients were recruited between March 2006 and May 2006 from the patients with COPD that had completed PR in 2004.

Intervention

Patients with CHF were randomised to seven weeks of pulmonary rehabilitation or seven weeks of normal care. Both interventions are described in chapter two. Patients with COPD were recruited to pulmonary rehabilitation for the observational comparative trial between COPD and CHF and a further group of COPD were recruited for seven weeks of normal care.

Outcome measures

Venous blood for the analysis of serum N-terminal pro Brain Natriuretic Peptide and C-reactive peptide was sampled before and immediately after the cardiopulmonary exercise test (CPX), before and after the intervention period for patients with COPD and CHF. Twenty mls venous blood was sampled at rest and immediately after exercise from a 14G cannula. It was drawn into prechilled tubes with 0.25mls aprotinin and 80µmls of 1M EDTA. After centrifugation at 3000rpm for 20 mins at 4°C, plasma was separated and stored at -80°C until analysis.

All the analysis was undertaken by Pauline Quinn supervised by Professor LL NG from the Department of Cardiovascular sciences, University of Leicester, Leicester UK. The details of the analysis of NTBNP and CRP are in appendix VII.

Other outcome measures before and after the intervention period

A cardiopulmonary exercise test (CPX), incremental Shuttle Walk test (ISWT), isometric quadriceps strength and body composition were all assessed as per the methods described in chapter two.

Statistical analysis

The baseline NTBNP and CRP levels were not normally distributed. Any comparison with the baseline values used non parametric tests.

The NTBNP and CRP levels were log transformed and changes with an intervention were assessed by the appropriate parametric tests. Pearson's correlation coefficient was used for the LOG transformed data when comparing to another normally distributed variable and Spearman's correlation coefficient when the other variable was not normally distributed.

Results

The results are presented in four sections

- 1) the baseline COPD and CHF results and correlation with disease severity and physical performance
- 2) the effect of maximal exercise on plasma NTBNP in COPD and CHF
- 3) the effect of exercise training on plasma NTBNP and CRP in CHF
- 4) the effect of exercise training on plasma NTBNP and CRP in COPD

39/55 patients with COPD and 41/44 patients with CHF had venous blood sampling. There was a delay in the availability of the reagents which meant that the first 13 patients with COPD were not recruited to this part of the study. There were six patients that did not have blood analysed; three in each group. The reasons were;

- i x1 broken tube in the centrifuge
- ii x1 delay in samples being frozen after centrifuge therefore they were discarded
- iii x2 unable to gain venous access
- iv x1 declined

There was no significant difference between the baseline demographics and exercise performance between the patients with COPD and CHF (table 7.1). As noted in chapter five the FFMI was significantly higher in patients with CHF than COPD.

Baseline plasma NTBNP in COPD and CHF

The baseline plasma NTBNP (fmol/ml) level was significantly lower in COPD compared to CHF; COPD 100 (57 to 251)fmol/ml vs. CHF 935 (350 to 1988)fmol/ml $p < 0.0005$ (figure 8.1). Two patients with CHF had an undetectable plasma NTBNP

level. Four patients with COPD had a [NTBNP] >500. Their mean (SD) FEV₁ percent predicted was similar to the whole group; 45.6 (20.1)% compared to 41.8 (15.8)%.

	<i>COPD n=39</i>	<i>CHF n=41</i>	<i>p value</i>
Age (yrs)	70.8 (10.4)	69.1 (8.7)	0.428
Gender	66% male	49% male	0.121
FEV ₁ % predicted	41.8 (15.8)	79.8 (21.8)	<0.0005*
LVEF %		33.5 (9.3)	
MRC scale grade †	3.0 (3.0 - 4.0)	2.0 (2.3 – 4.0)	0.101
FFMI (kg/m ²)	17.0 (2.5)	19.4 (2.8)	<0.0005*
Quadriceps Strength (Nm)	116 (48)	112 (47)	0.723
ISWT (m)	229 (145)	230 (123)	0.180
Peak VO ₂ (L/min)	0.96 (0.37)	0.86 (0.30)	0.961

*p<0.05, Mean (SD) unless †median IQ range

Left ventricular ejection fraction (LVEF), Fat free mass index (FFMI), Incremental shuttle walk test (ISWT), Peak VO₂ derived from the CPX on a cycle ergometer.

Table 8.1. Comparison of the baseline demographics and physical performance between patients with COPD and CHF

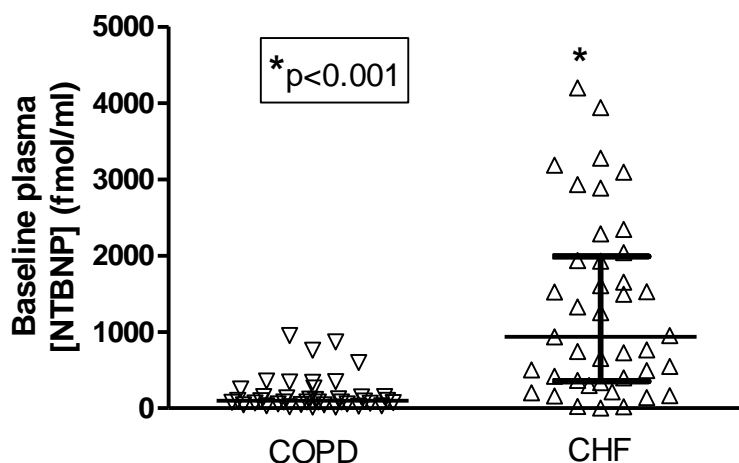


Figure 8.1. Comparison of the baseline plasma NTBNP level between COPD and CHF

Correlation between plasma NTBNP and disease severity, physical performance and functional status in COPD and CHF

Table 8.2 shows the above results of the correlations between plasma NTBNP and the above measurements in COPD and CHF. Plasma NTBNP correlated significantly and positively with age, and negatively with disease severity, degree of disability due to dyspnoea and peak exercise capacity for CHF. There was a trend towards a positive correlation with age and an inverse correlation with peak exercise capacity in COPD.

Quadriceps strength was moderately inversely correlated with plasma NTBNP in patients with COPD²⁹, but there was no correlation in patients with CHF (figure 8.2).

²⁹ When the outlier with isometric quadriceps strength of 261Nm was removed the significance decreased -0.319 p=0.058

	<i>COPD</i>		<i>CHF</i>	
	LOG ₁₀ plasma [NTBNP] fmol/ml	p value	LOG ₁₀ plasma [NTBNP] fmol/ml	p value
Age (yrs)	0.299	0.064	0.354	0.023*
FEV1 % predicted	-0.125	0.453		
LVEF %			-0.432	0.012*
FFMI (kg/m ²)	-0.245	0.133	-0.336	0.032*
Quadriceps strength (Nm)	-0.378	0.021*	-0.118	0.468
ISWT (m)	-0.093	0.577	-0.166	0.305
Peak VO ₂ (L/min)	-0.315	0.051	-0.510	0.001*
MRC dyspnoea scale grade	-0.092	0.583	0.335	0.032*
NYHA class			0.472	0.002*

*p<0.05, N-terminal Brain Natriuretic Peptide (NTBNP), left ventricular ejection fraction (LVEF), Fat free mass index (FFMI), incremental shuttle walk test (ISWT), peak VO₂ derived from the CPX on a cycle ergometer

Table 8.2. Correlation coefficients between plasma NTBNP and baseline demographics, disease severity, physical performance and functional status for COPD and CHF

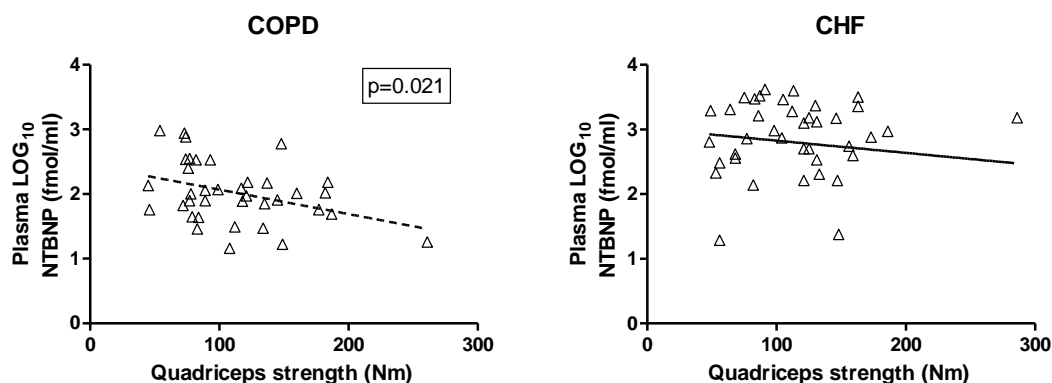


Figure 8.2. Scatter plot comparing isometric quadriceps strength with plasma NTBNP in COPD and CHF

There was a moderate but negative correlation between the resting heart rate and plasma NTBNP in patients with COPD and no correlation in CHF (figure 8.3). The heart rate at the end of exercise had no correlation with plasma NTBNP in neither COPD nor CHF; -0.027 $p=0.842$ and -0.049 $p=0.767$. Neither resting nor end-exercise oxygen saturation were correlated with plasma NTBNP in COPD; 0.283 $p=0.085$ and 0.031 $p=0.853$.

