AN ADAPTED REHABILITATION PROGRAMME FOR A CROSS SECTION OF SOUTH AFRICAN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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DECLARATION

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

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Signature Date

ABSTRACT (ENGLISH)

The benefits of exercise training for patients with chronic obstructive pulmonary disease (COPD) are well-documented. In South Africa, exercise programmes for COPD patients are limited and often expensive and inaccessible to the broader community. The purpose of this study was to assess the responses of COPD patients to an exercise programme and to determine if the same results can be obtained through a less costly programme. In the primary programme of the study, 22 subjects were subjected to 12 weeks of exercise training. Each subject underwent comprehensive pre- and post-intervention assessments, which included the measurement of overall health status by a physician, level of dyspnoea, forced expiratory lung function, exercise capacity, body mass index and health-related quality of life. Exercise sessions included aerobic and strength training exercises and involved three, hour-long exercise sessions a week. In the modified programme, 18 subjects were randomly divided into an experimental and control group. Eleven subjects were included in the experimental group and seven subjects in the control group. Subjects had to complete 32, hour-long exercise sessions in a 10-week period. The experimental group's exercise programme was adapted so that no specialised equipment was used, while the control group exercised in a well-equipped exercise- and rehabilitation centre. All subjects were subjected to the same pre- and post-intervention assessment as in the primary programme. In the primary programme, there were significant improvements in the physician's evaluation of overall health status ($p < 0.0001$), level of dyspnoea ($p < 0.05$), exercise capacity ($p < 0.000001$) and health-related quality of life ($p < 0.001$). No significant changes occurred in the forced expiratory lung function and body mass index. In the modified programme, there were significant improvements in the physician's evaluation of overall health status ($p < 0.000001$), level of dyspnoea ($p < 0.0001$), exercise capacity ($p < 0.000001$) and health-related quality of life ($p < 0.001$). Consistent with the primary programme, no significant changes occurred in the forced expiratory lung function and body mass

index. There was no significant difference between the results obtained by the experimental and control group on the physician's evaluation of overall health status ($p = 0.96$), level of dyspnoea ($p = 0.99$), exercise capacity ($p = 0.30$), health-related quality of life ($p = 0.50$), lung function and body mass index ($p = 0.23$). The study concluded that a 12-week exercise programme, that included aerobic and strength training, improves the overall health-status, level of dyspnoea, exercise capacity and health-related quality of life of patients with COPD. Furthermore, the same results can be obtained through a low-cost programme that utilises no specialised equipment. The implementation of low-cost exercise programmes in South Africa has great potential benefit for all patients with COPD.

OPSOMMING (AFRIKAANS)

Verskeie navorsing is al gewy aan die voordele wat oefenprogramme inhou vir pasiënte met kroniese obstruktiewe lugweg siekte (KOLS). In Suid-Afrika is soortgelyke programme egter uiters beperk en meestal ontoeganklik en onbekostigbaar vir die breë publiek. Die doel van hierdie studie was om die uitwerking van oefening op KOLS pasiënte te bepaal, sowel as om te bepaal of dieselfde resultate deur ‘n goedkoper program bereik kan word. Twee-en-twintig proefpersone was in die primêre program van die studie ingesluit, waartydens proefpersone onderwerp was aan ‘n 12-weke oefenprogram. Omvattende evaluasies is voor en na die intervensieprogram uitgevoer. Metings tydens hierdie evaluasies het ingesluit die evaluasie van persone se algemene gesondheidstoestand deur ‘n internis, omvang van asemnood, geforseerde ekspirasie longfunksie, oefeningskapasiteit, liggaamsmassa-indeks en gesondheidsverwante lewenskwaliteit. Oefensessies wat aerobies- and versterkingsoefeninge ingesluit het, is drie maal per week vir ‘n uur lank uitgevoer. In die aangepaste program is 18 proefpersone lukraak in ‘n eksperimentele- en kontrolegroep ingedeel. Die eksperimentele groep het elf persone bevat, terwyl daar sewe persone in the kontrole groep was. Hierdie proefpersone moes 32 oefensessies, van ‘n uur elk, in ‘n 10-week periode voltooi. Die eksperimentele groep se oefenprogram is so aangepas dat geen gespesialiseerde toerusting gebruik is nie, terwyl die kontrole groep in ‘n goed-toegeruste oefen- en rehabilitasiesentrum geoefen het. Al die proefpersone is aan dieselfde evaluasie voor en na die intervensieprogram onderwerp. In die primêre program is beduidende verbeterings gevind in die internis se evaluasie van persone se algemene gesondheidstoestand ($p < 0.0001$), omvang van asemnood ($p < 0.05$), oefeningskapasiteit ($p < 0.000001$) en gesondheidsverwante lewenskwaliteit ($p < 0.001$). Geen beduidende verskille is gevind in longfunksies en liggaamsmassa-indeks nie. In die aangepaste program was daar beduidended verbeterings in die internis se evaluasie van persone se algemene gesondheidstoestand ($p < 0.000001$), omvang van asemnood ($p < 0.0001$), oefeningskapasiteit ($p <$

0.000001) en gesondheidsverwante lewenskwaliteit ($p < 0.001$). Soos met die primêre program, was daar geen beduidende verskille in longfunksie en liggaamsmassa-indeks nie. Daar was geen beduidende verskille tussen die eksperimentele en kontrole groepe in die internis se evaluasie van persone se algemene gesondheidstoestand ($p = 0.96$), omvang van asemnood ($p = 0.99$), oefeningskapasiteit ($p = 0.30$), gesondheidsverwante lewenskwaliteit ($p = 0.50$), longfunksie en liggaamsmassa-indeks ($p = 0.23$) nie. Die gevolgtrekking van hierdie studie is dat ‘n 12-week oefenprogram, wat aerobies- en versterkingsoefeninge insluit, beduidende verbeterings in die algemene gesondheidstoestand, omvang van asemnood, oefeningskapasiteit en gesondheidsverwante lewenskwaliteit van persone met KOLS tot gevolg het. Soortgelyke voordele kan verkry word deur ‘n goedkoper oefenprogram wat geen gespesialiseerde toerusting vereis nie. Die implementasie van sulke koste-effektiewe oefenprogramme hou groot potensiële voordele in vir persone met KOLS in Suid-Afrika.

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LIST OF ABBREVIATIONS

6MWT	Six Minute Walk Test
6MWD	Six Minute Walk Test Distances
AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
AAT	Alpha-1 Antitrypsin
ACCP	American College of Chest Physicians
ACSM	American College of Sports Medicine
AIDS	Acquired Immunodeficiency Syndrome
ANOVA	Analysis of Variance
ATS	American Thoracic Society
ATP	Adenosine Triphosphate
BDI	Baseline Dyspnoea Index
BMI	Body Mass Index
BTS	British Thoracic Society
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Questionnaire
CT	Computed Tomography
DALY	Disability Adjusted Life Years
ERS	European Respiratory Society
$FEF_{25-75\%}VC$	Forced Expiratory Flow 25% to 75% of Vital Capacity
FEV_1	Forced Expiratory Volume in one second
FIV_1	Forced Inspiratory Volume in one second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRQL	Health Related Quality of Life

IC	Inspiratory Capacity
kPa	Kilo Pascal
LVRS	Lung Volume Reduction Surgery
MEFV	Maximal Expiratory Flow Volume
MP	Modified Programme
MVV	Maximum Voluntary Ventilation
mmHg	Millimetre Mercury
MRC	Medical Research Council
O_2	Oxygen
PaO_2 / PO_2	Partial Pressure of Oxygen
$PaCO_2$ / PCO_2	Partial Pressure of Carbon Dioxide
$PEEP_i$	Intrinsic Positive End-Expiratory Pressure
PEF	Peak Expiratory Flow
PP	Primary Programmes
RPE	Rate of Perceived Exertion
RV	Residual Volume
SATS	South African Thoracic Society
SBC	Stellenbosch Biokinetics Centre
SE	Standard Error
SD	Standard Deviation
SGRQ	St. Georges Respiratory Questionnaire
TB	Tuberculosis
TDI	Transitional Dyspnoea Index
THR	Training Heart Rate
TLC	Total Lung Capacity
V_E	Expired Ventilation per Minute
V_A/Q	Ventilation/Perfusion
VC	Vital Capacity
VO_2	Oxygen Consumption
VO_2max.	Maximal Oxygen Uptake
V_T	Tidal Volume

V_r	Volume of air in the lungs at rest
WHO	World Health Organisation

To my loving husband

CHAPTER I: INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), which encompasses both chronic bronchitis and emphysema, is one of the leading causes of death and disability in both the developed and developing world (Jindah *et al.*, 2006; Bateman *et al.*, 2004; Pinto-Plata *et al.*, 2004; Mannino, 2002; Pauwels *et al.*, 2001; Hurd, 2000; Petty & Weinmann, 1997; Curtis *et al*., 1994). COPD poses an enormous burden to society both in terms of direct cost to healthcare services and indirect costs to society through loss of productivity (Mannino, 2002; Hurd, 2000). "COPD is a common, costly and preventable disease that has implications for the global health, of the public and the individual" (Petty & Weinmann, 1997). Reasons for the major impact that COPD has on public health include the high mortality rates, large affected populations, the increase in prevalence and the impact that it has on daily living (Toshima *et al.*, 1990).

The information available on COPD is limited by various factors. It is difficult to differentiate between COPD and chronic severe asthma and patients with mild to moderate disease may not be identified as suffering from COPD (Lundback *et al.*, 2003). Various sources advise that statistics on COPD should be interpreted with caution because of underestimation (Chan-Yeung *et al.*, 2004; Cerveri *et al.*, 2001; Hurd, 2000; Mannino *et al.*, 2000; American Thoracic Society (ATS), 1995; Isoaho *et al.*, 1994; Bakke *et al.*, 1991). Furthermore, most information concerning COPD comes from developed countries and limited data is available for developing countries (Jindah *et al.*, 2006).

Various risk factors have been identified that contribute to the development of COPD. Tobacco smoking is regarded as the most important risk factor in the development of chronic respiratory disorders (Behrendt, 2005; Bateman *et al.*, 2004; Croxton *et al.*, 2002; Senior & Anthonisen, 1998; British Thoracic Society (BTS), 1997; ATS, 1995). A family history of COPD seems to be another significant risk factor, although insufficient evidence exists to determine whether this relationship is as a result of genetic or environmental factors, or a combination of both (Behrendt, 2005; Senior & Anthonisen, 1998; BTS, 1997; Petty &

Weinmann, 1997; ATS, 1995). According to Ehrlich and associates (2004), although tobacco smoking is a risk factor that cannot be overlooked in South Africa, the high prevalence of tuberculosis has "emerged as a powerful predictor of chronic bronchitis, much stronger than smoking".

Despite the high prevalence and enormous cost to healthcare and society, COPD has received scant attention in comparison to other respiratory conditions such as asthma and lung cancer. This is due to the fact that COPD is thought of as a self-inflicted disease with few effective treatments. Furthermore, it mainly affects the more elderly and therefore less vocal population. COPD is not an obvious killer such as lung cancer and therefore receives a less emotive response (O'Donnell *et al.*, 2002). According to MacNee (1997), the following statement had already been made in 1923 and is still true today:

> "The trite observation that familiarity breeds contempt is essentially true with regard to the outlook of chronic bronchitis; those afflicted are inclined to accept the complaint as inevitable…those called upon to treat it do not find it sufficiently interesting to study it closely."

Respiratory physicians around the world now believe that the attitude that "little can be done for this self inflicted disease" is not justifiable. Attempts have been made to redress this deficit with the recent introduction of guidelines in the management and care of patients with COPD (O'Donnell *et al.*, 2002). COPD is not only a frustrating disease for patients, but for physicians as well. This is due to the fact that medical treatment can only partially alleviate symptoms and functional improvements are limited (Clark, 1995:527).

COPD is one of the most widespread lung diseases in the world and the major reason for the development of pulmonary rehabilitation programmes (ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997). Today, pulmonary rehabilitation is seen as an integral part of the clinical management of patients with chronic respiratory conditions. The improvement of quality of life and functional ability, through the management of symptoms and the increase in

participation in physical and social activities, are the basis on which pulmonary rehabilitation was established. Pulmonary rehabilitation deals with problems that might not be adequately addressed by conventional medical treatment. These problems include deconditioning, social isolation, psychological symptoms, muscle wasting and weight loss. The complex interaction between these problems is illustrated in figure 1.1. A positive intervention in any one of these problems would translate into positive gains in the other aspects (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2006).

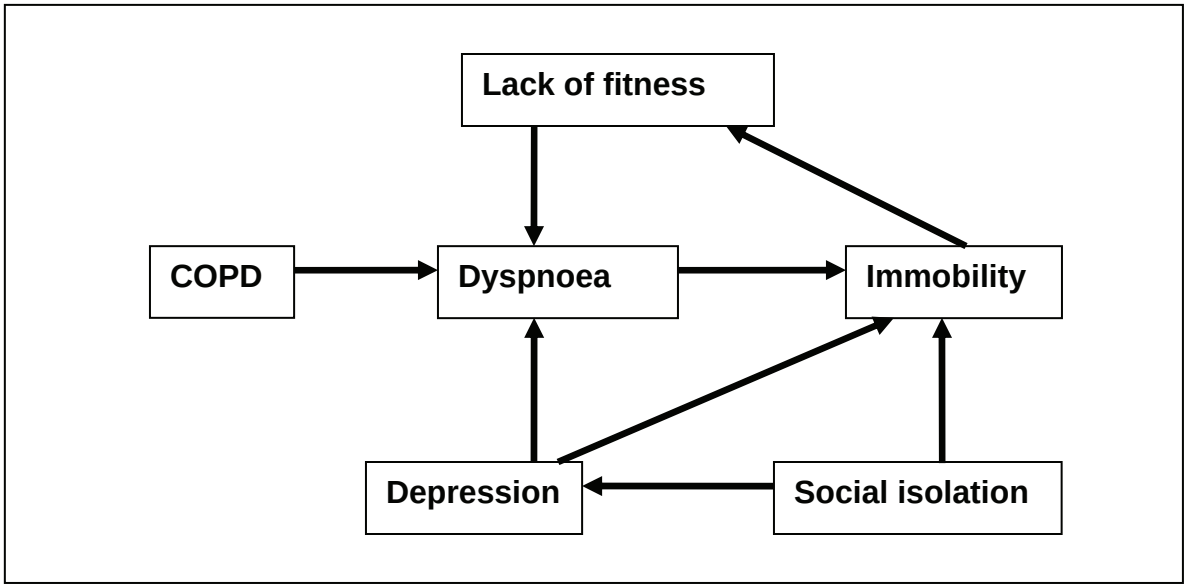

Figure 1.1 The cycle of physical, social and psychosocial consequences of COPD (GOLD, 2006).

Well-structured programmes consists of various components that all contribute to the achievement of treatment goals. Although exercise training is seen as the cornerstone of pulmonary rehabilitation, other components include education of family members and patients, psychosocial intervention and various forms of symptom and co-morbidity management (Morgan, 2003; BTS, 2001; McArdle *et al.*, 2001:953; ATS, 1999; Carrieri-Kohlman *et al.*, 1996; Belman, 1993; Holden *et al.*, 1990).

The positive outcomes of pulmonary rehabilitation in combination with medical treatment are well documented. These benefits include improved health status and functionality, a decrease in dyspnoea and a reduction in health care costs and hospitalisations (Bauldoff *et al.*, 2002; McArdle *et al.*, 2001:953; Guell *et al.*, 2000; Troosters *et al.*, 2000; Strijbos *et al.*, 1996; ATS, 1995; Celli, 1995; Reardon *et al.*, 1994; Cox *et al.*, 1993; Holden *et al.*, 1990; Busch & McClements, 1988).

Initially, physicians adopted a very conservative approach to exercise for COPD patients. In most cases exercise was limited or discouraged (Belman, 1993). Exercise was then later regarded as a last effort to manage these patients with little hope for success (ATS, 1999). A conjoined report by the American College of Chest Physicians (ACCV) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AAVCPR) recommended that exercise training should be included as a standard treatment modality in the rehabilitation of COPD patients (ACCV/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997). This report was later supported by the ATS and the BTS (BTS, 2001; ATS, 1999). At the present time, exercise is promoted for the improvement of quality of life and forms an integral part in the management of patients with respiratory disease (Nici *et al.*, 2006; Rochester, 2003; ATS, 1999; Ries *et al.*, 1995; Belman, 1993).

Controversy still exists regarding the optimal use of exercise training for COPD patients. A wide range of exercise programmes exist with vast differences regarding training mode, frequency and intensity (American College of Sports Medicine (ACSM), 2000:343; Maltais *et al.*, 1997; ATS, 1995; Celli, 1995; Belman, 1993). Despite the wide variety in exercise programmes, the fact that patients who adhere to these programmes are more committed to maintaining their own health and are more independent, remains constant (Ries *et al.*, 1995).

Research on the success of low-cost programmes is limited. According to Belman (1993) programmes without the benefit of complex testing and training methods, have previously been successfully implemented.

This study therefore aimed to contribute to the existing literature on the effects of exercise training on COPD patients, but with the focus on a South African setting. Furthermore, this study hoped to improve the accessibility of pulmonary rehabilitation to a broader community, by focusing on the feasibility of a low-cost programme.

Motivation for the study

- To assess the improvement of functional ability of COPD patients through exercise.
- To determine if the same results can be obtained through a less costly adapted rehabilitation programme.

Problem Statement and Objectives

1. Research Statement

There should be a significant difference between the following pre- and post test scores:

- Six minute walk test for distance (6MWT)
- St. Georges Respiratory Questionnaire (SGRQ)
- Baseline Dyspnoea Index (BDI) and Transitional Dyspnoea Index (TDI)
- Physician's Global Evaluation
- Forced Expiratory Volume in one second (FEV_1)
- Forced Inspiratory Volume in one second (FIV_1)
- Body Mass Index (BMI)
- Number of acute exacerbations

In the second part of the study, the results obtained (as measured by the variables stated above) by the modified programme (MP) and the Primary Programme (PP) should statistically be equivalent.

2. Objectives

- The aim of the study is to create exercise programmes that can be used successfully by all levels of health care professionals and COPD patients alike.
- The study aims to design an adapted model for the rehabilitation of COPD patients that is less expensive than the conventional method, but ultimately produces the same results.
- The study aims to use the results of the 6MWT for the prescription of exercise intensity of each individual subject.
- COPD patients will be encouraged to continue such a programme at home.
- This study will concentrate on exercise training, independent of other pulmonary rehabilitation components, such as education and psychological intervention.

CHAPTER II: LITERATURE REVIEW

Chronic obstructive pulmonary disease (COPD) is defined as a progressive, irreversible disease, characterised by partly reversible airflow obstruction and essentially encompasses two closely related respiratory disorders, namely chronic bronchitis and emphysema. An abnormal inflammatory response to noxious particles or gases is usually associated with COPD (Behrendt, 2005; Croxton *et al.*, 2002; Eisner *et al.*, 2002; Wouters, 2002; Pauwels *et al.*, 2001; Senior & Anthonisen, 1998; Petty & Weinmann, 1997; ATS, 1995). Although this definition was widely accepted for many years, the recent report of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) revised this definition to:

> "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 characterised 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."

The majority of COPD patients are current or former smokers; although the disease is not limited to smokers (GOLD, 2006; Behrendt, 2005; Croxton *et al.*, 2002; Eisner *et al.*, 2002; Wouters, 2002; Pauwels *et al.*, 2001; Senior & Anthonisen, 1998; Petty & Weinmann, 1997; ATS, 1995). Although the current working definition of the GOLD report does not include FEV_1 characteristics of COPD, FEV_1 is still central to the diagnosis and grading of COPD (see table 2.1).

Chronic bronchitis is clinically defined, whereas emphysema is defined in terms of anatomical pathology. A diagnosis of chronic bronchitis is based on two major symptoms, namely a chronic cough and sputum production. Chronic bronchitis is defined as a long-standing inflammation of the airways with the presence of a productive cough for at least three months a year for two consecutive years. All other causes of a chronic cough must be ruled out before the diagnosis can be made (Bateman *et al.*, 2004; McArdle *et al.*, 2001:950; Fishman, 1998:683; ATS, 1995). Chronic bronchitis is generally characterised by obstruction of the small airways (Wouters, 2002).

Emphysema is defined as a morbid condition of the lungs, where there is permanent abnormal enlargement of the airspaces distal to the terminal bronchioles, with destruction and reduced elastic recoil of the alveolar walls. It is accompanied by a lack of uniformity in the pattern of airspace enlargement without evident fibrosis (Bateman *et al.*, 2004; Wouters, 2002; McArdle *et al.*, 2001:951; Fishman, 1998:684; Senior & Anthonisen, 1998; ATS, 1995; Calverley & Pride, 1995:14; Dorland's Illustrated Medical Dictionary, 1967:481). Emphysema and chronic bronchitis do not form part of the GOLD definition of COPD. According to the most recent GOLD report, emphysema only describes one of several structural abnormalities present in COPD patients. Although chronic bronchitis is seen as a clinically and epidemiologically useful term, it does not reflect the major impact of airflow limitation on the morbidity and mortality of COPD patients. This report further emphasised that chronic cough and sputum production, that form the essential part of the definition of chronic bronchitis, may be present without airflow limitation or airflow limitation may be present without being preceded by a chronic cough or sputum production.

In the past, asthma formed part of the COPD complex. Due to the reversibility and participation of cellular and chemical mediators in the inflammation process, it has been separated from COPD. It is important to note that COPD has in many cases, a large reversibility component and an asthmatic may develop an irreversible airflow obstruction that is not distinguishable from COPD (Petty & Weinmann, 1997; ATS, 1995). Asthma may coexist with COPD and it is not always easy to distinguish between the two diseases (GOLD, 2006).

Staging or grading of COPD severity is vital to standardise the categorisation of this population and to optimise management. Disease severity should ideally be based on the interrelationship between the sensation of breathlessness, impairment in airflow and derangement in gas exchange. There is however, no data available to quantify this interrelationship and the widely accepted system for

classification of COPD is in terms of FEV_1 (Pauwels *et al.*, 2001; Berry *et al.*, 1999; ATS, 1995). The GOLD guidelines advised that the use of a staging system should be limited to educational purposes and as a general indication of the approach to initial management (GOLD, 2006). Various staging systems grade COPD severity based on FEV_1. Differences in these systems impede comparisons between different studies (Weiss *et al.*, 2003).

The most widely accepted staging system is the GOLD criteria for classification of COPD severity. COPD classification according to the GOLD criteria is summarised in table 2.1 (GOLD, 2006). This system is based on post-bronchodilator FEV_1. Although the cut-off points for the different stages are not clinically validated, these cut-off points are used for simplicity purposes. The use of a fixed ratio for FEV_1/FVC was based on a study by Johannessen and co-workers (2006), who found that the FEV_1/FVC ratio exceeds 0.70 in healthy adults of all age groups.

The previous GOLD guidelines (Pauwels *et al.*, 2001) included a "Stage 0: At Risk", which identified individuals who are at risk for the development of COPD based on symptoms and risk factors. This stage was, however, not included in the revised guidelines, because of insufficient evidence to suggest that all individuals that are at risk would progress into Stage I (GOLD, 2006).

Stage I COPD is characterised by mild airflow limitation. Individuals with Stage I COPD may not be aware of their lung function impairment and it usually has no effect on their quality of life. Chronic cough and sputum production may be present in these patients, but it is not always the case. Patients generally seek medical attention when the disease progresses to Stage II, due to the worsening of airflow limitation and chronic symptoms. Patients diagnosed with Stage III COPD experience severe impairment of quality of life, increased fatigue, a decrease in exercise capacity and an increase in dyspnoea and exacerbations (GOLD, 2006; Pauwels *et al.*, 2001). Stage IV COPD is characterised by severe airflow limitation and severely impaired quality of life. Exacerbations experienced by these patients

are often life threatening. According to Antonelli-Incalzi and co-workers (2003), this classification correlates with differences in health status.

Table 2.1 Classification of COPD severity according to the GOLD criteria.

Stage	**Characteristics**
I: Mild COPD	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
II: Moderate COPD	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
III: Severe COPD	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
IV: Very Severe COPD	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure*

* Respiratory failure: $Pa_{O2} < 8.0$ kPa (60 mmHg) with of without $Pa_{CO2} > 6.7$ kPa (50 mmHg) while breathing air at sea level.

According to the classification system proposed by the American Thoracic Society (1995), Stage I COPD is where FEV_1 is greater or equal to 50% of the predicted value, Stage II COPD is where FEV_1 is between 35 and 49% of the predicted value and Stage III COPD is where FEV_1 is less than 35% of the predicted value. Patients with Stage I COPD rarely experience severe hypoxaemia and arterial blood gas measurements are not required. The majority of COPD patients would classify as having Stage I of the disease. These patients generally have minimal impact on their health-related quality of life (HRQL) and rarely experience severe dyspnoea. The smallest group of patients are those with Stage II and Stage III COPD, respectively. In these patients, the oxygen and carbon dioxide tensions, in addition to arterial blood gas measurements, should be stated. Patients with Stage II COPD experience a significant impact on their HRQL, whereas HRQL is severely impacted in patients with Stage III COPD (ATS, 1995).

The criteria defined by the British Thoracic Society correlates with the GOLD criteria (BTS, 1997), but does not include FEV_1 criteria. According to Lundback and co-workers (2003), the ATS criteria are not as distinct as the GOLD, BTS and European Respiratory Society (ERS) criteria.

The staging system defined by the South African Thoracic Society (SATS) is similar to the GOLD criteria, but with differences in the cut-off points. Apart from FEV_1 criteria, the staging system of the SATS includes dyspnoea or functional impairment, six minute walk test distances (6MWD) and BMI (Bateman *et al.*, 2004).

Epidemiology

Due to its origin in early Europe, COPD was known as the "British Disease". One possible explanation for the high prevalence of COPD in the United Kingdom the past 30 years is high pollution levels. The prevalence of COPD was at least twice as high in the United Kingdom than any other country with the same tobacco smoking habits (Pride & Soriano, 2002).

According to the American Thoracic Society (1995), the available statistics with regards to the prevalence of COPD are incomplete and only estimations can be given. Varying age distributions, extensive use of the term COPD and the fact that it encompasses different conditions are among the reasons for misclassification and omission from statistics. Therefore, data on the prevalence and mortality of COPD must be interpreted with caution (Chan-Yeung *et al.*, 2004; Cerveri *et al.*, 2001; Hurd, 2000; Mannino *et al.*, 2000; Isoaho *et al.*, 1994; Bakke *et al.*, 1991). Celli and co-workers (2003) illustrated that variation in measurement approaches could alter prevalence estimations of COPD by 200%. According to Jindah and co-workers (2006), statistics on the prevalence of COPD are vastly underestimated. Furthermore, the majority of data available on the prevalence of COPD originates

from developed countries and little is known about the extent of the disease in developing countries (Pauwels *et al.*, 2001). According to Lomas (2002), there is a rise in COPD in developing countries such as India, Mexico, Cuba, Egypt, China and South Africa. This could be attributed to increasing tobacco export to and local tobacco production in these countries and consequently, an increase in tobacco consumption (Lomas, 2002). Furthermore, due to the rise in litigation in industrialised countries, tobacco companies are now focusing on less litigious countries. Mortality statistics of COPD can be improved by creating greater awareness of the disease, improvement of early diagnosis and rectifying biases toward COPD (Jensen *et al.*, 2006; Mannino *et al.*, 1997).

According to Lundback and co-workers (2003), the prevalence of COPD correlates strongly with smoking habits and advancement in age. In the western world, COPD is probably the fourth most common cause of death in middle aged to elderly men after ischemic heart disease, lung cancer and cerebrovascular disease (GOLD, 2003; Lundback *et al.*, 2003; Pauwels *et al.*, 2001; Hurd, 2000; ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997). According to statistics produced by the American Lung Association, 15 million Americans suffer from COPD and it claimed the lives of 87,000 Americans in 1992 (Mak, n.d.). According to the ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel (1997), four to six percent of white adult males and one to three percent of white adult females in the United States suffers from COPD. The prevalence increases to 15% in adults older than 55 years.

According to Mak (n.d.), the prevalence of COPD in the United Kingdom is estimated at 18% for males and 14% for females aged 40-68 years. In the U.S.A., 13.6% of males and 11.8% of females aged 65 to 74 years are thought to have COPD. Feenstra and co-workers (2001) developed a population model to illustrate the projected increase of COPD in the Netherlands from 1994 to 2015. According to this model the prevalence of COPD in the Netherlands will increase by 40% among males and 140% among females (Feenstra *et al*., 2001).

In the United Kingdom, the prevalence of COPD was higher in women than in men from 1990 to 1997 (De Torres *et al.*, 2005). In non-smokers, the prevalence of COPD is greater among women than men till the age of 60, where after the prevalence is the same for male and female non-smokers (Behrendt, 2005). McAllister (2002) attributed the rise in COPD among men after the age of 60 to smoking habits of the last 40 years. In the last 40 years, smoking was more popular among men than women and those smoking patterns now manifest in an increase in COPD among men after the age of 60. The rise in the prevalence of COPD among western women could be attributed to the increase in the popularity of smoking among these women (Lomas, 2002).

In a recent systematic review on the global prevalence of COPD, Halbert and co-workers (2006) illustrated that nine to ten percent of adults, 40 years and older, are diagnosed with COPD as defined by airflow limitation. These findings were consistent with an earlier qualitative review by Halbert and co-workers (2003) who reported the global prevalence of COPD as between four and ten percent. The World Health Organization (WHO) (2002) reported that the global prevalence of COPD in 2001 was between 1013 and 1206 for every 100 000 men and 810 for every 100 000 women. This estimation, however, includes all age groups and therefore totally underestimates the true prevalence.

A study by Cerveri and co-workers (2001) investigated the prevalence of chronic bronchitis in young adults aged 20 to 44. Data from 16 countries (13 European countries, USA, Australia and New Zealand) were analysed for this study. These authors found chronic bronchitis to be a significant health problem in young adults. The average prevalence of this disease was 2.6% in all the countries analysed, with the prevalence in individual countries ranging from 0.7 to 9.7%.

Statistics on the prevalence of COPD in South Africa are not readily available. According to Halbert and co-workers (2006), no spirometric studies exist on the

prevalence of COPD in any African country. A household survey done by Ehrlich and co-workers (2004) provided cross-sectional data on the prevalence of chronic bronchitis on a representative sample of the non-institutionalised South African population. This study indicated that the overall prevalence of chronic bronchitis is 2.3% in men and 2.8% in women (Ehrlich *et al.*, 2004). These figures are misleading due to the fact that adults between the ages of 15 and 44 years were included in the sample. COPD usually develops in the fifth decade of life (Bateman *et al.*, 2004; McArdle *et al.*, 2001:948); therefore, inclusion of such a young age group will result in a low prevalence percentage. Furthermore, patient-reported diagnoses generally underestimated disease prevalence (Halbert *et al.*, 2006).

1. Mortality

COPD has developed into an important cause of morbidity and mortality (Calverley, 2001; ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997; Curtis *et al.*, 1994). In 1996, COPD was the fourth leading cause of death in the U.S.A. and accounted for 4% of all deaths. At that time the mortality rates for men and women were the same up to age 55, whereafter the mortality rates for men rose sharply (Hurd, 2000; Petty & Weinmann, 1997; ATS, 1995). According to De Torres and co-workers (2005), there was a fivefold increase in the mortality rate of women with COPD from 1971 to 2000.

According to Statistics South Africa (2002), respiratory disease accounted for 4% of all deaths in South Africa in 2001. This figure increases to 6% in the Cape Town area for the same period (South African Medical Research Council, 2003).

Economic impact

It is estimated that by the year 2020, COPD will be under the top five conditions that bear the highest health burden on worldwide society (Hurd, 2000). Although only about five percent of people in the working population (age 18 to 64) will

develop COPD, it is still a costly disease (Eisner *et al.*, 2002). In 1985 COPD accounted for 5% of visits to physicians and more than 13% of hospitalisations in the United States (ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997).

Costs of COPD can be divided into primary and secondary care. Primary care involves consultations, prescriptions and oxygen, whereas secondary care encompasses hospital admissions and absenteeism from work (Pride & Soriano, 2002). COPD is responsible for severe impairment of health status and work disability (Eisner *et al.*, 2002). In the United Kingdom, respiratory conditions are the third most common cause of chronic disease in working people aged 45-64 years and are the most common cause of respiratory related death and COPD accounts for 56% of days of certified incapacity due to respiratory conditions in males. Hospital admissions account for the largest cost of COPD. In the United Kingdom, this cost is estimated at £2.5 billion per year (Morgan, 2003). In 1989, an estimated $7 billion was spent on provision of care for patients with COPD in the USA, with a further cost of $8 billion due to the loss of productivity (O'Donnell *et al.*, 2002; Petty & Weinmann, 1997). The total cost of COPD has increased sharply in 1999, in the USA, to more than $14 billion (Hurd, 2000). Table 2.2 illustrates the relative economic burden of COPD in four developed countries; unfortunately, no such data is available for developing countries (Pauwels *et al.*, 2001).

Table 2.2 Direct and indirect costs of COPD.

Country	Year	Direct costs (US$ millions)	Indirect costs (US$ millions)	Total (US$ millions)
U.K.	1996	778	3 312	4 090
Netherlands	1993	256	Not available	Not available
Sweden	1991	179	281	460
U.S.	1993	14 700	9 200	23 900

Pathology of COPD

According to McAllister (2002), an overlap exists between the disease processes of chronic bronchitis, emphysema and chronic asthma. The airflow limitation experienced by COPD patients is the result of small airway disease (obstructive bronchiolitis) and destruction of the lung parenchyma (emphysema), of which the degree of contribution varies between individuals (figure 2.2) (GOLD, 2006). Inflammation leads to structural changes, narrowing of the small airways and destruction of lung parenchyma.

Typical structural changes include fibrosis, epithelial disruption, thickening of basement membrane, smooth muscle hypertrophy and mucus hypersecretion. The destruction of lung parenchyma leads to the loss of alveolar attachments to the small airways and the loss of elastic recoil of the lung. This leads to impaired gas exchange, because of the diminished ability of the airways to remain open during expiration and insufficient alveolar surface. Chronic gas exchange abnormalities can lead to respiratory failure (GOLD, 2006; McAllister, 2002; ATS, 1995).

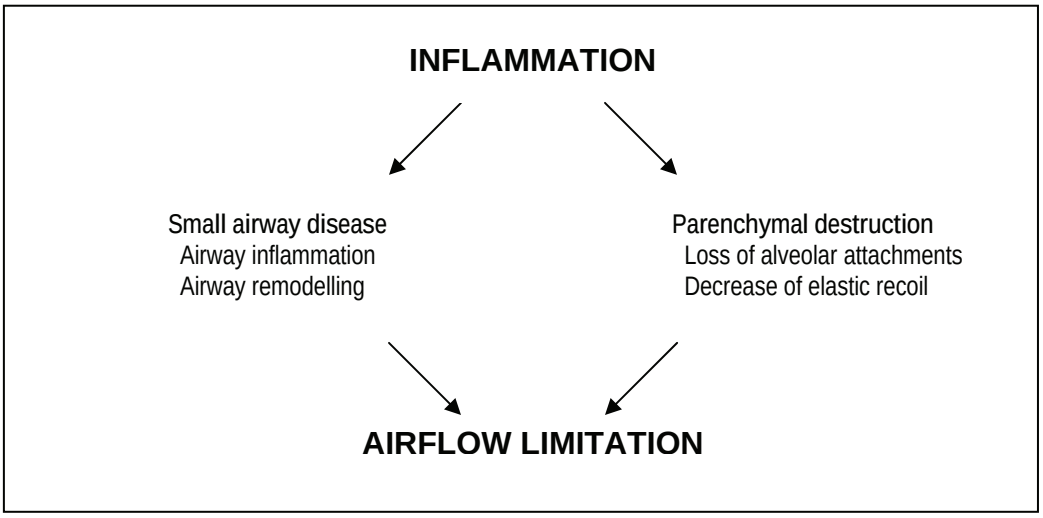

Figure 2.2 Mechanisms underlying airflow limitation in COPD (GOLD, 2006).

The inflammatory process in the respiratory bronchioles is mainly lymphocyte and polymorph mediated. Membranous bronchioles less than 2mm in diameter are important sites for airflow obstruction. This obstruction includes varying degrees of plugging with mucus, goblet-cell metaplasia, inflammation, increased smooth muscle and distortion due to fibrosis. The cross-sectional area of these bronchioles is decreased due to these changes together with the loss of alveolar attachments from the destructive process of emphysema. Bronchoconstriction is another mechanism that could explain airflow obstruction in the COPD patient. This is however, reversible in one third of patients by the administering of an inhaled beta-adrenergic agonist (ATS, 1995).

1. Emphysema

In emphysema, the lung parenchyma is affected by destruction of the alveolar walls. This destruction causes permanent enlargement of the distal airspaces and contributes to narrowing of the small airways through disruption of the alveolar attachments. The collapsing of the small airways leads to air trapping and consequent hyperinflation.

Due to the fact that emphysema is classified in terms of structural or anatomical pathology, three pathological changes should be considered when making a diagnosis. The first consideration is the size of the airspaces, which is also the primary consideration for classifying disease severity and identifying subtypes. Secondly, there should be evidence of destruction, which can be detected in early stages of the disease, before other pathological changes occur. Lastly, fibrosis should be minimal, which is important for the exclusion of other pathological conditions (Calverley & Pride, 1995:14). As a result of alveolar wall destruction, the main characteristics of emphysema include the loss of lung elasticity and elastic recoil pressure (ACSM, 1998a:317).

There are three types of emphysema described in the literature, *centriacinar emphysema*, *panacinar emphysema* and *distal acinar emphysema* (Fishman, 1998:684; ATS, 1995). It is important to note that in most patients it is impossible to distinguish the type of emphysema, since it is common for all three types to be present in one patient. *Centriacinar emphysema* starts in the respiratory bronchioles and spreads peripherally. There are two types of *centriacinar emphysema*, namely *centrilobular emphysema* and *focal emphysema*. *Centrilobular emphysema* tends to occur in the upper lobes, is usually associated with cigarette smoking and is commonly associated with dilatation and destruction of respiratory bronchioles. *Focal emphysema* is more widely distributed compared to *centrilobular emphysema* and is less severe. This type of *centriacinar emphysema* occurs in coal workers' pneumoconiosis (Hogg & Senior, 2002; Fishman, 1998:684; ATS, 1995).

Panacinar emphysema tends to occur in the lower lobes of the lungs and the entire alveolus is involved uniformly. It is difficult to differentiate between healthy lungs and lungs with mild *panacinar emphysema* and it only become significant in severe stages of this emphysema. This type of emphysema is associated with smoking and homozygous alpha-1 antitrypsin (AAT) deficiency (Hogg & Senior, 2002; Fishman, 1998:684; ATS, 1995).

Distal acinar emphysema is also known as *paraseptal emphysema* and involves distal airway structures, alveolar ducts and alveoli. Airflow is often well preserved in this type of emphysema, but because the process is localised adjacent to the fibrous septa or pleura, apical bullae may cause spontaneous pneumothorax (Fishman, 1998:684; ATS, 1995).

McLeod's syndrome or unilateral emphysema is caused by severe childhood infection as a result of rubella or adenovirus. Newborn babies can be affected by congenital lobar emphysema, which is a developmental abnormality. The term irregular emphysema is used for emphysema without any special distribution

pattern and emphysematous spaces form around the margins of scars (Hogg & Senior, 2002; Calverley & Pride, 1995:15).

1.1 Pathophysiological sequelae of cigarette smoking

Cigarette smoking directly and indirectly imposes oxidative stress on the lungs. Reactive species in cigarette smoke are directly responsible for oxidative damage in the lungs, while oxidative stress can indirectly increase through the activation of inflammatory cells (Croxton *et al*., 2002; Wouters, 2002). Oxidants are released from inflammatory leukocytes and alter the oxidant/antioxidant balance (Fishman, 1998:678). If the oxidant/antioxidant balance is shifted in favour of oxidants, through the presence of an excess of oxidants or a depletion of antioxidants, oxidative stress occurs. The effects of oxidative stress on the lungs include the activation of inflammatory genes, inactivation of antiproteases, stimulation of mucus secretion and increased plasma exudation (GOLD, 2006).

The pathogenesis of emphysema is commonly explained by the proteinase-antiproteinase hypothesis. According to this hypothesis proteinase activity is responsible for destruction of the alveolar walls (Hogg & Senior, 2002).

Neutrophils release the proteolytic enzyme neutrophil elastase, which is the major (not the only) proteinase involved in emphysema. Smoking results in an increase in neutrophils in the lung capillary bed, which will increase the concentration of neutrophil elastase. Adding to the pathology, cigarette smoke has been found to elicit an inflammatory response in the lungs and stimulates the release of elastase from these cells (Hogg & Senior, 2002; Wouters, 2002; Betsuyaku *et al.*, 1995; Bates, 1989:152). Elastase breaks down elastin, a normal structural component of lung tissue. Neutrophils are not the only inflammatory cells responsible for pathogenesis of lung destruction. Hogg and Senior (2002) implicated macrophages, T-lymphocytes and eosinophils as part of this process, as well.

In healthy individuals, the lung is protected from the destructive effect of elastase by an inhibitor, AAT. This protective action of AAT is however, inactivated by cigarette smoke, which results in destruction of the alveolar walls due to proteinase activity (Hogg & Senior, 2002; Fishman, 1998:699). Contrary to the majority of studies, Bates (1989:152) stated that AAT levels are not affected by cigarette smoke.

2. Chronic bronchitis

Chronic bronchitis is clinically defined in terms of sputum production and cough (ACSM, 1998a:315; Calverley & Pride, 1995:13). Pathological features of chronic bronchitis include enlargement of mucus-secreting glands in the airways, an increase in mucus glands in relation to serous glands, accumulation of mucus in the airways, narrowing of small airways, diverticula in the airways and colonisation by *Streptococcus pneumoniae* and *Haemophilus influenzae* (George *et al.*, 1990:174).

Hypersecretion of mucus is the result of an increase in the mass of submucosal glands and an increase in goblet cells in the surface epithelium (Calverley & Pride, 1995:13). Dilation of the ducts of submucosal glands further contributes to hypersecretion of mucus (Murray *et al.*, 2000:1203; George *et al.*, 1990:174). The increase in the volume of submucosal glands is the result of cigarette smoke and other irritants (it may also be present in asthma), while the increase in goblet cells may occur due to chemical stimuli. In healthy individuals, goblet cells are predominantly found in the proximal airways. In smokers, goblet cells are found in the peripheral airways and may increase or decrease in the proximal regions (Calverley & Pride, 1995:13). Smoking cessation leads to decreased sputum production (McAllister, 2002).

Increased smooth muscle, inflammation and the loss of alveolar attachments further contribute to increased mucus in the airways (Murray *et al.*, 2000:1203).

Mucus hypersecretion is accompanied by inflammatory changes, which results in scarring, fibrosis and distortion of peripheral airways (McAllister, 2002). Diverticula in the walls of the airways are predominantly found in the larger airways (George *et al.*, 1990:175).

Pathophysiology of COPD

Pathophysiology describes the physiological impact of pathological changes (Dorland's Illustrated Medical Dictionary, 1967:1112). In terms of COPD, it describes the distorted physiological characteristics of the disease that emanate from pathological changes in the lungs. These pathological changes include airflow limitation, mucus hypersecretion, ciliary dysfunction, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, cor pulmonale (Pauwels *et al.*, 2001) and ventilation-perfusion mismatching (Fishman, 1998:663).

The airflow during forced expiration is the result of the interaction between elastic recoil and airway resistance. Elastic recoil promotes airflow, whereas airway resistance limits airflow (Fishman, 1998:662). The primary physiological change of COPD is expiratory airflow obstruction, which is the result of airway obstruction and consequently the increase in airway resistance and loss in elastic recoil. The destruction of alveolar attachments contributes to expiratory airflow obstruction, but is secondary to airway obstruction, airway resistance and elastic recoil abnormalities (Pauwels *et al.*, 2001; Fishman, 1998:662-663). The reduction in FEV_1 experienced by patients with COPD is primarily the result of inflammation, fibrosis and luminal exudates in the small airways (GOLD, 2006).

The pathological origin of chronic cough and sputum, both key symptoms of COPD, is mucus hypersecretion and ciliary dysfunction (Pauwels *et al.*, 2001). In hyperinflation, the relaxation volume of the respiratory system (*Vr*) is raised above the functional residual capacity (FRC) due to changes in the elastic properties of

the lungs and chest walls (Gibson, 1996). The elastic recoil pressure increases as the lung volume increases to preserve maximum expiratory airflow. This causes an increase in the work of breathing and a decrease in ventilatory efficiency, which will contribute to dyspnoea (Fishman, 1998:664).

Abnormalities in gas exchange are the result of peripheral airway obstruction, parenchymal destruction and pulmonary vascular abnormalities. These abnormalities will lead to hypoxaemia and hypercapnia (Pauwels *et al.*, 2001). Hypercapnia and hypoxaemia can induce renal and hormonal abnormalities, which can lead to oedema (McAllister, 2002).

Various studies suggested that chronic low oxygen levels would cause vasoconstriction of the pulmonary arterioles, which results in pulmonary hypertension (McAllister, 2002; Pierson, 2000; Fishman, 1998:663). Eventually, pulmonary hypertension can result in structural changes such as intimal hyperplasia and smooth muscle hypertrophy (GOLD, 2006). Since these structural changes of the pulmonary arteries are seen in patients without hypoxaemia, this traditional view have been challenged. Other studies proposed that various inflammatory proteins play an important role in the regulation of pulmonary artery pressure (Joppa *et al.*, 2006; Wright *et al.*, 2005; Barbera *et al.*, 2003; Peinado *et al.*, 1999; Barbera *et al.*, 1994; Stevens *et al.*, 1992). Joppa and co-workers (2006) proposed that apart from chronic local inflammation in the airways and lung parenchyma, systemic inflammation could also play a role in the pathogenesis of pulmonary hypertension. Further studies are needed to address this in more detail.

Pulmonary hypertension can lead to cor pulmonale and right ventricular failure (McAllister, 2002; Pierson, 2000; Fishman, 1998:663). Cor pulmonale refers to “alterations in the structure and function of the right ventricle” consequent upon increased pressure, which results from disease of the lungs (Pierson, 2000). This is only evident in patients with a FEV_1 that is 25% or less of the predicted value or

during chronic hypoxaemia (marked by Pa_{O2} less than 55 mmHg). It is common for patients with mild COPD to experience a slight increase in pulmonary pressure during exercise (Fishman, 1998:663). An inverse relationship exists between pulmonary hypertension and the prognosis of COPD patients. Therefore, an increase in pulmonary hypertension results in a poorer prognosis (Pierson, 2000).

Ventilation-perfusion (V_A/Q) mismatching is common pathology in COPD and affects the airways and lung parenchyma (Fishman, 1998:663; Scharf, 1992:309). Two distinct V_A/Q profiles of COPD patients have been identified. Type A patients ("pink puffers") are characterised by a V_A/Q profile where a "substantial amount of ventilation is distributed to high V_A/Q regions". Type B patients ("blue bloaters") are characterised by a substantial amount of pulmonary blood flow perfusion in the low V_A/Q regions. Most patients cannot be classified into one of these profiles because they have both high and low V_A/Q regions (Fishman, 1998:663). Type B patients usually suffer from hypoxaemia, which can be easily corrected by oxygen administration (Pierson, 2000). V_A/Q abnormalities generally arise from disease in the small airways and would therefore not be reflected in lung function tests. The translation of V_A/Q inequalities into hypoxaemia depends on cardiac output (Scharf, 1992:311).

Cooper (2001b) describes the pathophysiology of COPD as "highly complex", due to interdependence of the pulmonary, cardiovascular and musculoskeletal systems. This interdependence is illustrated in figure 2.3.

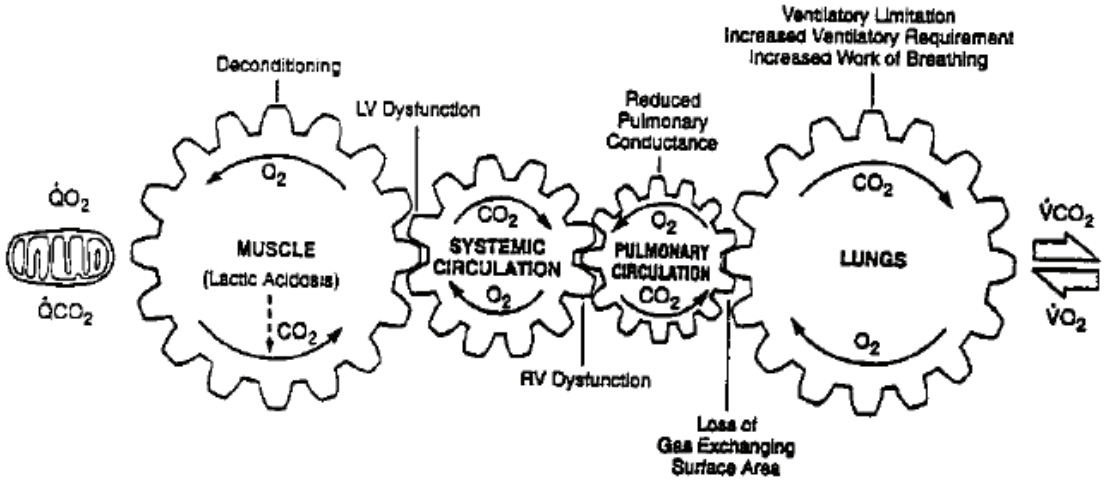

Figure 2.3 An illustration of the complex pathophysiology of COPD (Cooper, 1995).

Chronic hypoxia will increase mortality regardless of the degree of airflow obstruction. Hypoxia can result in increased ventilation, which can be perceived as dyspnoea. Hypercapnia can lead to alveolar hypoventilation, which will contribute to hypoxaemia. Hypoxaemia may increase the severity of dyspnoea, but results are variable (Pierson, 2000).

1. Ventilation and pulmonary mechanics

Abnormalities of ventilation and pulmonary mechanics are some of the primary limits to exercise performance (Rochester, 2003; Haccoun *et al.*, 2002; Belman, 1993; Casaburi *et al.*, 1991). Obstruction of expiratory flow due to alveolar wall destruction and bronchiolar narrowing and the consequent increase in airway resistance place a significant limitation on exercise performance (Rochester, 2003; Belman, 1993).

Deconditioning and peripheral muscle dysfunction can cause ventilation of COPD patients to be higher than expected. This is due to increased dead space ventilation, impaired gas exchange and increased ventilatory demands.

Airflow limitation can be severe enough to result in a maximal expiratory flow equal to resting expiratory flow (Murariu *et al.*, 1998; Belman, 1993). Prolonged expiration, together with an increased breathing frequency, lead to hyperinflation. A reduction in FEV_1 leads to an increased end expiratory lung volume (Nici *et al.*, 2006; Rochester, 2003; O'Donnell *et al.*, 2001; Gallagher, 1994; Belman, 1993). Hyperinflation can be static or dynamic. Static hyperinflation is caused by loss of elastic recoil pressure, while dynamic hyperinflation is the result of air trapping and increased inspiratory muscle activity during expiration (Gosselink, 2003). Dynamic hyperinflation is one of the most significant factors that cause exercise intolerance (O'Donnell *et al.*, 2002). Dynamic hyperinflation can be defined as an abnormal lung volume at the end of tidal expiration (Murariu *et al*., 1998; Gibson, 1996).

Dynamic hyperinflation can also lead to Intrinsic Positive End-Expiratory Pressure ($PEEP_i$). $PEEP_i$ is identified when alveolar pressure is positive at the end of tidal volume expiration, because of expiratory flow limitation. Because of dynamic hyperinflation, there is insufficient time for complete expiration to the resting volume, before the next inspiration. Alveolar pressure will not reach atmospheric pressure, which will result in positive pressure throughout expiration. As a result, intrathoracic pressure may increase high enough to impair venous return, limit cardiac output and lead to hypotension, barotrauma and pneumothorax (Fitting, 2001; Dueck, 2000).

Moderate hyperinflation is defined as the ratio between functional residual capacity (FRC) and total lung capacity (TLC) exceeding 0.6 and/or a residual volume (RV)/TLC ratio exceeding 0.5. Severe hyperinflation is characterised by a FRC/TLC ratio above 0.8 (200% of the predicted value) and/or a RV/TLC ratio above 0.7 (180% of the predicted value) (Dueck *et al.*, 1999; Gelb *et al.*, 1996a).

Hyperinflation limits tidal volume, increases elastic load of inspiratory muscles and forces inspiratory muscles into a shortened position (especially the diaphragm) (Rochester, 2003; Fitting, 2001; Mador *et al.*, 2000b; Fishman, 1998:664). Hyperinflation can be detected radiographically by the presence of a depressed diaphragm without its normal curvature and enlargement of the retrosternal airspace. The consequence of hyperinflation includes an abnormal distribution of resting tidal breathing between the rib cage and abdominal compartments, distortions of the chest wall motion and a reduced mechanical advantage of the diaphragm and the inspiratory muscles (Fishman, 1998:664; Gibson, 1996). The flattening of the diaphragm places it in a mechanically disadvantaged position and results in what is known as Hoover's sign. Hoover's sign is the constriction of the lower rib cage due to the abnormal pressure exerted by the flattened diaphragm, particularly during inspiration (Scharf, 1992:278). According to Gibson (1996), Hoover's sign is the best recognised distortion of the rib margin.

Dynamic hyperinflation is one of the main consequences of expiratory flow limitation and has a three-way effect on inspiratory loading. Firstly, inspiratory workload is increased through a decrease in static compliance, because patients breathe along the shallower portion of the pressure-volume curve. Secondly, the inspiratory threshold load is increased. Inspiration can only occur after respiratory muscles have generated enough force to overcome the elastic recoil pressure. Lastly, there is a greater dependence on breathing frequency, rather than breathing volume (O'Donnell *et al.*, 2001; Bauerle *et al*., 1998; Eltayara *et al.*, 1996; Belman, 1993).

According to Belman (1993), dynamic hyperinflation is "a necessary evil for without it the patients with COPD would not be able to increase ventilation to meet the demands of exercise". Ventilation is increased by the increase in end-expiratory lung volume. An increase in end expiratory lung volume results in patients that demonstrate breathing along the higher portion of the expiratory flow-volume curve

and an increase in maximum expiratory airflow (figure 2.4). This adaptive response does however, put the respiratory muscles at a mechanical disadvantage (Fishman, 1998:664; Carter, *et al.*, 1993).

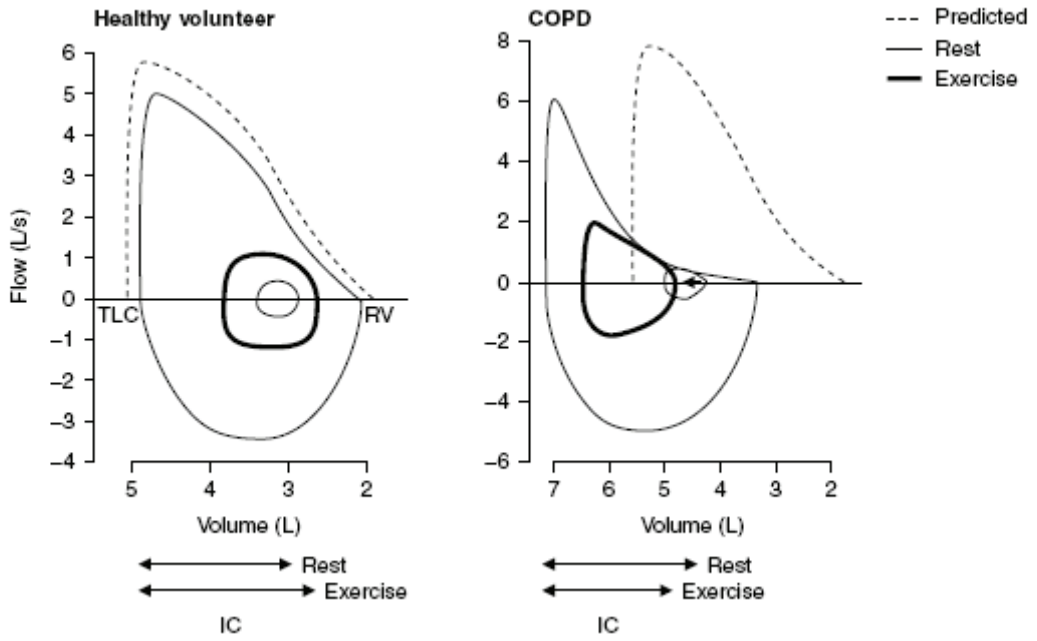

Figure 2.4 Tidal and maximal flow-volume loops at rest and during exercise of a healthy individual and a typical COPD patient (McConnell & Romer, 2004).

To generate the added force to overcome the elastic recoil pressure of a hyperinflated chest, patients recruit abdominal and expiratory muscles of the rib cage during expiration. However, expiration becomes an active action, rather than a passive action, which increases oxygen utilisation during this, usually passive, breathing phase. This results in a reduction of breathing efficiency (Belman, 1993). According to Casaburi and co-workers (1991), if the ventilatory requirements for a certain work rate can be reduced, exercise tolerance will increase.

Lung function can also limit exercise performance of COPD patients (Gosselink *et al.*, 1996). They reported that FEV_1 and the transfer factor for carbon monoxide were determining factors for exercise performance. Murariu and co-workers (1998)

found that lung function, based on resting inspiratory capacity (IC), contributes significantly to exercise intolerance of COPD patients.

2. Impaired gas exchange

Impaired gas exchange during exercise is the result of an increased physiologic dead space, ventilation-perfusion mismatch and reduced diffusing capacity. An increase in the physiologic dead space results in an increase in ventilatory demand (Rochester, 2003; Gallagher, 1994).

Hypoxaemia is a common feature of COPD and is especially significant during exercise. Desaturation during exercise can largely be attributed to a reduction in mixed venous PO_2 and hypoventilation. Reduced alveolar ventilation results in an increase in total minute ventilation to maintain efficient carbon dioxide output (Gallagher, 1994; Belman, 1993). High CO_2 levels in the blood have been implicated as a factor affecting exercise tolerance (Carter *et al*., 1993). Arterial hypoxaemia has an influence on exercise tolerance, because of impaired oxygen delivery to working muscles. Hypoxaemia can also indirectly influence exercise tolerance because ventilatory limitation is experienced at an increasingly lower work rate (Gallagher, 1994). According to Mak and co-workers (1993), oxygen desaturation during exercise is not a determining factor for submaximal exercise capacity.

V_E in patients with COPD is higher during exercise compared to healthy individuals. This increase is, however, seldom enough to compensate for the increased physiological dead space to V_T ratio, resulting in higher Pa_{CO2} during exercise. Increased Pa_{CO2} limits exercise performance by impairing hyperventilation when metabolic acidosis develops (Gallagher, 1994).

3. Hypoxaemia and hypoxia

According to Pierson (2000) no explicit definitions exist for hypoxaemia and hypoxia and that, an interrelationship exists between the two conditions. The Dorland's Illustrated Medical Dictionary (1967:717) defines hypoxaemia as a "deficient oxygenation of the blood". Hypoxaemia is usually the result of ventilation/perfusion mismatching. Hypoxaemia results in an increase in ventilatory drive, dilatation of the vascular bed, tachycardia, vasoconstriction of pulmonary vasculature and an increase in cardiac output. As heart rate, cardiac output and oxygen use by contracting muscles increase during exercise, the transit time of the blood through the capillary bed decreases. This will accentuate the hypoxaemic abnormalities, which will result in reduced exercise capacity (Soo Hoo, 2003; Okubadejo *et al.*, 1996). Hypoxaemic patients' exercise capacity is directly limited by the reduced oxygen delivery to the working muscles (Gallagher, 1994). Another possible explanation for the relationship between hypoxaemia and reduced exercise capacity is the fact that chronic hypoxaemia results in muscle wasting (Degache *et al.*, 2003).

Hypoxia is a decrease in the oxygen supplied to the tissue (Dorland's Illustrated Medical Dictionary, 1967:717). Hypoxia results in impaired cardiac function by decreasing myocardial contractility and maximum cardiac output, which will translate into reduced exercise tolerance (Pierson, 2000). When subjected to chronic hypoxia, adaptations occur in the skeletal muscles. These adaptive responses result in vulnerability towards oxidative stress, which causes malfunction in adenosine triphosphate (ATP) generation. This malfunction impairs exercise capacity (ATS & ERS, 1999).

4. Hypercapnia and acidosis

Lactic acid production during incremental exercise is dependant on circulatory function and fitness level (Belman, 1993). A build-up of lactic acid occurs when the

production of lactate exceeds the oxidation in the muscle cells and energy requirements cannot be met aerobically (McArdle *et al*, 2001:160). It was previously thought that COPD patients could not exercise at sufficient levels to elicit a lactic acid response (Belman, 1986; Hughes & Davison, 1983; Belman & Kendregan, 1981). However, other studies (Maltais *et al.*, 1996b; Casaburi *et al.*, 1991; Sue *et al.*, 1988) did record lactic acidosis at low work rate levels. It has been reported that COPD patients develop lactic acidosis at lower work rate levels than healthy individuals (Casaburi *et al*., 1991; Gallagher, 1994). Casaburi and co-workers (1991) attribute this phenomenon to two factors, reduced oxygen supply to working muscles and a sedentary lifestyle. Maltais and co-workers (1996b) demonstrated that there is an excessive increase in lactic acid in COPD patients. This was attributed to altered skeletal muscle oxidative capacity. They also found a relationship between increased lactic acid and impaired activity of mitochondrial enzymes. The decrease in enzyme activity is the result of a decrease in the number of mitochondria due to a reduction in muscle mass.

Respiratory acidosis develops as a result of carbon dioxide retention (Dorland's Illustrated Medical Dictionary, 1967:27). Increased carbon dioxide will decrease the serum pH, which is known as respiratory acidosis. Respiratory and metabolic acidosis stimulate ventilation because of the fall in arterial pH. Ventilation can also be indirectly stimulated by acidosis through an increase in CO_2 production (Maltais *et al.*, 1996b; Gallagher, 1994).

As with healthy individuals, the lactic acid threshold (the point at which the level of lactic acid rises) in COPD patients is preceded by an increase in minute ventilation (Belman, 1993). According to McArdle and co-workers (2001:291), exercise performance is influenced by the onset of blood lactate accumulation. The same is true for COPD patients (Rochester, 2003).

Peak lactate levels in COPD patients will be reduced because of their overall reduction in exercise capacity. A rise in lactic acid levels in these patients is as a

result of working limb muscles and not respiratory muscles. This is illustrated by the fact that low lactic acid levels are present in patients with severe obstruction and consequently high respiratory muscle work rates (Belman, 1993).

Hypercapnia is defined as excessive carbon dioxide in the blood (Dorland's Illustrated Medical Dictionary, 1967:700). The degree of hypercapnia is determined by abnormalities in minute ventilation (V_E), physiologic dead space and CO_2 output. Hyperinflation (resting and dynamic) contributes to hypercapnia through its influence on breathing patterns, inspiratory muscle function and neuroregulatory control (O'Donnell *et al.*, 2002). Hypercapnia at rest has been associated with poor survival (Hogdkin, 1990). The impact of hypercapnia on respiratory muscle function is still unclear. A recent study found that hypercapnia and consequent respiratory acidosis, could contribute to diaphragmatic fatigue (Jonville *et al.*, 2002). Mador and co-workers (1997) found that acute, moderate hypercapnia results in a decrease in the contractibility of limb muscle, which will impact exercise capacity. Hypercapnia did not have any impact on diaphragmatic contractibility (Mador *et al.*, 1997). Another study illustrated that exercise capacity is not affected by hypercapnia, although hypercapnic patients achieved lower ventilation during exercise. Furthermore, it was found that hypercapnia is the result of the lung's inability to increase ventilation and could not be attributed to respiratory muscle weakness or dysfunction (Montes de Oca & Celli, 2000).

5. Malnutrition

According to the American Thoracic Society (1995), 60% of patients that are critically ill with COPD are malnourished. Malnutrition varies according to the grade of pulmonary limitation. Typically, the incidence of malnutrition increases with an increase in the severity of pulmonary limitation (ATS, 1995; Donahoe *et al.*, 1989).

One of the adverse effects of malnutrition is that it is associated with muscle wasting, which leads to weakness of respiratory muscles (Franssen, 2003; Marquis *et al.*, 2002; ATS, 1995; Schols *et al.*, 1991; Farber & Mannix, 1989). Malnutrition can result in a reduction of diaphragmatic mass due to the loss of cross sectional area of the muscle fibres (Schols *et al.*, 1991). Engelen and co-workers (1994) reported a significant loss in skeletal and respiratory muscle strength in patients that suffered from depletion of fat-free body mass. Efthimiou and co-workers (1988) showed a loss in muscle strength and an increase in fatigability of the sternomastoid muscle in underweight COPD patients. These changes were explained by a decrease in local energy stores. Donahoe and co-workers (1989) found an increase in oxygen consumption of the ventilatory muscles as patients' body weight reduced. Depletion of fat-free body mass is only significant in physical performance when this mass reduces significantly (Baarends *et al.*, 1997; Schols *et al.*, 1991). Wilson and co-workers (1989) found a linear relationship between body weight and exercise tolerance.

It is not just underweight COPD patients who are at risk, Schols and co-workers (1993) reported that depletion of fat-free body mass and muscle wasting could occur in normal weight COPD patients. Body weight is not necessarily influenced by changes in body composition and may remain unchanged or even increase despite the presence of muscle wasting (Schols *et al.*, 1993). Body weight is therefore not a reliable indicator of nutritional status (Mador, 2002). Obese patients and patients with fluid retention are especially susceptible to this phenomenon (Marquis *et al.*, 2002).

Malnutrition influences exercise tolerance in three ways. Firstly, the atrophy of fast twitch fibres predisposes the diaphragm to fatigue. Secondly, the decrease in local energy stores of the peripheral muscles, results in an increase in muscle fatigability. Lastly, the increase in oxygen consumption of the ventilatory muscles decreases the total available oxygen for the exercising muscles (Schols *et al.*, 1991).

Efthimiou and co-workers (1988) reported that increased dietary intake in COPD patients, results in improved respiratory muscle strength, handgrip strength, dyspnoea and distance on the six-minute-walk test (6MWT).

Clinical features of COPD

The natural course and clinical features of COPD is not the same in all patients. It is a progressive disease and symptom manifestation in patients may vary greatly (GOLD, 2006).

1. Patient history

Most importantly when assessing a patient's history, is the consideration of exposure to COPD risk factors (Pauwels *et al.*, 2001). Patients with COPD usually have a history of smoking 20 or more cigarettes per day for 20 or more years. When symptoms develop, they typically present with a productive cough or an acute chest illness (ATS, 1995).

Primary symptoms that should be considered are a chronic cough with sputum production, wheezing and dyspnoea (Mahler, 1990:12). Sputum production is initially only in the morning and only becomes purulent with an exacerbation. A history of wheezing and dyspnoea can lead to the incorrect diagnosis of asthma (ATS, 1995). It is important to consider that COPD is not a stable condition and symptoms and functionality may vary from day to day (Morgan, 2003). As the disease progresses, acute exacerbations become more frequent and at later stages may lead to hypoxaemia with cyanosis. Morning headaches suggest hypercapnia which may lead, together with hypoxaemia, to cor pulmonale with right heart failure and oedema. Haemoptysis may be due to carcinoma, but usually is an indication of mucosal erosion (ATS, 1995).

2. Physical examination

A physical examination is not considered a very effective diagnostic tool for COPD (Pauwels *et al.*, 2001). Slow expiration and wheezing with forced expiration may be the only findings in the initial chest examination (ATS, 1995). Pursed-lip breathing is usually a sign of hyperinflation and an impaired FEV_1 (McAllister, 2002; Calverley & Pride, 1995:313). As the disease progress findings will include limited motion of the diaphragm, an increase in breathing frequency, a decrease in breath sounds, prolonged expiration, distant heart sounds, coarse crackles at the lung bases and frequent wheezes. An increased anteroposterior diameter of the chest or a barrel shaped chest may be a further indication of hyperinflation (McAllister, 2002; ATS, 1995). Some patients increase their breathing frequency to compensate for the reduction in oxygen levels. Although these patients experience severe dyspnoea, cyanosis is not present, hence they are classified as “pink puffers” (Type A). Generally, these patients are able to maintain oxygen levels late into the disease process. Patients that are not breathless, but appear blue are classified as “blue bloaters” (Type B) (McAllister, 2002). Blunted hypoxic drives explain the lack of dyspnoea in type B patients (Pierson, 2000). These patients are not able to increase breathing frequency to compensate for falling oxygen levels and have to rely on very low oxygen levels to maintain respiratory drive (McAllister, 2002). Type B patients might develop cor pulmonale earlier than type A patients (Pierson, 2000).

Findings during end-stage COPD will include pursed-lip expiration, cyanosis, full use of accessory respiratory muscles of the neck and shoulder (especially the sternomastoid muscles) and neck vein distension. An enlarged, tender liver may indicate right heart failure and asterixis may be seen with severe hypercapnia (ATS, 1995). Other clinical signs of right heart or respiratory failure include central cyanosis, swelling of the ankles and increased jugular vein pressure (McAllister, 2002; Pauwels *et al.*, 2001).

Diagnostics

Several objective measures are widely used for the diagnosis of COPD and other respiratory diseases. These include spirometry (flow and volume tests), chest imaging and cytologic and haematologic tests (McArdle *et al.*, 2001:953). Chronic bronchitis usually does not have physiologic or radiographic evidence of hyperinflation and diffusion tests are generally normal. Emphysema is characterised by abnormal diffusion tests and radiographic and pulmonary measures show evidence of hyperinflation (Petty & Weinmann, 1997).

1. Spirometry

Spirometry plays a key role in the diagnosis and management of patients with COPD. It is useful in the assessment of severity and monitoring of the progression of COPD (Van Schalkwyk *et al.*, 2004; ATS, 1999; ATS, 1995). Pauwels and co-workers (2001) suggest that spirometry should be performed on patients with a chronic productive cough and a history of exposure to risk factors, even if dyspnoea cannot be detected.

Flow volume measurement is the foundation of spirometry and plays a vital role in the management of expiratory flow limitations (Dueck, 2000). Pulmonary function tests should include FEV_1, FVC and the ratio between the two (Pauwels *et al.*, 2001). The degree of partially reversible or irreversible airflow obstruction forms an integral part in the diagnosis of COPD. Therefore, most studies use FEV_1 and lung function tests as patient population descriptors, rather than outcome measures (ATS, 1999; ATS, 1995).

COPD patients experience a reduction in ventilatory capacity because of airflow obstruction. In advanced stages of the disease, patients adjust their pulmonary mechanics to compensate for this reduced ventilatory capacity (Carter *et al.*, 1993).

Carter and co-workers (1993) also found that even patients with mild COPD experience ventilatory limitations.

1.1 Forced expiratory volume in one second (FEV_1)

FEV_1 reflects the airflow obstruction and is defined as the volume of air expired in the first second. A degree of airflow limitation is usually used to predict morbidity and mortality (Celli *et al.*, 2004; Pinto-Plata *et al.*, 2004; Nishimura *et al.*, 2002; BTS, 1997; Petty & Weinmann, 1997).

Irreversible airflow obstruction is diagnosed when the post-bronchodilator FEV_1 is less than 80% of the predicted value, together with a FEV_1/FVC ratio of less than 70% (Pauwels *et al.*, 2001). FEV_1 does not describe all the negative attributes and systemic manifestations of COPD (Celli *et al.*, 2004; Pinto-Plata *et al.*, 2004; Nishimura *et al.*, 2002). The benefits of using FEV_1 includes, that it has little variability, is easily measured and can be accurately predicted according to age, gender and height. FEV_1 cannot however, distinguish between emphysema and chronic bronchitis (ATS, 1995). The value of FEV_1 is specific for the diagnosis of an existing airflow limitation and has little value for early diagnosis (Petty & Weinmann, 1997).

In non-smokers without respiratory disease, FEV_1 begins to decline at the age of 35 at a rate of 25 to 30ml per year. In smokers that are susceptible to cigarette smoke, this decline is more severe and the heavier the smoking the more severe the decline (Scanlon *et al.*, 2000; Senior & Anthonisen, 1998; ATS, 1995). These smokers experience a decline twice as fast as non-smokers (50 to 60ml per year). However, the average decline that smokers experience is not significant enough to cause symptomatic airflow obstruction, until FEV_1 reaches a level below 50% of its predicted value. This leads to the conclusion that the decline in FEV_1 which COPD patients experience, is significantly larger compared to the average smoker. There is a direct relationship between the initial FEV_1 level and the slope of FEV_1 decline.