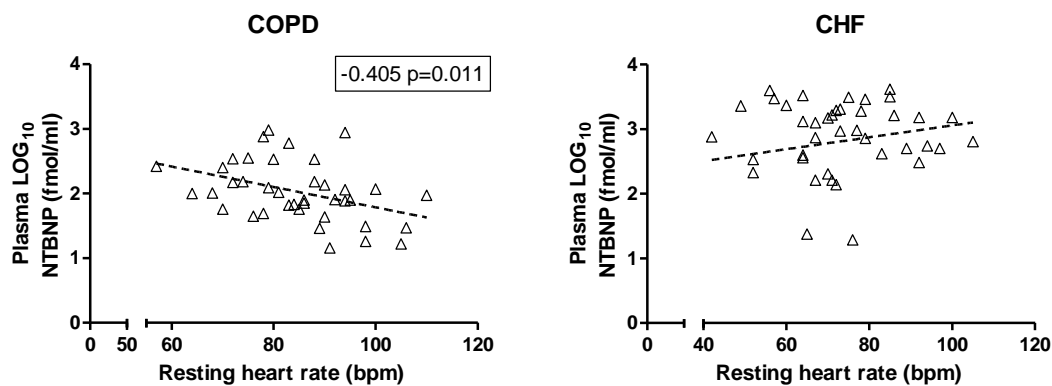


Figure 8.3. Graph to show the relationship between resting heart rate and [NTBNP] in COPD and CHF

Baseline plasma CRP level in COPD and CHF

The median (IQ range) plasma CRP level was significantly higher in CHF than COPD; 4.5 (0.9 to 4.5)mg/ml vs. 3.6 (2.7 to 5.7)mg/ml $p=0.02$ (figure 8.4). There was no correlation between plasma LOG_{10} NTBNP and plasma LOG_{10} CRP in CHF; 0.234 $p=0.141$ or COPD; 0.088 $p=0.596$.

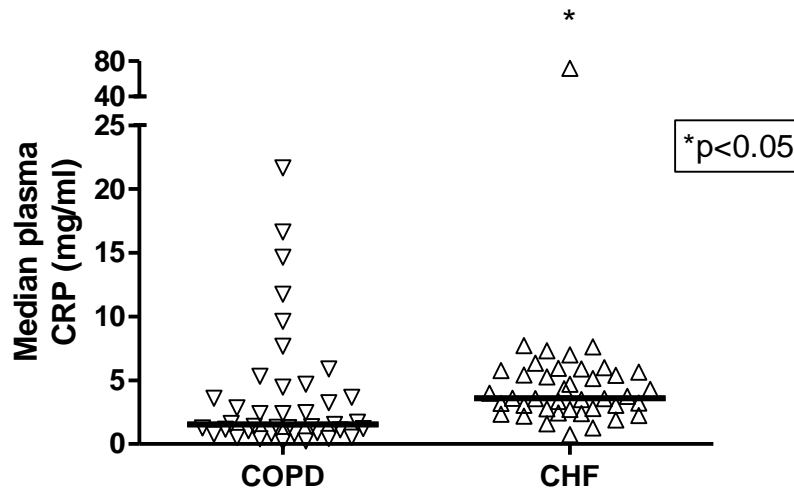


Figure 8.4. Graph to show the range of plasma CRP levels for COPD and CHF

Correlation between plasma CRP and disease severity, dyspnoea and physical performance in COPD and CHF

There was a significant moderate correlation between plasma CRP and disease severity and functional status assessed by either the NYHA classification or MRC dyspnoea scale and a trend towards a weak correlation with exercise capacity in patients with CHF (table 8.3). Plasma CRP did not correlate with disease severity, functional status, quadriceps strength or exercise capacity in patients with COPD.

	<i>COPD</i>		<i>CHF</i>	
	LOG ₁₀ plasma [CRP] mg/ml	p value	LOG ₁₀ plasma [CRP] mg/ml	p value
Age (yrs)	0.044	0.788	-0.050	0.756
FEV ₁ % predicted	-0.125	0.453		
LVEF %			-0.350	0.046*
FFMI (kg/m ²)	0.101	0.540	-0.080	0.618
Quadriceps strength (Nm)	0.083	0.626	-0.094	0.564
ISWT (m)	-0.114	0.495	-0.263	0.101
Peak VO ₂ (L/min)	-0.035	0.831	-0.292	0.079
MRC dyspnoea scale grade †	0.069	0.680	0.390	0.012*
NYHA class			0.386	0.013*

*p<0.05, pearson correlation coefficient except for † spearman's correlation coefficient
C-reactive protein (CRP), left ventricular ejection fraction (LVEF), Fat free mass index (FFMI),
incremental shuttle walk test (ISWT), peak VO₂ derived from the CPX on a cycle ergometer,
New York Heart Association (NYHA).

Table 8.3. Correlation coefficients between plasma CRP and baseline demographics,
disease severity, physical performance and functional status for COPD and CHF

Response of plasma NTBNP to exercise in COPD and CHF

There was no mean change in plasma LOG_{10} NTBNP (fmol/ml) after a maximal exercise test (CPX) for COPD; 2.04 (0.45) to 2.02 (0.60) $p=0.733$ or CHF; 2.77 (0.76) to 2.78 (0.76) $p=0.444$. There was a small amount of individual variability (figure 8.5).

After seven weeks of training all patients performed another CPX with NTBNP levels measured before and immediately after the exercise test. In patients with COPD there was no significant change in the LOG_{10} NTBNP level (fmol/ml) with exercise after PR; 2.07 (0.44) to 1.94 (0.15) $p=0.128$ although the trend was towards a lower NTBNP level. In patients with CHF, there was a significant increase in LOG_{10} NTBNP (fmol/ml) with exercise after PR; 2.63 (0.87) to 2.67 (0.86) $p=0.002$.

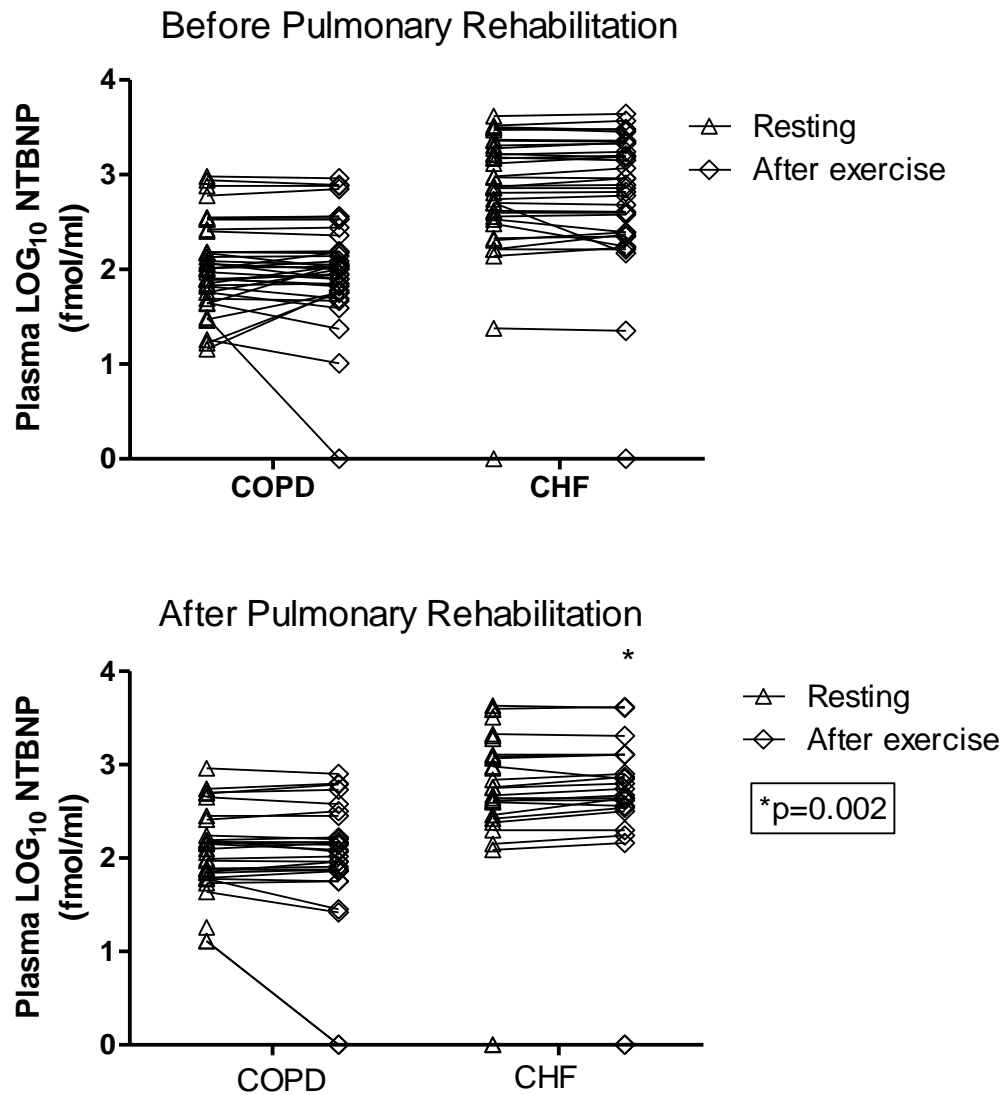


Figure 8.5. Individual variability of plasma NTBNP levels before and after exercise in COPD and CHF, before and after pulmonary rehabilitation

The effects of exercise training on plasma NTBNP in CHF

The results of the randomised controlled trial of pulmonary rehabilitation vs. normal care were described in chapter four. The patients who completed seven weeks of exercise training (pulmonary rehabilitation [CHF-PR]) made significant improvements in exercise performance compared to normal care; mean change in ISWT performance; 62 m vs -6 m $p < 0.0005$ respectively. 24/27 patients in the CHF-PR group and 16/17 patients who completed seven weeks of normal care (CHF-NC) had complete pairs of before and after plasma NTBNP levels. The baseline plasma median (IQ range) NTBNP (fmol/ml) levels were similar between the two groups; 943.8 (397.4 to 2116.4) vs. 429.2 (249.2 to 1570.7) $p = 0.132$.