In men, there is a stronger relationship between FEV_1/FVC and declining FEV_1. Age, smoking history and number of cigarettes currently smoked are all factors that would contribute to a more rapid decline in FEV_1. After smoking cessation, the FEV_1 decline returns to that of a non-smoker, although actual FEV_1 does not return to that of a non-smoker (Senior & Anthonisen, 1998; ATS, 1995).

1.2 Forced vital capacity (FVC)

FVC is the maximum volume of air that can be forcefully exhaled after maximal inspiration. For a successful test, complete exhalation is required (Stewart, n.d.:24). In COPD patients, FVC can be reduced. FVC is typically assessed in conjunction with FEV_1 and expressed as a ratio of these two measurements (FEV_1/FVC). A positive diagnosis for COPD requires a reduced FEV_1 in combination with the FEV_1/FVC ratio reduced below 70%. FEV_1/FVC is a more sensitive measure for airflow obstruction and measurements below 70% can be measured before FEV_1 is reduced to a significant level. Due to this, FEV_1/FVC has immense value in early detection of COPD (Pauwels *et al.*, 2001; O'Brien *et al.*, 2000).

1.3 Maximum voluntary ventilation (MVV)

MVV differs from other dynamic lung function tests in that it assesses maximal effort throughout a preset interval (12 seconds), whereas most other tests focus on a single manoeuvre. Important information obtained from this test includes, "an overall assessment of effort, coordination and the elastic and flow-resistive properties of the respiratory system" (Fishman, 1998:547). Some patients cannot perform this test, due to the effort necessary to continue maximal ventilation for 12 seconds. A normal MVV test rules out moderate to severe COPD and restrictive disease (Fishman, 1998:547). According to Efremidis and co-workers (2005), MVV is a good predictor of peak VO_2 or exercise tolerance in COPD patients.

Exercise tolerance is determined by expressing V_E as a fraction of MVV. A limitation to this method is that MVV varies according to V_T and end-expiratory lung volume. Therefore, there will be a considerable difference between MVV at rest and MVV during exercise. Another factor to consider is that the pattern of respiratory muscle activation differs from rest to exercise. Another limitation is that MVV during exercise may be underestimated due to bronchodilatation during exercise. Therefore, MVV values of individual patients vary according to different situations (Gallagher, 1994).

The ratio between MVV and $V_E$max is diagnostically more useful than MVV alone. This ratio can contribute to distinguishing between COPD and restrictive lung disease (Gallagher, 1994).

1.4 Peak expiratory flow (PEF)

PEF measurements are useful for assessment of the impact of different factors on the airways. This test is easy to perform, inexpensive and well tolerated by patients. PEF measurements are useful when a series of measurements are needed for a particular patient (Bellia *et al.*, 2003; BTS, 1997).

FEV_1 and PEF are similar in that both require a forced expiratory manoeuvre. PEF differs from FEV_1 in that it is "measured on the first effort-dependent portion of the forced expiratory manoeuvre", while FEV_1 "reflects airway resistance at different sites in the airways" (Bellia *et al.*, 2003). PEF measurements cannot distinguish between obstructive and restrictive disease and tend to underestimate airflow obstruction in COPD patients (BTS, 1997).

1.5 Inspiratory capacity (IC)

Recent studies determine that resting IC measures could be used to predict exercise capacity in COPD patients (Diaz *et al.*, 2000b; Murariu *et al.*, 1998). IC

can also be used to determine the extent of dynamic hyperinflation and therefore, give an indication of disease progression (Marin *et al.*, 2001; Murariu *et al.*, 1998). According to Diaz and co-workers (2000b), FEV_1/FVC is the best predictor of exercise capacity in patients without airflow limitation; however, this test gives little insight into exercise capacity of patients with airflow limitation. Their study demonstrated that IC is the best predictor of exercise capacity in patients with airflow limitation.

Albuquerque and co-workers (2006) argued that IC measurements alone do not give sufficient information about actual elastic load during exercise. Casanova and co-workers (2005) reported that static hyperinflation, as expressed by IC as a ratio of total lung capacity (TLC) (named "inspiratory fraction"), is an independent mortality predictor in patients with moderate and severe COPD. Albuquerque and co-workers (2006) found post-bronchodilator inspiratory fraction to be an independent predictor of maximal exercise capacity in COPD patients. According to these authors, inspiratory fraction gives a better indication of the impact of air trapping combined with hyperinflation. Furthermore, they found a correlation between inspiratory fraction and BMI, which could be a possible explanation for the relationship between low BMI and mortality.

1.6 Lung volumes

The measurements of total lung capacity (TLC) should be considered for patients with a FVC less than 80% of the predicted value. TLC can rule out restrictive disease and assess the severity of hyperinflation (Dueck, 2000). If elastic recoil is decreased, TLC will be increased. Residual volume (RV) can also be increased due to airway closure at higher volumes. An increase in RV subsequently results in a decrease in FVC and IC. The RV/TLC ratio is also useful as a predictor of airway obstruction, which is frequently found in COPD patients (Murray *et al.*, 2000:1191).

2. Chest radiography

Chest radiography is the most extensive used pulmonary assessment technique. The value of chest radiography includes screening for abnormalities; provides a baseline for future assessments and monitors disease progression (McArdle *et al.*, 2001:952). Chest radiographs are only accurate in severe emphysema cases and are not reliable for the diagnosis of mild emphysema (ATS, 1995). Chest radiographs are however, valuable in the exclusion of other causes of dyspnoea (Pauwels *et al.*, 2001).

Radiographic images provide the best indication of the presence of emphysema. Evidence of the presence of emphysema on a posteroanterior (PA) and lateral chest radiograph includes a low, flat diaphragm, increased retrosternal airspace, a long narrow heart shadow and rapid tapering of the vascular shadows, accompanied by hypertransradiancy of the lungs. Right ventricular hypertrophy and pulmonary hypertension cause the hilar vascular shadows to be prominent and the heart shadow to interrupt the retrosternal space (ATS, 1995).

3. Computed Tomography (CT)

CT scans are more sensitive in the diagnosis of emphysema than chest radiography. These scans can be used to identify the specific anatomic type of emphysema, as well as the assessment of the size of emphysematous bullae. The knowledge of the specific type of emphysema has no effect on therapy and thus limits the value of CT in the routine care of the COPD patient. It is, however, useful for the diagnosis of complicating bronchiectasis and to predict the benefit of pulmonary resection for giant bullous disease (Pauwels *et al.*, 2001; ATS, 1995).

4. Magnetic resonance imaging (MRI)

Although MRI scans are sometimes used in the management of COPD patients, the value of these scans are limited, this is due to the fact that large sections of the lungs have insufficient density to create a clear MRI image (McArdle *et al.*, 1996:693).

5. Sputum examination

If chronic bronchitis is stable, sputum is mucoid with occasional macrophages, as opposed to an exacerbation where sputum becomes purulent with neutrophils. Gram's stain would reveal an increased number of organisms. The most frequent pathogens cultured from sputum are *Steptococcus pneumoniae* and *Haemophilus influenzae*. Causes of exacerbations include viral infections or other oropharyngeal flora, such as *Moraxella catarrhalis* (ATS, 1995).

6. Arterial blood gas analysis

Arterial blood gas analysis has little value in the early stages of COPD, because Pa_{O2} usually remains unchanged until FEV_1 reaches a level below 50% of the predicted value. Pa_{CO2} is expected to stay normal until FEV_1 reaches a level below 25% of the predicted value (Fishman, 1998:663). Blood gas abnormalities will however, occur before cyanosis manifests (McAllister, 2002). In the early stages of COPD, the analysis of arterial blood gasses can be beneficial to detect mild hypoxaemia, particularly after exercise (Murray *et al.*, 2000).

This diagnostic tool is, however, of importance in advanced stages of COPD and is indicated when FEV_1 reduces below 40% of the predicted value or if respiratory or right heart failure is suspected. "Respiratory failure is indicated by Pa_{O2} < 8.0 kPa (60 mm HG) with or without Pa_{CO2} > 6.0 kPa (45 mm Hg) while breathing at sea level" (Pauwels *et al.*, 2001).

7. Other

Additional investigations for patients with moderate or severe COPD may have added value. Pauwels and co-workers (2001) suggested that bronchodilator reversibility testing is important to exclude asthma as a diagnosis, to establish a patient's best attainable lung function, to determine prognosis and to guide treatment decisions. However, according to the revised GOLD guidelines, although "post-bronchodilator FEV_1/FVC and FEV_1 measurements are recommended for the diagnosis and assessment of severity of COPD, the degree of reversibility of airflow limitation…is no longer recommended for diagnosis, differential diagnosis from asthma, or predicting the response to long-term treatment with bronchodilators or glucocorticosteroids (GOLD, 2006)."

Alpha-1 Antitrypsin (AAT) deficiency screening may be indicated in patients who develop COPD before 45-years of age. This screening can also be useful for families with a strong history of COPD (Pauwels *et al.*, 2001).

Aetiology

1. Risk factors

The identification of risk factors is essential for the prevention and management of any disease (GOLD, 2006). In most countries, tobacco smoking is regarded as the most important risk factor in the development of COPD (Behrendt, 2005; Croxton *et al.*, 2002; Senior & Anthonisen, 1998; BTS, 1997; ATS, 1995). Research suggests that contributing risk factors cannot explain the fact that not all smokers develop COPD. A family history of COPD seems to be the most significant risk factor, although insufficient evidence exists to determine whether this relationship is as a result of genetic or environmental factors, or a combination of both (Behrendt, 2005; Senior & Anthonisen, 1998; BTS, 1997; Petty & Weinmann, 1997;

ATS, 1995). In a survey done by Ehrlich and co-workers (2004) it was determined that in South Africa a history of tuberculosis holds a greater risk for COPD than tobacco smoke. Other important contributing risk factors for South Africa are ambient air pollution (i.e. domestic use of biomass fuel) and occupational factors (i.e. industrial and mining dust) (South African Medical Research Council, 2002; Hnizdo *et al.*, 2000).

1.1 Tobacco smoke

Tobacco smoking accounts for 80 to 90% of the risk for developing COPD (Jindah *et al.*, 2006; McAllister, 2002; ATS, 1995). The risk for developing COPD is five times higher for smokers compared to non-smokers and 50% of elderly smokers develop COPD (Jindah *et al.*, 2006).

According to the World Health Organisation (WHO) (1999:65), the current global smoking trends will result in an increase in mortality from tobacco use, from four millions deaths in 1998 to 10 million deaths in 2030. Half of these deaths will occur in productive individuals between the ages of 35 and 69, and 75% will be as a result of chronic bronchitis and emphysema (WHO, 1999:66). In South Africa, smoking contributes to one in 10 adult deaths; most of these deaths are a result of respiratory disease (Leeman, 2006).

In many countries, COPD was an uncommon disease before tobacco smoking became popular. The incidence of tobacco smoking in the United Kingdom was at its highest between 1940 and 1970. During this time, it was reported that 70% of adult males were regular smokers. A decrease in the popularity of tobacco smoking resulted in a decline in cigarette consumption after 1970. In 1970, 44% of adult women in the United Kingdom were regular smokers, after which there was a decline in the prevalence. Generally, men have larger average cigarette consumption than women (Pride & Soriano, 2002). Although the incidence of smoking is relatively low in Africa, tobacco consumption is growing at an alarming

rate. Tobacco consumption in Africa increased by 3.2% in 2000, while consumption only increased by 2.7% in other developing countries (Chan-Yeung *et al.*, 2004). A household survey in South Africa established that 42.3% of men and 10.7% of women smoked in 1998 (Department of Health & Medical Research Council, 1998).

Cigarette smoke is associated with higher death rates from chronic bronchitis and emphysema, a higher prevalence of spirometry abnormalities and respiratory symptoms. A greater annual decline in FEV_1 is probably one of the most significant effects of tobacco smoke (Pauwels *et al.*, 2001; Petty & Weinmann, 1997; ATS, 1995; Bates, 1989:152 & 157). The effect of aging and tobacco smoke on FEV1 is illustrated in figure 2.5. The maximal expiratory flow volume (MEFV) curve is thought to be the most sensitive reflection of the respiratory abnormalities in smokers. Respiratory abnormalities can be detected on the MEFV curve before changes in FEV_1 are observed (Bates, 1989:155-156). According to Bates (1989:77), smoking results in impaired tracheal clearance; this is most likely due to the loss of organised ciliary function. This impairment is partly reversible and mucociliary clearance will improve after three months in the event of smoking cessation. In some smokers, there is a permanent increase in residual volume (Bates, 1989:158). As a result of this increase in residual volume increased closing volumes can be measured. This increase in closing volume can occur before any FEV_1 abnormalities are detected (Bates, 1989:160). Conflicting evidence exists regarding the loss of elastic recoil of lung tissue in smokers. According to Bates (1989:160-161) some studies found a decrease in elastic recoil as a result of smoking, where other studies reported normal lung recoil pressures. Smoking has a significant effect on airway reactivity, as shown by a reduced $FEF_{25-75\%}$VC in smokers (Bates, 1989:161).

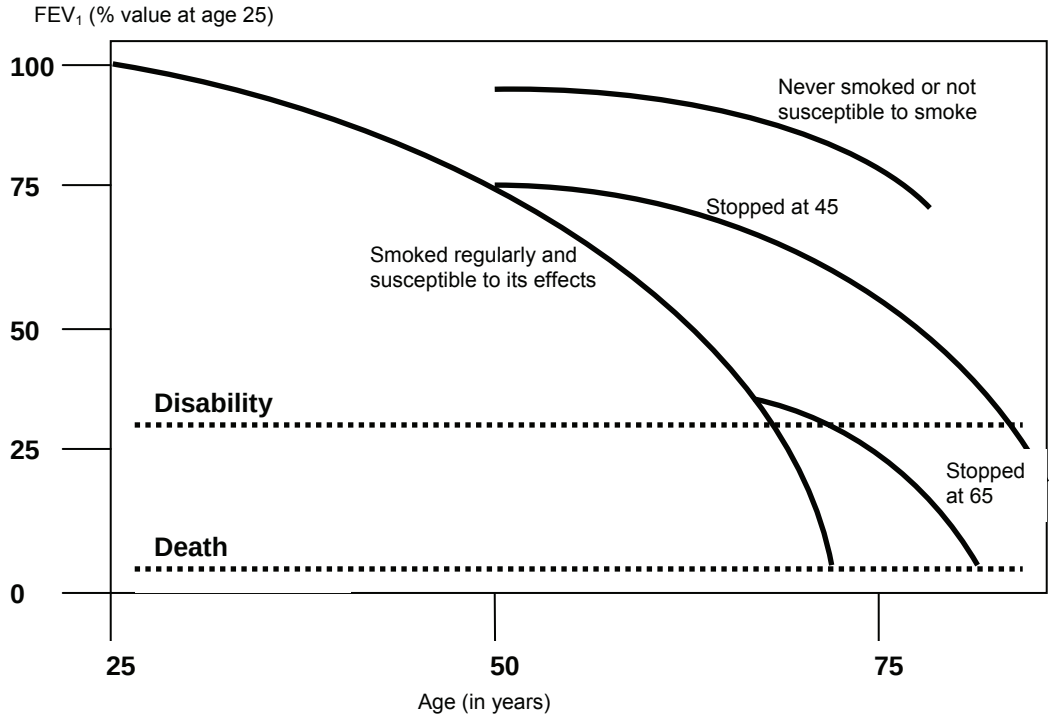

Figure 2.5 Decline in FEV_1 with age (adapted from Fletcher and Peto, 1977).

Pipe and cigar smoking are not as big a risk for COPD than cigarette smoking, although there is still an increased risk for the development of COPD when compared to non-smokers (Pauwels *et al.*, 2001; ATS, 1995).

Not all people who smoke, however, develop COPD; and not all patients with COPD are smokers or have smoked in the past. Genetic factors (Pauwels *et al.,* 2001) and occupational exposures (Bergdahl et al., 2004) have been implicated for this inconsistency. According to previous studies (Barnes, 2003; Scanlon *et al.*, 2000; ATS, 1995), only 15% of smokers develop clinically significant COPD. According to a study by Lundback and co-workers (2003), 50% of smokers may develop COPD and not 15 to 20%, as previously believed. These authors attributed the differences in prevalence to different diagnostic criteria. In the United States, the prevalence of a chronic cough is reported by 24% of smokers, 4.7% of ex-smokers and 4.0% of people who never smoked (Jindah *et al*., 2006). Watson and co-workers (2002) found that individuals with a smoking history of ten pack

years or more, combined with a low dietary intake of fruit and vegetables are at greater risk for the development of COPD. These authors suggested that low fruit and vegetable intake might be a possible explanation for the inconsistency in the development of COPD.

There seems to be a varying susceptibility to lung damage due to cigarette smoke within the general population. Only a proportion of smokers show a decline in lung function that is enough to result in severe impairment. Susceptible subjects have an accelerated rate of decline of lung function (50-90ml of FEV_1 per year compared with 20-30ml of FEV_1 per year after the age of 30 in non-smokers), as illustrated in figure 2.5 (BTS, 1997). According to the GOLD guidelines, not all individuals experience the decline in FEV_1, as illustrated in figure 2.5 (GOLD, 2006). Lundback and co-workers (2003) found that the prevalence of COPD in female smokers, aged 61 to 62 is higher than in male smokers of the same age. Recent studies suggest that women are more susceptible to the effects of cigarette smoke than men (Petty & Weinmann, 1997; Xu *et al.*, 1994).

According to Bates (1989:163) some pathologies caused by smoking are partly reversible after cessation. As mentioned previously, an improvement in tracheal mucus velocity can be measured three months after cessation. A significant improvement in FEV_1 and VC has been reported five months after cessation. The rate of disease progression is slowed down by half after smoking cessation, compared to the progression seen in smokers (Hoogendoorn *et al.*, 2005; Petty & Weinmann, 1997). The rate of FEV_1 decline can return to normal after smoking cessation, although normal lung function is not regained (McAllister, 2002; BTS, 1997). The British Thoracic Society (1997) reported that 90% of smokers would experience a cessation of excessive sputum production after smoking cessation.

Diverse acute effects of cigarette smoking have been reported. These acute effects include a small increase in airway resistance, an increase in residual

volume, flow becomes more dependent on gas density and an increase in tidal volume (due to stimulation of irritant receptors) (Bates, 1989:154).

Factors affecting the degree of the risk involved with tobacco smoke include the quantity of smoking, age of starting, total pack-years and current smoking status (ATS, 1995). According to the British Thoracic Society (1997), most COPD patients have a smoking history of between 10 and 20 pack years. One pack-year equals 20 cigarettes, one joint of cannabis or 15g or pipe tobacco per day, for one year (Bateman *et al.*, 2004).

1.1.1 Environmental Tobacco Smoke (ETS)

ETS is an important risk factor for all non-smokers (Jindah *et* al., 2006). ETS may contribute to the development of respiratory symptoms and COPD (GOLD, 2006). Children of parents who smoke are at the greatest risk to ETS and these children are more likely to take up smoking at some stage in their life. These children have a higher prevalence of respiratory symptoms and disease as well as measurable spirometry deficiencies (Jindah *et al.*, 2006; Steyn *et al.*, 2000; ATS, 1995). In South Africa, urban, coloured children are at the highest risk for exposure to ETS (Steyn *et al.*, 2000).

1.2 Tuberculosis (TB)

Tuberculosis (TB) is a contagious, infectious disease caused by the airborne mycobacterium, *Mycobacterium tuberculosis.* Other mycobacteria that have been implicated in the development of TB are *Mycobacterium bovis and Mycobacterium africanum*. An individual diagnosed with TB has a five percent chance to develop an active infection within one to two years. This risk increases substantially, if an individual contracts the AIDS-virus and becomes infected with TB (Merck Manual, 2003).

According to the Health Systems Trust (2006) the prevalence of TB in South Africa increased from 411 individuals per 100 000 in 1990 to 670 individuals per 100 000 in 2004. In developing countries, TB is more prevalent in younger individuals, whereas in developed countries, TB is predominantly diagnosed amongst older individuals. Eight million new cases of symptomatic TB are reported world wide each year (Merck Manual, 2003). Due to the high occurrence of TB in South Africa, a large population of South Africans who suffer from TB are at risk of developing COPD (Hnizdo *et al.*, 2000).

TB generally affects the lungs, although any other organ can be involved (Merck Manual, 2003). Damage to lung tissue after TB treatment includes fibrosis, bronchovascular distortion, emphysema and bronchiectasis. Pulmonary TB results in chronic impairment of pulmonary function. This adverse relationship between pulmonary TB and COPD has already between described in a study in South Africa in 1989 (Willcox & Ferguson, 1989). According to Hnizdo and co-workers (2000), recurrent TB episodes result in escalating lung function impairment. In their study, 18% of subjects with one TB episode, 27% of subjects with two TB episodes and 35% of subjects with three TB episodes, developed chronic lung function impairment (Hnizdo *et al.*, 2000). According to the WHO (1999:66), TB's mortality figures are doubled in smokers, compared to non-smokers.

The GOLD guidelines advised that in countries where the prevalence of TB is high, a diagnosis of TB should always be considered in patients with COPD symptoms (GOLD, 2006).

1.3 Genetic factors

A well established risk factor is the deficiency of the protective protease inhibitor, AAT (Pauwels *et al.*, 2001; Fishman, 1998:662; ATS, 1995). This inherited autosomal recessive disorder is rare in the general gene pool. The AAT deficiency gene increases the risk for the development of COPD 40 times (Chan-Yeung *et al.*,

2004). Despite significantly increasing the risk for COPD, AAT deficiency accounts for less than 1% of all cases of COPD (BTS, 1997; ATS, 1995).

AAT is a serum protein that is produced by the liver and usually found in the lungs (ATS, 1995). AAT protects the alveoli against destruction of structural proteins due to the actions of elastase. Destruction of the alveoli eventually develops into emphysema (ACSM, 1998a:317; ATS, 1995).

Emphysema is the result of proteolytic activity due to insufficient levels of AAT. Patients with AAT deficiency may not develop emphysema, but AAT deficient individuals who smoke have a greatly increased risk of developing emphysema, especially at an early age (Hogg & Senior, 2002).

1.4 Ambient air pollution

Ambient air pollution is considered another risk factor for COPD. However, the exact role of high levels of urban air pollution is not known. When compared to tobacco smoke, the risk seems small (Pauwels *et al.*, 2001; ATS, 1995). According to Jindah and co-workers (2006), ambient air pollution is an important factor in chronic respiratory morbidity. Air pollution has been associated with increased exacerbations and cardiovascular and respiratory mortality (McAllister, 2002).

Indoor air pollution has been implicated as a risk factor for developing COPD. The burning of biomass fuel in ill ventilated dwellings, poses a great risk for persons that are continuously exposed (Pauwels *et al*., 2001). Grobelaar and Bateman (1991) studied women in rural areas of South Africa. Their study found a relationship between COPD and biomass fuels, particularly cow dung and grinding procedures (resulting in mixed dust pneumoconiosis) used in ill ventilated houses.

1.5 Chest infections

Reduced lung function and respiratory symptoms have been associated with severe childhood respiratory infections (Tager *et al.*, 1988). According to Barnes and Godfrey (1997:3), there is an association between chest infections in the first year of life and the development of COPD at a later stage.

In COPD patients, an exacerbation is defined as "sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD" (Burge & Wedzicha, 2003). Senior & Anthonisen (1998) reported that acute exacerbations have no long-term effect on the decline rate of FEV_1. The belief that recurring chest infections can lead to COPD is described as the "British hypothesis". This hypothesis has been refuted by Fletcher and colleagues (1976) who reported that repetitive chest infections had no long-term effects on the rate of FEV_1 decline. Additionally, a study by Seemungal and co-workers (1998) found that exacerbations have a negative effect on the quality of life of patients with COPD. This study further found that previous exacerbations increase the risk for future exacerbations in COPD patients. Patients with a productive cough may also be more susceptible to chest infections and environmental risk factors (Seemungal *et al.*, 1998). Repeated chest infections may also contribute to the pathogenesis and progression of COPD (GOLD, 2006).

1.6 Occupational factors

There are certain occupational factors that can increase a person's risk for developing COPD. Mine, textile and cement workers are especially at risk for exposure to coal, silica, cotton and heavy metals (especially cadmium). Constant exposure to these substances is associated with an increase in the prevalence of COPD (especially emphysema), increased rates in FEV_1 decline and higher mortality rates (McAllister, 2002; ATS, 1995). Exposure to dust is considered more

hazardous than exposure to gas or fumes (McAllister, 2002). Hazardous airborne substances cause an increase in airway responsiveness and promote the destructive effects of cigarette smoke (McAllister, 2002; ATS, 1995). Bergdahl and co-workers (2004) showed that one out of every ten deaths, attributable to COPD, can be prevented through the reduction of exposure to inorganic dusts alone. Trupin and co-workers (2003) found that occupational exposures can increase the risk for the development of COPD by more than 100%, even after tobacco consumption is taken into account. Although the mechanisms through which dust exposure increases the risk for COPD remain unclear, scarring or fibrosis of the smaller airways and parenchyma could be a possible explanation (Bergdahl *et al*., 2004).

1.7 Gender and race

Generally, it is believed that men, compared to women, are more at risk of developing COPD (Fishman, 1998:662; Petty & Weinmann, 1997; ATS, 1995). The fact that tobacco use is higher among men is responsible for this misconception. According to Senior and Anthonisen (1998), women are more prone to airway reactivity and rapid decline of FEV_1, which increase their risk for the development of COPD. Recent studies have shown that females are more likely to experience respiratory symptoms than males (Dales *et al.*, 2006; De Torres *et al.*, 2005). Furthermore, females are more likely to be diagnosed with chronic airway disease and respiratory medication is more frequently prescribed. A possible explanation for gender differences in COPD diagnoses, is the fact that females might express their experience of respiratory symptoms as more severe, compared to males. This might result in unintentional gender-related biases by physicians (Dales *et al.*, 2006). According to De Torres and co-workers (1995), women develop significant airflow obstruction at a younger age with a lower smoking history, compared to men. These authors also found that women have more exacerbations than men. Although symptoms experienced by women might be more severe, women with COPD tend to have better survival rates than men. A

possible explanation for this is the fact that women have higher Pa_{O2} and lower Pa_{CO2} levels than men with similar FEV_1 values.

Mortality rates are higher among white females compared to other races. The difference between white males and other races is smaller (ATS, 1995).

1.8 Socio-economic status

It appears that there is a decline in the prevalence of COPD with an increase in socio-economic status. This difference may however, be attributed to higher exposure to air pollutants, crowding and poor nutrition in lower socio-economic classes (McAllister, 2002; Pauwels *et al.*, 2001; ATS, 1995). Cooking in ill ventilated kitchens or single room houses may contribute to indoor air pollution and result in a significant increase in risk for the development of respiratory disease (Jindah *et al*., 2006). Other factors that can cause the apparent correlation between low socio-economic status and the risk for COPD, is poor housing, exposure to secondary smoke, popularity of active smoking, increased lower respiratory tract infections during childhood and occupational exposures (McAllister, 2002).

1.9 Acquired Immune Deficiency Syndrome (AIDS)

Limited studies exist on the relationship between COPD and HIV (Human Immunodeficiency Virus) or AIDS. A number of HIV-seropositive individuals experience respiratory symptoms, such as dyspnoea, coughing and sputum production, which cannot be explained by AIDS-related pulmonary complications. Evidence exists to suggest that HIV infection can contribute to the damaging effects of tobacco smoking and consequently increases the risk for the development of COPD (Diaz *et al.*, 2003). Diaz and co-workers (2000a) reported that HIV infection is associated with an increased rate in the onset of smoking-related emphysema.

1.10 Reactivity of airways

One possibility to account for differences in the susceptibility to develop COPD, is that there is a genetically determined predisposition to develop allergy and bronchial hyperresponsiveness, the *"Dutch Hypothesis"* (Pauwels *et al.,* 2001; Scanlon *et al*., 2000; ATS, 1995). According to this hypothesis, asthma, emphysema and chronic bronchitis are different manifestations of a single disease process. Whether an individual develops asthma, bronchitis or emphysema, is a result of genetic and environmental factors that are modulated by age and gender. An alternative school of thought is the *"Two-type Hypothesis"*, which includes a Dutch-type limb termed *"Chronic Asthmatic Bronchitis"* or *"Overlap Syndrome"* and a more insidious form which leads to chronic bronchitis and emphysema. Both schools of thought, however, emphasise the interrelationship between bronchial hyperreactivity, infection and smoking. Recently, the focus was placed on identifying the population most at risk of developing COPD (Fishman, 1998:662).

Non-specific airway reactivity might be a risk factor for COPD. Reactivity is inversely related to FEV_1 and may be predictive of an accelerated rate of decline of spirometry in smokers. The specific role that it plays in the development of COPD is unclear and might be attributable to inflammation (Senior & Anthonisen, 1998; Petty & Weinmann, 1997; ATS, 1995). Airway reactivity is more common in women than in men and the rate of decline in FEV_1 is also more severe in women (Senior & Anthonisen, 1998; Tashkin *et al.*, 1992). In some cases there is a relationship between exposure to tobacco smoke or other noxious particles and gases and hyperresponsiveness of the airways (Pauwels *et al.*, 2001).

2. Symptoms

COPD patients experience various symptoms, some of which could be attributed to co-morbidities (ATS, 1999). Generally, symptoms only occur late in the disease

process (once patients have lost more than 50% of their lung function). Chronic coughing, excessive sputum production, dyspnoea and functional impairment are among the most frequent complaints (McAllister, 2002; Murariu *et al*., 1998; O'Donnell *et al*, 1995). Other common symptoms include weight loss, sleep disturbance, depression and anxiety (McAllister, 2002). This section will concentrate on dyspnoea, functional impairment and weight loss; other symptoms will be discussed elsewhere.

2.1 Dyspnoea

Dyspnoea is defined as an uncomfortable awareness of breathing or an increase in respiratory effort that is regarded as abnormal by the patient and can lead to functional impairment (Lareau *et al.*, 1994; Mahler, *et al.*, 1984). Dyspnoea is a common symptom of patients with COPD and can be distressing and disabling despite optimal medical therapy. Increased intrinsic mechanical loading of inspiratory muscles, increased mechanical restriction of the chest wall, functional weakness of inspiratory muscles, increased ventilatory demand, gas exchange abnormalities, cardiovascular limitations and dynamic hyperinflation are contributing factors to exertional dyspnoea (Franssen, 2003; Gosselink, 2003; Marin *et al*., 2001; ATS, 1999; Carrieri-Kohlman *et al.*, 1996; Lareau *et al*., 1994). Other factors that contribute to dyspnoea include hypercapnia, hypoxaemia (Fishman, 1998:665), loss of alveolar tissue and skeletal muscle weakness (Franssen, 2003). According to Nishimura and co-workers (2002), dyspnoea classification is a better indicator of mortality than FEV_1.

It is important to quantify the impact of dyspnoea on patients to evaluate medical therapy and for successful individualisation of rehabilitation programmes (ATS, 1999; Lareau *et al.*, 1994). Dyspnoea can be assessed through psychophysical methods and clinical scales (Mahler *et al.*, 1984). Instruments for the measurement of the effect of dyspnoea on functional status and daily activities include the Medical Research Council dyspnoea questionnaire, the Baseline and

Transitional Dyspnoea Indexes (BDI and TDI) and the Pulmonary Functional Status and Dyspnoea Questionnaire (PFSDQ). Mahler and co-workers (1984) found dyspnoea ratings to be effective in assessing and quantifying breathlessness, although no correlation was found between dyspnoea ratings and pulmonary function. Various scales and questionnaires exist for the measurement of exertional dyspnoea. Most commonly used are the Borg scale of perceived exertion (Borg RPE scale) (Appendix A) and the visual analogue scale (VAS) (ATS, 1999; Carter *et al.*, 1993; Borg, 1982).

Dyspnoea leads to impaired functional capacity, a decline in the ability to perform daily tasks and consequently, impaired quality of life (Boueri *et al.*, 2001). The impact of dyspnoea may vary. Dyspnoea may only be associated with activities; it can limit activities or activities may be eliminated altogether (ATS, 1999). Patients with mild COPD do not typically complain of dyspnoea, probably due to the body's ability to adapt to minor reductions in pulmonary function. However, the daily function of these patients may be impaired (Carter *et al.*, 1993). Dyspnoea often results in lack of confidence to perform physical activities. This causes patients to refrain from physical activities that they are physically capable of performing (Wigal *et al.*, 1991).

Pulmonary rehabilitation programmes are essential to improve exercise tolerance (Boueri *et al.*, 2001). Programmes that focus on education and exercise training play a vital role in assisting patients to manage dyspnoea (Scherer & Schmieder, 1997).

2.2 Impairment of functional capacity

Dyspnoea and impaired functional capacity are interrelated (Franssen, 2003; Carter *et al.*, 1993). As dyspnoea increases, patients tend to develop sedentary lifestyles, which in turn will contribute to impaired functional capacity (Carter *et al.*, 1993).

Assessment of functional capacity in COPD patients is vital to management and understanding the impact of the disease. The 6MWT, that was adapted from the 12-minute walk test, is most frequently used for this purpose (Pinto-Plata *et al.* 2004; Carter *et al.*, 2003).

Generally, the use of the 6MWT is limited to the assessment of the functional status of patients living with COPD. The 6MWT is normally influenced by two main physiological factors, namely the degree of airflow limitation (FEV_1) and the single breath carbon monoxide diffusion capacity (Marin *et al.*, 2001). Benefits in using the 6MWT are that it is simple to administer, requires no specialised equipment, has been standardised and reflects the capacity to perform day-to-day activities (Carter *et al*., 2003; Enright *et al.*, 2003).

Pinto-Plata and co-workers (2004) illustrated that the 6MWT is a better indicator of mortality than FEV_1 and BMI. This study also found that a decline in 6MWDs occurs independently of changes in lung function.

2.3 Weight loss

It is widely accepted that COPD is accompanied by weight loss (Wilson *et al.*, 1989). According to Engelen and co-workers (1994), between 20% and 70% of COPD patients, are estimated to be underweight. Weight loss and a low body weight are associated with increased morbidity and a poor diagnosis for COPD patients (Farber & Mannix, 2000; Engelen *et al.*, 1994). According to Wouters (2002), a loss of more than 40% of metabolising tissue, will result in death. This was confirmed by other retrospective survival studies that reported that low body weight is associated with higher mortality rates (Schols *et al.*, 1998; Gray-Donald *et al.*, 1996; Wilson *et al.*, 1989). According to Gray-Donald and co-workers (1996), body mass index (BMI) is a strong predictor of mortality. Baarends and co-workers (1997) indicated that BMI is not sensitive to changes in muscle mass and therefore

not suitable for mortality prediction or indication of exercise capacity. Weight loss in COPD patients can be attributed to the loss of muscle mass and not fat, as in the case of starvation (Mador, 2002). According to Marquis and co-workers (2002), muscle wasting is the actual indicator of mortality and not weight loss *per se*. Muscle wasting can occur in the absence of weight loss and therefore body weight might be a false reassurance of survival. The correlation between muscle wasting and mortality is explained by the presence of important amino acids in muscle tissue. Depletion of these amino acids impairs vital physiological functions, such as immune defence and tissue regeneration (Kotler, 2000).

Due to the increased energy requirements of the respiratory muscles, COPD patients have increased resting energy requirements. It is of vital importance that patients with COPD are educated on good dietary habits. Well-balanced dietary habits are essential to maintain an ideal body weight (Schols *et al*., 1998; ATS, 1995). Several studies have shown that the implementation of good dietary habits in malnourished COPD patients, lead to an increase in body weight, fat-free body mass, respiratory muscle function, and subsequently higher survival rates (Rochester, 2003; Schols *et al*., 1998; Schols *et al.*, 1995; Rogers *et al*., 1992; Whittaker *et al.*, 1990; Efthimiou *et al*., 1988).

Treatment

The three most important goals in the treatment of COPD patients, according to the American Thoracic Society (1995), are to lessen airflow limitation, to prevent and treat secondary medical complications and to improve quality of life by decreasing respiratory symptoms. Pauwels and co-workers (2001) summarised the goals for treatment of COPD patients as: “(1) prevent disease progression, (2) relieve symptoms, (3) improve exercise tolerance, (4) improve health status, (5) prevent and treat complications, (6) prevent and treat exacerbations and (7) reduce mortality”. Petty and Weinmann (1997) also emphasised the importance of the alteration of disease progression and alleviation of symptoms.

Currently medical treatment for COPD has only partial success when it comes to reduction of symptoms and the improvement of functional capacity (Calverley & Pride, 1995:528). Management of patients with COPD should therefore include a wide range of treatment modalities; these include patient education, preventive care, smoking cessation, pharmacological and oxygen therapy, ventilatory muscle training and exercise rehabilitation (Pinto-Plata *et al.*, 2004; Guyatt *et al.*, 1984). Figure 2.6 illustrates the approach to the management of COPD according to the American Thoracic Society (1995).

It is important to note that patients respond differently to different treatment modalities and certain treatments may result in benefits in more than one area. Therefore, treatment goals need to be adjusted according to a patient's specific needs and responses (Pauwels *et al.*, 2001).

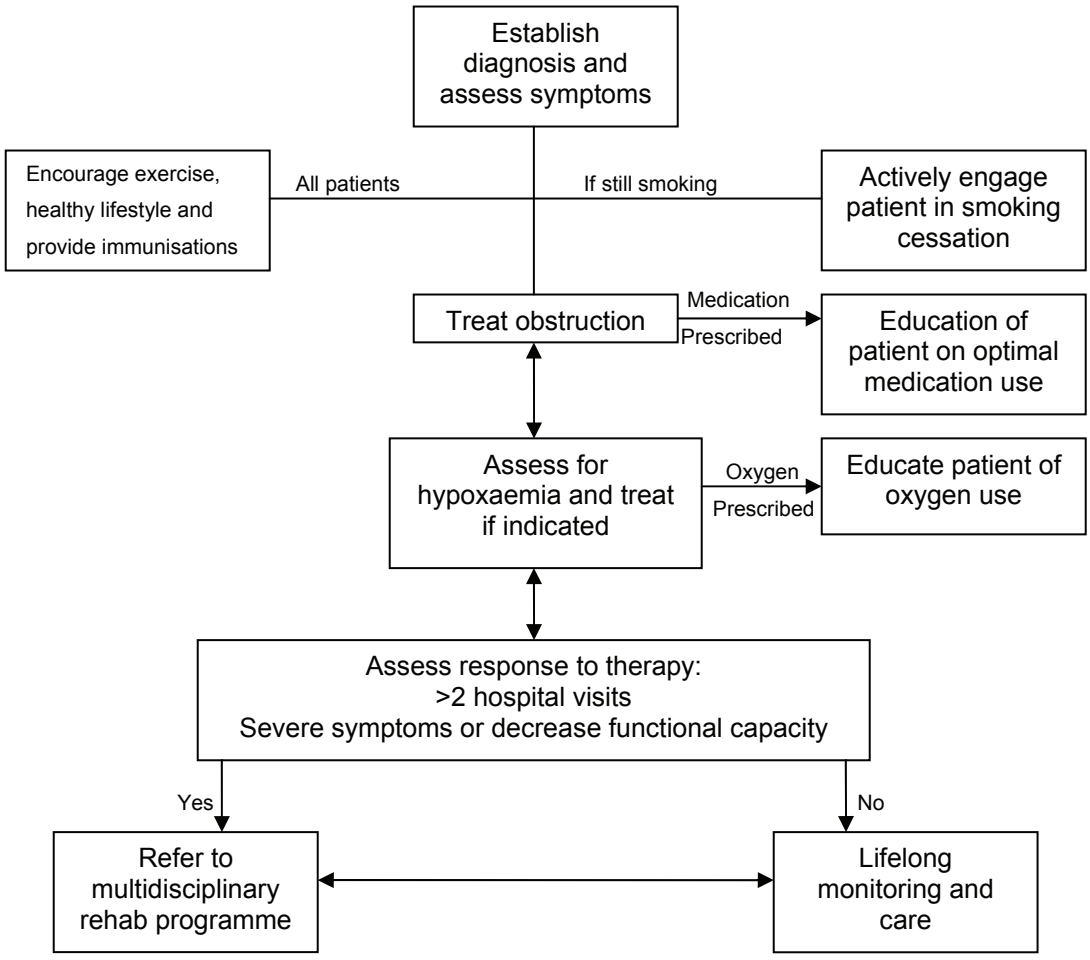

Figure 2.6 Management of COPD (ATS, 1995).

1. Drug and inhaler treatments

According to the American Thoracic Society (1995), there is no evidence to suggest that early regular use of pharmacotherapy can alter the progress of COPD.

1.1 Bronchodilators

Most COPD patients respond to bronchodilator therapy (Petty & Weinmann, 1997). Bronchodilators are effective in reducing dyspnoea, coughing intensity and wheezing (Calverley, 2001). The use of a bronchodilator results in a significant increase in FEV_1 in most patients with COPD (Senior & Anthonisen, 1998). According to O'Brien and co-workers (2000), bronchodilators can reduce pulmonary hyperinflation even if no change in FEV_1 is observed. Both short- and long-acting beta2-agonists and anticholinergic agents are generally effective (Calverley, 2001; Petty & Weinmann, 1997). Szafranski and co-workers (2003) found that the use of budesonide/formoterol was effective for the management of moderate to severe COPD. In their study, the use of this long-acting beta-antagonists reduced exacerbations, improved lung function, symptoms and HRQL (Szafranski *et al.*, 2003). Because COPD patients are typically, older patients it is important to bear in mind that they may have less tolerance to sympathomimetic-induced tremors and cardiac side effects. Due to fewer side effects, slower onset and longer action, a long-acting anticholinergic agent might be more effective than a long-acting $beta_2$-agonist (ATS, 1995). Calverley and co-workers (2007) found that the use of combination therapy, with a long-acting beta-antagonist/corticosteroid combination, was effective in reducing exacerbations and improved health status and lung function. No statistically significant improvement in mortality was documented (Calverley *et al.*, 2007). According to Senior and Anthonisen (1998) although bronchodilators have short-term benefits for COPD patients, insufficient evidence exists to conclude that this therapy will alter the long-term course of the disease.

Despite theophylline's potential for toxicity, it still has a vital role to play in the treatment of COPD patients, if careful dosing is applied. It has the most value in the patient who cannot use aerosol therapy optimally. Due to its long-acting nature, theophylline can be taken once or twice a day (ATS, 1995). It improves respiratory muscle function, improves cardiac output, reduces pulmonary vascular

resistance and improves perfusion of ischemic myocardial muscle (Petty & Weinmann, 1997; ATS, 1995).

Tantucci and co-workers (1998) found that salbutamol significantly reduced FRC and increased inspiratory capacity. This improvement originates from a reduction in hyperinflation.

1.2 Anti-inflammatory therapy

COPD is characterised by constant airway inflammation. In advanced stages of this disease the number of neutrophils in the alveolar structures increase, which warrants anti-inflammatory therapy, in the form of either oral or inhaled corticosteroids (Calverley, 2001). According to the American Thoracic Society (1995), the role of anti-inflammatory treatment in the COPD patient is unclear. This society proposed that insufficient evidence exists to suggest that anti-inflammatory agents will have added benefits for the COPD patient already on a regular bronchodilator. Other studies reported that inhaled corticosteroids had no effect on the decline of FEV_1 (Burge *et al.*, 2000; The Lung Health Study Research Group, 2000; Vestbo *et al.*, 1999). According to the GOLD report, the use of corticosteroids should be considered in patients with a FEV_1 less than 50% of the predicted value if they experience at least one exacerbation per year. Inhaled corticosteroids will reduce the frequency of exacerbations and improve health status in this population (GOLD, 2006; Pauwels *et al.*, 2001).

In the event of an acute exacerbation, a short course of oral corticosteroids is mandatory (GOLD, 2006; Petty & Weinmann, 1997; ATS, 1995). Side effects of systemic corticosteroids in the older population include skin damage, cataracts, diabetes, osteoporosis and secondary infection; therefore, long-term use is not recommended (GOLD, 2006; ATS, 1995).

1.3 Antibiotics

The use of a broad spectrum antibiotic for the treatment of acute exacerbations is widely accepted (Petty & Weinmann, 1997; ATS, 1995). According to the guidelines of the South African Thoracic Society, antibiotics "should be prescribed where there is clear evidence or strong suspicion of an infection (marked sputum purulence and/or fever)" (Bateman *et al.*, 2004). The presence of *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* (organisms commonly involved in infection) could be confirmed by sputum Gram stain, but is not essential. Resistance to macrolides and doxycycline should be kept in mind when prescribing an antibiotic. Alternative agents include amoxycillin/clavulanate, cefuroxima or quinolones (Bateman *et al.*, 2004). According to Petty and Weinmann (1997), sputum cultures may be misleading and broad spectrum antibiotics should be given on an empiric basis (Petty & Weinmann, 1997). There is no evidence to suggest that antibiotics have any benefits in the prevention or treatment of COPD exacerbations due to the fact that the cause of these exacerbations is unknown. However, symptoms of an infection, such as fever and changes in the chest radiograph, will justify a course of antibiotics (Senior & Anthonisen, 1998; ATS, 1995). In the case of severely ill patients, or recurrent infections, treatment should be continued for 10 to 14 days (Bateman *et al.*, 2004). The benefits provided by flu vaccines suggest that exacerbations are partly due to airway infections. Antibiotics can also be useful in the treatment of recurrent infections (Senior & Anthonisen, 1998; ATS, 1995).

1.4 Other pharmacologic agents

In younger, non-smoking patients with a severe AAT deficiency, with associated emphysema, AAT augmentation therapy may be justified (ATS, 1995). Immunisations with pneumococcal and influenza vaccines are recommended to prevent exacerbations and infections of the respiratory tract (Calverley, 2001; ATS, 1995).

1.5 Adjustment of therapy

Vital to the success of pharmacologic therapy is a dynamic relationship between the physician and the patient. Patients must be educated on therapy possibilities and become actively involved in treatment (ATS, 1995).

2. Oxygen therapy

Supplemental oxygen could be life preserving for COPD patients. Oxygen is administered to correct or prevent hypoxaemia (Soo Hoo, 2003; Petty & Weinmann, 1997; ATS, 1995). Oxygen therapy has a positive affect on mortality and the more continuous the therapy, the larger the effect (Soo Hoo, 2003; Senior & Anthonisen, 1998). Figure 2.7 illustrates how oxygen therapy increased survival in a study conducted by the Medical Research Council Working Party (1981).

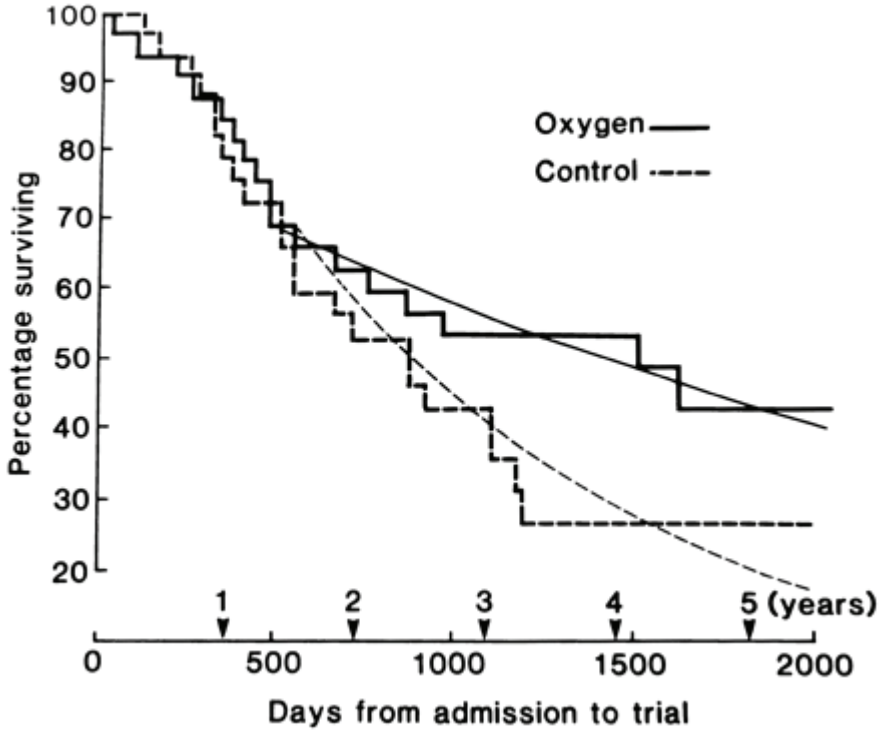

Figure 2.7 Results of British trials of home oxygen therapy in hypoxemic chronic obstructive pulmonary disease. Survival is plotted against time of follow-up.

2.1 Benefits of oxygen therapy

Long-term oxygen therapy holds various benefits for the hypoxaemic patient. Physiological benefits include reversal of secondary polycythemia, alleviation of right heart failure (caused by cor pulmonale), strengthening of cardiac function and improvement of pulmonary hypertension and enhancement of neuropsychological function. Other benefits for the patient include an increase in body weight, a decrease in hospitalisations, an improvement in exercise ability and improved quality of life. It was furthermore found that long-term, continuous oxygen therapy improves the survival of hypoxaemic COPD patients and reduces overall mortality (Fujimoto *et al.*, 2002; ATS, 1995). Other benefits of supplemental oxygen during exercise is summarised in table 2.3.

Table 2.3 Benefits of supplemental oxygen for COPD patients during exercise (Soo Hoo, 2003).

Treatment	**Mechanism of benefit**
Oxygen	Prevents oxygen desaturation
	Decreases pulmonary artery pressure
	Improves right ventricular function
	Decreases minute ventilation
	Decreases dyspnoea
	Decreases or delays diaphragmatic fatigue
	Decreases diaphragmatic work
	Increases exercise endurance
	Decreases serum lactate levels
	Decreases tachycardia
	Reverses hypoxia-induced bronchoconstriction
Hyperoxia	All of the above (probably dose-related effect)
	Decreases ventilatory drive
	Slows respiratory rate
	Decreases dynamic hyperinflation

Most studies concerned with oxygen therapy focused on COPD patients with severe hypoxaemia, due to the belief that oxygen therapy would have little effect on mild hypoxaemia (Fujimoto *et al*., 2002). A study by O'Donnell and colleagues (1997) found that patients with mild hypoxaemia, at rest, could experience improved exercise tolerance and dyspnoea during exercise with supplemental oxygen. Fujimoto and colleagues (2002) further documented significant improvements in exercise performance of COPD patients who experienced mild hypoxaemia at rest. The factor that determines the extent of the improvement of exercise performance during oxygen inhalation is the degree of airflow obstruction and not the degree of hypoxaemia (Fujimoto *et al.*, 2002).

2.2 Mechanisms of improvement

The mechanisms in the reduction of the mortality of COPD patients by the administration of long-term oxygen therapy, are not yet fully understood. It may be explained by the reduction in pulmonary arterial pressures. The pulmonary arterial pressures tend to increase in chronic hypoxaemic patients and oxygen therapy causes a reduction in these pressures. However, these pressures are not lowered to normal levels, but the reduction is enough to improve cardiac output and tissue oxygen delivery.

Oxygen inhalation can improve pulmonary hypertension in patients with moderate to severe airflow obstruction. The mechanism of this improvement is related to the inhibition of hypoxic vasoconstriction and a reduction in pulmonary artery occlusion pressure (Fujimoto *et al.*, 2002).

2.3 Oxygen therapy during exercise

Activity or exercise is encouraged in COPD patients. Some hypoxaemic patients experience an increase in hypoxaemia during exercise and others, who are not hypoxaemic during rest, develop it during exercise. Although it is not supported by research, home supplemental oxygen is often prescribed for patients who are hypoxaemic only during exertion. Immediate benefits of oxygen during exercise include the reduction of dyspnoea and improvement in exercise tolerance and minute ventilation during submaximal workloads (Fujimoto *et al.*, 2002; ATS, 1995).

2.4 Hazards of oxygen

Generally, oxygen therapy is considered safe. There are, however, some dangers that should be taken into account when prescribing oxygen therapy. These include oxygen toxicity, CO_2 retention and physical hazards (ATS, 1995).

2.4.1 CO_2 retention

CO_2 retention is not a common risk in low-flow oxygen therapy. Supplemental oxygen may suppress the ventilatory drive which can lead to aggravation of hypercapnia, respiratory acidosis and CO_2 narcosis (McAllister, 2002; ATS, 1995). Patients with an intact renal system will be able to tolerate CO_2 retention (ATS, 1995).

2.4.2 Physical hazards

Fires and explosions are the major physical risks of oxygen therapy. Smoking during oxygen therapy is, in most cases, the cause of these fires. Explosions could occur if an oxygen canister is knocked over. These fires and explosions are rare and with proper education of patients, family and caregivers, can be avoided (ATS, 1995).

3. Surgical treatments

Due to an increased risk for mortality and morbidity in surgical treatment of the COPD patient, it is important to assess the risk-benefit ratio prior to surgery to assure that the benefits outweigh the risks. Pulmonary function studies are important to assess physiological operability prior to surgery (ATS, 1995).

3.1 Lung transplantation

Lung transplantation can be lifesaving for some patients and has shown to improve quality of life and functional capacity of patients with severe COPD (Pauwels *et al.*, 2001; ATS, 1995). According to Pauwels and co-workers (2001) patients should be considered for lung transplantation when their FEV_1 lowers to below 35% of the predicted value, their Pa_{O2} lowers to 7.3 to 8.0 kPa (55 to 60 mm Hg), their Pa_{CO2} rises above 6.7 kPa (50 mm Hg) and secondary pulmonary hypertension is

diagnosed. However, this procedure is impeded by high costs, donor availability and requires lifelong immunosuppression (ATS, 1995).

3.2 Lung volume reduction surgery

As a result of the loss of elastic recoil, the conducting airways may collapse. Collapsed airways will lead to severe expiratory flow limitation, dynamic hyperinflation and intrinsic positive end-expiratory pressure ($PEEP_i$) (Dueck, 2000).

Lung volume reduction surgery (LVRS) is a surgical procedure in which parts of the lung are resected to reduce hyperinflation. This improves mechanical efficiency of the respiratory muscles by improving the effectiveness of pressure generation (as measured by length/tension relationship, curvature or diaphragm and area of apposition). LVRS can significantly improve the elastic recoil, which will increase the diameter of the collapsed airways, and therefore improves expiratory flow rates (GOLD, 2006; Gelb *et al*., 1996b).

According to Hamacher and co-workers (2002), apart from improvements in dyspnoea, walking distance and pulmonary measures, LVRS is associated with significant improvements in quality of life. Furthermore, their study indicated that quality of life improvements are maintained for at least two years.

However, insufficient evidence exists to fully understand the role and benefits of LVRS and the high cost involved limits this procedure to a small population (GOLD, 2006; Pauwels *et al.*, 2001).

3.3 Resection of large bullae

In the patient where large bullae are compressing normal tissue, this surgery can relieve dysfunction and dyspnoea (Pauwels *et al.*, 2001; ATS, 1995). Computed tomography is generally used to differentiate between large bullae and non-

compressive destructive emphysema (ATS, 1995). CT scans, together with arterial blood gas analyses and comprehensive respiratory function tests, are essential for determining a patient's suitability for surgery (Pauwels *et al.*, 2001).

4. Smoking cessation

Smoking cessation is one of the key elements in the treatment of patients with not just COPD, but all lung conditions (Willemse *et al.*, 2004; Buist, 2003). According to Senior and Anthonisen (1998), smoking cessation is the best way to change the disease process of COPD. The success rate of cessation is as low as 27% and multiple interventions are sometimes necessary for successful smoking cessation. Table 2.4 summarise the elements of successful smoking cessation (ATS, 1995).

Table 2.4 Protocol for smoking cessation (ATS, 1995).

1	Initiation	Physician or health care worker should initiate quitting, explaining risks of cigarette smoking for the individual and including strong admonition. Encourage establishment of a definite quit date. Offer referral for self-help or group programme.
2	Early follow-up	Telephone patient within three to five days after quit date. Review progress and counsel regarding recruitment of support person. Call again one to two weeks after quit date. Repeat as needed.
3	Continuing reinforcement	Further follow-up should be arranged by physician or health care worker. Next regular visit should be less than two months after initiating cessation programme; assess progress with expired air and/or cotinine in urine, blood or saliva. If absent, review and reward success and reinforce prior warnings. May follow up by phone monthly until next visit; continue follow-up at increasing intervals for 12 months after quit date.
4	Failure	If a patient fails to achieve abstinence or does so but relapses, physician or health care worker should review programme with patient, emphasising elements of success and identifying circumstances of failure; explore alternatives. Nicotine replacement may be used to control withdrawal symptoms; infrequently other pharmacologic therapy, such as clonidine of buspirone, may be discussed. Hypnosis may be considered, but is of little value when applied as a single-session recourse. Acupuncture is not recommended.

Despite the emphasis from all parties concerned to promote smoking cessation, 26% of COPD patients have never been advised to quit smoking (Sherman *et al.*, 2003).

4.1 Factors influencing cessation

Factors that influence the success rate negatively include the addictive potential of nicotine, conditioned response, depression, poor education, low income and forceful promotional campaigns by the tobacco industry (ATS, 1995). The latter

will not be considered in the South African setting, due to the tobacco laws. Sherman and co-workers (2003) found equal success rates for smoking cessation in COPD and non-COPD patients, despite the fact the COPD patients are more often referred to smoking cessation programmes. Factors contributing to unsuccessful cessation in COPD patients include depression, poor education and the perception among COPD patients that it is more difficult for them to quit than for the average person (Sherman *et al.*, 2003).

4.2 Pharmacotherapy

Today there are numerous pharmacotherapies available to assist patients in smoking cessation. Research has shown that any form of nicotine replacement therapy is effective for smoking cessation and long-term abstinence (Calverley, 2001; Lancaster *et al.*, 2000). Other pharmacotherapies that have shown success are antidepressants and the antihypertensive drug clonidine. Clonidine is associated with various side effects that limit its usefulness (Lancaster *et al.*, 2000). Antidepressants with dopamine agonist properties (e.g. bupropion), have been highly successful in assisting in smoking cessation (Calverley, 2001). These agents are however, only of value if smokers are adequately motivated to discontinue their habit.

4.3 The effects of cessation on lung function

A study by Scanlon and co-workers (2000) investigated the effects of smoking cessation on the lung function of 5 887 COPD patients with mild to moderate airflow obstruction. One of their key findings was that the annual FEV_1 decline in patients, who quit smoking, was half that of patients that continued smoking, over a four year period. Patients who continued smoking had an average decline of 62ml per year, compared to the 31ml per year in quitters. According to this study, the factors that influence the improvement or stabilisation of FEV_1 include baseline pulmonary measures, baseline bronchodilator responsiveness, race and age.

Factors that are responsible for a greater improvement, during the first year of cessation, include greater airway responsiveness, lower initial lung function, younger age, heavy smoking and the female gender. Importantly, women who continued smoking had a greater loss of lung function compared to men with similar smoking rates (Scanlon *et al*., 2000). This could be explained by the fact that women are more susceptible to the harmful effects of cigarette smoking (Petty & Weinmann, 1997; Xu *et al*., 1994). Willemse and co-workers (2004) demonstrated that smoking cessation improves airway hyperresponsiveness.

5. Pulmonary rehabilitation

Rehabilitation is defined by the British Thoracic Society (BTS) (1997) as "the restoration of the individual to the fullest medical, mental, emotional, social and vocational potential of which he/she is capable". The American College of Chest Physicians (ACCP) defines pulmonary rehabilitation as "an art of medical practice wherein an individually tailored, multidisciplinary programme is formulated, which through accurate diagnosis, therapy, emotional support and education, stabilizes or reverses both the physiology and psychopathology of pulmonary diseases and attempts to return the patient to the highest possible functional capacity allowed by this pulmonary handicap and overall life situation" (ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997).

The most recent definition adopted by the ATS and ERS is:

> "Pulmonary rehabilitation is an evidence-based, multidisciplinary and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation and reduce health care costs through stabilizing or reversing systemic manifestations of the disease" (Nici *et al.*, 2006).

The use of pulmonary rehabilitation to enhance standard therapy of patients with COPD, is well documented and widely accepted. It also forms an essential part of the clinical management and health maintenance of these patients (Nici *et al.*,

2006; Rochester, 2003; ATS, 1999; American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), 1998; Fishman, 1998; ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997; Celli 1995; Ries *et al.*, 1995; Curtis *et al*., 1994; Cox *et al.*, 1993). According to Mahler (1998), several factors played a role in the renewed interest in pulmonary rehabilitation that was experienced in recent years. The key factors, according to this author, were the marked increase in the prevalence of COPD and a greater awareness of the deconditioning of these patients (Mahler, 1998). The ATS and ERS attribute the rise in interest towards pulmonary rehabilitation to an increase in the number of patients referred to programmes and the support of well-designed clinical trials, which provided a scientific basis for the implementation of these programmes. Improved understanding of the pathophysiology of chronic respiratory diseases, further contributes to possibilities and applicability of pulmonary rehabilitation (Nici *et al.*, 2006).

The main aim of pulmonary rehabilitation is to reduce respiratory symptoms, decrease disability and improve health status, functional capacity, independence and overall quality of life, while diminishing health care costs (Nici *et al.*, 2006; BTS, 2001; McArdle *et al.*, 2001:953; ATS, 1999; Mahler, 1998; Gosselink *et al*., 1997; Petty & Weinmann, 1997; Ries *et al.*, 1995; Belman, 1993; Jones *et al.*, 1992). Apart from the financial implications of hospital admissions, frequent admissions contribute to inactivity and dependence on others. Therefore, the prevention of hospital admissions and management of risk factors for admissions should be an essential treatment goal when treating COPD patients. Risk factors for hospital admissions include previous admissions, a low FEV_1, hypoxaemia and inactivity (Morgan, 2003; Osman *et al.*, 1997; Ries *et al.*, 1995).

Pulmonary rehabilitation programmes may include an array of therapeutic modalities. These include education of the patient and family members, treatment of bronchospasm and bronchial infection, treatment of congestive heart failure, oxygen therapy, physical and occupational therapy, breathing technique training,

psychosocial therapy and exercise training (Nici *et al.*, 2006; Morgan, 2003; BTS, 2001; McArdle *et al.*, 2001:953; ATS, 1999; Belman, 1993; Holden *et al.*, 1990). Exercise training is seen as the foundation of pulmonary rehabilitation (ATS, 1999; Bernard *et al.*, 1999; Berry *et al.*, 1999; Make, 1986; ATS, 1981). These intervention strategies collaborate into the lifelong management of patients with chronic respiratory disease (Nici *et al.*, 2006). According to Ries and co-workers (1988), education alone is not as effective as a programme that includes exercise training. This was confirmed by Carrieri-Kohlman and co-workers (1996) who stated: “Exercise is the key to improvement…”

According to Morgan (2003) only about three percent of COPD patients are referred for pulmonary rehabilitation, while only 14% of this three percent actually receive it. Another fact of concern is that pulmonary rehabilitation is usually prescribed when patients are in an advanced stage of the disease. Most patients that end in programmes could be classified as having moderate COPD. Patients with mild COPD are rarely encountered in pulmonary rehabilitation, despite the fact that these patients already experience a significant loss in functionality and quality of life. Although the impairment that patients with mild COPD experience, is not as debilitating as with moderate and severe COPD, these patients can still benefit from these programmes and physical function and HRQL can be improved. This was established by Berry and co-workers (1999), who found that there is no significant difference in the benefits obtained from participating in a pulmonary rehabilitation programme through all stages of COPD (Berry *et al*., 1999). Figure 2.8 illustrates the cycle of disabling symptoms experienced by COPD patients and the importance of pulmonary rehabilitation in the management of these symptoms.

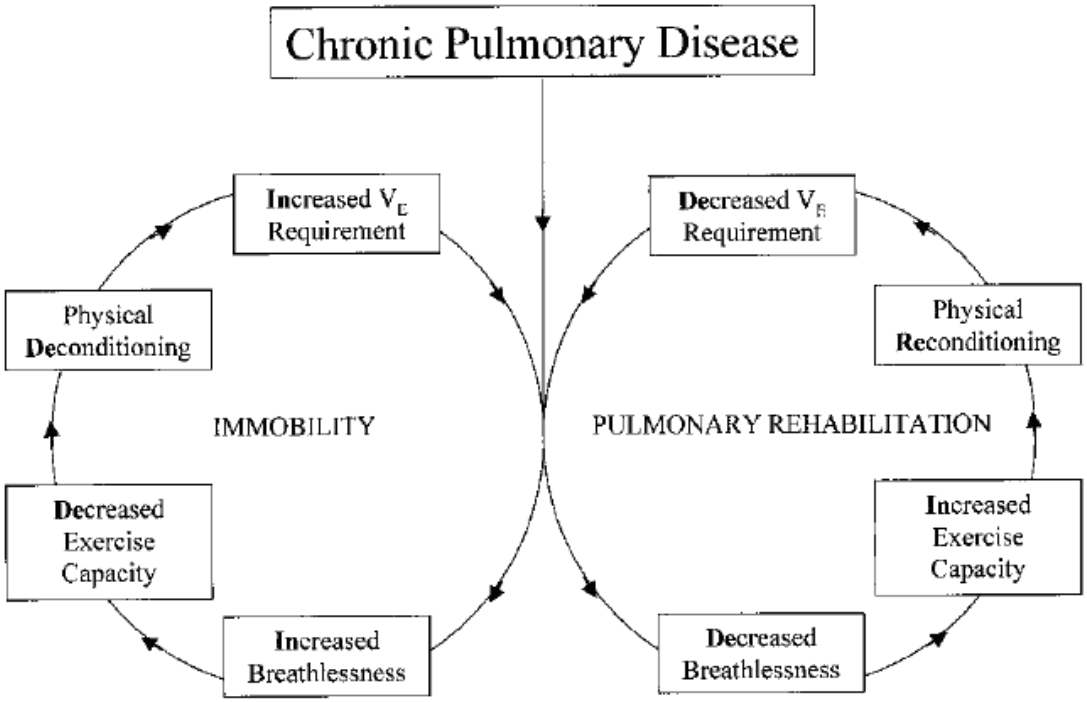

Figure 2.8 A diagram to illustrate the cycles of COPD with and without exercise orientated pulmonary rehabilitation (Cooper, 2001b).

5.1 Collaborative self-management

Collaborative self-management is the education of patients and family members to become actively involved in their treatment and to assume charge of their own care. Education plays a key role in order for patients to understand their disease, recognise symptoms and learn practical ways to cope with and treat these symptoms. It is important that the educational component of a rehabilitation programme be tailored to the needs of each individual patient (ATS, 1995). A randomised, controlled study by Monninkhof and co-workers (2003) found that a comprehensive self-management programme had no effect on the quality of life, walking distance, symptoms or exacerbation frequency of COPD patients. These authors suggest that in order for self-management programmes to succeed, an exercise component needs to be incorporated. Based on previous literature, these

authors, furthermore, concluded that a self-management programme would be more effective in patients with severe COPD.

5.2 Exercise training

Initially, physicians adopted a very conservative approach to exercise for COPD patients. In most cases exercise was limited or discouraged (Belman, 1993). Exercise was then later regarded as a last effort to manage these patients with little hope for success (ATS, 1999). A conjoined report by the American College of Chest Physicians (ACCV) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AAVCPR) recommended that exercise training should be included as a standard treatment modality in the rehabilitation of COPD patients (ACCV/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997). This report was later supported by the ATS and the BTS (BTS, 2001; ATS, 1999). At the present time, exercise is promoted for the improvement of quality of life and forms an integral part of the management of patients with respiratory disease (Rochester, 2003; ATS, 1999; Ries *et al.*, 1995; Belman, 1993).

Dyspnoea is usually one of the foremost reasons for the decrease in physical activity amongst COPD patients. Inactivity results in deconditioning, which aggravates dyspnoea at ever lower work levels (Steiner & Morgan, 2001; Celli, 1995; Folgering & van Herwaarden, 1994). Deconditioning further contributes to inability to perform daily tasks, which will lead to social isolation, depression and dependence on others. Improvement of physical capacity is therefore important to prevent this vicious cycle (Steiner & Morgan, 2001).

The success of exercise training can be attributed to the fact that most of the disabilities experienced by these patients result from secondary morbidities that are often treatable. Exercise training does not improve the degree of obstruction or hyperinflation of COPD patients, but the muscle conditioning together with pacing,

enable patients to walk further with less breathlessness (ATS, 1999). Secondary consequences of respiratory disease are summarised in Table 2.5.

Table 2.5 Consequences of respiratory disease (ATS, 1999).

Types of secondary morbidity	**Mechanism(s)**
Peripheral muscle dysfunction	Deconditioning, steroid myopathy, ICU neuropathy, malnutrition, decreased lean body mass, fatigue, effects of hypoxaemia, acid-base disturbance, electrolyte abnormalities
Respiratory muscle dysfunction	Mechanical disadvantage secondary to hyperinflation, malnutrition, diaphragmatic fatigue, steroid myopathy, electrolyte abnormalities
Nutritional abnormality	Obesity, cachexia, decreased lean body mass
Cardiac impairment	Deconditioning, cor pulmonale
Skeletal disease	Osteoporosis, kyphoscoliosis
Sensory deficits (impaired vision, hearing, etc.)	Medications (e.g., steroids, diuretics, antibiotics)
Psychosocial	Anxiety, depression, guilt, panic, dependency, cognitive deficit, sleep disturbance, sexual dysfunction

Contrary to prior belief (Belman, 1986), COPD patients can exercise at a sufficient intensity to instigate physiological adaptations (Maltais *et al.*, 1996a). Due to the wide range of exercise tolerance experienced by COPD patients, outcome objectives have been diversified. The first refers to patients that are able to train at a sufficient intensity to produce physiological adaptations. The second refers to patients that are limited by dyspnoea and other symptoms. These patients cannot sustain exercise intensities sufficient to produce physiological adaptations. Therefore, the objective for these patients would be to improve mobility within these constraints. To address the needs of all patients, it is of vital importance to individualise exercise programmes (Clark *et al.*, 1996).

Table 2.6 Evidence-based guidelines for exercise training in COPD (Rochester, 2003).

Training / Candidacy	BTS	ATS	ACCP/AACVPR
Lower extremity training	Endurance and strength training recommended: • 20-30 min • 3-5 times per week • Intensity of 60-70% of VO_2max where possible • Maintain O_2 saturation above 90%	Endurance and strength training recommended: • 20-30 min • 2-5 times per week • Intensity of 60% of VO_2max where possible	Recommended as part of pulmonary rehabilitation: optimal specific prescription not defined
Upper extremity training	Strength and endurance training may be included	Strength and endurance training recommended	Strength and endurance training recommended
Ventilatory muscle training	Non-essential	Role unclear	Evidence does not support routine use. May be considered in some patients with decreased respiratory muscle strength and dyspnoea

The basic principles for exercise prescription apply for both healthy individuals and COPD patients, namely mode, frequency, intensity and duration (ACSM, 2000:343; ATS, 1995; Celli, 1995). These principles greatly influence the degree of the training effect experienced (Celli, 1999:195). Table 2.6 summarises the clinical guidelines for exercise training according the BTS, ATS and the ACCP/AACVPR (BTS, 2001; ATS, 1999; ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997).

5.2.1 Training intensity

Training intensity ascertains that improvement or a training effect will only be observed if a load higher than the baseline is induced (Celli, 1995). Athletes

usually train at the maximum tolerated intensity to achieve maximum benefits from a session. Adjustment to exercise intensity to suit individual needs are, however, common practice in exercise prescription (Celli, 1999:195).

The recommended exercise intensity for healthy individuals is 60 to 90% of the predicted maximal heart rate or 50 to 80% of the maximal oxygen uptake (McArdle *et al.*, 2001:954; ACSM, 2000:145; ATS, 1999; ACSM, 1998b; ACSM, 1990). Until recently, it was thought that COPD patients cannot exercise at these intensities and the prescribed intensities were between 30 and 50% of the predicted maximal heart rate. However, these intensities are below the anaerobic threshold and beneficial physiologic adaptations are minimal. Today it is accepted practice to exercise respiratory patients at 60 to 75% of maximal work rate (ATS, 1999; Coppoolse *et al.*, 1999; Folgering & van Herwaarden, 1994). A recent study by Probst and co-workers (2006) confirmed that COPD patients could easily exercise within the prescribed intensities for healthy individuals.

For patients who cannot sustain the prescribed intensity for a prolonged period, interval training is recommended. Interval training consists of several high intensity exercise bouts that are alternated with rest periods (ATS, 1999). An added benefit of interval training is that it correlates better to daily activities than continuous training. The effectiveness of interval training for COPD patients has been confirmed (Vogiatzis *et al.*, 2004; Vogiatzis *et al.*, 2002; Coppoolse *et al.*, 1999). Vogiatzis and co-workers (2002) reported that interval training could improve quality of life and exercise tolerance. One of the important benefits of interval training is that patients can exercise at their maximal intensity with a significant decrease in their perception of dyspnoea (Vogiatzis *et al.*, 2002).