There was no change in resting plasma LOG_{10} NTBNP level with either PR; 2.76 (0.83) to 2.77 (0.83) $p = 0.901$ or NC; 2.66 (0.63) to 2.68 (0.55) 0.772 (figure 8.6).

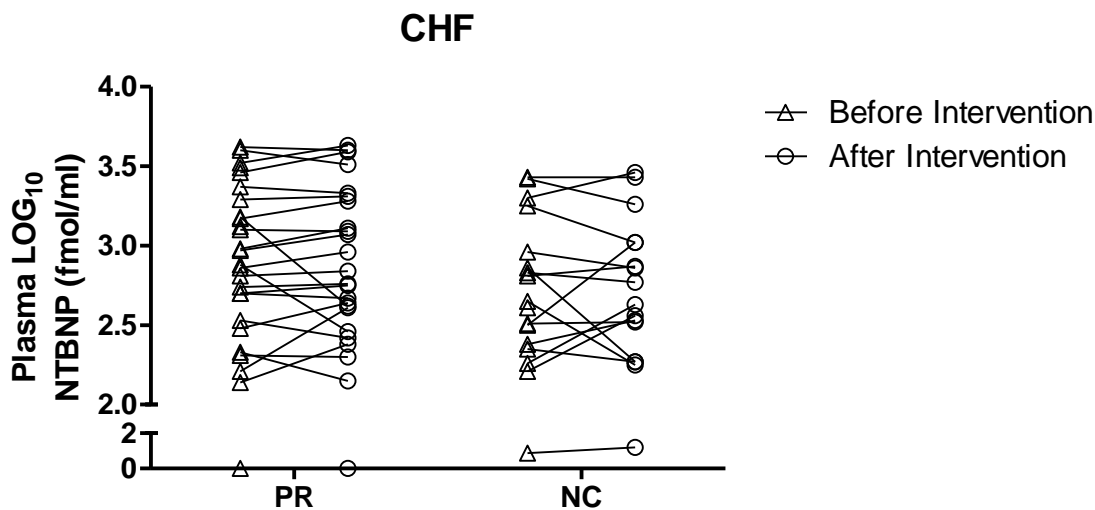


Figure 8.6. Graph to show the individual variability of plasma NTBNP levels before and after pulmonary rehabilitation (PR) and normal care (NC).

The effect of exercise training on plasma CRP in patients with CHF

There was no significant difference between the baseline median (IQ range) plasma CRP (mg/ml) levels for either group; 3.86 (2.75 to 5.81) vs. 3.74 (2.27 to 5.13) 0.370. There was no change in plasma LOG_{10} CRP levels with either exercise training (PR); 0.62 (0.19) to 0.59 (0.35) $p=0.736$ or normal care (NC); 0.44 (0.39) to 0.48 (0.42) $p=0.508$ (figure 8.7).

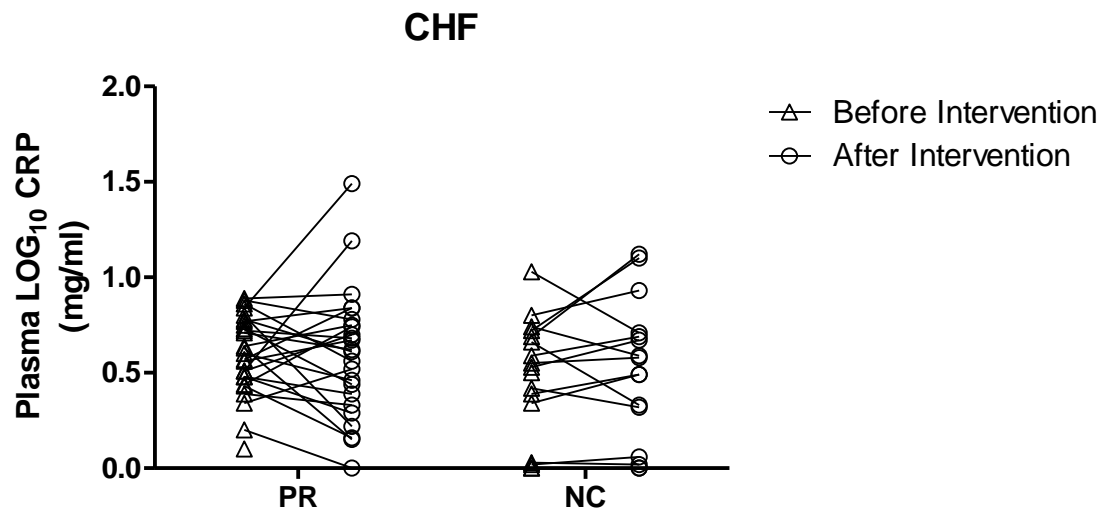


Figure 8.7. Graph to show the individual variability of plasma CRP levels before and after pulmonary rehabilitation (PR) and normal care (NC).

The effect of exercise training on plasma NTBNP in patients with COPD

39/55 patients with COPD who were recruited for the observational comparative trial of PR between COPD and CHF (described in chapter five) had venous blood sampling before PR (COPD-PR). 14 patients with COPD were recruited to seven weeks of normal care (COPD-NC).

The median (IQ range) plasma NTBNP (fmol/ml) was similar between the two groups; COPD-PR 99.7 (57.3 to 250.6) fmol/ml vs. COPD-NC 116.4 (71.9 to 215.3) fmol/ml $p=0.672$. The median (IQ range) plasma CRP level for the COPD-PR group was 1.53 (0.89 – 4.37) ng/ml. The COPD group receiving normal care did not have plasma CRP analysed³⁰.

30 patients completed PR with complete paired venous sampling and 14 patients completed normal care. There was no significant difference in the baseline demographics and exercise performance between the two groups (table 8.4). The mean (SD) ISWT improved from 250 (121)m to 313 (314) $p<0.0005$ for the COPD-PR group. The ISWT was unchanged before and after normal care (COPD-NC); 226 (74) to 224 (76) $p=0.904$.

The mean (SD) plasma LOG_{10} NTBNP level was unchanged after seven weeks of exercise training; 2.02 (0.46) to 2.05 (0.45) fmol/ml $p=0.642$ and was also unchanged after seven weeks of normal care; 2.06 (0.45) to 2.09 (0.49) $p=0.595$. The individual variability is shown in figure 8.8.

³⁰ Originally the NTBNP samples were analysed in two separate batches and this led to inaccuracies in the results so they were reanalysed altogether. It was unnecessary to repeat the CRP analysis, but the samples for the normal care group were not available at the first analysis.

	<i>COPD-PR</i> <i>n=30</i>	<i>COPD-NC</i> <i>n=14</i>	<i>p</i>
Age	67.9 (8.0)	66.4 (8.4)	0.569
Gender	46.6%	42.8%	0.831
FEV1 % predicted	42.6 (16.5)	43.2 (14.8)	0.767
MRC grade†	3 (3-4)	3 (3-4)	0.950
ISWT (m)	250 (121)	226 (74)	0.488

* $p < 0.05$. † median (IQ range). Pulmonary rehabilitation (PR), normal care (NC), Incremental Shuttle Walk Test (ISWT).

Table 8.4. Comparison of the baseline demographics and exercise performance between patients with COPD completing PR or NC

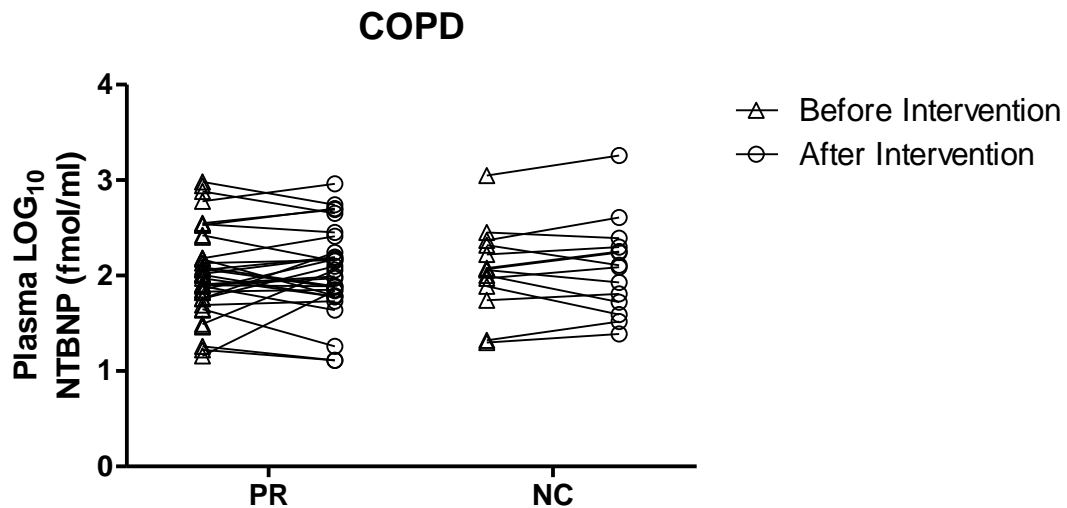
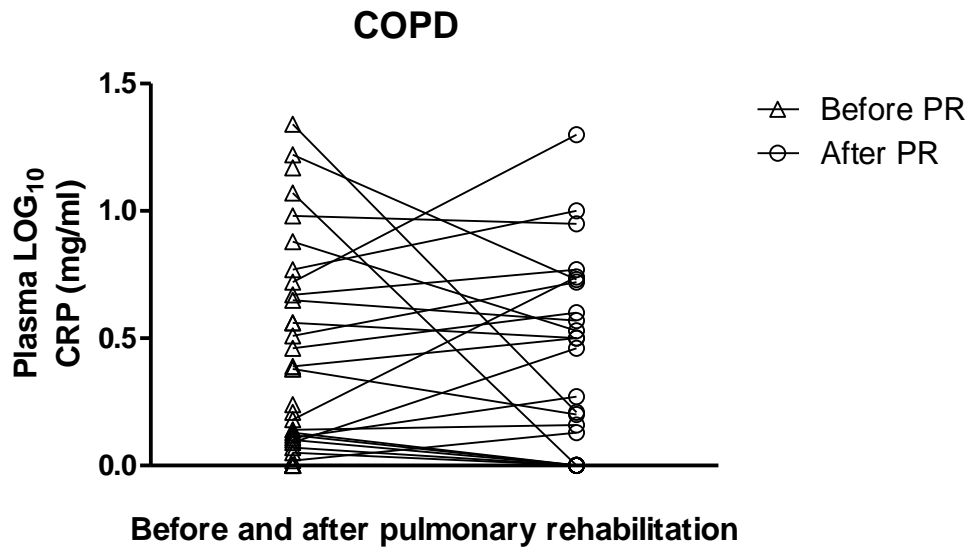