Casaburi and co-workers (1991) confirmed that COPD patients that trained at a higher intensity, demonstrated a significantly lower cardiac frequency after two months of aerobic training, compared to patients that trained at a lower intensity. In contrast, Clack and co-workers (1996) established that low intensity training

could improve exercise tolerance and dyspnoea in COPD patients. Ries and co-workers (1995) recorded an improvement in treadmill endurance with low intensity training, despite the absence of VO_2max improvement. In a study by Maltais and co-workers (1997), 88% of subjects could not tolerate high intensity training. However, they did show an improvement in exercise capacity with low intensity training. These authors recommend low intensity training for patients with moderate to severe COPD and higher intensities for patients with mild COPD. According to Celli (1999:196), any exercise intensity above 50% of maximal work rate can instigate a training effect, after which intensity can be increased as exercise tolerance improves. Table 2.7 illustrates the criteria that should be taken into account when prescribing exercise intensity to COPD patients (Cooper, 2001a).

Table 2.7 Intensity criteria for aerobic exercise prescription.

Criteria	**Definition**
Target	Minimum intensity necessary to produce a clinically meaningful response
Range	Span of training intensity from the target to maximum intensity safely tolerated by subject
Progression	Maintenance of the intensity stimulus in the face of training adaptations

It is important to note that predicted heart rate is not always the best indicator to use when determining exercise intensity for these patients. Peak exercise levels can be reached well below prescribed work rates due to ventilatory limitation (ATS, 1999; Horowitz *et al.*, 1996; Belman *et al*., 1991; Casaburi *et al*., 1991). Controversy still exists as to what the best approach is; suggested alternatives are dyspnoea ratings or the Borg RPE scale (Appendix A) (ATS, 1999; Glass *et al.*, 1992; Belman *et al*., 1991; ACSM, 1990). The Borg RPE scale is the preferred method of exercise prescription, but should be paired with heart rate readings (Cooper, 2001a; ACSM, 1990). Two studies (Mejia *et al.*, 1999; Horowitz *et al.*, 1996) have found that dyspnoea ratings are effective in the prescription of exercise intensity in COPD patients. The pitfall of this method according to Cooper (2001a)

is that patients may not exercise at sufficient intensities due to the fact that dyspnoea will decrease with training.

It is important to note that any exercise is better than none. Even if patients can only tolerate low intensity exercise, benefits can still be observed when compared to doing no exercise at all (ZuWallack *et al.*, 1991).

5.2.2 Training frequency and duration

Training frequency and duration prescribed for healthy individuals are 30 to 45 minutes per day, three to five times per week. In order for a training programme to elicit a physiological response, the programme must be continued for five to eight weeks (ACSM, 1990; Yerg *et al.*, 1985; Seals *et al*., 1984). Casaburi and co-workers (1991) argued that the same principles apply to COPD patients. Guidelines according to the ATS (1999) and BTS (2001) recommend 20 to 30 minute sessions, two to five times per week over an eight to 12 week period. Clark (1994) acknowledged that significant improvements can be observed after six weeks of exercise training, but suggests that the minimum programme duration for COPD patients should be 12 weeks. An extended programme could ensure adherence to exercise after the programme is completed (Clark, 1994).

The recommended exercise prescription for COPD patients according to McArdle and co-workers (2001:954) is three times per week, with each session lasting 20 minutes. If exercise duration needs to be reduced, frequency needs to be increased, e.g. if sessions are five to 15 minutes, frequency should be adapted to five to seven days a week. Cooper (2001a) recommends 30 minutes of aerobic exercise, at least three days per week for six to eight consecutive weeks.

According to Cooper (2001a), the greater the frequency and duration of exercise training, the greater the benefits will be. The minimum frequency and duration for COPD patients to obtain benefits, in terms of exercise capacity, is not known.

Ringbaek and co-workers (2000) concluded that exercise sessions twice a week are not sufficient to produce a significant improvement in six-minute-walk-test distances. It is generally accepted that three exercise sessions weekly, are the required minimum (BTS, 2001; Ringbaek *et al.*, 2000). Green and co-workers (2001) found that a seven week rehabilitation programme is more effective than a four week rehabilitation programme. The seven week programme showed greater improvements in health status and exercise assessments (Green *et al.*, 2001). Rossi and co-workers (2005) compared the effectiveness of 10 and 20 exercise sessions, respectively. This study found that 20 exercise sessions are more effective in improving exercise tolerance, symptoms and HRQL in mild-to-moderate COPD patients.

5.2.3 Training specificity

Specificity of training is the physiological principle that refers to improvement only in the exercise or skill practised (Celli, 1995) and training is only beneficial to the muscle or muscle group being trained (Celli, 1999:195). It is important that the exercises included in the exercise programme closely relate to the individual's daily activities (Bernard *et al.*, 1999; ATS, 1995).

5.2.4 Reversibility of training

Reversibility of training refers to the phenomenon that once training is suspended, the training effect will disappear. The majority of research does not focus on the long-term effect of exercise training in COPD patients and therefore existing evidence is inconclusive (Celli, 1995). However, Ries and co-workers (1988) demonstrated that aerobic benefits obtained through treadmill walking, persisted up to 16 months after the programme was completed. A more recent study by Cambach and co-workers (1997) confirmed these results. In this randomised controlled study, 99 subjects exercised 90 minutes, three times a week, over a three month period. Subjects were evaluated after three and six months.

Improvements in exercise tolerance and quality of life were documented after three and six months.

5.2.5 Pre-exercise evaluation and outcome assessments

Most COPD patients have a history of smoking. This, together with the fact that these patients are generally older patients, puts them at risk for cardiovascular disease. One of the main reasons for conducting pre-exercise evaluation is to exclude any cardiovascular disease (ATS, 1995). Furthermore, pre-exercise evaluations give an objective assessment of the impact of the disease on functionality of the patients (Johnson, 2004).

Pre-exercise evaluations also assist in the formulation of clear exercise goals for each individual. Important to formulation of these goals, is the assessment of the severity of respiratory impairment. To determine respiratory impairment, a physical examination is conducted and clinical history and spirometry records are reviewed (ATS, 1999). This evaluation should include a cardiac stress test and spirometry to ensure the safety of the patients (ATS, 1995).

The determination of baseline exercise capacity is important for various reasons. Firstly, it is important to assist in exercise prescription to determine the optimal exercise intensity for each individual. Secondly, exercise induced hypoxaemia and other abnormal responses can be evaluated, and proper precautions can be taken. Thirdly, the cardiac response to exercise can be evaluated and abnormalities can be detected. It is furthermore important to assess the VO_2-work rate relationship. Psychological limitations and the impact that it has on exercise training, can also be assessed (Gallagher, 1994; ATS, 1999).

Outcome assessments are vital to determine the overall effectiveness of an exercise programme and serve as a motivational tool. Exercise tests play a vital role in the outcome assessment of an exercise programme. Various tests are used

for this purpose, of which the six-minute walk test is probably the most frequently used in pulmonary rehabilitation (Turner *et al.*, 2004; ATS, 1999).

Dyspnoea is a common symptom of COPD and therefore an important variable to measure in an outcome assessment. Various scales and questionnaires can be used for this purpose; these include the Borg RPE scale (Appendix A), the Baseline and Transitional Dyspnoea Indexes (BDI and TDI) and the Pulmonary Functional Status and Dyspnoea Questionnaire (ATS, 1999).

The measurement of HRQL of life has two vital applications in the pulmonary rehabilitation context. Firstly, it is an important instrument in determining the benefits and effectiveness of various programmes and secondly, it is valuable in evaluating new methodologies (ATS, 1999).

Supplemental to the measurement of HRQL is the measurement of respiratory-specific functional status. Functional status can be described as the interaction between what a patient is capable of doing (capacity), what a patient is actually doing (performance), the difference between capacity and performance (reserve) and capacity utilisation. Rehabilitation should focus on increasing a patient's reserve and motivating patients to utilise this added ability (ATS, 1999).

Evaluation of functional status of the respiratory patient should focus on how well a patient can perform daily activities. Daily activities should be divided into basic and instrumental activities. Basic activities include eating, bathing and dressing, whereas instrumental activities are the activities needed to adapt to the environment. Instrumental activities are closely related to a patient's independence and include shopping and walking outdoors (ATS, 1999).

5.2.6 Aerobic training

It is accepted that aerobic capacity will decline with age as a result of the natural aging process. In COPD patients, this decline is aggravated by physical inactivity and deconditioning. As exercise capacity declines and the patient advances in age, so does the potential of improvement of the absolute work capacity (Cooper, 2001a). A decline in exercise capacity of a COPD patient, is accompanied by a decline in airway function (Palange *et al.*, 2000; Fletcher & Peto, 1977). Lacasse and co-workers (1996) did a meta-analysis of 11 studies concerned with aerobic training of COPD patients. They found an improvement in exercise capacity after endurance training. Therefore, aerobic or endurance training is fundamental to any exercise programme prescribed to COPD patients (Cooper, 2001a; O'Donnell *et al.*, 1995).

An aerobic exercise training programme will improve the exercise endurance of COPD patients, although the mechanism of improvement is not fully understood (BTS, 2001; ATS, 1999; ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997; Strijbos *et al.*, 1996; Celli, 1995; O'Donnell *et al.*, 1995; Ries *et al.*, 1995; Wijkstra *et al.*, 1994; Toshima *et al.*, 1990). Belman and Kendregan (1981) suggested that endurance is improved because of desensitisation towards dyspnoea. This study found no changes in the oxidative enzyme content of trained muscles after six weeks of exercise training, despite a significant improvement in aerobic endurance. In contrast, Casaburi and co-workers (1991) showed a reduction in exercise lactic acidosis and ventilation following eight weeks of exercise training, which suggests that physiological adaptations occurred. Maltais and co-workers (1997) suggested that the improvement in endurance is the result of an accumulation of several factors, namely better motivation, desensitisation towards dyspnoea, improvement in mechanical skill and enhanced respiratory muscle function. O'Donnell and co-workers (1995) reported significant improvements in dyspnoea, after endurance exercise training, which far exceeded improvements recorded by any other therapeutic intervention. Possible

explanations for their findings include a reduction in ventilatory demand, improved ventilatory muscle strength, improved mechanical efficiency and psychological improvements. Another important finding was an increase in resting IC, which was explained by an increase in inspiratory muscle strength (O'Donnell *et al.*, 1995). A study by Porszasz and co-workers (2005) found a 300% increase in aerobic capacity after seven weeks of endurance training, which was ascribed to a decrease in dynamic hyperinflation. Cooper (2001a) argued that due to the effectiveness and the backing of numerous studies, aerobic training should occupy most of the time allocated to a pulmonary rehabilitation programme.

A wide array of programmes has been studied through the years with varied success. Consensus is still to be reached regarding the most advantageous exercise frequency, intensity, duration and mode. Uncomplicated, low activity programmes have been successfully implemented and successful exercise programmes have varied anything from two to six sessions a week, with session duration varying from one to three hours (ATS, 1999; O'Donnell *et al.*, 1995; Belman, 1993). Table 2.8 summarise the guidelines for endurance training according to Clark (1994).

Table 2.8 Guidelines for endurance training.

Frequency	Minimum of three times weekly
Duration	Minimum of 20 minutes
Intensity	No less than two thirds of the exercise intensity achievable without lung disease.
Timescale	Minimum of six weeks.

With reference to functional capacity, upper-extremity endurance training is not as effective as lower-extremity endurance training (Lake *et al.*, 1990). Walking or treadmill walking is the most preferred mode of endurance exercise, because it translates best to daily activities (Cooper, 2001a). Other authors also promote walking as an exercise modality on the basis that it resembles daily activities (Gosselink *et al.*, 1997; Maltais *et al.*, 1997). Celli (1999:199) promotes treadmill

walking as an exercise modality on the basis that it produces a higher oxygen uptake. Some patients with arthritis, joint deformities and obesity may prefer stationary cycling to walking, due to the added stress on the joints during walking (Cooper, 2001a). Gosselink and co-workers (1997) demonstrated that stationary cycling can improve walking distances and therefore, can be beneficial to activities of daily living.

Casaburi and co-workers (1991) ascribe the lack of physiological adaptations recorded by various pulmonary rehabilitation programmes to discrepancies in training frequency, duration and intensity. Traditionally, patients with severe COPD are not referred for exercise training. The typical patient in these programmes has mild to moderate COPD. Previous studies did, however, show that exercise training can be beneficial for patients with severe COPD (Bernard *et al.*, 1999; Niederman *et al.*, 1991; ZuWallack *et al.*, 1991).

5.2.7 Strength training

According to Wouters (2002), the loss of muscle strength is a common problem experienced by COPD patients. Hamilton and co-workers (1995) found that the average muscle strength of COPD patients is only 81% of that of healthy, age-matched controls. Strength training will result in an increase in myofibrils in muscle fibres (Celli, 1999:195). The aim of strength training for the COPD patient should be "to reduce the effects of major skeletal muscle deconditioning and the loss of function due to enforced inactivity and poor nutritional status" (Clark, 1994). COPD patients will obtain the same improvement in muscle strength from strength training as healthy individuals (Mador *et al.*, 2004). Strength- or resistance training is especially important for individuals who present with specific muscle weaknesses, since muscle weakness contributes to exercise limitation. In individuals who do not demonstrate muscle weakness, strength training is still important to maintain muscle strength (Spruit *et al.*, 2002; ATS, 1999; ATS, 1995; Simpson *et al.*, 1992). According to Belman (1993), a structured strength training programme can improve

cycle endurance and quality of life of COPD patients. This was confirmed by other studies (Clark *et al.*, 1996; Simpson *et al*., 1992). Clark and co-workers (1996) subjected 32 subjects to a 12-week exercise programme that focused on conditioning of peripheral skeletal muscles. They found a significant improvement in the treadmill walking endurance, despite the fact that the programme only focused on peripheral muscle conditioning and that maximal cardiorespiratory fitness remained unchanged. In a study by Clark and co-workers (2000), muscle function and treadmill endurance improved after a programme that only included weight training of the upper- and lower extremities. Patients included in this study suffered from mild COPD and the programme demonstrated to be effective for patients with impaired isokinetic muscle function prior to training (Clark *et al.*, 2000). Spruit and co-workers also found a cross-over effect between endurance and resistance training. These authors found that endurance training could result in significant increases in peripheral muscle force, while resistance training resulted in an increase in 6MWD and peak workload. Contrary to these findings, other studies found that apart from improving muscle strength, strength training has no added benefits, in terms of quality of life and exercise endurance, for COPD patients above a structured endurance programme (Bernard *et al.*, 1999; Mador *et al.*, 2004).

Strength training is safe and well-tolerated by COPD patients and does not inhibit endurance training (Mador *et al.*, 2004). Benefits for including strength training exercises in an exercise programme for COPD patients, include the fact that dyspnoea is limited during these exercises, which results in improved exercise tolerance (Bernard *et al.*, 1999; Clark *et al.*, 1996; Simpson *et al.*, 1992). Furthermore, cardiopulmonary stress during strength training is significantly lower compared to walking, cycling and stair climbing (Probst *et al.*, 2006). According to Dekhuijzen and Decramer (1992), a well structured strength training programme is vital for COPD patients being treated with corticosteroids to prevent steroid-induced myopathy to some extent. The variety of strength training exercises provides for an interesting exercise programme that adds to motivation of patients.

Another added benefit is that strength training helps to combat osteoporosis and promotes bone density (Bernard *et al.*, 1999; Clark *et al.*, 1996; Simpson *et al.*, 1992).

Decramer and co-workers (1997) explored another potential benefit of strength training, when their research showed a correlation between peripheral muscle weakness and health care costs. This relationship can possibly be explained by the fact that health care utilisation and muscles weakness are indicators of disease severity. Muscle weakness could also be associated with recurrent complaints, which can result in hospitalisations that are more frequent. A final possible explanation is that there is an interrelationship between health care utilisation and muscle weakness. Frequent hospitalisations and subsequent bed rest, combined with more frequent treatment with corticosteroids and subsequent steroid-induced myopathy, may result in muscles weakness. It could then be proposed that an improvement in muscle weakness will not only result in improved exercise tolerance and functional status, but also lead to reduced health care costs (Decramer *et al.*, 1997).

In a systematic review of strength training in COPD patients, O'Shea and co-workers (2004) concluded that strength training is both safe and appropriate for these patients. It is however, of vital importance to thoroughly screen patients before prescribing a strength training programme due to the possibility of co-morbidities. A possible limitation to the feasibility of strength training for COPD patients, is the availability and access to equipment. According to O'Shea and co-workers (2004), only one study evaluated the use of free weights and resistance bands as a simple alternative to expensive equipment. Further research is required into more cost-effective strength training methods (O'Shea *et al.*, 2004).

5.2.7.1 Lower extremity training

Several studies have shown that lower extremity exercises are beneficial for COPD patients (Mahler, 1998; Ries *et al.*, 1995; Wijkstra *et al.*, 1994; Hughes & Davison, 1983; Moser *et al.*, 1980; Christie, 1968; Paez *et al.*, 1967). According to Bernard and co-workers (1999), lower extremity aerobic training improves exercise tolerance in COPD patients, but has no effect on muscle weakness and muscle atrophy. This supports the use of lower extremity strength training. An increase in muscle strength will result in an improvement of exercise tolerance.

The perception of muscle fatigue can be reduced by increasing the strength of the quadriceps femoris muscles. Strength training in healthy, older, individuals results in an increase of the skeletal muscle's oxidative capacity, improved peripheral muscle strength and an increase in muscle volume and muscle cross-sectional area (McArdle *et al*., 2001:535 & 882; Bernard *et al.*, 1999). The same benefits can be obtained in patients with moderate to severe COPD. Muscle hypertrophy and improved neural recruitment can explain the increase in muscle strength after a strength training programme, for healthy individuals as well as COPD patients (Bernard *et al.*, 1999).

5.2.7.2 Upper extremity training

Various upper extremity muscles or muscle groups have both respiratory and postural functions. These include the upper and lower *trapezius*, *latissimus dorsi*, *serratus anterior*, *subclavius*, *pectoralis major* and *pectoralis minor*. With severe COPD, the diaphragm's ability to generate force diminishes and the above-mentioned muscles become increasingly important in the generation of inspiratory pressures (Celli, 1999:200; Lareau *et al.*, 1992).

Dyspnoea associated with upper extremity activities, at lower intensities than with lower extremity activities, are common among COPD patients. Upper extremity

work is associated with a higher ventilatory demand compared to the same workload for the lower extremities (Fishman, 1998:714; Mahler, 1998; ATS, 1995; Belman, 1993; Couser *et al.*, 1993; Ries *et al.*, 1988). This can be explained by the stabilising role that the muscles of the shoulder girdle have during respiration. Upper extremity exercises may cause dyssynchronous breathing because of the loss of this stabilising effect (Celli, 1999:200; Clark, 1995:529). Certain upper extremity actions elicit more dyspnoea than others do. These actions include activities that require sustained, unsupported arm extension (i.e. washing hair) and activities that restrict diaphragmatic movement (i.e. forward bending) (Lareau *et al.*, 1992). Exercise benefits are specific to the muscle group involved in training, therefore the inclusion of upper extremity exercises in an exercise programme is vital for the alleviation of these symptoms (ATS, 1995; Belman, 1993; Ries *et al*., 1988).

According to Celli (1999:200), during arm exercises, pressure generation is shifted from the inspiratory muscles to the diaphragm and abdominal muscles. Regular upper extremity exercises result in a decrease in metabolic and ventilatory demand for these exercises (Celli, 1999:200; ATS, 1995; Belman, 1993; Couser *et al.*, 1993). Therefore, a patient's capacity to perform these exercises should increase (Celli, 1999:200). This was confirmed by Couser and co-workers (1993) who illustrated that metabolic and ventilatory demand for arm elevation decreases after an eight week rehabilitation programme that includes upper extremity training. The 14 subjects recruited for their study reported a decrease in dyspnoea after an eight week training programme. According to the American Thoracic Society (1999), training of the upper extremities should not only focus on strength, but in addition, should have an endurance component. Mahler (1998) noted that patients should be instructed on proper breathing techniques during upper body movements. Coordination of movement and breathing could facilitate breathing. Expiration should occur during the part of the movement that requires the most effort, which generally is the extension of the arms.

Previous studies concluded that upper extremity training alone does not improve performance in arm activities used in daily living. Furthermore, quality of life benefits are only observed during a combination of upper and lower extremity training (Lake *et al.*, 1990; Ries *et al.*, 1988). Improved performance from upper extremity training is task specific; activities of daily living therefore play an integral part in the exercise prescription process (Celli, 1995). Contrary to previous studies, Hamilton and co-workers (1995) found a relationship between upper body and thoracic muscle strength and maximal exercise capacity. This was confirmed by a recent study that reported that the strength of the thoracic muscles is a predictor of functional capacity, as determined by the 6MWT (Dourado *et al.*, 2006).

5.2.8 Pursed-lip breathing

The goal of pursed-lip breathing is to relieve or control dyspnoea and to counteract hyperinflation. It is often unconsciously used by patients to enhance exercise tolerance (Gosselink, 2003; ATS, 1999; ATS, 1995).

The aim of pursed-lip breathing is to alter the breathing patterns of symptomatic patients (Celli, 1995). This is achieved by slowing the respiratory rate, decreasing minute ventilation and carbon dioxide level, increasing tidal volume and oxygen saturation, preventing dynamic airway compression, improving respiratory synchrony of abdominal and thoracic musculature and improvement of gas exchange (ATS, 1999; ATS, 1995). It is still unclear whether pursed-lip breathing actually alleviates dyspnoea, despite the physiological improvements (ATS, 1999).

Instructions for pursed-lip breathing according to the American Thoracic Society (1995) are as follows: “Breathe in slowly and deeply through the nose; purse the lips lightly, as if to whistle; then breathe out slowly through the pursed lips, taking twice as long to exhale as to inhale.”

Diaphragmatic breathing is another technique sometimes taught to COPD patients to optimise ventilatory function (Rochester, 2003). During this technique, patients are told to move the abdominal wall during inspiration, while limiting upper rib cage movement. The aim of diaphragmatic breathing is to "improve chest wall motion and the distribution of ventilation, decrease the energy cost of breathing, the contribution of rib cage muscles and dyspnoea and improve exercise performance" (Gosselink, 2003). According to Gosselink and co-workers (1995), diaphragmatic breathing can increase inspiratory loading and dyspnoea in some COPD patients. Rochester (2003) noted that patients with a low tidal volume (V_T) and rapid breathing rate could benefit from this technique.

5.2.9 Ventilatory muscle training

Inspiratory muscles are affected by COPD and there is a relationship between the condition of these muscles and quality of life and mortality (Senior & Anthonisen, 1998). Ventilatory muscle weakness can contribute to fatigue, dyspnoea, exercise limitation, hypercapnia and even respiratory failure (Rochester, 2003; ATS, 1999; ATS, 1995a). The aim of ventilatory muscle training is to improve gas exchange and ventilation, improve respiratory muscle function, decrease dyspnoea, increase exercise tolerance and ultimately improve quality of life (Gosselink, 2003). Controversy still exists as to whether weakened inspiratory muscles should be strengthened through exercise, or rested; assuming weakness is as a result of fatigue (Senior & Anthonisen, 1998).

Training of these weakened inspiratory muscles will result in a training response, which will translate into improved respiratory muscle function (McConnell & Romer, 2004; Celli, 1995). Scherer and co-workers (2000) found that respiratory muscle training improved respiratory muscle endurance, exercise performance, HRQL and dyspnoea. This study found that respiratory muscle training had no effect on pulmonary function. Weiner and co-workers (1992 & 2004) found that an exercise programme that includes inspiratory threshold loading training, showed significantly

better results than a programme that focuses on general exercise training alone. Results included improved inspiratory muscle strength and endurance and an increase in exercise tolerance. Hart and co-workers (2002) emphasised that attention should be given to respiratory muscle endurance and not just respiratory muscle strength. In the study by Scherer and co-workers (2000), there was a 258% improvement in respiratory muscle endurance after respiratory muscle training.

Respiratory muscle strength can be improved through high-intensity, low-frequency stimuli. This is achieved through increasing inspiratory pressures by inspiring against a closed glottis or shutter. Inspiratory muscle strength will also improve through endurance training for the inspiratory muscles (Celli, 1995). Hill and co-workers (2006) established that high-intensity inspiratory muscle training improved inspiratory muscle strength and endurance, dyspnoea and exercise capacity.

Respiratory muscle endurance is improved by low-intensity, high-frequency stimuli (Celli, 1995). Methods of training inspiratory muscles include resistive loading, threshold loading, voluntary isocapnic hyperventilation or controlled breathing strategy (Gosselink, 2003; Rochester, 2003; ATS, 1999; ATS, 1995a; Celli, 1995). In resistive loading, the load is increased by narrowing of the inspiratory hole size, provided the frequency, tidal volume and inspiratory time remain unchanged. Threshold loading training is independent of inspiratory flow rate (Celli, 1995). The benefits of threshold loading include that it is easily quantified and training load can be adjusted (Rochester, 2003). In voluntary isocapnic hyperpnoea, high levels of ventilation are maintained for 15 minutes, two to three times a day (Celli, 1995). These techniques improve inspiratory muscle strength and endurance in COPD patients, but it is unclear whether these improvements result in alleviation of symptoms (ATS, 1999). Insufficient research exists to fully understand the role of respiratory muscle training and the benefits it holds for COPD patients.

Weiner and co-workers (2004) emphasised the importance of a maintenance programme after a short-term ventilatory muscle training programme. These authors found that the benefits obtained through ventilatory muscle training, gradually decline over 12 months in the absence of a maintenance programme. Studies concerned with resting ventilatory muscles found that this is very impractical and difficult to achieve and that no significant benefits are attained (Senior & Anthonisen, 1998; Albert, 1997).

5.3 Exercise tolerance

Exercise tolerance and its prediction are of vital importance when it comes to training individuals with COPD (Rochester, 2003; Pauwels *et al*., 2001; Gosselink *et al.*, 1997; Gallagher, 1994; Decramer, 1992). Killian and co-workers (1992) studied exercise limiting symptoms in 97 COPD patients and compared it to the response of 320 healthy individuals. An important finding of this study was that both the average COPD patient and healthy individual, stopped exercising when leg effort or dyspnoea reached an intensity of 7 (very severe) on the revised Borg RPE scale. The difference between the COPD patients and the control group was that the COPD patients reached the mentioned intensity at a much lower workload.

According to a study by Efremidis and co-workers (2005) exercise tolerance, as expressed by peak VO_2, can be accurately predicted through resting pulmonary measurements. The most consistent predictors of peak VO_2 were expiratory airflow limitation and inspiratory-expiratory strength measures (Efremidis *et al.*, 2005). The prediction of exercise tolerance in COPD patients is important for disability evaluations and to establish the cause of exertional symptoms and limitations (Efremidis *et al.*, 2005; Pauwels *et al.*, 2001).

Various pathologies are implicated in the limitation of exercise performance of COPD patients. These pathologies include abnormalities of ventilatory mechanics, respiratory muscles, alveolar gas exchange and cardiac function, as well as leg

fatigue, dyspnoea and chronic deconditioning (O'Donnell *et al.*, 2002; Etnier *et al.*, 1999; Bauerle *et al.*, 1998; Gosselink *et al.*, 1996; Hamilton *et al.*, 1995). According to the ATS and ERS, the primary symptoms that limit exercise performance are dyspnoea and fatigue. Dyspnoea and fatigue may result from the other pathologies mentioned (Nici *et al.*, 2006). According to Foglio and co-workers (2000), the most important predictors of exercise capacity are pulmonary hyperinflation, dyspnoea and age. It was previously thought that FEV_1 is the primary cause or indication of exercise intolerance. However, patients with similar FEV_1 values display a wide range in exercise capacity (Maltais *et al.*, 1996b). According to Montes de Oca and Celli (2000), the exact impact of deconditioning, hypoxaemia, hyperinflation, muscle weakness and haemodynamic compromise has on exercise tolerance remains unclear.

Treatment aimed at reducing these limitations will improve exercise performance (Rochester, 2003; Aliverti & Macklem, 2001; Belman, 1993; Carter *et al.*, 1993; Killian *et al.*, 1992). It is important to note that physiological factors that limit one form of exercise (i.e. incremental work loads) may not necessarily limit other forms of exercise training (i.e. constant work load) (Gallagher, 1994).

Due to the complex interaction between the different variables that limit exercise performance, it is often difficult to isolate these variables. For example, deconditioning would result in peripheral muscle fatigue and peripheral muscle fatigue could contribute to deconditioning (Nici *et al.*, 2006). The variables that contribute to exercise intolerance are discussed separately. The interrelationship between these factors will also be addressed.

5.3.1 Respiratory muscle dysfunction

COPD patients often exhibit weakness of the respiratory muscles. Weakness in the skeletal muscles of COPD patients can often be explained by deconditioning. However, because the respiratory muscles of COPD patients are under constant

mechanical loading, other factors than deconditioning are responsible (Orozco-Levi, 2003).

Extrinsic and intrinsic factors result in muscle weakness in COPD patients. Extrinsic factors include hypoxia, hypercapnia, malnutrition, electrolyte disturbances, steroid myopathy and dynamic hyperinflation (Orozco-Levi, 2003; Rochester, 2003; Fitting, 2001; Gibson, 1996; Folgering & van Herwaarden, 1994; Belman, 1993). Intrinsic factors include changes in fibre size, sarcomere length, muscle mass and muscle metabolism (Orozco-Levi, 2003).

Dynamic hyperinflation shortens the diaphragm fibre sarcomere and reduces the zone of apposition, which results in weakened diaphragmatic function. The diaphragm can shorten sufficiently to eliminate the zone of apposition altogether (Scharf, 1992:278). Upper body actions place further limitations on diaphragmatic function, due to the fact that the stabilising effect of the shoulder girdle on the thorax is lost during these movements. This restriction on the diaphragm results in a decrease in exercise capacity and an earlier onset of dyspnoea (Rochester, 2003; Fitting, 2001; Gibson, 1996; Folgering & van Herwaarden, 1994; Belman, 1993). Clinical signs of diaphragmatic dysfunction include dyspnoea, which is aggravated in a supine position, elevation of the diaphragm and abnormalities in the chest wall motion (Scarf, 1992:285). Weakness of respiratory muscles is assessed by measuring the pressures, expiratory flows and lung volumes during the MVV test (Scharf, 1992:286).

O'Donnell and co-workers (1995) reported that ventilatory muscle weakness would limit exercise performance. They suggested that a six-week exercise training programme that trains at near maximal ventilation levels, should improve ventilatory muscle strength and endurance, which will translate into improved exercise performance. Contrary to these findings, Belman (1993) reported that the effect, if any, that ventilatory muscle training has on exercise performance, is insignificant (Belman, 1993).

5.3.2 Respiratory muscle fatigue

Muscle fatigue is defined as “an exertion-induced, reversible decrease in muscle strength or in the force exerted by the muscles in response to a given stimulus or load” (Scharf, 1992:283). According to Belman (1993), the role of respiratory muscle fatigue in the toleration of exercise in the COPD patient is unclear. Insufficient evidence exists to suggest that the respiratory muscles are fatigued in COPD patients after prolonged exercise. Rochester (1991) emphasises that inspiratory muscle weakness plays a more significant role than muscle fatigue. According to Wijkstra and co-workers (1994), inspiratory muscle strength can limit exercise performance. Respiratory muscle weakness can lead to hypercapnia, which can further limit performance (Begin & Grassino, 1991). Contrary to Rochester’s (1991) findings, Hart and co-workers (2002) emphasised the role of inspiratory muscle endurance. According to Gallagher (1994), the susceptibility to fatigue varies between different respiratory muscles. Therefore, recorded fatigue in a specific respiratory muscle cannot necessarily be transferred to other respiratory muscles.

According to Mador and co-workers (2000b), COPD patients are predisposed to respiratory muscle fatigue during exercise. These authors attribute this predisposition to the imbalance between inspiratory load and capacity during exercise (Mador *et al.*, 2000b; Belman, 1993). Mador and co-workers (2000b) studied diaphragmatic fatigue and found that some COPD patients experience fatigue during high-intensity, constant load cycle exercise. They hypothesised that dynamic hyperinflation may have been the determining factor. Important to their findings was that the majority of their subjects did not experience any diaphragmatic fatigue.

5.3.3 Peripheral muscle dysfunction and fatigue

Exercise tolerance cannot be explained by ventilatory limitations alone. Therefore, other possible factors have been explored, including peripheral muscle dysfunction (Storer, 2001). The relationship between exercise tolerance and the condition of the skeletal muscles has recently received considerable attention (Haccoun *et al.*, 2002; Casaburi, 2001; Gea *et al.*, 2001; Storer, 2001; Clark *et al.*, 2000; Mador *et al.*, 2000a; Murariu *et al.*, 1998; Gosselink *et al.*, 1996; Maltais *et al.*, 1996b; Casaburi *et al.*, 1991). Previous studies demonstrated that the determining factor in exercise tolerance is leg effort and not dyspnoea, as expected (O'Donnell *et al.*, 1995; Killian *et al.*, 1992). Physiological attributes of peripheral and respiratory muscles are identical and they show the same decrements in strength (Carter *et al.*, 2003; Aliverti & Macklem, 2001; Bernard *et al.*, 1999; O'Donnell *et al.*, 1995; Belman, 1993; Killian *et al.*, 1992). According to Franssen (2003), muscle dysfunction experienced by COPD patients is not homogeneously distributed over different muscle groups. Mador and co-workers (2000a) found that contractile fatigue is specific to the exercising muscles and that muscle fatigue contributes significantly to exercise intolerance.

Various factors contribute to the dysfunction of skeletal muscles of COPD patients. Muscle mass, strength and endurance will decrease as a result of inactivity, aging, hypoxaemia, hypercapnia, malnutrition, steroid myopathy, atrophy of type I and type IIa muscle fibres, reduction in muscle fibre capillarisation, reduced oxidative enzyme capacity and impaired muscle metabolism (Franssen, 2003; Casaburi, 2001; Gea *et al.*, 2001; Mador *et al.*, 2000a; ATS & European Respiratory Society (ERS), 1999; Baarends *et al.*, 1997; Maltais *et al.*, 1996b; Jakobsson & Jorfeldt, 1995; Engelen *et al.*, 1994). Decrease in muscle mass is also associated with an increase in mortality (Schols *et al.*, 1998; Gray-Donald *et al.*, 1996). Peripheral muscle dysfunction leads to increased ventilatory demand and excessive muscle fatigue (Gosselink *et al.*, 1996; Hamilton *et al.*, 1995).

The cause of muscle dysfunction in COPD patients is not fully understood. Possible causes for dysfunction include systemic inflammation, low anabolic hormone levels, reactive oxygen species, deconditioning, malnutrition, ageing, hypoxia (Wouters *et al.*, 2002; Debigare *et al.*, 2001; ATS & ERS, 1999) and steroid myopathy (Rochester, 2003). Muscle wasting is also the result of an increased proteolytic/antiproteolytic ratio. Proteolytic activity can increase due to inactivity and proinflammatory cytokines (Debigare *et al.*, 2001). The continual reduction in the availability of oxygen at cellular level can also contribute to skeletal muscle dysfunction (Maltais *et al.*, 1996b). A study done on healthy individuals also found that constant exposure to hypoxaemia is detrimental to the oxidative capacity of skeletal muscle cells (Howald *et al.*, 1990). According to Graham and co-workers (1980), respiratory acidosis may also contribute to impaired muscle oxidative capacity.

Exercise tolerance can be improved by a structured, lower extremity aerobic and strength training programme (Rochester, 2003; Bernard *et al.*, 1999; Celli, 1995). Belman (1993) also emphasised the importance of nutritional status on both peripheral and respiratory muscles.

5.3.4 Cardiovascular function

Restriction of exercise performance as a result of cardiovascular limitation is frequently observed in COPD patients (O'Donnell *et al.*, 2001; Sietsema, 2001). Thickening of the intimae, narrowing of the lumens of arteries and arterioles, emphysematous destruction of vascular bed, alveolar hypoxia, increased alveolar pressure, increased haematocrit and acidosis result in an increase in pulmonary vascular resistance and pulmonary artery pressures (O'Donnell *et al.*, 2001; Sietsema, 2001; Gallagher, 1994; Belman, 1993). Cardiac output may be further limited by the decrease in right ventricular preload. This decrease is related to hyperinflation, which impairs the stroke volume of the right ventricle. The decrease in cardiac output will result in a decrease in exercise tolerance (O'Donnell *et al.*,

2001; Sietsema, 2001; Gallagher, 1994). There may also be an increase in the heart rate/VO_2 ratio, which means that estimation of exercise intensity by means of heart rate can be inaccurate (Gallagher, 1994; Belman, 1993).

5.3.5 Deconditioning

Chronic inactivity in COPD patients is an aggravating factor for exercise intolerance (Belman, 1993). The level of obstruction is not the only factor that influences the extent of dyspnoea, as varying levels of dyspnoea have been observed in patients with similar airway obstruction (O'Donnell & Webb, 1992). Impaired pulmonary function can only account for part of the reduced exercise capacity experienced by COPD patients. Carter and co-workers (1993) implicated deconditioning as another contributing factor.

Prolonged periods of bed rest and inactivity are common amongst COPD patients. This prolonged inactivity and disuse result in deconditioning and consequent impaired muscle strength and endurance (Franssen, 2003; ATS & ERS, 1999).

5.3.6 Steroid-induced myopathy

One of the well-known side effects of continuous use of corticosteroids is steroid-induced myopathy and muscle atrophy (Dekhuijzen & Decramer, 1992). Cardiac decompensation, malnutrition, electrolyte imbalances and blood gas abnormalities all contribute to muscle weakness in COPD patients. Due to already weakened muscles, COPD patients may be more susceptible to steroid-induced myopathy (Decramer *et al.*, 1996). Steroid-induced myopathy may also affect the diaphragm. Diaphragm function of the COPD patient may already be limited by the effects of hyperinflation, hypoxaemia, hypercapnia, malnutrition and inactivity, increasing the susceptibility for steroid-induced myopathy (Dekhuijzen & Decramer, 1992).

Decramer and co-workers (1996) confirmed that steroid-induced myopathy contributes to peripheral as well as respiratory muscle weakness, which in turn will result in aggravation of dyspnoea. In that study, patients with steroid-induced myopathy had a reduced BMI and increased mortality rates.

5.3.7 Psychological factors

Depression, anxiety and fear of exercise are very important factors to consider when exercise tolerance is addressed in COPD patients. Patients' perception and reaction to dyspnoea varies widely and must be taken into account (Nici *et al.*, 2006; Rochester, 2003; Belman, 1993; Belman *et al*., 1991). Poor motivation should also be considered an important factor of exercise intolerance (Nici *et al.*, 2006).

5.3.8 Other

In addition to the factors mentioned above, Rochester (2003) includes optimisation of medical therapy, breathing strategies and oxygen therapy as factors that can improve exercise tolerance.

5.4 Mechanisms of improvement

According to Belman (1993), there is to date no conclusive evidence to indicate the main mechanism of improved exercise performance in COPD patients. It has however, been proven by numerous studies, that exercise has no influence on pulmonary mechanics and gas exchange (McArdle *et al.*, 2001:953; ATS, 1995a; Casaburi *et al.*, 1991; Busch & McClements, 1988; Belman, 1986; Belman & Wasserman, 1981). Strijbos and co-workers (1996) suggested that possible mechanisms of improvement in exercise capacity include physiological changes, improved efficiency, better co-ordination of neuromuscular activity and desensitisation to dyspnoea.

5.4.1 Improved aerobic capacity

In healthy individuals, an improvement in endurance capabilities can be ascribed to physiological and metabolic adaptations. These adaptations included an increase in mitochondrial density (size and number), an increase in the activity and concentration of aerobic enzymes, an increase in capillary density and enhanced oxidation of lipids and carbohydrates. Functional adaptations included a decrease in exercise and resting heart rate and enhanced stroke volume and cardiac output (Rochester, 2003; McArdle *et al.*, 2001:467-468; Belman, 1993; Casaburi *et al.*, 1991; Belman & Kendregan, 1981).

In a study done by Belman and Kendregan (1981) 15 patients showed an improvement in overall exercise endurance after six weeks of exercise training, but no changes in muscle oxidative enzyme activity and cardiac frequency were recorded. Due to the fact that these changes are not observed in COPD patients, it is concluded that exercise intensities during the training of these patients are not enough to attain a true aerobic response (Belman, 1993). Bernard and co-workers (1999) recorded a reduction in cardiac frequency, V_E and blood lactate concentration for a specific workload, after a 12-week exercise programme for COPD patients that included aerobic and strength training. O'Donnell and co-workers (1995) reported that increased aerobic capacity could be attributed to reduced ventilatory demand.

5.4.2 Increased motivation

Belman (1993) found that an increase in maximal V_E or heart rate could indicate an increase in a patient's motivation. However, improvements in these variables are not consistent. The importance of motivation amplifies during submaximal steady state exercise tests (Belman, 1993). McGavin and co-workers (1977) regarded

patient motivation and the enthusiasm of health care providers a vital aspect of improved performance.

5.4.3 Reduction in dyspnoea

The perceived reduction in dyspnoea after regular exercise training can be the result of various factors. The measurement of the intensity of dyspnoea is an integral part of pulmonary rehabilitation. Due to the subjective nature of available scales and questionnaires, there is a strong correlation between improvements in wellbeing and reduction in dyspnoea (Belman, 1993; Belman *et al*., 1991; Belman and Kendregan, 1981). According to Scherer and Schmieder (1997), there is enough evidence to conclude that a patient's perception towards dyspnoea will influence physical endurance. According to Fishman (1994), patients' perceptions of the intensity of dyspnoea may change without any physiological changes. In a study by Reardon and co-workers (1994), 30 patients experienced a reduction in dyspnoea that could not be explained by an improvement in exercise efficiency alone. They concluded that the improvement in dyspnoea was a result of altered perceptions of dyspnoea and increased motivation, which enabled patients to improve their exercise endurance more than expected.

Another factor responsible for the reduction of this symptom is desensitisation to dyspnoea (Mahler, 1998; Reardon *et al.*, 1994; Belman, 1993; Belman *et al*., 1991; Belman and Kendregan, 1981). Therefore, a decrease in dyspnoea may be the result of repeated exposure to this symptom. Improved exercise performance results in more efficient movement and a decrease in ventilation, which will influence the perception of dyspnoea (Scherer & Schmieder, 1997; Carrieri-Kohlman *et al.*, 1996; O'Donnell *et al.*, 1995; Holden *et al.*, 1990; Cockcroft *et al.*, 1981; Moser *et al*., 1980). A study by Belman and co-workers (1991) found an improvement in dyspnoea after just 10 days of exercising. This improvement in dyspnoea was explained by desensitisation towards dyspnoea, because minute ventilation and oxygen consumption remained unchanged.

A study by O'Donnell and co-workers (1995) unexpectedly reported an improvement in lung function. They established that an increase in inspiratory reserve volume or a decrease in end-inspiratory lung volumes would translate into reduced exertional dyspnoea.

Cox and co-workers (1993) ascribe the improvement in dyspnoea to reliable intake of medication, development of better coping strategies and a decrease in smoking habits. When patients exercise under supervision of health professionals, they may experience more confidence in their abilities, which will improve their perception of dyspnoea (Make, 1990; McGavin *et al.*, 1977).

5.4.4 Improved mechanical skill

Early studies identified improved mechanical skill as a means of improving performance (McGavin *et al.*, 1977). Paez and co-workers (1967) attributed this improvement to better neuromuscular co-ordination. Improvement of mechanical skill improves the efficiency of oxygen utilisation and ventilatory requirements. Although improvement of mechanical skill will have an effect on exercise endurance, there is no benefit with regards to pulmonary function and gas exchange (Belman, 1993; ATS, 1987).

Improvement of mechanical skill has frequently been associated with treadmill exercise. However, Casaburi and co-workers (1991) have illustrated that physiological response plays a greater role in improvement than "learning" the skill of efficient treadmill walking.

5.5 Benefits of pulmonary rehabilitation

The benefits of pulmonary rehabilitation include improved health status, a decrease in dyspnoea and a reduction in health care costs. Although pulmonary rehabilitation consists of various important components, exercise training was

found to be the “cornerstone” of benefits obtained (BTS, 2001; Carrieri-Kohlman *et al.*, 1996).

The benefits of regular exercise training for healthy individuals have been studied extensively. These benefits include an increased maximal oxygen uptake, an increase in muscular strength and endurance, improved muscle co-ordination, positive changes to body composition and an improved sense of wellbeing (Celli, 1999:195; O’Donnell *et al.*, 1995; Ries *et al.*, 1995; Goldstein *et al.*, 1994; Casaburi *et al.*, 1991).

Significant evidence exists to validate the use of exercise training to have physiological and psychological benefits for the COPD patient (ATS, 1995a). Patients with mild to moderate COPD respond similarly to exercise as healthy individuals. Patients with severe airflow obstruction will have a limited improvement in maximal oxygen uptake (Celli, 1999:195). Various studies have reported on the improvement of exercise endurance after pulmonary rehabilitation (Niederman *et al.*, 1991; ZuWallack *et al.*, 1991; Ries *et al.*, 1988; Belman, 1986; Cockcroft *et al.*, 1981). Exercise training in conjunction with medical therapy has had great success in improving the quality of life and functional capacity of COPD patients. Exercise training is not aimed at reversing symptoms, but at minimising disability and dependence and increasing involvement in physical and social activities (ATS, 1999; Berry *et al.*, 1999; ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997; Wijkstra *et al.*, 1994; Niederman *et al.*, 1991; ZuWallack *et al*., 1991).

Physiological benefits of exercise training for the COPD patient include an increased capacity for physical activity and exercise performance; even though changes in conventional pulmonary function are seldom documented (Bauldoff *et al.*, 2002; McArdle *et al.*, 2001:953; Guell *et al.*, 2000; Troosters *et al.*, 2000; Strijbos *et al.*, 1996; ATS, 1995a; Celli, 1995; Reardon *et al.*, 1994; Cox *et al.*, 1993; Holden *et al.*, 1990; Busch & McClements, 1988). Belman & Kendregan (1982) demonstrated that exercise has no influence on ventilatory muscle function.

McGavin and co-workers (1977) reported, after reviewing early studies on exercise, that improvement in exercise tolerance is a universal conclusion when COPD patients are subjected to exercise. In addition to improving exercise tolerance, pulmonary rehabilitation is beneficial for improving dyspnoea and HRQL (Rochester, 2003; Guell *et al.*, 2000; Troosters *et al.*, 2000; ATS, 1999; O'Donnell *et al*., 1995; Ries *et al.*, 1995; Wijkstra *et al.*, 1995; Goldstein *et al.*, 1994; Reardon *et al*., 1994). In several studies, patients have noted an improvement in quality of life variables (sense of wellbeing, self-esteem and self-efficiency), a functional improvement in respiratory muscle function, less coughing and a decrease in sputum. A decrease in dyspnoea is an essential benefit of exercise training for these patients (Boueri *et al*., 2001; BTS, 2001; McArdle *et al*., 2001:953; ATS, 1999; Foglio *et al.*, 1999; ACCP/AACPR Pulmonary Rehabilitation Guidelines Panel, 1997; Benstrup *et al.*, 1997; Scherer & Schmieder, 1997; Lacasse *et al.*, 1996). An increase in oxidative enzyme activity and a decrease in lactic acid production have also been recorded (Celli, 1999:195; Maltais *et al.*, 1996a; Casaburi *et al.*, 1991). A study by Coppoolse and co-workers (1999) found a decrease in leg pain and an increase in maximal inspiratory pressure after pulmonary rehabilitation. Cardiovascular benefits of exercise training in COPD patients have been reported by Costes and co-workers (2004). Increased survival rates have been reported by Bowen and co-workers (2000) as a result of improved functional status. Ries and co-workers (1995) recorded a decrease in mortality rates after pulmonary rehabilitation. Holden and co-workers (1990) reported that the increased attention by different health care providers during pulmonary rehabilitation, could bestow functional benefits on COPD patients. Make (1990) suggested that the increased attention by health care providers improves patients' confidence in their abilities, which reflects as an increase in exercise capacity.

The decrease in the number of hospitalisations and the number of hospital days after pulmonary rehabilitation, has been documented by several studies (McArdle *et al*., 2001:953; Griffiths *et al.*, 2000; ATS, 1999; AACVPR, 1998; Fishman, 1998; Bendstrup *et al.*, 1997; Celli, 1995; Cox *et al.*, 1993). This decrease in

hospitalisations, combined with the decrease in medical costs, result in considerable savings in total healthcare (Decramer *et al.*, 1997; ATS, 1995a). This was confirmed by Cox and co-workers (1993) who reported that the number of working days increased after 12 weeks of pulmonary rehabilitation. In this study, the 44 patients in the experimental group's working days increased from 2.1 ± 0.4 to 3.4 ± 0.4 days per week, whereas the working days of the control group decreased. According to Griffiths and co-workers (2000), pulmonary rehabilitation does not only decrease the number of hospital admissions, but decreases the length of hospital stay. A randomised controlled study by Guell and co-workers (2000) found a decrease in the number of exacerbations after a pulmonary rehabilitation programme, which contributed significantly to savings in health care costs. Celli (1995) noted that more scientific research is needed to determine exactly what the effect of pulmonary rehabilitation is in terms of healthcare savings.

According to Brooks and co-workers (2002), benefits obtained through pulmonary rehabilitation are irrespective of the type of programme used. The same benefits can be obtained through inpatient, outpatient and community-based programmes. In contrast, Strijbos and co-workers (1996) found that exercise maintenance is better with home-based exercise programmes, compared to outpatient programmes. Wijkstra and co-workers (1995) also obtained positive results with home-based rehabilitation sessions. In their study, the quality of life benefits obtained through the home-based programme were sustained for 18 months. This was supported by Hernandez and co-workers (2000) who found significant improvements in quality of life, exercise tolerance and dyspnoea after a simple, 12-week, home-based exercise programme.

One of the main concerns regarding the effectiveness of pulmonary rehabilitation is the limited duration of benefits achieved (Rochester, 2003; Ries *et al.*, 1995). Various studies showed that quality of life benefits obtained through pulmonary rehabilitation are retained for months after completion of the programme (Cambach *et al*., 1997; Wijkstra *et al.*, 1995; Cox *et al.*, 1993; Vale *et al.*, 1993). Ketelaars

and co-workers (1997) reported that HRQL benefits decline nine months after completion of a programme. Other studies confirmed the presence of training benefits up to two years after completion of a training programme (Verrill *et al.*, 2005; Ries *et al.*, 2003; Guell *et al.*, 2000; Troosters *et al.*, 2000; Foglio *et al.*, 1999; Ries *et al.*, 1995). Toshima and co-workers (1990) recorded improved exercise endurance six months after completion of a training programme. Cockcroft and co-workers (1981) found that improvements in functional capacity, as measured by the 12-minute walk test, were sustained for seven months after completion of pulmonary rehabilitation. In a long-term study by Casanova and co-workers (2007), they found that the average annual decline of walking distance, measured by the 6MWT, is only 12.5m. According to these authors, the largest decline in functional capacity is found among patients with severe COPD (Casanova *et al.*, 2007). Vale and co-workers (1993) found that even though improvements in quality of life and exercise endurance significantly reduced after 11 months, the follow-up measurements were still higher than the baseline values. Cox and co-workers (1993) attribute this to the positive effect that pulmonary rehabilitation has on patients' lifestyles. According to these authors, the patients in their study engaged more frequently in leisure activities and made other positive lifestyle changes. It is important to note that even in healthy individuals the benefits obtained through an exercise programme decline once exercise is discontinued (ACSM, 1998b).

5.6 Cost involved in pulmonary rehabilitation

Despite the established benefits of exercise for COPD patients, the use of exercise as a treatment modality for these patients has been challenged by Albert (1997). According to Albert (1997), exercise rehabilitation is not cost effective and undoubtedly the most expensive component of pulmonary rehabilitation. In contrast, Griffiths and co-workers (2001) illustrated that pulmonary rehabilitation is cost effective when considering health care utilisation of patients not engaged in a programme. Senior and Anthonisen (1998) reported that a need exists for the

development of an inexpensive alternative to conventional pulmonary rehabilitation.

5.7 Adherence after pulmonary rehabilitation

Due to poor self-management and self-discipline and a lack of adherence to treatment protocols, the benefits obtained through a pulmonary rehabilitation programme tend to diminish after completion of the programme (Griffiths *et al*., 2000; Celli, 1999:196). Benefits gained from pulmonary rehabilitation tend to last for 18 months after completion of a programme, after which improvements decline. These declines are evident despite follow-up programmes to promote adherence. Patients with lower pre-rehabilitation walking distances seem to experience greater declines compared to other patients (Brooks *et al*., 2002; Ketelaars *et al.*, 1997).

Greater adherence is seen in programmes where patients perform supervised exercise routines, compared to behaviourally-orientated programmes where the focus is on education. Other factors that may influence adherence include age, socio-economic status, anxiety, duration and difficulty of exercises, type of exercises and social support. Adherence tends to be better with exercises that patients can easily incorporate into their daily routine (Norweg *et al.*, 2005; Brooks *et al.*, 2002). Gosselink (2002) added motivation, logistics of living environment and disease stability to the above mentioned factors that influence exercise adherence. Disease stability is considered the most important factor in determination of exercise adherence. Frequent exacerbations impede exercise continuation and lead to a decline in functional capacity. A significant obstacle, for patients and clinicians alike, is how to maintain exercise performance despite frequent exacerbations (Gosselink, 2002). Foglio and co-workers (2001) raised the question whether severity and frequency of exacerbations has an influence on the long-term outcomes of pulmonary rehabilitation. Their research established that patients admitted to pulmonary rehabilitation on a yearly basis experienced repeated improvements in exercise tolerance and a reduction in exacerbations.

Improvements in exercise tolerance had, however, the same duration after completion of each programme and repeated pulmonary rehabilitation did not result in extension of benefits (Foglio *et al.*, 2001).

Several studies addressed the effectiveness of a maintenance programme after completion of a pulmonary rehabilitation programme (Ries *et al.*, 2003; Bauldoff *et al.*, 2002; Brooks *et al.*, 2002; Ketelaars *et al.*, 1997; Wijkstra *et al.*, 1995; Vale *et al.*, 1993). The results of the effectiveness of maintenance programmes are inconsistent. In general, these programmes are valuable in promoting exercise adherence for the duration of the maintenance programme (usually 12 months), where after adherence is equivalent to patients not engaged in such a programme (Rochester, 2003). Ketelaars and co-workers (1997) reported that patient selection for maintenance programmes is important. According to these authors, not all patients need to follow a maintenance programme after completion of pulmonary rehabilitation. Patients who have shown little improvement or those with poor baseline values will probably not benefit from a maintenance programme (Ketelaars *et al.*, 1997). Bauldoff and co-workers (2002) found that the use of distractive stimuli, in the form of music, could result in increased success of maintenance programmes.

Ries and co-workers (2003) addressed possible factors responsible for the modest effects of maintenance programmes. They found that it is unlikely that the weakness of outcome measures could be responsible. Another possible explanation is that maintenance intervention is not sufficient to produce long-term change. The effectiveness of maintenance programmes depends on how well it can equip patients with coping strategies. They found that due to the unstable nature of the health status of COPD patients, it is very difficult to sufficiently adapt maintenance programmes to the complex behaviour changes of these patients. Therefore, ineffectiveness of maintenance programmes can be a key factor responsible for the relative low success rates of these programmes. Finally, it is important to remember that COPD is a progressive disorder and that disease

progression may play a major role in a patient's decline, despite the level of adherence after completion of a pulmonary rehabilitation programme (Ries *et al.*, 2003; Brooks *et al*., 2002).

Healthy related quality of life (HRQL)

While the improvement of survival time is still an important treatment goal, health care providers have shifted their focus from quantity of life to quality of life in the treatment process of COPD patients. The term HRQL is preferred when referring to chronic diseases, since quality of life can be influenced by factors other than health status (i.e. financial status, social status, employment) (Curtis & Patrick, 2003; Curtis *et al.*, 1994). The term "functional status" is often used alongside HRQL. There is, however, a clear distinction between the two. Functional status refers to a person's ability to perform tasks of daily living, whereas HRQL refers to a person's subjective experience of the impact that disease has on one's quality of life (Ketelaars *et al.*, 1996; Curtis *et al.*, 1994; Lareau *et al.*, 1994). According to Lareau and co-workers (1994), functional status is in some settings regarded "synonymous with physiologic measures of airway obstruction". COPD generally affects older individuals that usually consider the ability to enjoy life (i.e. HRQL) more important than task performance (i.e. functional status). Although HRQL is a subjective measure, it is of vital importance to optimise treatment and management of COPD patients (Curtis *et al.*, 1994).

It is important to note that improvements in physiological measures, such as FEV_1 and oxygen saturation, do not necessarily translate to improvements in HRQL (Ketelaars *et al.*, 1996; Curtis *et al.*, 1994). The opposite is also true; improvement in HRQL does not necessarily reflect an improvement in physiological measures (Curtis *et al.*, 1994). According to Ketelaars and co-workers (1996), HRQL consists of four components, namely "symptoms", "activities", "impacts" and "wellbeing", as developed in the St. George's Respiratory Questionnaire (SGRQ). According to these authors, improvements in pulmonary function have little effect

on the HRQL of the COPD patient. A good correlation was found between exercise performance and HRQL, although it did not account for all the variability in HRQL (Ketelaars *et al.*, 1996; Okubadejo *et al.*, 1996).

Many physiological factors influence the quality of life of patients with COPD. According to Okubadejo and co-workers (1996), the quality of life of COPD patients will be impacted by hypoxaemia. A good correlation was found between Pa_{O2} and quality of life. Osman and co-workers (1997) found a significant correlation between poor quality of life and hospital re-admission. Shoup and co-workers (1997) found that both high and low body weight was associated with poor HRQL. Furthermore, this study reported a significant correlation between dyspnoea and HRQL as measured by the baseline dyspnoea index (BDI) and the SGRQ, respectively. Mahler and co-workers (1992) also found dyspnoea to be the most important predictor of HRQL. Exacerbations are another important factor that influences quality of life. Seemungal and co-workers (1998) found that an increased occurrence of exacerbations resulted in a decrease in HRQL. Spencer and co-workers (2004), who found that exacerbations had a cumulative effect on health status, confirmed this. Another study reported that an increase in quality of life is associated with an increase in survival rate (Bowen *et al.*, 2000).

Apart from this obvious impact that COPD has on HRQL, other less obvious issues, such as depression, anxiety and sleep deprivation, are sometimes overlooked. The interdependence between these issues and HRQL are apparent (Curtis *et al.*, 1994). According to Okubadejo and co-workers (1996) depression and anxiety correlates with HRQL as indicated by the SGRQ. Furthermore, they found anxiety and depression to be better indicators of HRQL than physiological measurements.

It is vital to assess the impact of interventions on the quality of life of patients with COPD (Boueri *et al*., 2001). Various scales and questionnaires have been developed to assess the impact of disease on the HRQL of patients (Osman *et al.*,

1997; Okubadejo *et al*., 1996). According to Okubadejo and co-workers (1996), disease-specific questionnaires that are specifically developed for patients with airflow obstruction, have a higher sensitivity than general health measures. The most popular questionnaires used for COPD patients include the Chronic Respiratory Questionnaire (CRQ) and the SGRQ. These questionnaires focus on a patient's subjective experience of symptoms, the impact of symptoms on a patient's life and the level of distress and anxiety caused by the disease. Although these questionnaires do not correlate well with physiological measures, they are important, because quality of life is central to the management of these patients (Osman *et al.*, 1997).

The SGRQ includes three subscales, namely symptoms, impacts and activities. According to Osman and co-workers (1997), female COPD patients experience greater limitation in activities and greater levels of distress than male patients do. These authors also demonstrated that younger patients experienced a greater psychological impact due to their illness, compared to older patients.

CHAPTER III: METHODOLOGY

Ethical approval

This study was an extension of a similar study by J.L. Brown (Stellenbosch University). The Ethics Committee of Human Research of the Faculty of Health Sciences of Stellenbosch University was informed of the extension and initially no further approval was needed as approval for the initial study was obtained, reference number 2002/C076. An adjustment to the protocol necessitated further approval. The adjusted protocol gained consent from the Ethics Committee and was added to the original approval as an amendment.

The eight subjects that comprised the study of J.L. Brown were also reported on in the current study. The decision to include those subjects was made on the basis that not all the variables included in the current study were reported on in the study by J.L. Brown. The current researcher was also involved in the testing and evaluation of those patients and additional evaluations were added to the original protocol.

Subject selection

According to the American Thoracic Society (1999), exercise as part of the management of COPD patients is indicated for patients, who despite optimal medical treatment, experience a restriction in daily activities and exercise capability. Indications for referral is summarised in Table 3.9.

Table 3.9 Common indications for referral for pulmonary rehabilitation (ATS, 1999).

Respiratory disease resulting in: • Anxiety engaging in activities • Breathlessness with activities • Limitations with social and leisure activities, indoor and/or outdoor chores, basic or instrumental activities or daily living • Loss of independence

Subjects mainly came from the Helderberg, Tygerberg and Oostenberg municipal areas. The study was advertised in local newspapers, pharmacies and through radio interviews. General practitioners and physicians were informed of the study and asked to refer appropriate patients for screening by a physician. A total of 25 subjects were identified as suitable for the primary programme (PP) of the study, according to the inclusion and exclusion criteria. Three of these subjects did not complete the study. A further 21 subjects were identified by a physician for the extension of the study according to the inclusion and exclusion criteria. These patients were randomly divided into an experimental and control group. The ten subjects in the control group followed the same protocol as in the PP, whereas the eleven subjects in the experimental group followed the MP. Three subjects in the control group did not complete the study. Reasons for non-completion will be discussed later in this chapter. Figure 3.9 illustrates how subjects were divided into different groups.

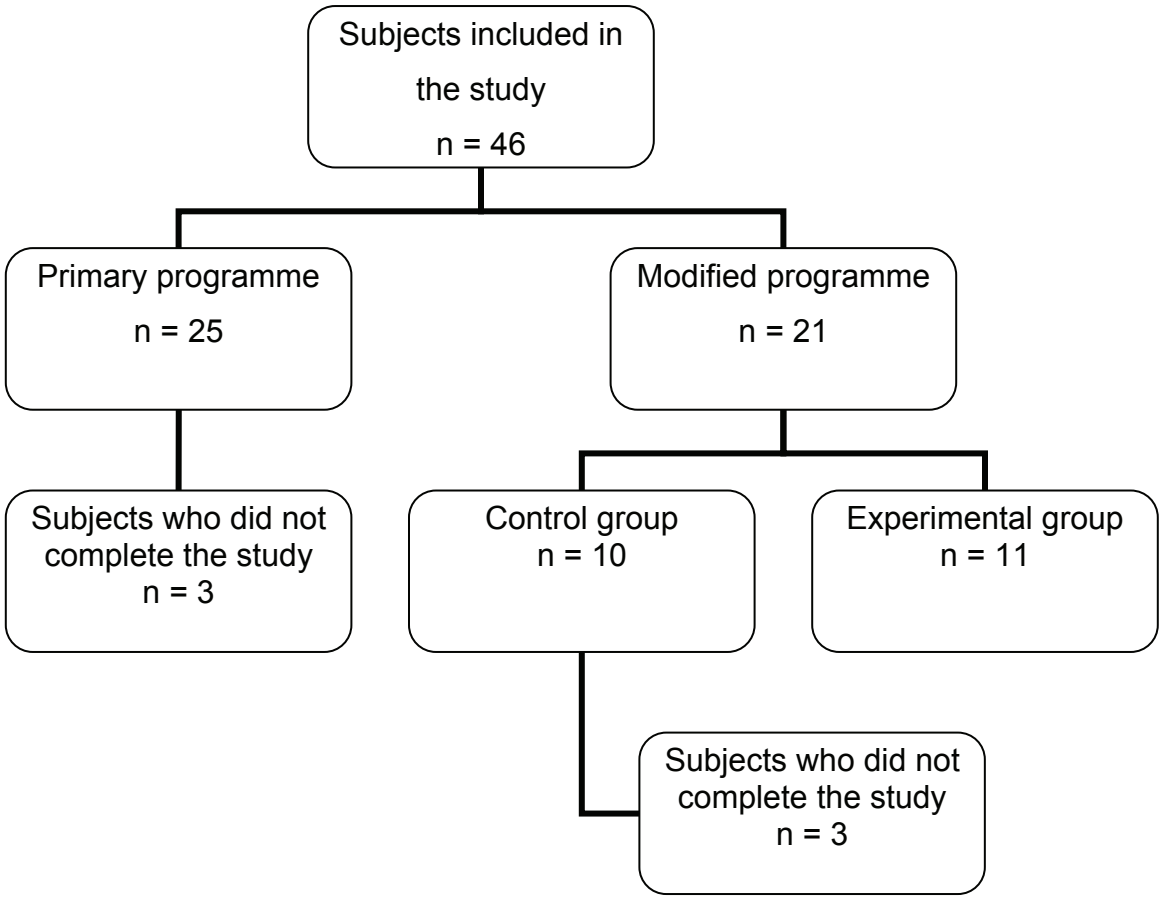

Figure 3.9 Subjects included in the study.

Subjects were encouraged to continue other forms of treatment and medication. All subjects had to be correctly medicated before the date of initial testing. Current medication was assessed by a senior physician and optimised where necessary. Subjects were encouraged to maintain daily routines and disruptions were to be avoided for the duration of the study. General practitioners and physicians were informed if one of their patients enrolled in the study and of any modification to their medication.

As with similar studies (Berry *et al.*, 1999, Foglio *et al.*, 1999, Scherer & Schmieder, 1997; Couser *et al.*, 1993, Holden *et al.*, 1990) no control group was used for the initial part of the study. The decision not to include a control group was made on ethical grounds. Numerous studies have illustrated the benefits of exercise training for COPD patients (Rochester, 2003; Bauldoff *et al.*, 2002; Boueri

et al., 2001; BTS, 2001; Griffiths *et al.*, 2000; Guell *et al.*, 2000; Troosters *et al.*, 2000; Celli, 1999:195; Foglio *et al.*, 1999; AACVPR, 1998; Fishman, 1998; ACCP/AACPR Pulmonary Rehabilitation Guidelines Panel, 1997; Benstrup *et al.*, 1997; Scherer & Schmieder, 1997; Carrieri-Kohlman *et al.*, 1996; Lacasse *et al.*, 1996; Strijbos *et al.*, 1996; Celli, 1995; O'Donnell *et al.*, 1995; Ries *et al.*, 1995; Wijkstra *et al.*, 1995; Goldstein *et al.*, 1994; Reardon *et al.*, 1994; Cox *et al.*, 1993; Casaburi *et al.*, 1991; Niederman *et al.*, 1991; ZuWallack *et al.*, 1991; Holden *et al.*, 1990; Busch & McClements, 1988; Ries *et al.*, 1988; Belman, 1986; Cockcroft *et al.*, 1981). Adding a control group would have denied beneficial treatment to patients that are also in desperate need of help. Therefore, each subject served as his or her own control.

In the MP, the group that followed the same programme as the PP represented the control group. No placebo group was included based on the same reasons that no control group was included in the PP.

1. Inclusion Criteria

Subjects are diagnosed with COPD according to the GOLD criteria

According to the GOLD criteria, COPD can be diagnosed if the FEV_1 is less than 80% of the predicted value in combination with a FEV_1/FVC ratio of less than 70%, which is not reversible by the use of a bronchodilator. Reversibility is defined as an increase in FEV_1 exceeding 12% or an absolute increase of 200ml after the inhalation of a bronchodilator (Pauwels *et al*., 2001:1257; Berry *et al*., 1999).

Subjects are mobile and can walk unaided

Since one of the primary aims of the study was to assess functional capacity, the 6MWT represented an essential part of the assessments. Furthermore, walking was the main cardiovascular component of the exercise programmes. For the

study to be successful, it was important that subjects exercised at an intensity that was sufficient to elicit a physiological response. Therefore, the inability to walk unaided would have prevented subjects obtaining the full benefits of the exercise intervention.

Subjects must own telephonic communication

It was important to be able to communicate with the subjects throughout the intervention programme. Telephonic communication was especially important in the event of absenteeism. Subjects knew that they were likely to be called if they missed a session, so sessions were only missed for essential reasons. Furthermore, it was important to be able to reach patients for rescheduling of sessions or reporting of any complaints or illness. Subjects that did not own a personal telephone, but had access to a reliable neighbour or family member's telephone were allowed to participate in the study.

Subjects must be willing to follow a 10-week rehabilitation programme

Subjects in the initial part of the study had to exercise three times a week for 12 weeks. Subjects who missed more than six sessions were excluded from the study. In the MP, subjects had to complete 32 exercise sessions in a 10-week period. To encourage adherence to the programme, subjects were allowed to schedule sessions around their daily programme. It was each subject's responsibility to ensure that they have sufficient time to complete the prescribed sessions in the allowed time. Subjects who could not commit to the 10-week programme, due to travel or business engagements, were excluded from the study.

Age of 45 years and older

An age specification was included to homogenise subjects. COPD is generally diagnosed in the fifth or sixth decade of life (Weiss *et al.*, 2003; WHO, 1999); therefore, subjects were unlikely to be excluded based on their age.

Consent and support of the subjects' personal physician

Since a physician was part of the study, consent from the subjects' personal physician was essential for ethical reasons. It was vital that physicians had a positive impression of the study and did not feel that patients were taken away from their practices. Physicians were well informed of the study protocol and feedback was given when necessary. Consent from personal physicians was also required to promote adherence. It was thought that subjects would have more confidence in the programme if it was recommended or supported by their personal physician.

Completion and signature of an informed consent document

Subjects were informed about the study protocol and what was expected of them by a physician. Subjects were allowed time to study the patient-information-and-consent documents thoroughly (Appendix D). Subjects that agreed to participate had to sign the consent form before the initial evaluation. One of the signed copies was given to the subject, while a second signed copy was kept by the researchers in the subject's file.

2. Exclusion Criteria

Serious illnesses or co-morbidities

Subjects with serious illnesses or co-morbidities, such as cancer, chronic arthritis, uncontrolled hypertension, congestive cardiac failure or uncontrolled angina, were excluded from the study to ensure that the results reflect the impact of the intervention programme on COPD status. Furthermore, certain co-morbidities could prevent subjects from completing the exercise programme, i.e. painful arthritic joints may prevent weight bearing exercises.

Serious psychological disorders

Patients with serious psychological disorders that would have interfered with the rehabilitation process, for example an inability to learn, severe depression or disruptive behaviour, were excluded from the study. Although the exercise programme was easy to understand and subjects exercised under constant personal supervision, a certain level of motivation and intellectual capacity were required from the subject. Although depression is common among COPD patients (Rochester, 2003; Curtis *et al.*, 1994; Belman, 1993; Belman *et al*., 1991), severe, untreated depression could have affected a subject's ability to participate and/or complete the study. Serious psychological disorders may have impaired a subject's ability to understand the study protocol completely. Psychologically unstable or disruptive subjects may have hindered other subjects from completing exercise sessions or would not have been able to complete sessions in the allowed time.

Known or suspected cases of ischemic heart disease and right or left heart failure

Serious cardiac conditions can place a patient at unnecessary risk during exercise training (ATS, 1999). Although exercise training can be beneficial for these conditions, a cardiac rehabilitation programme would be better suited for these patients to minimise their risk for complications.

One year or less post – Tuberculosis

Current tuberculosis would have obscured the results of the study, since changes in health status could possibly be attributed to TB medication and not the exercise intervention. To ensure homogeneity among subjects, these patients were excluded.

Smokers of less than 8 pack years

Smoking history is important, although not essential, in COPD diagnosis. COPD patients without a smoking history were excluded to ensure homogeneity among subjects.

Any known alcohol or drug addictions

Alcohol and drug addictions would have interfered with the exercise programme. Addictions could have prevented subjects from attending all exercise sessions or from exercising optimally. Furthermore, subjects had to be as healthy as possible prior to the initial evaluation to ensure that evaluations were not obscured by other conditions.

Subjects who are in respiratory failure or desaturated to below 80% during the pulmonary evaluation

Oxygen saturation levels were continuously monitored during the initial 6MWT. In the initial part of the study, subjects who desaturated below 85% were given supplemental oxygen while completing the test. Supplemental oxygen was given to these subjects during the exercise intervention. In the MP, subjects who desaturated below 80% were excluded from the study. This was because it was thought that supplemental oxygen would not be readily available to the broader community of South Africa and would therefore not be realistic for the modified programme. It would also not be feasible to supply oxygen to participants who underwent their exercise training outside of the confines of the formal rehabilitation area.

Research timeline

The data collection for the PP started in September 2002 and the last patient was admitted to the study during July 2004. Patients were evaluated and underwent a 12-week intervention programme. The post-intervention assessment was repeated after six months.