Figure 8.8. Graph to show the individual variability of the change in plasma NTBNP with pulmonary rehabilitation and normal care.

The effects of exercise training on plasma CRP in patients with COPD

There was no change in the mean (SD) plasma LOG_{10} CRP level with PR; 0.33 (0.49) to 0.26 (0.50) $p=0.369$. The individual variability is shown in figure 8.9.



Discussion

There are similar systemic manifestations between COPD and CHF. Neurohumoral activation although more commonly associated with CHF may also be present in COPD. Systemic inflammation has been reported in both conditions. The presence of neurohumoral activation or systemic inflammation is associated with a worse prognosis in CHF. Patients with COPD have an increased cardiovascular mortality even accounting for confounding factors such as age and smoking. The current work reports the baseline plasma NTBNP and CRP levels, and the response both to an exercise challenge and to seven weeks of exercise training in COPD and CHF.

The patients with CHF had a significantly higher baseline plasma NTBNP level than patients with COPD supporting an overall difference in the underlying pathology. Two patients with CHF had an undetectable NTBNP level. One patient had a BMI of 54 and obesity is associated with lower levels of NTBNP (542). The left ventricle function had been reported as moderately impaired in both patients. When they were reanalysed by the single operator (described in chapter two) the LVEF could not be assessed accurately in the patient with the BMI of 54 and the other LVEF was 55%³¹.

There are no normal reference values for the plasma NTBNP levels from the same laboratory. However, median (range) levels were 42.5(5.7 – 1166.4) fmol/ml in healthy subjects which is slightly lower than the median for the COPD group in this study 99 (14.5 – 950.7)fmol/ml (543). The levels are affected in healthy subjects by age, gender (higher in females) and heart rate (544). In one study an NTBNP level <160

³¹ This patient had significant breathlessness on exertion with normal lung function and neither CVS nor ventilatory limitation to exercise on the CPX with an adequate effort. An LVEF of between 35-60% is considered mild heart failure by some category's.

pg/ml made a diagnosis of symptomatic LVSD less likely (545)³². In healthy subjects aged <50yrs the 99th percentile is 88 ng/ml for men and 153ng/ml for females. There is no data for the negative predictive value of NTBNP in right heart failure (the study by Leuchte et al used BNP).

The NTBNP level correlated with peak exercise capacity (peak VO₂) and functional status in CHF which supports previous studies. Williams et al described a correlation between peak VO₂ and plasma NTBNP level of $r=0.64$ $p<0.001$ (546) and Kruger et al described a similar correlation of $r=0.54$ $p<0.001$ (198). The mean age of these patients was 55yrs and 60 yrs respectively, but the relationship is still present in the older population of the current study. The data from the current study also showed a significant correlation between NTBNP and functional status (NYHA class). However there was no relationship with ISWT distance. Hogenhuis et al showed a weaker relationship between BNP and NYHA class in 229 patients with CHF $r=0.20$ $p<0.01$ and no correlation between the six minute walk test distance and plasma BNP level (547).

In the COPD group there was a trend towards a weak correlation between NTBNP and exercise capacity, but no relationship with functional status. There was a moderate correlation between NTBNP and quadriceps strength³³. This was not seen in the CHF group although there was a weak correlation with FFMI. The plasma CRP level did not correlate with quadriceps strength in COPD or CHF and there was no correlation between NTBNP and CRP levels in either group. This does not support systemic inflammation as a potential link between the NTBNP level and quadriceps strength.

³² The values fmol/ml from the laboratory for the current study are very similar to the Roche Elecys NTBNP assay pg/ml

³³ This became a trend only, with the removal of one outlier and therefore would need confirming in a larger study

The negative relationship between resting heart rate and NTBNP level in COPD is not easily explained. It became non significant when the two patients with low NTBNP levels and a resting heart rate of >100 bpm were removed, but they were not obvious outliers. The lack of relationship between resting heart rate and NTBNP in CHF is perhaps explained by beta blockade therapy. In healthy subjects NTBNP increases with resting heart rate. The majority of the patients with COPD were on long acting beta agonists and some were on long acting anticholinergics, both of which can increase the heart rate. This might explain some of the variability. If patients with COPD had overstimulation of the sympathetic nervous system by neurohumoral activation then a positive relationship between resting heart rate and NTBNP would have been expected. There was also no relationship between peak heart rate and NTBNP level. If the NTBNP level reflected left or right ventricular dysfunction or pulmonary hypertension in the COPD group then a positive relationship may have been expected, although this was also not seen in the patients with CHF. Both the heterogeneity of COPD and poor characterisation of the patients, in this study regarding left and right heart function, limit further interpretation.

Increased sympathetic nervous system activity has been reported in patients with chronic lung disease. In a small study, patients with COPD or pulmonary fibrosis and respiratory failure, the muscle sympathetic nervous activity (MSNA) was higher than healthy controls (206). In primary pulmonary hypertension there is increased MSNA and this did correlate with resting oxygen saturation, but it did not fully correct to normal with hyperoxia (548). BNP and resting heart rate are possibly not specific enough

markers of neuroendocrine activation and more detailed assessments are probably necessary.

The current study showed there was no overall change in plasma NTBNP after a maximal exercise test for COPD or CHF. This supports other data in CHF reporting no overall change in BNP levels with exercise (549;550). After exercise training there was no change in NTBNP after exercise in COPD, but a small significant increase was seen in CHF³⁴. The CPX results after PR were discussed for COPD and CHF in chapter five; in summary there was no improvement in peak exercise capacity (peak VO₂), but there was a significant increase in exercise duration (>30 secs) with exercise training. Venous sampling at isotime would have been better to assess whether there was any modulation in the exercise response after training. The increase in NTBNP at peak exercise could simply be reflecting the increase in work.

In some patients with COPD and CHF the NTBNP level decreased with exercise and this was more evident in COPD after training. A decrease in BNP level with exercise has previously been reported in 16% of a cohort of patients with severe CHF (550). The patients with a decrease in BNP with exercise were older and had more severe disease (higher NYHA class) in that study. The mechanisms postulated were that the synthetic capacity of the ventricles might be overwhelmed and therefore lead to a state of relative deficiency or that there was a higher clearance of BNP by enhanced degradation of BNP by neutral endopeptidase (NEP). Although the enzyme is concentrated in the kidneys, the renal function was similar between the patients who had an increase and a decrease in BNP to exercise in the study by Kruger. NEP is also concentrated in the lung so there maybe increased release during exercise leading to

³⁴ Data logged

increased breakdown and maybe more common in patients with COPD. This is entirely speculative and would need further investigation.

The increase seen in CHF and not COPD after training may just simply be a reflection of the LVSD in all the patients with CHF and an increase in cardiac myocyte stretch. In COPD only a subgroup would have cor pulmonale and a potential increase in NTBNP with exercise through increased cardiac myocyte stretch.

Other studies have shown an increase in BNP with exercise in CHF. One of the few mechanistic studies investigating the change in BNP with exercise suggested that impaired left ventricular function was the main factor leading to an increase in BNP (551). Two groups were compared; dilated cardiomyopathy vs mitral stenosis with similar pulmonary wedge pressures and BNP increased more with exercise in the patients with dilated cardiomyopathy. A further study showed that symptomatic patients had a larger increase in BNP with exercise than patients with asymptomatic LVSD³⁵(552). However BNP at peak exercise did not improve risk stratification in a subsequent study (553). The differences in the outcome between the various studies discussed are likely due to small numbers and different disease severity.

In young healthy subjects the response of BNP to exercise has been shown to both increase with exercise (554) and stay the same (550;555). In healthy elderly subjects BNP has been shown not to increase after maximal exercise (556). NTBNP was significantly increased after a marathon and a mountain bike marathon in athletes (557). This increase was not related to an increase in cardiac troponin and therefore was less likely to be caused by myocardial damage. The authors postulated that the raised NTBNP

³⁵ Left ventricular systolic dysfunction

may have 'cytoprotective and growth regulating effects'. This has yet to be further evaluated in healthy subjects or CHF.