The data collection for the MP started May 2005 and the last subject was admitted to the study during October 2006. The pre- and post-intervention assessments were separated by eight to ten weeks of exercise training. No follow-up assessment was included in this part of the study.

Pre-intervention assessment procedure

In the MP, a pre-evaluation was included to ensure that only candidates suitable for the study underwent the pre-intervention assessment. Suitable subjects

identified at the local Stellenbosch regional hospital were invited to attend the first meeting at the senior physician's practice.

All subsequent screening and testing took place at an independent practice of a senior physician. Contact numbers of this practice was supplied in all advertisements and interested individuals contacted the practice directly. Other possible subjects were referred to the practice by their personal physicians. Interested individuals were screened on appointment at the practice and were given more information on the study and what was to be expected.

On arrival, the study protocol and what was required of the subjects, were explained to interested individuals by a physician. Before commencing the screening process, possible subjects were issued with patient-information-and-consent documents (Appendix D). Time was allowed for individuals to study these documents and any questions or uncertainties were addressed. Subjects that agreed to participate had to sign the consent form before the screening began. Copies of these signed documents were kept on file and one signed copy was handed to each of the subjects.

All subjects that signed the consent forms were then clinically screened. Screening included documentation of the subject's history, a medical screening and an examination. After the initial screening, the BDI and physician's global evaluation were completed.

All subjects received four inhalations of Combivent (480µg salbutamol and 80µg Atrovent) prior to spirometry. A clinical technologist advised the subject on the correct use of an inhaler and made sure that the bronchodilator was administered correctly. A minimum of ten minutes were allowed for the bronchodilator to take effect before testing lung function. Next, the subject's height and weight were measured and recorded by a clinical technologist using a standard Paramedic 2m stadiometer and a Soehnle Certified-150kg scale (serial number: 6176). Lung

function testing procedures (including the Borg-RPE-scale) were thoroughly explained to the subject by a clinical technologist. Three correct lung function tests were performed and the best effort was recorded. A Jaeger Master Lab system (serial number: 700707-02A250046) was used to measure lung function. The system was calibrated prior to the tests using a three litre syringe. After lung function testing, a resting ECG was recorded, using a Cardio Perfect MD ECG machine (serial number: 015219). Subjects with normal resting ECG were required to perform the 6MWT. The procedure of the 6MWT was thoroughly explained to the subject by a clinical technologist and any questions were addressed. Since the 6MWT was performed on a StarTrac treadmill (model: ST 2005-EZ; serial number: 206759), subjects were allowed time to familiarise themselves with the machine. When the subject was comfortable walking on the treadmill, the subject was rested till cardiovascular parameters (heart rate, blood pressure and breathing rate) returned to normal. The subject was guided through the test by the clinical technologist, who encouraged the subject throughout according to the ATS standards. The walking distance and time was measured by the treadmill. Oxygen saturation levels were monitored throughout the test with a BCI Oxi Pulse oximeter (catalogue number: 3301; serial number: 320014739). In the PP, subjects who desaturated below 85% during the first 6MWT were given supplemental oxygen. Subjects in the MP who desaturated below 80% were excluded from the study. Blood pressure and heart rate were measured and recorded after the test. Blood pressure was measured using a standard Surgifix mercury sphygmomanometer. Two tests were initially performed. If the distances in each test differed by more than 10%, a third test was performed. The best distance was recorded. Subjects were rested between tests till cardiovascular parameters returned to normal and they felt that their legs were well rested. After the test, a clinical technologist again explained the Borg-RPE-scale to the subject and recorded their Borg rating on the Modified Borg-RPE-scale after each test. After the subject was well rested, the investigator explained the SGRQ to the subject. The subject completed the SGRQ without help from the investigator.

Subjects who did not meet the inclusion and exclusion criteria during the initial evaluation process, were treated or referred to conform to the criteria, for possible inclusion at a later stage. Subjects that were current smokers were allowed into the PP, but were advised on how to quit. Since the benefits obtained in the PP were significantly less for current smokers, smokers were excluded from the MP until they successfully quit smoking.

After the evaluation, an appointment was made to begin the exercise programme at the Stellenbosch Biokinetics Centre (Department of Sport Science, Stellenbosch University, South Africa).

Intervention programme

1. Primary programme

The invention programme was staged over 12-weeks and subjects had to attend three, hour long exercise sessions per week. Subjects were not allowed to miss more than six sessions during the entire programme. The exercise programme was conducted at a fully equipped exercise- and rehabilitation centre. Subjects exercised under constant, one-to-one supervision of a Biokineticist or student-Biokineticist.

The exercise programme (Appendix B) included an aerobic component as well as upper and lower body strength training exercises. Programmes were individualised by adjusting the intensity and repetitions according to each subject's ability, but no changes to the type of exercises were allowed. The same programme was followed at every session and subjects had to complete all exercises at every session.

Subjects were advised to use their bronchodilator ten minutes prior to arrival for each exercise session. On arrival, subjects were fitted with Polar® heart rate

monitors and allowed to sit and rest for five to ten minutes before blood pressure was measured. Blood pressure and heart rate readings were recorded prior to and after each exercise session. If an abnormal blood pressure reading was obtained, the subject was instructed to sit and relax for a further five minutes until a normal reading could be obtained. If the blood pressure did not reach a safe level for exercise, the subject was advised to reschedule his/her appointment. In the event of repeated abnormal blood pressure readings, the subjects were referred to their physician or doctor for exercise clearance.

The aerobic component of the exercise session consisted of 20 minutes of treadmill walking (ten minutes in the beginning of the session and ten minutes at the end). Treadmill walking was used because it reflects the metabolic and ventilatory requirements of daily activities (Palange *et al.*, 2000). The intensity of the aerobic exercise was determined by using a percentage of the maximum heart rate, according to the Karvonen formula (Appendix E), in combination with the Borg-RPE-scale. The target intensity for subjects was 60 to 75% as described in previous literature (ATS, 1999; Coppoolse *et al.*, 1999; Maltais *et al.*, 1997; Folgering & van Herwaarden, 1994). A Borg rating of five (severe), was prescribed on the modified Borg scale (Appendix A). Horowitz and co-workers (1996) demonstrated the use of subjective rating scales to be effective in prescribing exercise intensity for COPD patients. Subjects had to exercise, for ten minutes, at which ever intensity they reached first. Some subjects reached their target heart rate before they considered the exercise as “severe”, while others could not reach their target heart rate, but exercised at a “severe” intensity on the Borg scale. Some subjects could not continuously walk for ten minutes. Subjects were allowed to rest and continue with the remainder of the prescribed minutes, if possible. For these subjects, the duration of their treadmill walks were gradually increased until they were able to walk continuously for ten minutes. As the subjects’ exercise capacity increased, the treadmill speed was adjusted to ensure that the prescribed intensity was achieved at each session.

After each treadmill walk, stretching of the large muscle groups of the legs was done. Subjects were assisted in these stretches to ensure maximal mobility and range of motion was retained throughout the intervention programme.

Stretches were followed by a combination of upper and lower body resistance training. Resistance exercises focused on the main muscle groups of the body and used a combination of free weights, gym equipment and own body weight as resistance. The aim was to complete three sets of ten repetitions for each of the prescribed exercises. Initially, some subjects were not able to complete all the sets, but gradually improved to the prescribed programme. As described by Horowitz and co-workers (1996) RPE-ratings were used to determine the heaviness of the weights. Resistance was prescribed as five (severe) on the modified Borg-RPE-scale. Resistance was continuously adjusted to reach the prescribed intensity. Heart rate and RPE-ratings were documented after each exercise for future reference.

2. Modified programme

In the MP subjects had to complete 32, hour long exercise sessions over an eight to ten week period. Subjects were allowed to schedule sessions three or four times a week, depending on their daily programmes. The investigator assisted subjects in the scheduling of sessions and ensured that the subjects completed the prescribed sessions in the allowed time. The control group exercised in a fully equipped exercise- and rehabilitation centre and followed the same exercise protocol as in the PP. The experimental group's exercise programme was adapted to be more cost-effective and accessible to individuals of all socio-economic backgrounds. The programme was designed in such a way that no specialised equipment was needed and that it could be easily implemented anywhere in South Africa.

Similar to the PP, the MP (Appendix B) included an aerobic component as well as upper and lower body strength training exercises. Subjects were also advised to use their bronchodilator ten minutes prior to arrival for each exercise session.

Although heart rate monitors are not affordable for the majority of South Africans, both the experimental and control groups wore Polar® heart rate monitors throughout the exercise sessions. Heart rate monitors were used for research and safety purposes, but are not essential to achieve successful results in an adapted programme. The same blood pressure and heart rate protocol was used as in the PP.

The protocol for the MP consisted of the same components as in the PP and the same supervising and monitoring principles applied. Similar to the PP, the intensity of each session was determined using heart rate and the Borg-RPE-scale.

For the experimental group, treadmill walking was replaced by walking on a flat surface. When the weather permitted it, walking was done outside, otherwise subjects walked inside a hall. Because the pre- and post-walk test assessments were done on a treadmill, a treadmill walk was brought into the experimental group's exercise programme every two weeks. This was done to ensure that the control group did not have any advantage regarding familiarity to a treadmill. Stretching of large muscle groups was done in the same way as in the PP. Resistance exercises mainly used body weight, sandbags and free weights. Similar to the PP, heart and RPE-ratings were documented after each exercise for future reference.

Safety measures

The following criteria for termination of the exercise test were used as a guideline to ensure that subjects were not placed under unnecessary risk during the 6MWT (ACSM, 2000:104).

Absolute indications:

1. Onset of moderate-to-severe angina (chest pain)
2. Drop in systolic blood pressure below standing resting pressure or drop in systolic blood pressure with increasing workload accompanied by signs of ischemia
3. Signs of poor perfusion (circulation or blood flow), including pallor (pale appearance of the skin), cyanosis (bluish discoloration), or cold and clammy skin
4. Severe or unusual shortness of breath
5. Central nervous system symptoms e.g., ataxia (failure of muscular coordination), vertigo (an illusion of dizzying movement), visual or gait (pattern of walking or running) problems, confusion
6. Patient's request (to stop)

Relative indications:

1. Drop in systolic blood pressure below standing resting pressure or drop in systolic blood pressure with increasing workload without signs of ischemia
2. An increase in chest pain
3. Physical or verbal manifestations of shortness of breath or severe fatigue
4. Wheezing
5. Leg cramps or intermittent claudication (grade 3 on a 4-point scale)
6. Hypertensive response (systolic blood pressure >260 mm Hg; diastolic blood pressure >115 mm Hg)
7. Less serious arrhythmias (abnormal heart rhythms) such as supraventricular tachycardia

All personnel involved in the exercise training of the subjects were trained in cardio-pulmonary resuscitation (CPR) and first aid. Emergency contact numbers were kept beside the telephone. A physician or general practitioner, from the Stellenbosch University Student Health Services, was always on standby during

the exercise sessions. If any abnormalities in heart rate or blood pressure were detected during exercise, the physician or general practitioner was contacted. Since heart rate and RPE-ratings were documented after each exercise, during every session, severe changes could easily be detected.

Contraindications to exercise, according to the ACSM (2000:167), were used to further ensure the subjects safety.

1. Unstable angina
2. Resting systolic blood pressure of more than 200mmHg or resting diastolic blood pressure of more than 100mmHg had to be evaluated on a case-by-case basis
3. Orthostatic blood pressure drop of more that 20mmHg with symptoms
4. Acute systemic illness or fever
5. Uncontrolled systemic atrial or ventricular arrhythmias
6. Uncontrolled tachycardia (more than 120 beats per minute)
7. Uncontrolled diabetes
8. Severe, acute orthopaedic conditions that would prohibit exercise

Facilities and equipment

Pre- and post rehabilitation assessments of subjects took place at a physician's practice in Stellenbosch using available facilities and testing equipment. Exercise sessions took place at the Stellenbosch Biokinetics Centre (Stellenbosch University), using their facilities and equipment. Equipment needed for the conventional programme included a sphygmomanometer, Polar® heart rate monitors, free weights, multigym equipment, stepping benches and treadmills. Equipment used in the adapted programme included a sphygmomanometer, Polar® heart rate monitors, free weights, chairs and sandbags.

Measurements

1. Six minute walk test for distance (6MWT)

1.1 Aim

A treadmill 6MWT was used to assess the exercise capacity of the subjects in this study. The 6MWT is considered a safe, effective, simple and inexpensive measurement of exercise capacity to assess the functional status of patients living with COPD. It is also used to assess the effectiveness of different treatment modalities (Johnson, 2004; Marin *et al*., 2001; Stevens *et al.*, 1999; Redelmeier *et al.*, 1997). According to Casanova and co-workers (2005), the 6MWT correlates well with dyspnoea, airflow obstruction and hyperinflation.

1.2 Description

The 6MWT can be performed on a treadmill or in a corridor. In the current study, a treadmill was used due to limited space at the evaluation centres. The use of a treadmill also facilitates the monitoring of subjects and the administration of oxygen during the test. During the 6MWT, patients are instructed to walk as far as possible in the allowed six minutes. Patients are allowed to stop and rest during the test, but rest periods form part of the six minute period (Redelmeier *et al.*, 1997). Most protocols (ATS, 2002) do not allow for the use of a treadmill, due to underestimation of exercise ability. Stevens and co-workers (1999) found that when using a treadmill, walking distance was shorter by a mean of 14%, compared to corridor distances. However, Johnson (2004) argued that the use of a treadmill is more versatile and gives a better indication of functional improvements. According to the American Thoracic Society (2002), treadmill tests are not interchangeable with corridor tests.

The 6MWT was performed after spirometric measures were completed. The clinical technologists that administered the tests were experienced in performing treadmill 6MWTs. The procedure of the 6MWT was thoroughly explained to the subject by a clinical technologist and any questions were addressed. If subjects were unfamiliar with a treadmill, time was given to adjust to walking on a treadmill. Subjects were seated before testing began. This time was used to document resting heart rate, blood pressure and oxygen saturation. The technologist adjusted the treadmill speed on the request of the subject (faster or slower). Verbal encouragement was given throughout the test. After completion of the test, blood pressure, heart rate and oxygen saturation were documented while subjects were still standing. Subjects were seated on a chair to rest, while their Borg rating [on the modified Borg scale (Appendix A)] was obtained.

A pulse oximeter was used to record oxygen saturation throughout the test. If patients (PP only) desaturated below 85%, supplemental oxygen was supplied during subsequent testing and exercise training. During the MP, patients that desaturated below 85% during the 6MWT were excluded from the study.

A minimum of two tests were performed per evaluation, with sufficient rest in between. If results of the two tests were not within 10% of each other, the test was repeated until results were within 10%. The longest distance of the completed tests was recorded. A threshold of 54m is considered as a significant improvement in functional status (Enright *et al.*, 2003; ATS, 1999; Redelmeier *et al.*, 1997; Guyatt *et al.*, 1984).

1.3 Reliability and validity

The 6MWT is considered reliable and valid for the assessment of functional capacity in COPD patients (Carter *et al.*, 2003; Mak *et al.*, 1993; Knox *et al.*, 1988). The 6MWT can be used in all patients, regardless of age, gender or level of literacy (Guyatt *et al.*, 1984).

1.4 Limitations

Carter and co-workers (2003) investigated the effect of body height and weight on the 6MWT. They concluded that body height might affect stride length, which in turn can influence the distance covered and the ambulatory efficiency. Furthermore, a direct correlation exists between body weight and energy expenditure. The heavier a person's body weight, the higher energy expenditure will be, which will have an influence on the distance covered in the walk test. A further limitation is that it does not allow for the assessment of maximal exercise capacity, which may be important in certain patients (Gallagher, 1994). Other limitations include that the 6MWT measures global function and gives no information on the cause of limitation. Furthermore, patients with mild disease will not be able to demonstrate their full exercise capability while walking on a flat surface. Improvement is the result of increased walking speed, which might limit some patients, since many patients have difficulty walking faster due to mechanical limitations (Johnson, 2004). The repeatability of the 6MWT when conducted by different supervisors is an issue which could influence the distance achieved. This issue was addressed in the MP by including an independent 6MWT at the post-intervention assessment (See "Post-intervention assessment").

2. Modified Borg RPE scale

2.1 Aim

The modified Borg RPE scale was used in this study to rate the effort of the 6MWT and to prescribe exercise intensity during the intervention programme. According to Belman and colleagues (1991), the Borg RPE scale is an effective and reproducible method to evaluate dyspnoea and determine exercise intensity for COPD patients, provided patients exercise at a high intensity or close to VO_2max.

2.2 Description

The Modified Borg scale (Appendix A) was used throughout this study to document subjects' perceived exertion. Subjects were shown the scale and asked to rate exertion on a scale from zero to ten. To limit being influenced by the tester, the instructions described in Appendix A were given to the subject. Subjects had to identify a single number; a range (i.e. a five to a six) was not acceptable.

2.3 Validity and reliability

Glass and co-workers (1992) demonstrated the validity and clinical application of the Borg-RPE-scale in prescribing exercise intensity. There is a high correlation between exertion ratings, heart rate and workload (ACSM, 2000:78).

3. St. George's Respiratory Questionnaire (SGRQ)

3.1 Aim

The SGRQ was used in this study to assess health related quality of life of the subjects. The aim of the SGRQ is to provide a standardised measurement of the limitations that respiratory disease place on a patient's daily life. This questionnaire was proven sensitive in patients with airflow obstruction (Okubadejo *et al.*, 1996).

3.2 Description

The SGRQ (Appendix F) is a self-administrated questionnaire that contains 50 items, with 76 weighted responses, that measures frequency of symptoms, activities that cause or are limited by dyspnoea and impact on daily life (employment, panic, disturbance and medication) (Wedzicha *et al.*, 1998; Curtis *et al.*, 1994). This questionnaire produces three component scores, which range from

0 to 100 and a total score. Scores are converted to a percentage where 100 indicates maximum disability. A difference of 4% is considered significant for any of the components or the total score (Jones, 2002; Wedzicha *et al.*, 1998; Osman *et al.*, 1997; Okubadejo *et al.*, 1996; Jones *et al.*, 1991). According to Okubadejo and co-workers (1996), the SGRQ can distinguish between mild, moderate and severe COPD.

The SGRQ was explained to the subject by the investigator and questions were addressed. The subject was left alone in a quiet room to complete the questionnaire. Any further questions were addressed after completion of the questionnaire to limit the influence of the investigator on the subject's responses. The questionnaires were available in English and Afrikaans.

After completion, the scores were calculated using the method described in Appendix F.

3.3 Validity and reliability

The SGRQ is reproducible, valid and responsive and correlates well with a range of established measures of disease activity (Jones *et al.*, 1992). The SGRQ is a standardised questionnaire, which allows for comparison between different studies and interventions (Curtis & Patrick, 2003; Finnerty *et al.*, 2006).

3.4 Limitations

Although this questionnaire is comprehensive, it cannot address all possible disturbances (Okubadejo *et al*., 1996).

4. Baseline Dyspnoea Index (BDI) and Transitional Dyspnoea Index (TDI)

4.1 Aim

In this study, the BDI and TDI (Appendix G) were used to assess breathlessness and the impact it has on quality of life. The BDI and TDI are dyspnoea measurement instruments designed by Mahler and co-workers (1984). The aim of the BDI and TDI is to measure the degree of dyspnoea and the impact it has on an individual's life (Curtis *et al*., 1994).

4.2 Description

The BDI is the initial assessment, whereas the TDI is related to the BDI, but assesses changes after an intervention programme. These indexes include three scales of measurement, namely functional impairment (the degree to which activities of daily living are impaired), magnitude of task needed to evoke dyspnoea (the intensity of activity) and magnitude of effort needed to evoke dyspnoea (the overall effort exerted to perform activities) (Mahler *et al.*, 1984). According to a patient's history, an interviewer rates the patients in each category. Ratings of each category are combined to obtain a central BDI or TDI score. The total score of the BDI is 12. Four points per scale of measurement can be obtained, where zero is considered a very severe impairment and four is considered no impairment. Therefore, the higher the score, the less the impact of dyspnoea is. The TDI is measured after the intervention programme and can receive three positive or negative points per scale of measurement. Plus three is considered a major improvement, while minus three is considered a major deterioration. Therefore, the TDI score can range from minus nine to plus nine. A change of one unit from the BDI to the TDI score is considered a clinically significant change (Witek & Mahler, 2003). The BDI and TDI were measured by a senior physician during the pre- and post-intervention assessments.

4.3 Validity and reliability

The BDI and TDI are valid and reliable for the assessment of dyspnoea amongst COPD patients; it correlates well with pulmonary function measures and is sensitive to treatment effects (Mahler *et al.*, 1992; Mahler *et* al., 1987; Mahler *et al.*, 1989; Mahler *et al.*, 1984).

5. Flow-volume spirometry

5.1 Aim

Flow-volume spirometry was used in this study to measure FVC, FEV_1, FEV_1 predicted and FIV_1. A Jaeger Master Lab system was used to perform spirometry.

5.2 Description

The variables mentioned above were tested using a maximal test according to the ATS/ERS standards (Miller *et al.*, 2005). Maximum effort by the subject was essential for a valid test. A clinical technologist explained and demonstrated the testing procedure to the subject and any questions were addressed. The subject was seated in front of the system and a nose clip was used to prevent air from escaping through the nose. The test started with a period of quiet breathing (tidal volume), followed by a rapid breath in (forced inspiration), after which the subject had to exhale as hard as possible for as long as possible. The test was ended with a rapid inhalation. The subjects were continuously and loudly encouraged throughout the manoeuvre.

The test was repeated three times and the best result was recorded. If the results of the three tests differed by more than 5% or 100 to 150ml, the test was repeated until the results were satisfactory. The results of the test were compared to the predicted values that are calculated based on age, gender and height.

5.3 Validity and reliability

Flow-volume spirometry is considered essential in the diagnosis and assessment of disease severity in COPD patients (Dueck, 2000; ATS, 1999; ATS, 1995a). It is essential that the test be performed by adequately trained persons using a regularly calibrated spirometer of approved standard and quality (Van Schalkwyk *et al.*, 2004).

5.4 Limitations

Flow-volume spirometry is highly dependent on the subject's cooperation and effort. Since results are dependent on patient cooperation, results can only be underestimated, never overestimated (Lalloo *et al.*, 1991).

6. Body mass index (BMI)

6.1 Aim

In this study, BMI was used to assess the subjects' weight and any weight changes. BMI is an expression of weight relative to height. Since there is a strong correlation between weight loss, mortality and exercise tolerance in COPD patients, the evaluation of weight changes are essential (Farber & Mannix, 2000; Gray-Donald *et al.*, 1996; Engelen *et al.*, 1994).

6.2 Description

BMI is calculated by dividing body mass (kilograms) by height (metres) squared.

BMI (kg/m^2) = body mass (kg) / height $(m)^2$

Standing height was measured in metres, to the nearest millimetre with the use of a stadiometer. Height was taken without shoes. Subjects were instructed to stand erect with their arms hanging to their sides. The subjects' head was adjusted into the Frankfort Plane. (Frankfort Plane is achieved by aligning the lower edge of the eye socket in the same horizontal plane as the notch superior to the tragus of the ear.) Subjects were instructed to look straight ahead while taking a deep breath. At the end of inhalation, the clinical technologist measured the highest point on the skull.

Body weight was measured with a Soehnle Certified-150kg scale to the nearest 0.5kg. Body weight was measured without shoes, while subjects were wearing light clothing.

6.3 Validity and reliability

BMI assessment is commonly used by researchers and clinicians (McArdle *et al.*, 2001:755). BMI is considered a reliable measure providing that the same scale is used for every measurement (ACSM, 2000:63).

6.4 Limitations

BMI gives no indication of body composition and has a large standard error of estimating percentage body fat (± 5%). The standard error of BMI increases in individuals that are grossly over- or underweight (McArdle *et al.*, 2001:758; ACSM, 2000:63).

7. Physician's global evaluation

7.1 Aim

This study used the physician's global evaluation to assess the overall condition of the subjects.

7.2 Description

The same physician evaluated the subjects at the pre- and post-intervention assessments and recorded a physician's global score for each subject (Appendix H). This score ranged from one to eight, with one falling into the poor category and eight falling into the excellent category. This score was based on the physician's evaluation of the subject's concomitant therapy, number and severity of exacerbations, severity of cough, ability to exercise and amount of wheezing since the last visit.

7.3 Validity and reliability

The physician's global evaluation is frequently used in chronic disease research and by physicians and pulmonologists. Numerous published studies and drug trials have used this evaluation with success (Donohue, 2005). A study by Falcone and co-workers (2005) reported a good inter-observer agreement in the physician's global assessment of patients with juvenile idiopathic arthritis.

Limitations

Although this evaluation provides important information regarding disease severity and prognosis, further investigation is needed into the elements that influence severity and the predictive validity (Kroenke *et al.*, 2006).

8. Exacerbations

Although the measurement of the number of acute exacerbations was not included in the study protocol, a secondary analysis was conducted on the number of acute exacerbations. For this purpose, an exacerbation was defined as an increase in pulmonary symptoms that was severe enough to prevent a subject from attending an exercise session. Furthermore, exacerbations reported by subjects in the SGRQ were also analysed, by evaluating the subjects' response to Question 5 in Part 1: "Over the last 3 months, how many severe or very severe unpleasant attacks of chest trouble have you had?"

Post-intervention assessment

The same protocols and procedures were followed at the post-intervention assessments. In the MP, an additional 6MWT assessment was included to confirm repeatability of this test when conducted by independent supervisors. After completion of the intervention programme, a 6MWT was performed at the Stellenbosch Biokinetics Centre (SBC), using the same protocol as in the pre-intervention assessment at the physician's practice. The clinical technologist, who administered the 6MWT at the post-intervention assessment, was not informed of the results obtained at the SBC 6MWT. After completion of the post-intervention assessment, subjects received feedback on their results. Subjects were educated on exercise adherence. Some subjects chose to continue exercising at the current facility at their own expense, while others joined gymnasiums or exercised at home. For subjects included in the PP an appointment was made for a six month follow-up assessment. After six months, the subjects in the PP were evaluated again, using the same protocol and procedures as in the post-intervention assessment.

Absenteeism and complications

As with previous studies (Troosters *et al.*, 2000; Cambach *et al.*, 1997; Goldstein *et al.*, 1994; Busch & McClements, 1988), a number of patients who met the inclusion criteria did not finish the programme. Three female subjects dropped out of the PP and three male subjects dropped out of the MP (all three were in the control group).

Two of the female subjects developed depression and lacked motivation. Despite various attempts to keep them motivated, they eventually ceased to attend the exercise sessions. The third female subject suffered from several prolonged exacerbations that forced her to withdraw from the study. Attempts were made to keep her in the study, but due to the exacerbations, she was restricted to four weeks of bed rest. This would have negatively influenced the results of the intervention programme. Although she was excluded from the study, the researchers allowed her to continue to exercise at the facility when possible.

One of the male subjects that did not finish the study was a farm worker at a wine farm. Due to harvesting, he was not able to attend sessions for three months. The second male subject developed TB and had to be excluded from the study. The third male subject was initially motivated to exercise, but did not receive any support from his family. His spouse was convinced that the exercise would not be beneficial to him and he eventually withdrew from the study.

Other subjects missed sessions, but continued to be motivated and completed the programme without missing more than six sessions or within the allowed time. Reasons for absenteeism included business and travel engagements, holiday arrangements, acute exacerbations and hypertension.

Data analysis

The Centre of Statistical Consultation (Stellenbosch University) assisted in analysing the data. The Statistica 7.1 software was used. Repeated measures ANOVA and correlations were used to analyse the data. The significance was set at 5%.

The repeated measures ANOVA was used to test if the mean measurements of the different groups and/or different evaluations were equal to each other. In cases where this hypothesis was rejected, the Bonferroni correction was used to distinguish which means differed from each other.

For the correlations, the p-values were reported. The r-values (to indicate how strong the relationship between two variables was) were insignificant, due to the small number of subjects included in the study.

CHAPTER IV: RESULTS

Subject Demographics

A total of 22 subjects completed the PP, 15 males and seven females. Although all subjects were encouraged to quit smoking, five subjects continued smoking despite advice to the contrary. Three of the subjects were black and 19 were caucasian. Four subjects exercised with supplemental oxygen. According to the GOLD criteria, three subjects were classified with very severe COPD, 11 with severe COPD and eight with moderate COPD.

A total of 18 subjects completed the MP, nine males and nine females. Of the seven subjects in the control group, three were male and four were female. Of the eleven subjects in the experimental group, six were male and five were female. Smokers were excluded from the MP. Five of the subjects in the experimental group were black and six were caucasian. One subject in the control group was black and six were caucasian. Four subjects in the experimental group and three in the control group had severe COPD. Seven subjects in the experimental group and four in the control group had moderate COPD. Classification was also done according to the GOLD criteria (See Chapter II).

See Appendix I.

Results

Frequency histograms are included for the baseline values of the variables tested. These histograms illustrate the overall frequency distribution of the variables for all the subjects at baseline level. These graphs give further insight in the subjects' demographics at baseline level. ANOVA graphs are included for all the variables to illustrate the statistical difference between the baseline, three month and six month evaluations (where applicable). In these graphs, the means of the data are illustrated by a small circle (°). The vertical bars on either side of these circles illustrate the confidence intervals. Correlations are calculated between certain

variables. Box plots are included for certain variables. Medians, 25th and 75th percentiles, ranges and outliers can be identified on these plots. Medians are indicated by a small square (□). The bottom and top lines of the large square indicate the 25th and 75th percentiles, respectively. The vertical bars (whiskers) on either sides of the square indicate the range of the data. Outliers are represented by a small circle (°). The results of the different parts of the study will be discussed separately.

1. Primary programme

1.1 Frequency histograms of baseline data

1.1.1 Six minute walk test

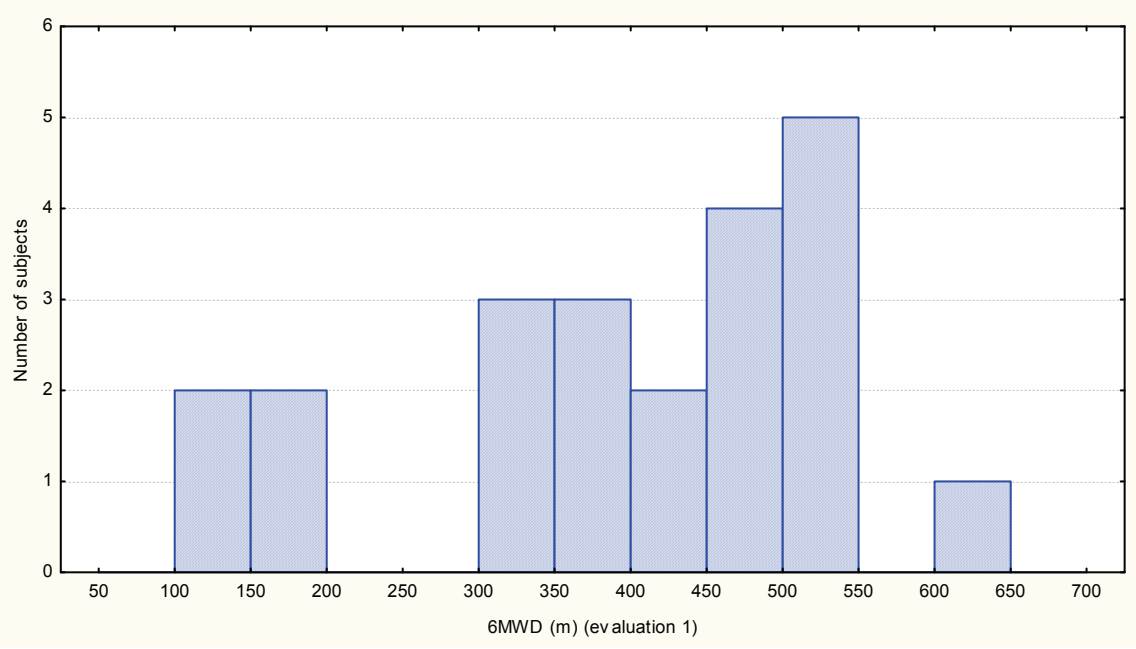

Figure 4.10 A frequency histogram of the subjects' baseline distances on the 6MWT.

There was a marked variability in the physical capability of the subjects at the baseline evaluation. This is clearly illustrated in figure 4.10. The shortest distance covered in six minutes was 120m and the longest distance was 620m.

1.1.2 Baseline dyspnoea index

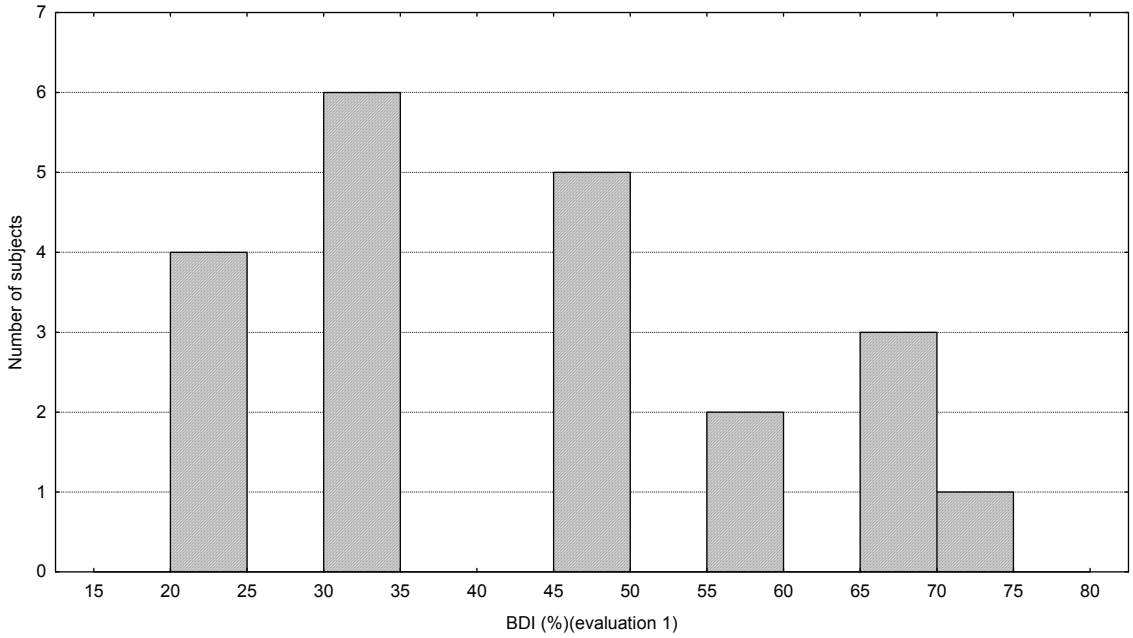

Figure 4.11 A frequency histogram of the subjects' BDI values.

Again, there was a very wide distribution for the BDI scores at the baseline evaluation. The scores were converted to a percentage. The lowest score was 25% and the highest score was 75%.

1.1.3 St. George's Respiratory Questionnaire

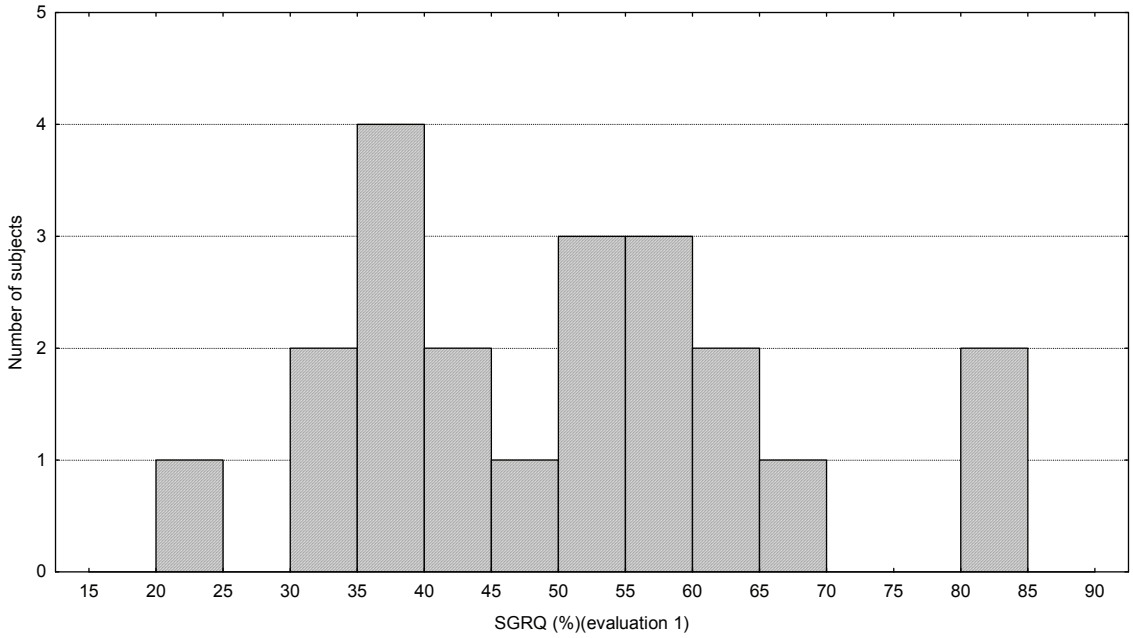

Figure 4.12 A frequency histogram of the subjects' baseline scores on the SGRQ.