There was no change in NTBNP level with seven weeks of high intensity exercise training in either COPD or CHF. To date this is the first report of the effect of exercise training in COPD on NTBNP. This data supports the safety of exercise training in these groups as there was no overall increase in NTBNP representing myocardial stress from either left or right ventricular dysfunction. Subsequent to the current study being conducted Conraads et al reported a significant reduction in NTBNP levels with four months of combined resistance and endurance training in CHF compared to four months of normal care (558). There was a significant decrease in left ventricular end-systolic diameter with training. The numbers of patients were similar to the current study, but they were younger and fitter (peak VO_2 18.4 ml/min/kg). A further RCT reported similar significant reductions in NTBNP after 3 months of supervised training at 60-70% peak VO_2 , three times per week (559). The main modality was cycling. Passino et al reported reductions in NTBNP with nine months of exercise training in CHF and also showed modulation of the sympathetic nervous system with reduced levels of noradrenalin after exercise training (295). The improvements in peak VO_2 were correlated with the reduction in NTBNP. However the reduction in NTBNP was not correlated with the improvement in LVEF, but was correlated with the reduction in noradrenalin supporting that exercise training does modulate neurohumoral activation in CHF.

All the reported studies above demonstrated a reduction in NTBNP with exercise training in CHF in contrast with the current study. They were all for a longer duration;

three to nine months than the current study of seven weeks. Serial measurements of NTBNP were not performed in any of the studies to see when the reductions started to occur. The patients were fitter; peak VO_2 14 to 18 ml/min/kg compared to <11 ml/kg/min for the current patients. In contrast one group recruited more disabled patients with a mean peak VO_2 of 11 ml/kg/min and showed no change in NTBNP after 18 weeks of training despite improvements in exercise capacity. The effect of exercise training on neurohumoral activation may alter depending on the degree of disability. This would need confirming in a larger trial.

Plasma CRP was unaltered with short term endurance training in COPD and CHF. In the introduction (chapter one) the variable results from studies reporting the effect of serum inflammatory markers (TNFalpha and IL6) were described. The majority of studies were negative. Variable results of skeletal muscle levels of expression of TNFalpha and IL6 from exercise training have also been reported. The changes in the serum and muscle can be dissociated and therefore results cannot be extrapolated.

In COPD, plasma CRP did not correlate with disease severity, functional status or physical performance. This is in contrast with the results Garrod et al reported where plasma CRP was correlated with the MRC grade and six minute walk distance (560). The patients were of a similar age and disease severity compared to the current work and similar subject numbers. In the study by Garrod one patient with a high CRP level at baseline was removed. In the current work four patients with COPD had a plasma CRP level >10 mg/ml. Although the logged data was analysed there is a possibility these patients skewed the data. CRP had a moderate inverse correlation with disease severity in CHF which supports the literature (539). There was one patient with CHF with a very

high CRP level >80mg/ml. They were stable at the time of entry to the study and therefore were included in the data analysis.

There were major limitations of this work. The major limitation to the interpretation of the baseline values of NTBNP in COPD is the lack of characterisation of pulmonary hypertension and cor pulmonale, and the lack of definitive exclusion of LVSD. The lack of normal reference values for the NTBNP levels meant that the absolute values of NTBNP were compared. However it is known that age, gender and creatinine clearance affect NTBNP. These variables were not accounted for which could have affected the data. Plasma NTBNP and CRP are a limited measure of neurohumoral activation and systemic inflammation. More detailed assessments of both processes are needed. CRP is an acute phase protein and more stable measurements maybe appropriate e.g IL6 and fibrinogen. Another limitation was that skeletal muscle levels of TNFalpha and IL6 were not measured.

The medication in the patients with COPD was not standardised which may have affected some of the data. The samples were frozen for longer than planned and for a variable time period as all the samples had to be analysed together. Evidence shows that the results are stable after six months of storage, but some of the samples in the current study were stored for two years. However the data regarding exercise capacity and NTBNP in CHF is entirely in keeping with previous studies which would be unlikely if there was a significant deterioration from storage.

Although the short term training programme used for this work is effective at improving exercise performance and health status longer term training maybe necessary to augment some of the systemic manifestations of these diseases.

In summary the data in **this chapter** has not contributed further to the understanding of if or how neurohumoral activation or systemic inflammation in COPD and CHF are affected by exercise training. Overall NTBNP and CRP plasma levels were unaffected by exercise training in COPD and CHF .The review of the literature in heart failure has shown that in fitter patients exercise training appears to reduce NTBNP levels and this can not solely be explained by improved left ventricular function

The current data has raised the possibility of increased neurohumoral activation in some patients with COPD evidenced by the higher NTBNP levels. The correlation between NTBNP and quadriceps strength in COPD needs confirming, but could be a further contributing factor to skeletal muscle dysfunction. The presence of neurohumoral activation in COPD would be worth further study involving thoroughly characterised patients, more detailed measurements of this process and assessing the prognostic significance. Subsequent larger studies could then investigate whether longer exercise training programmes affect this process.

- The **final chapter** discusses the main findings from this thesis and describes the possible future directions from this work

Chapter nine

Discussion

The aim of this thesis was to investigate whether combined training programmes for COPD and CHF were feasible. Exertional breathlessness and fatigue are common symptoms of COPD and CHF resulting in activity limitation. Both diseases are associated with comparable systemic manifestations including skeletal muscle dysfunction. This is a major contributing factor to reduced exercise capacity associated in both conditions. Exercise training has previously been shown to improve skeletal muscle dysfunction in COPD and CHF. Although pulmonary rehabilitation is integral to the management of COPD, a practical service involving exercise training has not developed in the same way as for CHF.

The hypothesis was that patients with CHF could make similar improvements in exercise performance and health status compared to COPD and that both groups of patients could be beneficially trained together. Two main trials were conducted;

1. A randomised controlled trial of pulmonary rehabilitation vs. normal care in patients with CHF, to explore if the model of PR could be applied to patients with CHF
2. A comparative observational study of pulmonary rehabilitation between COPD and CHF, to explore the feasibility of combined training programmes

The usual outcome measures for PR were applied to patients with CHF to develop generic outcome measures for COPD and CHF. The reproducibility (if not known) was

assessed for the measures of physical performance. The role of aspects of the systemic manifestations behind the improvements with exercise rehabilitation was explored.

Main findings

The study in **chapter four** demonstrated that patients with CHF made significant improvements in exercise performance and health status with pulmonary rehabilitation compared to normal care. The model of pulmonary rehabilitation can therefore be applied successfully to patients with CHF. This supports the literature of the beneficial effects of exercise training in patients with CHF. The training regimen was high intensity endurance training from the outset and was well tolerated. Serial measurements of ISWT and ESWT throughout the seven week training programme showed statistically significant improvements by week four (session 7). This shows potential early physiological improvements with high intensity exercise training.

Patients with COPD and CHF both made similar and statistically significant improvements in exercise performance and health status from a seven week course of pulmonary rehabilitation, described in **chapter five**. This is the first report to-date of a study demonstrating the feasibility of a combined training programme for COPD and CHF. The mean improvement in the ISWT with PR achieved the clinically important difference of the ISWT (reported for COPD) in both groups. Although patients with CHF made significant improvements in health status there was a trend to be lower than for COPD.

The education part of the programme was not adapted for patients with CHF. This part of the programme could be modified to provide all generic lectures. The

education included lectures on disease education and pharmacology. In the UK, community specialist nurses for COPD or heart failure undertake disease education as part of their role. It may not be necessary for disease specific education to also be undertaken during exercise rehabilitation. These services could be structured to complement each other.

Measures of exercise capacity and quadriceps strength were similar between COPD and CHF, supporting previous literature. The improvements in walking distance with PR were similar between the two groups despite some differences in the limitation to exercise (cardiovascular vs. ventilatory). Quadriceps strength correlated with peak and submaximal exercise capacity in COPD and CHF supporting a common limiting factor to exercise.

The presence of skeletal muscle dysfunction in COPD and CHF is well documented and exercise training can improve fibre type proportion towards type I fibres. The data in **chapter seven** demonstrated a lower proportion of type I fibres in COPD and CHF than reports for healthy adults. The subject numbers of CHF were too small to make any further conclusions. There was a trend towards an improvement in type I fibres in COPD with exercise training (as expected). The peroxisome proliferator-activated receptors are regulators of skeletal muscle oxidative capacity and a pilot study of the effect of exercise training on PPAR expression was conducted (chapter seven). PPAR delta mRNA expression significantly increased after exercise training. There is evidence of a beneficial role of skeletal muscle PPAR delta in exercise training in patients with diabetes and from animal models. To-date this is the first description of the changes in skeletal PPAR expression with exercise training in patients with COPD.

Chapter eight described the lack of effect on plasma NTBNP or CRP with exercise training in COPD and CHF. Although reviewing the literature of neuroendocrine activation and systemic inflammation in COPD and CHF added personal understanding of the systemic consequences of these diseases, the data has not furthered the understanding of the mechanisms or effects of exercise training in these groups.

A rehabilitation service includes an assessment, the programme and outcome measurements. The assessment for patients with CHF would need to include the exclusion of exercise induced arrhythmias which is not routinely done for COPD in the UK. This could be done either with a laboratory exercise test or by telemetry for field testing.

The outcome measures commonly used for COPD were applied to CHF. The reproducibility of the ISWT in CHF was reported in **chapter three** in an older group of patients than in previously reported studies. The ISWT is reproducible after a familiarisation test. This was the first report of the use of the ESWT in patients with CHF. A familiarisation test is also necessary.

Improving health status is an important goal of a rehabilitation programme. Self reported questionnaires are easier to administer for a clinical service. The literature supports comparability with interview led questionnaires. A self reported version of the CHQ was developed using a similar format to the CRQ-SR, described in **chapter six**. The questionnaire was reproducible and responsive. It was comparable, but not interchangeable with the CHQ-IL.

The PFSDQ-M assesses the impact on daily activities of breathlessness and fatigue and was originally designed for patients with COPD. It was applied to patients

with CHF described in **chapter six**. It was reproducible, but was not particularly responsive to the effects of pulmonary rehabilitation. There were no direct measures of physical activity for comparison.

The MRC scale has been used to indicate a threshold of disability for when PR maybe beneficial (grades 3-5) in COPD. It specifically assesses the effect of breathlessness on functional status and was therefore applied to CHF (described in **chapter six**). The MRC scale was discriminative for disability in CHF measured by exercise performance and health status. There was no significant difference in LVEF% between the grades supporting the existing literature that the degree of organ impairment has little effect on functional status.

Overall the common outcome measures used for patients with COPD were successfully applied to patients with CHF.

Limitations

The comparative observational study was underpowered for the original power calculation due to the lower numbers of patients with CHF recruited (discussed chapter five). Instead of 80% power, 72% power at the $p < 0.05$ level of significance was achieved. Although the results of the change in the ISWT with PR were very similar for COPD and CHF, the conclusions statistically are less robust.

The main outcome measures were exercise performance and health status. Although the improvements in these outcomes were similar for COPD and CHF, this may not be extended to other outcome measurements. A direct measurement of physical activity would have strengthened the data. A formal outcome measure for the

psychological component of rehabilitation would have also extended the understanding of the rehabilitation process between the two diseases.

A short term training programme was used and it can not be extrapolated that the outcome results would remain similar for longer training programmes. Only short term outcomes were measured and similarly it can not be assumed that the longer term outcomes would be similar for the two diseases.

Predominantly endurance based training was used and the similarities between the outcomes for the two diseases may not be extrapolated for resistance and combined resistance and endurance training.

The study designs for the work described in **chapters three and six** were added to the main study design. Although this was done to increase the scope of the overall project, the individual study designs were compromised because of the main study features. The study designs would have been slightly different if they were the only studies being conducted.

Future work

The work in this thesis supports the view of the similarity of the disability (activity limitation) caused by the comparable systemic manifestations of COPD and CHF. Common training programmes for COPD and CHF are feasible. Currently services for chronic diseases are usually organised around the particular organ involved. The work in this thesis highlights the possibility of targeting service provision around a common disability rather than organ impairment.

There was no economic analysis performed on the current study so the next step would be to investigate if combined training programmes for COPD and CHF provided economies of scale for both conditions. The recognition of diseases that may benefit from exercise training is increasing. It may not be feasible or necessary to set up individual exercise rehabilitation programmes for each disease. Developing generic exercise rehabilitation for exertional breathlessness is a potential solution.

An outpatient rehabilitation programme was used for the studies reported in this thesis. The results may not be extrapolated to other situations. Although exercise rehabilitation is successful for the majority of patients who complete a course, there is a significant dropout rate and a number of patients who decline the service. Other geographical locations may help attendance and compliance e.g community programmes, self management etc. It maybe that rather than individual programmes for different diseases, a range of different programmes for a given disability would be more efficacious or cost-effective.

International health care systems are funded differently, but in the UK resources are limited. Shorter duration programmes enable more patients to have access to the service. In patients with CHF, both the ISWT and ESWT performance had not plateau'd by seven weeks. The optimal length of programme is still unknown. Although short term benefits were seen it is recognised that these are not sustained after two years. Modifying behaviour long term is a difficult therapeutic objective, and further work on how to achieve this is necessary.

Despite the improvements in exercise performance and health status seen in both conditions, quadriceps muscle strength was unchanged. Quadriceps weakness is

associated with a poorer prognosis in both COPD and CHF. The current literature shows muscle strength is improved more with combined strength and endurance training than endurance training alone. However, there is no definitive evidence of an improvement in exercise performance or health status above endurance training alone. Whether improving muscle strength improves prognosis is unknown, but would be worthy of investigation. Improving physical activity is an ultimate goal of exercise rehabilitation. Although beneficial, improvements in exercise performance and health status do not directly translate to improvements in physical activity. Whether combined strength and endurance training programmes improve physical activity more than endurance alone would be worth investigating in both COPD and CHF.

Further work examining the role of the PPARs expression in skeletal muscle of COPD and CHF and the effects of exercise training might be useful. A study including healthy sedentary aged matched controls would be necessary. PPAR delta agonists are available. If the increase in PPAR delta expression in skeletal muscle with exercise training in COPD is confirmed then this could be a potential therapeutic target either on its own or for performance enhancement.

The introduction of this thesis discussed the similarity both in the systemic manifestations and their contributing factors between COPD and CHF, despite the majority of research being conducted separately. Targeting research towards a common disability irrespective of the primary disease may also help improve understanding of the mechanisms and potential therapies.

Targeting service provision for chronic disease around a common disability or symptom could extend from exercise rehabilitation to outpatient medical care. In the UK

patients presenting with exertional breathlessness will have limited investigations by the GP before either being given a diagnosis and management or being referred to a speciality clinic. In the introduction the common co-existence of COPD and CHF was highlighted and this is often under-recognised. A speciality clinic for exertional breathlessness might be diagnostically more accurate. Other aspects of chronic disease management are not disease specific e.g co-morbidity, polypharmacy, nutrition, breathing techniques, psychology, palliation and end of life care, and potentially could all be addressed within one generic multi-disciplinary team for breathlessness.

APPENDICES

Appendix I

Definitions of Chronic Obstructive Pulmonary Disease (COPD) and Chronic Heart Failure (CHF)

COPD

Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007 Sep 15;176(6):532-55

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

Stage I: mild COPD: Characterized by mild airflow limitation (FEV_1/FVC , 0.70, $FEV_1 > 80\%$ predicted). Symptoms of chronic cough and sputum production may be present, but not always. At this stage, the individual is usually unaware that his or her lung function is abnormal.

Stage II: moderate COPD: Characterized by worsening airflow limitation (FEV_1/FVC , 0.70, $50\% < FEV_1$, 80% predicted), with shortness of breath typically developing on exertion and cough and sputum production sometimes also present. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease.

Stage III: severe COPD: Characterized by further worsening of airflow limitation (FEV_1/FVC , 0.70, $30\% < FEV_1$, 50% predicted), greater shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations that almost always have an impact on patients' quality of life.

Stage IV: very severe COPD: Characterized by severe airflow limitation (FEV_1/FVC , 0.70, $< FEV_1$, 30% predicted or $< FEV_1$, 50% predicted plus the presence of chronic respiratory failure). Respiratory failure is defined as an arterial partial pressure of O_2 (PaO_2) less than 8.0 kPa (60 mm Hg), with or without an arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. Respiratory failure may also lead to effects on the heart such as cor pulmonale (right heart failure). Clinical signs of cor pulmonale include elevation of the jugular venous pressure and pitting ankle edema. Patients may have stage IV COPD even if their FEV_1 is greater than 30% predicted, whenever these complications are present. At this stage, quality of life is very appreciably impaired and exacerbations may be life threatening.

Chronic Heart Failure

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008
The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure
2008 of the European Society of Cardiology. *European Heart Journal* (2008) 29, 2388–2442

HF is a syndrome in which the patients should have the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest (Table 3).

A clinical response to treatment directed at HF alone is not sufficient for the diagnosis, but is helpful when the diagnosis remains unclear after appropriate diagnostic investigations. Patients with HF would usually be expected to show some improvement in symptoms and signs in response to those treatments from which a relatively fast symptomatic improvement could be anticipated (e.g. diuretic or vasodilator administration). The major and common clinical manifestations of HF are shown in Table 4.

Table 3 Definition of heart failure

Heart failure is a clinical syndrome in which patients have the following features:

† Symptoms typical of heart failure (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)and

† Signs typical of heart failure
(tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly) and

† Objective evidence of a structural or functional abnormality of the heart at rest (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

Table 4 Common clinical manifestations of heart failure

Dominant clinical feature	Symptoms	Signs
Peripheral oedema/congestion	Breathlessness tiredness, fatigue anorexia	Peripheral oedema, raised jugular venous pressure, pulmonary oedema, hepatomegaly, ascites, fluid overload (congestion), cachexia
Pulmonary oedema	Severe breathlessness at rest	Crackles or rales over lungs, effusion Tachycardia, tachypnoea
Cardiogenic shock (low output syndromes)	Confusion, weakness	Cold periphery Poor peripheral perfusion SBP <90 mmHg Anuria or oliguria
High blood pressure (hypertensive heart failure)	Breathlessness	Usually raised BP, LV hypertrophy, and preserved EF
Right heart failure	Breathlessness, fatigue	Evidence of RV dysfunction, raised JVP, peripheral oedema, hepatomegaly, gut congestion

Appendix II

Patient information leaflet and consent form

APPENDIX III

Home walking diary and description of the peripheral muscle exercises

APPENDIX IV

Questionnaires

Appendix V

**Reporting the peak oxygen consumption (peak VO₂)
and the reproducibility of the two CPX systems using a
biological control**

Reporting the peak oxygen consumption (peak VO₂)

Modern exercise testing systems use rapid response gas analysers to produce breath by breath data. This allows data to be reported by two methods; a rolling breath average or an average over a timed interval. Different approaches for presenting the expired gas data have the potential to affect the absolute results. The absolute peak VO₂ value is one of the criteria used for the assessment of heart transplantation in patients with CHF. An absolute value >14 ml/min/kg suggests that surgery can be safely deferred (561). A mixing chamber was used and expired gas was sampled every 30 seconds. In patients with lung cancer the peak VO₂ forms part of the functional assessment for surgery. A recent study demonstrated a worse outcome with patients with an absolute peak VO₂ of <15ml/min/kg (562). International guidelines for surgical resection for lung cancer recommend either non standard surgery or non operative options for patients with a peak VO₂ <10 ml/min/kg (563). As absolute values of peak VO₂ are included for guidelines in the assessment for surgery, it is important to understand whether the method of reporting the peak VO₂ affects the results.

For the study in this thesis the results for the MSX system had all been reported using a five breath rolling average. When the exercise system was changed to the Zan system only software for a timed interval summary was available. The question raised was whether the data could be combined.

The ATS statement on exercise testing (396) recommends that for systems using a mixing chamber ‘data should be averaged over 30 – 60 seconds’ and for breath by breath data the ‘data should be averaged over 30 – 60 second intervals although 20 second intervals may be acceptable’. There are no references for these

recommendations. It also states that erroneous breaths by swallowing, coughing should not be included. The computer generated reports will include all breaths so this relies on the operator removing these and reanalysing the data. The data is analysed in 30 second averages from the start (zero secs) to the end i.e it is not the final 30 seconds that is analysed. The final data point could be averaged over a range of 1 – 29 seconds and there is no guidance when to use the figure for the previous 30 seconds i.e if only five seconds of data is left then use the data for the previous 30 secs. Rolling breath data will be affected by the breathing frequency so the data ‘smoothing’ will alter as the exercise test progresses.

How the peak VO_2 is reported may potentially affect the absolute value, the reliability or the magnitude of change with an intervention. All these were outcomes for the work in this thesis. Therefore, whether different methods of reporting the peak oxygen consumption (VO_2) influenced 1) the absolute value 2) the stability of repeat testing or 3) the effect of an intervention was investigated.

Methods

24 patients with COPD; 12 male, mean (SD) age 67.0 (8.2) yrs, FEV₁ % predicted 38.6% (14.6) underwent three maximal, symptom limited, incremental cardiopulmonary exercise tests on a cycle ergometer using a 10W/min protocol as described in chapter two (MSX 671). The gas analysis was measured by mass spectrometry and calibrated before each use. The first two tests were performed between one to two weeks apart under the same conditions prior to starting seven weeks of pulmonary rehabilitation (described in chapter two) and the third test was performed within a week of completing the course. The peak VO₂ was calculated by rolling breath averages (1,5 and 9) and by averaged time intervals 10, 20 and 30 seconds from the end of exercise.

Statistical analysis

The different methods used to report peak VO₂ were compared using repeated measures. Repeated measures and Pillai's Trace were used to assess the overall difference between the six methods. Bonferroni's correction factor was applied to adjust for multiple comparisons. Paired t-tests were used to assess the difference in peak VO₂ between the two baseline tests and before and after exercise training. All analysis was completed using SPSS version 14.0

Results

Table Ai. shows the baseline values of VO₂ peak for one exercise test reported six different ways. These ranged from 11.4 – 13.0 mls/min/kg. There was a significant difference between all the values (p<0.001). The pairwise comparisons derived from repeated measures showed there was a significant difference (p<0.05) between each of

the six different methods, except between the 9 breath rolling average and the 10 second summary.

Different methods of calculating the peak VO₂

Method	Rolling breath average			Timed interval average		
	1 breath	5 breaths	9 breaths	10 secs	20 secs	30 secs
Method number	1	2	3	4	5	6
Peak VO ₂ (ml/min/kg)	13.0 (11.8-14.0)	12.0 (10.9-13.0)	11.7 (10.7-12.8)	11.7 (10.7-12.7)	11.5 (10.5-12.5)	11.4 (10.4-12.4)

Mean (95% CI). Peak oxygen consumption (peak VO₂)

Table Ai. Peak VO₂ measurements derived by six methods.

Tables Aii and Aiii show the difference in VO₂ peak, reported by six different methods, between the two baseline tests and before and after training. The change between the two baseline tests ranged from 0.33 to 0.76 mls/min/kg and before and after training -0.12 to 0.31 mls/min/kg. There was no overall difference between these values p=0.807 and p=0.687 respectively. Pairwise comparisons revealed no significant difference between any of the methods for both sets of data.

Different methods of calculating the peak VO₂

	Rolling breath average			Rolling breath average		
	1 breath	5 breaths	9 breaths	10secs	20secs	30secs
Change in peak VO ₂ (mls/min/kg)	0.43 (-0.21 to 1.08)	0.76 (-0.13 to 1.64)	0.38 (-0.13 to 0.97)	0.37 (-0.15 to 0.89)	0.36 (-0.20 to 0.91)	0.33 (-0.23 to 0.89)
†						
p	0.176	0.089	0.187	0.156	0.193	0.239

p<0.05 level of significance, †mean (95% CI), peak oxygen consumption (peak VO₂)

Table Aii. Effect of the different methods of reporting peak VO₂ on the change in peak VO₂ between two baseline exercise tests

Different methods of calculating the peak VO₂

	Rolling breath average			Rolling breath average		
	1 breath	5 breaths	9 breaths	10secs	20secs	30secs
Change in peak VO ₂ (mls/min/kg)	0.08 (-0.42 to 0.57)	-0.12 (-0.94 to 0.71)	0.28 (-0.20 to 0.76)	0.31 (-0.14 to 0.76)	0.25 (-0.23 to 0.73)	0.33 (-0.21 to 0.64)
†						
p	0.757	0.772	0.241	0.166	0.193	0.305

p<0.05 level of significance, †mean (95% CI), peak oxygen consumption (peak VO₂)

Table Aiii. Effect of the different methods of reporting peak VO₂ on the change in peak VO₂ before and after exercise training

Discussion

This data showed that different methods of reporting peak VO_2 significantly affected the absolute value in patients with COPD. The different methods are therefore not interchangeable. The rolling breath data produced higher values than the timed average intervals. This has implications for the standardisation of how the peak VO_2 is reported particularly when absolute values are used as part of assessment for certain surgical procedures.

This supports a subsequent study evaluating the sampling interval in patients evaluated for heart transplant (564). They assessed the effect of the sampling intervals; 15s, 30s and 60s averages, eight breath rolling average and breath by breath. The conclusion was the sample interval did affect the absolute peak VO_2 measurement and the authors recommended using larger rolling averages than single breath by breath analysis, or an interval less than 60 seconds for timed summary data.

Changes in peak VO_2 following repeated testing were independent of the reporting convention. Although the changes with the intervention (PR) were also not affected by the method of reporting peak VO_2 there was not a significant change in the mean value so it can not be extrapolated that large changes with an intervention would be similarly unaffected.

An agreed reporting convention for peak VO_2 would be helpful and a thirty second interval would seem reasonable. When the peak VO_2 is presented in studies as an outcome measure how it has been reported should be documented.

All the data for the main studies is therefore reported from thirty second summary data and the data from the MSX system was reanalysed by thirty second summary averages.

Comparison of the two different CPX systems used for the main studies

For the main studies reported in this thesis the results from a cardiopulmonary exercise test were a secondary outcome measure. Two different systems were used due to mechanical failure of the mass spectrometer. The first system was an MSX with expired gas analysed using a mass spectrometer and the second was a Zan with expired gas analysed using a mixing chamber. A small study was conducted to compare the results of CPX using both systems. The aim was to see if there was any difference between the two systems that needed to be accounted for in the results of the main study.

Methods

A healthy subject that was not actively training was used as a biological control; male aged 21 yrs, 83kg and 187cm. A full CPX using an incremental protocol was performed monthly. To compare the two systems the last three CPX using the MSX system were compared to the first three using the Zan system. The incremental protocol was exactly the same and the gas analysis was presented as one minute summary data. Independent t tests were used to compare the results between the two systems.

Results

Mean (SD)	MSX	Zan	Mean (95% CI) difference	p
VO ₂ max	3.09 (0.05)	3.17 (0.13)	0.08 (-0.15 to 0.31)	0.370
VCO ₂ max	3.51 (0.11)	3.57 (0.04)	0.06 (-0.13 to 0.24)	0.449
VE	95.9 (7.9)	91.1 (7.6)	-4.8 (-19.8 to 9.5)	0.404
Watts	247 (14)	255 (0)	8 (-15 to 31)	0.374
f_{Cmax}	170 (2)	171 (8)	-0.3 (-13.0 to 12)	0.945
RER	1.12 (0.01)	1.12 (0.03)	0.01 (-0.06 to 0.08)	0.746

Table Aiv. Comparison of the results of CPX between the two systems

The mean maximum heart rate and workload for the CPX were similar for both systems. There was no significant difference between each system for the parameters derived by expired gas analysis.

Conclusion

There was no significant difference in the results between the two systems for the healthy control. Based on the these findings the results of the CPX have not been adjusted for the system used, for the main studies presented in this thesis.

APPENDIX VI

**Does body mass index influence the outcome of
pulmonary rehabilitation in patients with COPD?**

Does body mass index influence the outcome of Pulmonary Rehabilitation in patients with COPD?

Evans RA, Hall ME, Steiner MC, Morgan MD, Singh SJ.
 Thorax 2005 Dec; 60 Supp II P40

Introduction

Patients with COPD are a heterogenous population including both obese and cachectic patients. Our Pulmonary Rehabilitation programme involves predominantly endurance walking exercises, which could be influenced by weight. We investigated whether body mass index (BMI) influenced the Incremental Shuttle Walk Test (ISWT) performance and whether it affected the outcome of Pulmonary Rehabilitation.

Methods

We retrospectively analysed data from 395 patients; 220 male, mean (SD) age 69.3 yrs (9.0), FEV₁ 1.05 (SD 0.48)L, BMI 26.5 (5.8), ISWT 176 (112)m. All patients underwent a seven week course of Pulmonary Rehabilitation and performed an ISWT before and after.

Results

Complete data was available in 358 patients. Patients were divided into 5 groups according to BMI shown with the baseline ISWT performance in the chart below.

Group	Grade	BMI	n	Mean (SD) ISWT m
1	Underweight	<20	35	177 (103)
2	Normal	>20-25	151	187 (114)
3	Overweight	>25-30	117	180 (121)
4	Obese	>30-40	77	146 (99)
5	Very Obese	>40	15	185 (98)

There was no significant difference in baseline ISWT distance overall by ANOVA $p=0.126$. However, post hoc analysis correcting for multiple comparisons with LSD showed the obese group had a significantly lower ISWT performance than the overweight and normal weight patients $-41m$ $p=0.045$ and $-34m$ $p=0.009$ respectively. The mean (95% CI) improvement in ISWT with rehabilitation for each group was Group 1 = 72 (50-94)m, Group 2 = 62 (51-72)m, Group 3 = 57 (49-65)m, Group 4 = 66 (52-81)m and Group 5 = 45 (17-73)m.

There was no statistical difference in the change in ISWT between the groups by ANOVA $p=0.485$ or with post hoc analysis. Very obese patients appeared to do less well, but this was a small group.

Conclusion

Over half of this COPD population were overweight. Obese patients seem to have a lower ISWT performance. This does not appear to affect the outcome of pulmonary rehabilitation in terms of exercise capacity.

APPENDIX VII

Laboratory analysis of NTBNP and CRP

Laboratory analysis of NTBNP and CRP

NTBNP

The N-BNP assay was based on a noncompetitive assay. Rabbit antibodies were raised to the N- and C-terminals of human N-BNP. The C-terminal-directed IgG was the capture antibody. The N-terminal IgG was affinity-purified and biotinylated. Samples or N-BNP standards were incubated in C-terminal IgG-coated wells with the biotinylated antibody for 24 hours at 4°C. Streptavidin labelled with methyl-acridinium ester was used to detect the bound biotinylated antibody. Within and between assays, coefficients of variation have previously been shown to be 2.3 and 4.8% respectively (531).

CRP

C-reactive protein was measured using an enzyme-linked immunosorbent assay plate immobilized monoclonal CRP antibody (100 ng/100 µL; Unipath PLC, Bedford, Bedfordshire, UK) and a rabbit polyclonal antibody (50 ng/100 µL; Merck BioSciences, Nottingham, UK). Detection used biotinylated antirabbit IgG (Sigma, Poole, UK; diluted 1:250 000) and methyl-acridinium ester-labeled streptavidin as previously described. The CRP assay had inter- and intra-assay coefficient of variation <10%, with lower limits of detection of 20 ng/mL (565).

APPENDIX VIII

**Definitions of Polymerase Chain Reactions and other
laboratory methodology for chapter seven**

**Laboratory methodology for the muscle biopsy
analysis; Gel electrophoresis and Quantitative PCR**

Definitions of Polymerase Chain Reactions and other laboratory methodology for chapter seven

Polymerase chain reaction (PCR)

PCR is a laboratory technique used to amplify a known piece of deoxyribonucleic acid (DNA). Oligonucleotide primers corresponding to each end of a DNA region of interest are synthesised first. DNA polymerase is then used to assemble a new strand of DNA from a single strand of the original double helix DNA. Thermal cycling (heating and cooling the PCR sample) is used to separate the strands of the original double helix. This process is repeated multiple times amplifying the specific DNA region of interest. The amplified segment is then abundant enough to be seen using an electrophoretic gel.

Gel electrophoresis

Gel electrophoresis separates molecules like DNA or ribonucleic acid (RNA) using an electric current applied to an agarose gel matrix. By placing the molecules in wells in the gel and applying an electric current, the molecules will move through the matrix at different rates, usually determined by their mass to charge ratio. The distance a band travels is approximately inversely proportional to the logarithm of the size of the molecule

Reverse transcriptase PCR (rt-PCR)

Reverse transcriptase PCR is a laboratory technique used to amplify a defined piece of a ribonucleic acid (RNA) molecule. The RNA strand is reverse transcribed into its DNA complement or complementary DNA (cDNA) using deoxyribonucleotides (dNTPs) and reverse transcriptase. Messenger RNA (mRNA) is single stranded so needs to be

converted to cDNA to then undergo PCR which is subsequently performed. The cDNA is then amplified by PCR as described above to then be 'read' by electrophoresis. Rt-PCR can be used to quantify mRNA from very small samples and can then give quantitative results on gene expression.

Real-Time PCR or quantitative PCR

Real time rt-PCR is also known as Quantitative PCR. It enables both detection and quantification of a specific sequence in a DNA sample (i.e done in the same process rather than having to quantify the gene expression subsequently with electrophoresis). It follows the same basic principles of PCR, but its key feature is that the amplified DNA is quantified as it accumulates in the reaction in real time after each amplification cycle. It is often used with reverse transcription PCR (rtPCR).

Two strategies are often used to quantify the results obtained by real time rtPCR; the comparative Ct method and the standard curves method. The comparative method was used in chapter seven.

Comparative C_t method

$$[\Delta] [\Delta]Ct = [\Delta] Ct \text{ sample} - [\Delta] Ct \text{ reference}$$

Where $[\Delta] Ct \text{ sample}$ is the Ct value for sample normalised to the endogenous housekeeping gene and $[\Delta] Ct \text{ reference}$ is the Ct value of the calibrator also normalised to the endogenous house keeping gene.

Ct is the cycle number

Transcription – copying of DNA by RNA polymerase into messenger RNA

Transcription factor – is a protein that binds to a specific sequence of DNA and regulates the transcription of genetic information from DNA to RNA. They contain one or more DNA binding domains which attach to the specific sequence of DNA adjacent to the genes they regulate. Transcription factors either perform this alone or with other proteins in a complex to either increasing (activators) or preventing (repressor) the presence of RNA polymerase.

Laboratory analysis of the muscle biopsies

Quantitative PCR for PPAR analysis

Total RNA was isolated from snap frozen human vastus lateralis muscle using RNA plus (Qbiogene) according to the manufacturer's protocol. First strand cDNA was then synthesised from 1 µg RNA sample using random primers (Promega) and PowerScript Reverse Transcriptase (BD Biosciences). Additional reactions were performed, in which the reverse transcriptase was omitted to allow for assessment of genomic DNA contamination and/or pseudogenes through 1.5% agarose electrophoresis inspection.

Taqman PCR was carried out using an ABI prism 7000 sequence detector (Applied Biosystems, USA), with 2 µl of cDNA, 18 µM of each primer, 5 µM probe, and Universal Taqman 2x PCR Mastermix (Eurogentec) in a 25 µl final volume. Each sample was run in duplicate. Primers and MGB TaqMan probes (Applied Biosystems) were designed such that probes spanned over exon-exon boundaries to avoid genomic

amplification. Hydroxymethyl bilane syllane (HMBS) was used as internal control, and all genes of interest were labelled with the fluorescent reporter FAM. The thermal cycling conditions used were: 2 min at 50°C, 10 min at 95°C, followed by 40 cycles at 95°C for 15 s and 60°C for 1 min.

Standard curves obtained by serial dilution of cDNA were run in an initial stage in duplicate in two separate reactions: one with the primer gene set of interest, and one with the HMBS endogenous gene. Ct (Cycle number) values of the target gene were normalized to Ct values of the internal placebo HMBS, and the final results were calculated according to the $2^{-\Delta\Delta Ct}$ method (chapter seven). The value of the initial biopsy (before exercise) was used as calibrator with a value of 1 for each subject.

Gel electrophoresis for the muscle fibre type proportion

Frozen muscles were homogenized in ice-cold homogenization buffer 250 mM sucrose, 100 mM KCl, 5 mM EDTA, and 20 mM tris(hydroxymethyl)-aminomethane (Tris), pH 6.81. Total protein was assayed according to the method of Bradford. The stacking gels were composed of 30% glycerol, 4% acrylamide-NJ/'-methylene-bis-acrylamide (his) (50:1), 70 mM Tris (pH 6.7), 4 mM EDTA, and 0.4% sodium dodecyl sulfate (SDS). The separating gels were composed of 30% glycerol, 8% acrylamide-bis (50:1), 0.2 M Tris (pH 8.8), 0.1 M glycine, and 0.4% SDS. The gel constituents were prepared from stock solutions, and polymerization was initiated with 0.05% N,N,N',N'-tetramethylethylenediamine and 0.1% ammonium persulfate. The upper running buffer consisted of 0.1 M Tris (base), 150 mM glycine, and 0.1% SDS. The lower running buffer consisted of 50 mM Tris (base), 75 mM glycine, and 0.05% SDS. Upper and

lower buffers were cooled to 4°C in a refrigerator before use, and the entire gel unit was placed in a Styrofoam box with ice to maintain the temperature below 10°C for the duration of the electrophoretic run. The gel was run for 24 h at 275 V. The amount of protein run on the gel was 0.5 µg of total protein per lane. The gels were stained with silver (Biorad silver stain plus kit). The stained gels were scanned using a Duo Scan T1200 Agfa scanner. Bands were identified and the optical density volume was calculated using the Quantity One programme (Bio-Rad).

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