The same pattern is seen with the SGRQ. Again there was a wide distribution, the lowest score (least impaired) was 24.87 and the highest score (most impaired) was 82.49.

1.1.4 Lung function variables

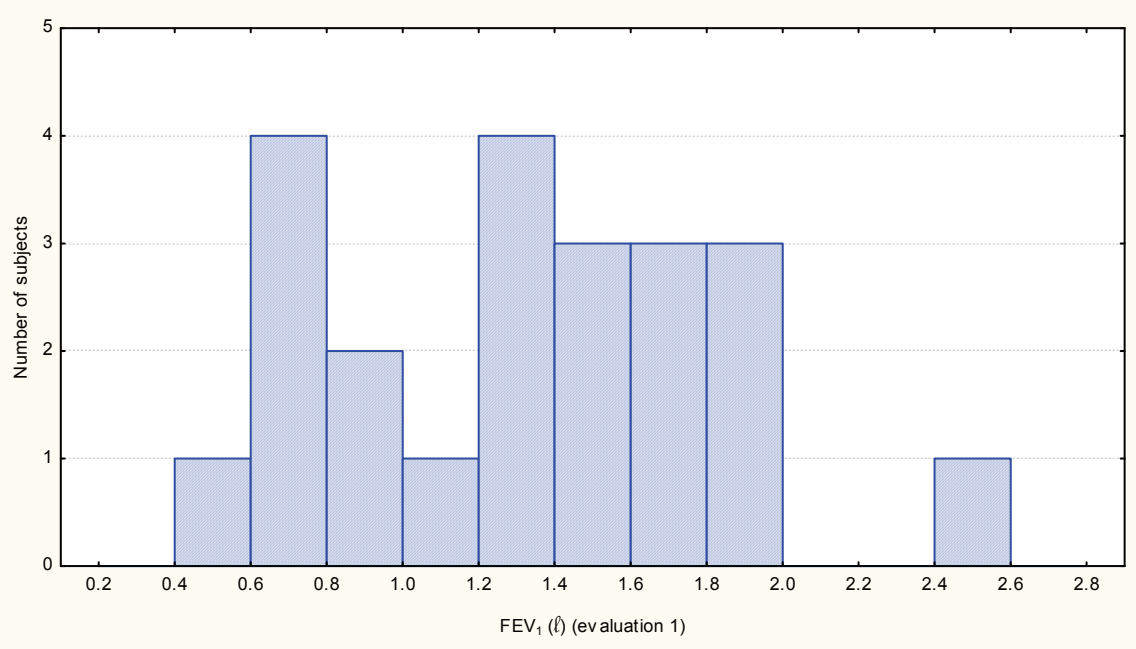

Figure 4.13 A frequency histogram of the subjects' baseline FEV_1.

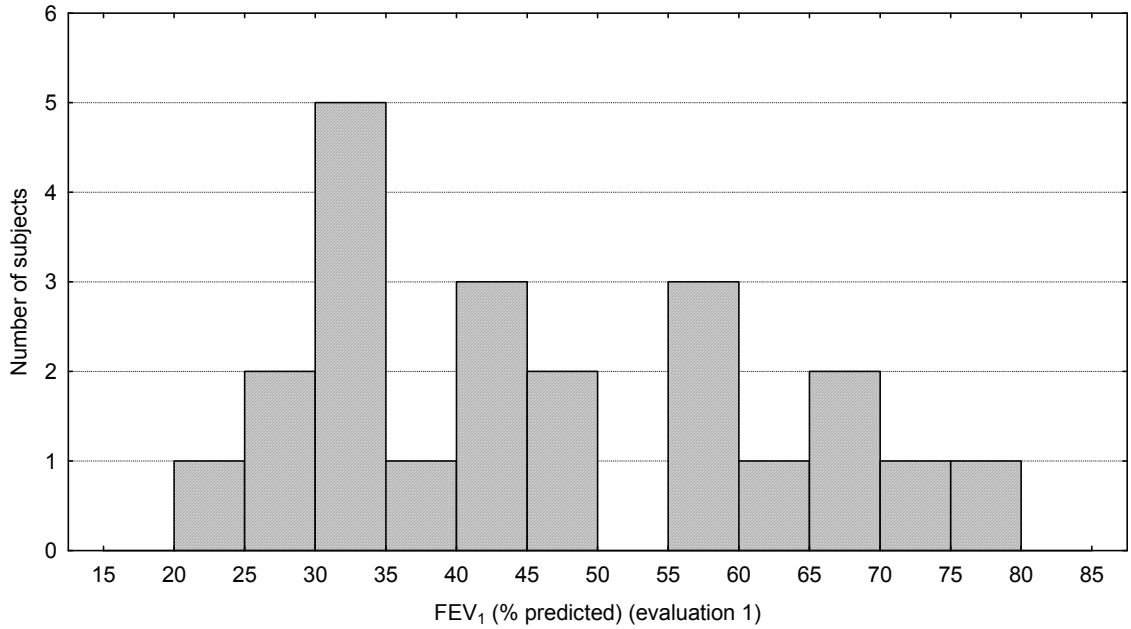

Figure 4.14 A frequency histogram of the subjects' baseline FEV_1 percentage of their predicted scores.

Due to the wide variety of subjects tested, it was expected that the FEV_1 scores and subsequently, the percentage of the predicted FEV_1 scores would vary greatly. The lowest FEV_1 was 0.59 ℓ and the highest was 2.52 ℓ. According to GOLD criteria (see Chapter II), no subjects with mild COPD were included in this part of the study, 36.36% of the subjects were classified as having moderate COPD and 63.63% had severe or very severe COPD. (The criteria from the SATS were not used because the GOLD criteria were more recently updated.)

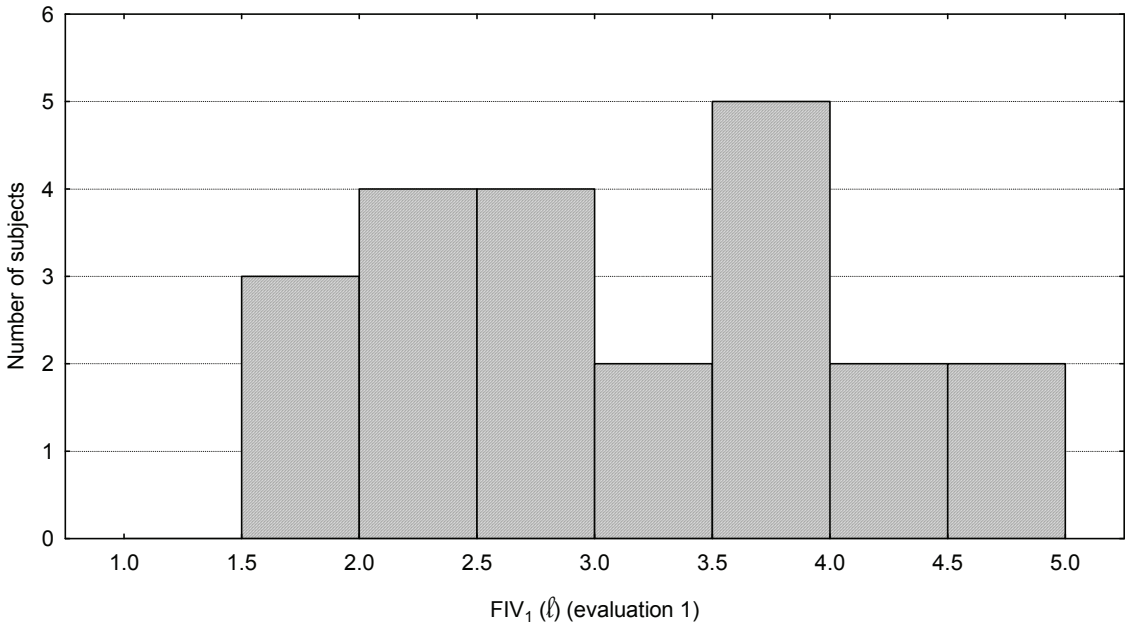

Figure 4.15 A frequency histogram of the subjects' baseline FIV_1 values.

Again, there was a wide distribution between these scores, although most of the scores were at the lower half of the histogram. The highest FIV_1 was 4.63 ℓ and the lowest was 1.62 ℓ.

1.1.5 Physician's global index

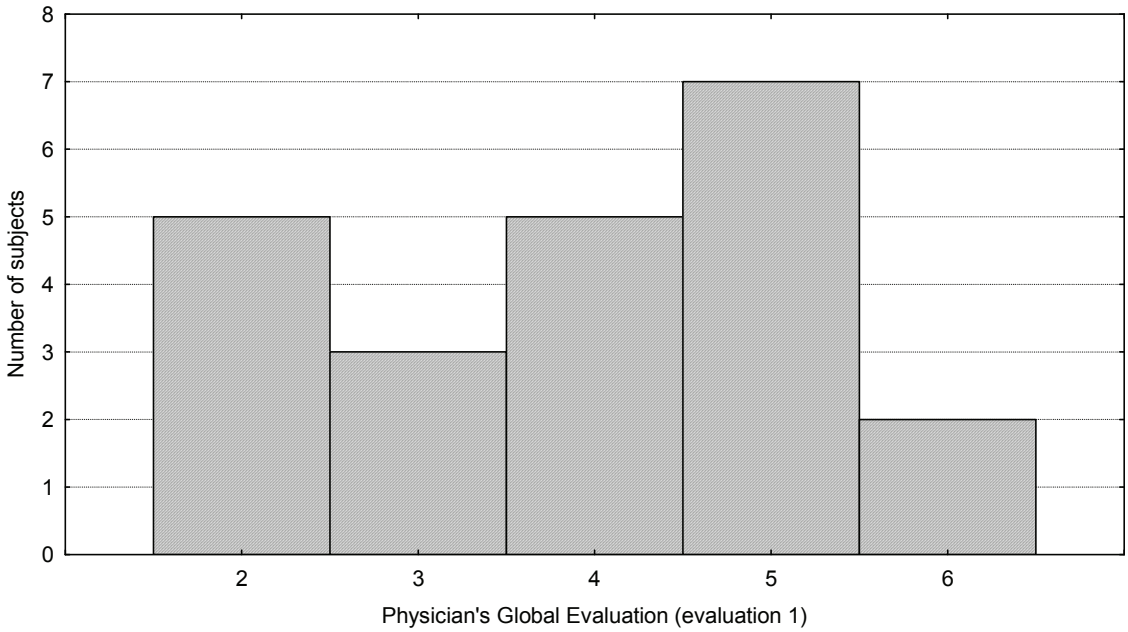

Figure 4.16 A frequency histogram of the subjects' baseline scores for the physician's global evaluation.

Figure 4.16 illustrates the distribution of the physician's global scores. The lowest score was two and the highest score was six out of a possible eight.

1.1.6 Body mass index

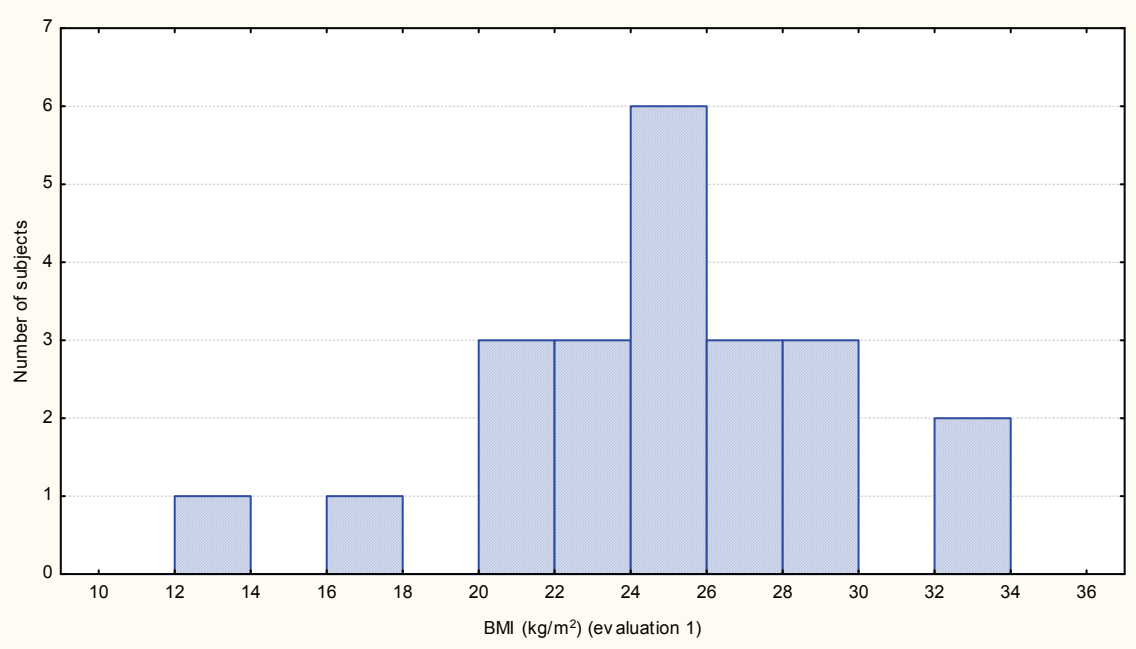

Figure 4.17 A frequency histogram of the subjects' baseline BMI's.

BMI scores are illustrated in figure 4.17. The encouraging finding here is that most of the scores are between 24 kg/m^2 and 26 kg/m^2 which are still an acceptable BMI. The lowest score was an alarming 13.19kg/m^2 and the highest score was 34.31kg/m^2.

Important questions raised by the frequency histograms presented were whether the highest and lowest scores were continuously obtained by the same subjects. When comparing the BDI-scores and the baseline FEV_1-values of the subjects, the subject that scored the highest (slight dyspnoea) on the BDI had one of the lowest FEV_1's, whereas the subject who scored the lowest (very severe dyspnoea) on the BDI had a baseline FEV_1 of 2.52 ℓ, which was also the highest FEV_1 tested. This was consistent with the finding of Mahler *et al.* (1992) who found that although patients who experience severe breathlessness have lower pulmonary function measures, this generalisation could not be uniformly applied to individual patients.

The subject that achieved the highest (most impaired) score on the SGRQ had a FEV_1 of 1.98 ℓ and a BDI-score of 50%. The subject that scored the lowest (least impaired) on the SGRQ had a FEV_1 of 0.95 ℓ, and a BDI-score of 25%. This was consistent with previous studies that found that pulmonary function has a small effect on HRQL (Ketelaars *et al.*, 1996; Curtis *et al*., 1994). Previous studies found a good correlation between exercise performance and HRQL (Ketelaars *et al.*1996; Okubadejo *et al.*, 1996). When looking at the frequency distribution of the 6MWDs and HRQL, the subject that demonstrated the best exercise performance, also scored fairly well on the SGRQ. The subjects with poor exercise performance demonstrated poor HRQL. Although the tendency was similar to previous studies, these subjects were not the outliers on the SGRQ.

1.2 Changes from the first to the third evaluation

1.2.1 Six minute walk test

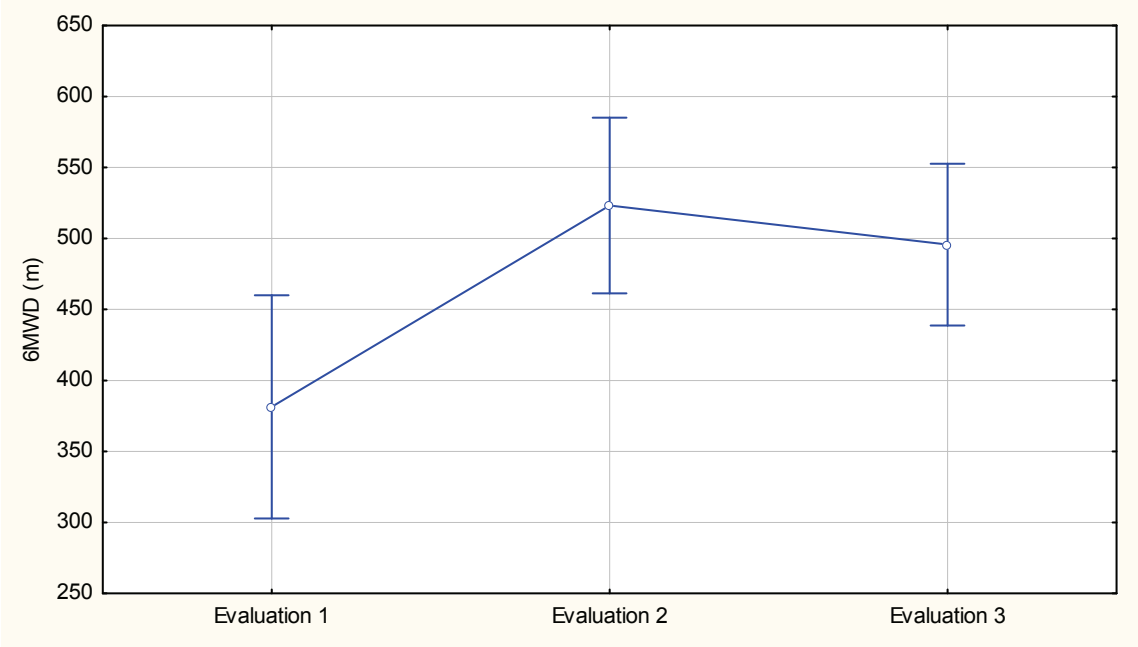

Figure 4.18 An ANOVA graph to illustrate the subjects' differences in the mean distance walked in the 6MWT in all three evaluations.

The repeated measures ANOVA test illustrated that there was a significant improvement in the six minute walking distance (6MWD) the subjects obtained from first to the second evaluation ($p < 0.000001$). There was a slight decline in 6MWD at the third evaluation, but the improvement was still significant if, compared to the baseline values ($p < 0.00001$). The mean 6MWD at the first evaluation was 381.42m (SD ± 137.20m; SE ± 36.40m), which improved to 523.21m (SD ± 101.56m; SE ± 28.66) at the second evaluation. The 6MWD at the third evaluation was 495.71m (SD ± 98.58m; SE ± 26.35m), which is not statistically lower than the mean distance of evaluation 2 ($p = 0.42$). The mean improvement from the first to the second evaluation was 142m (SD ± 69.37m). The mean improvement from the first to the third evaluation was 114.29m (SD ± 74.70m). Both these improvements are higher than the threshold of 54m that is necessary for an intervention to be significant (Enright *et al.*, 2003; ATS, 1999; Redelmeier *et al.*, 1997; Guyatt *et al.*, 1984).

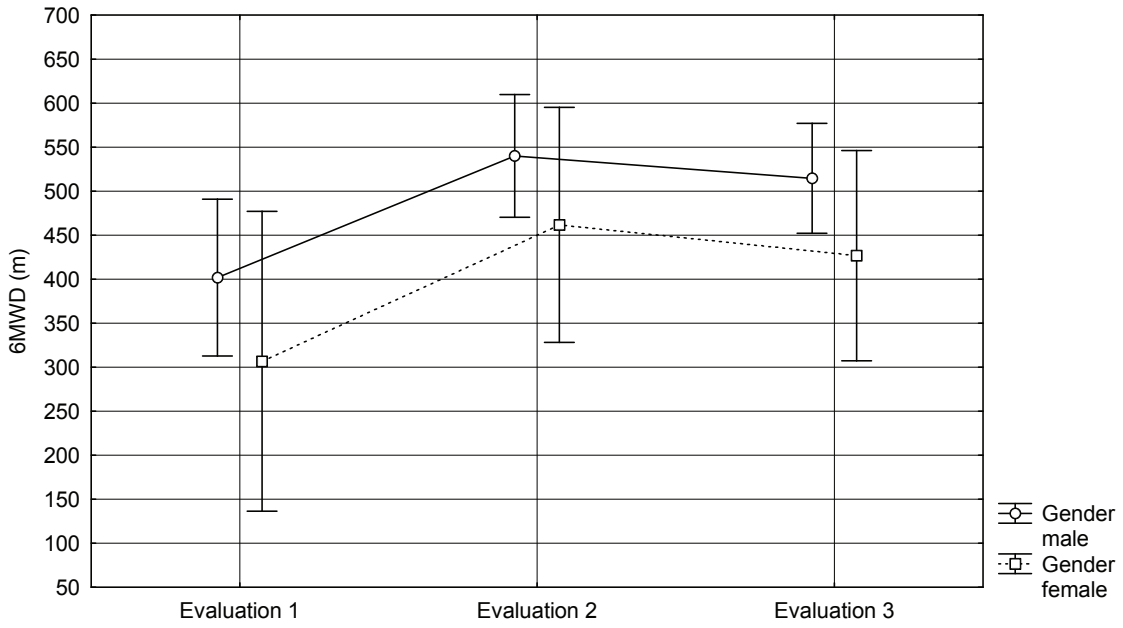

Figure 4.19 An ANOVA graph to illustrate the mean difference in 6MWD between males and females from first to the third evaluation.

The mean distance for the men at the first evaluation was 401.82m (SD ± 129.17m) and for the women it was 306.67m (SD ± 140.22m). These mean distances improved to 540m (SD ± 98.30) for the men and 461.67 (SD ± 85.46m) for the women from the first to the second evaluation. The mean distance for men at the third evaluation was 514.55m (SD ± 102.41m) and for women 426.67m (SD ± 40.41). Although the female subjects covered noticeably shorter distances on the 6MWT, there was no statistically significant difference between the performance of the two gender groups (p = 0.23).

1.2.2 Baseline and Transitional Dyspnoea Index

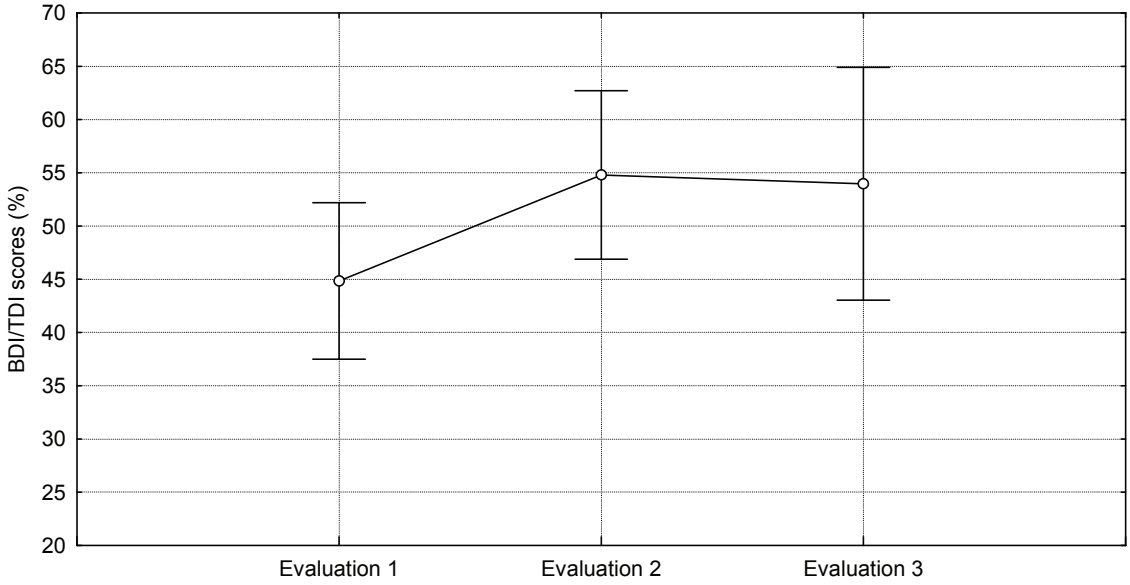

Figure 4.20 An ANOVA graph to illustrate the subjects' mean BDI-scores at the first evaluation and the mean TDI-scores at the second and third evaluations.

The TDI is the measure of change from the BDI. A repeated measures ANOVA test was used to analyse the BDI and TDI. The mean BDI-score at the first evaluation was 45.67% (SD ± 16.13%; SE ± 6.19%), which improved to 54.54% (SD ± 17.84; SE ± 8.78%). The mean TDI-score at the third evaluation was 54.36% (SD ± 18.93%; SE ± 7.31%). Figure 4.20 illustrates the significant

improvement from the first to the second evaluation ($p < 0.05$). Although the mean TDI-score was lower at evaluation 3, it was not statistically significant ($p = 1.00$).

1.2.3 St. George's Respiratory Questionnaire

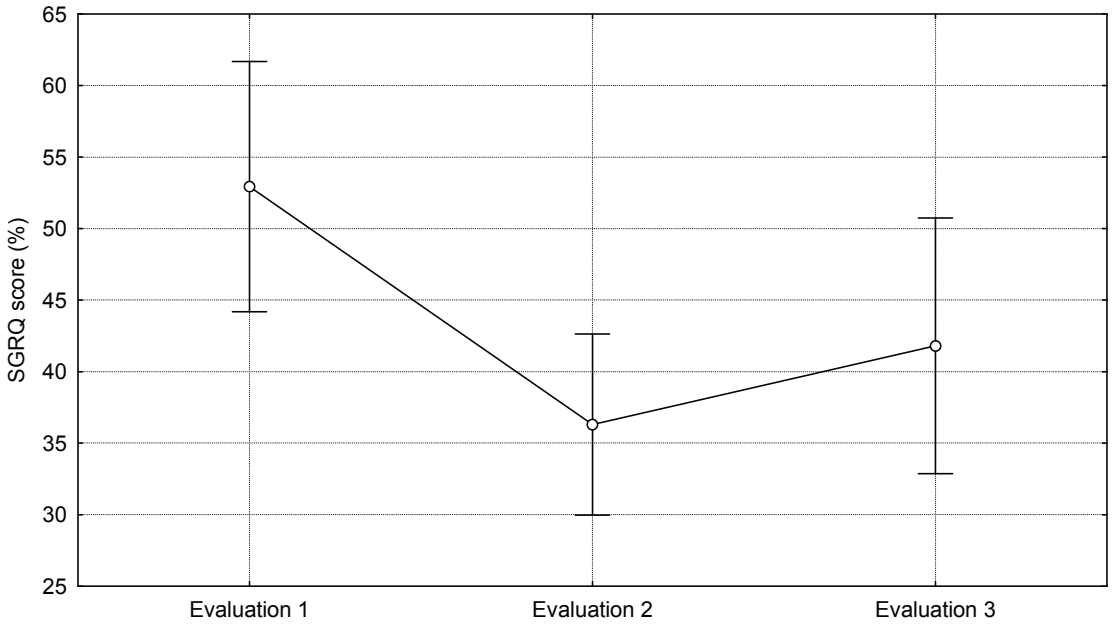

Figure 4.21 An ANOVA graph to illustrate the subjects' differences in mean scores on the SGRQ.

A repeated measure ANOVA test was used to analyse the scores the subjects obtained in the SGRQ. A high score indicates a low quality of life and a low score indicates a high quality of life. The mean score at the first evaluation was 52.94 (SD ± 15.21; SE ± 4.05) which lowered to 36.30 (SD ± 18.46; SE ± 2.93) at the second evaluation. This difference was statistically significant ($p < 0.001$). At the third evaluation the mean SGRQ-score increased to 41.81 (SD ± 14.65; SE ± 4.14). Although this increase was not statistically significant ($p = 0.48$), it was clinically significant as it exceeds four units, as determined by Jones (2002). Despite this clinically significant decrease in HRQL from the second to the third evaluation, the improvement from the first to the third evaluation remained statistically significant ($p = 0.02$).

1.2.4 Lung function variables

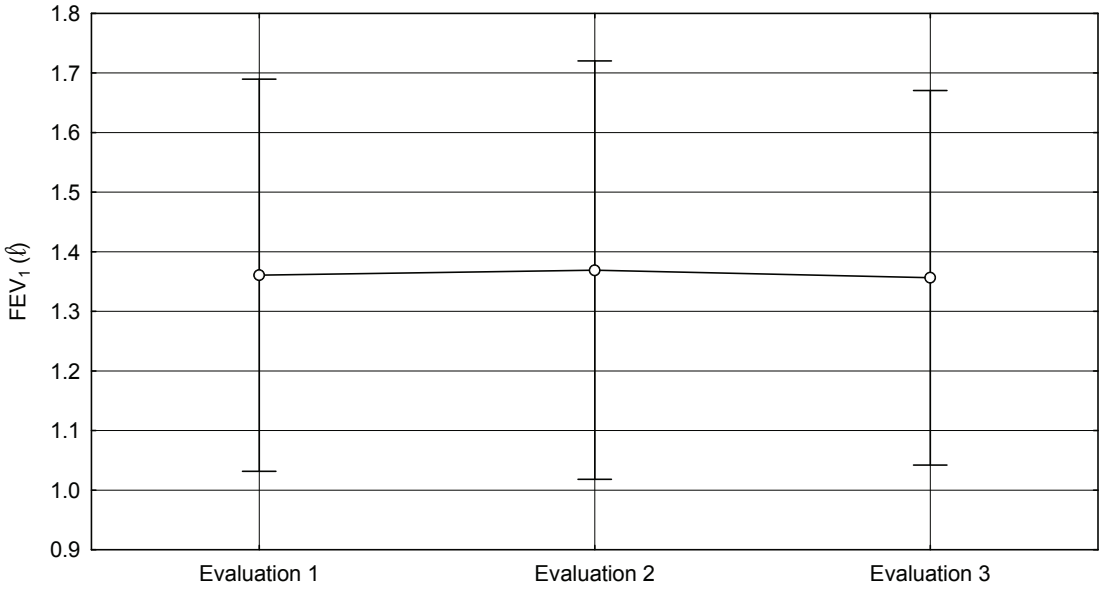

Figure 4.22 An ANOVA graph to illustrate the subjects' differences in mean FEV_1 from the first to the third evaluation.

A repeated measures ANOVA test was used to analyse the subjects' FEV_1-scores. There was no change in the subjects' mean FEV_1 ($p = 0.97$). As figure 4.22 illustrates and as previously noted, there was a wide range in FEV_1 throughout the evaluations. The mean FEV_1 at the first evaluation was 1.36 ℓ (SD ± 0.54 ℓ; SE ± 0.15 ℓ) which changed to 1.37 ℓ (SD ± 0.51 ℓ; SE ± 0.16 ℓ) at the second evaluation. At the third evaluation, the mean FEV_1 was 1.36 ℓ (SD ± 0.53 ℓ; SE ± 0.15 ℓ).

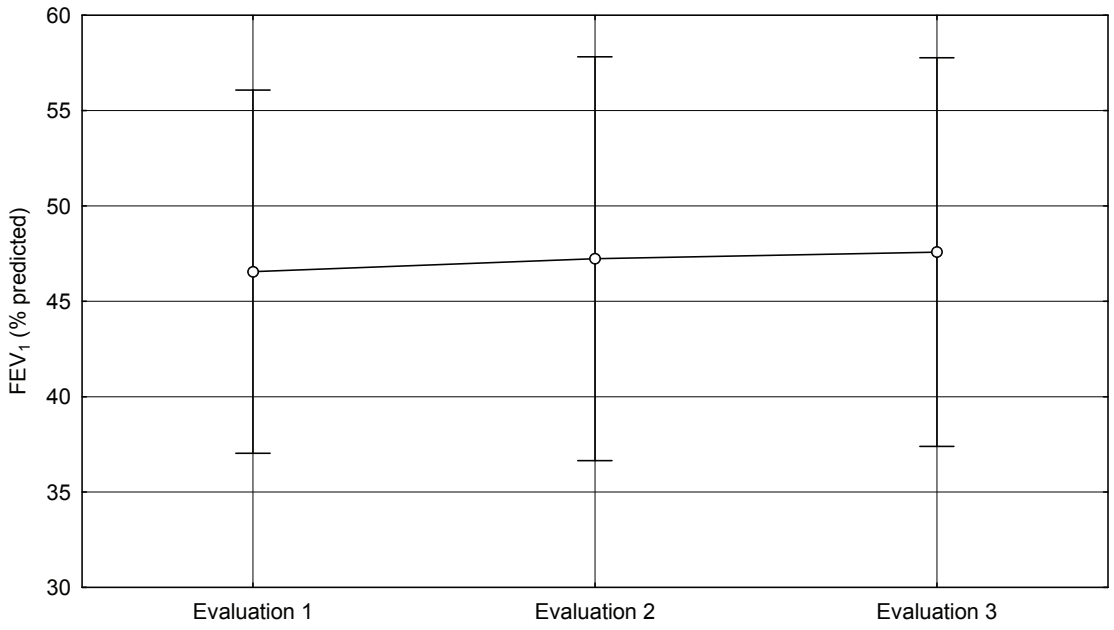

Figure 4.23 An ANOVA graph to illustrate the subjects' differences in mean percentage of predicted FEV_1 from the first to the third evaluation.

A repeated measures ANOVA test was used to analyse the subjects' percentage of predicted FEV_1's. There was no change in the subjects' mean percentage of predicted FEV_1 ($p = 0.85$). The mean predicted percentage at the first evaluation was 46.55% (SD ± 17.65%; SE ± 4.40%), which changed to 47.23% (SD ± 15.78%; SE ± 4.90%) at the second evaluation. At the third evaluation, the mean predicted percentage was 47.59% (SD ± 17.03%; SE ± 4.72%).

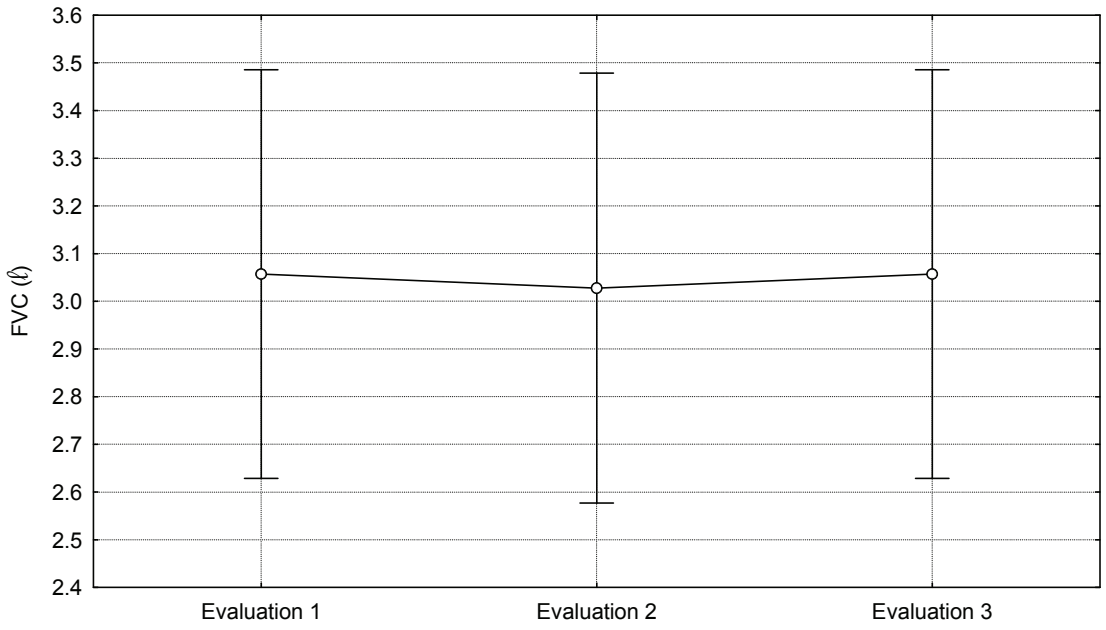

Figure 4.24 An ANOVA graph to illustrate the subjects' differences in mean FVC-values from the first to the third evaluation.

A repeated measures ANOVA test was used to analyse the subjects' FVC-values. There was no statistically significant change in the mean FVC from the first to the third evaluation ($p = 0.65$). The mean FVC at the first evaluation and second evaluation was 3.03 ℓ (SD ± 0.99 ℓ & 0.96 ℓ; SE ± 0.20 ℓ). At the third evaluation, the mean FVC was 3.03 ℓ (SD ± 0.99 ℓ; SE ± 0.20 ℓ).

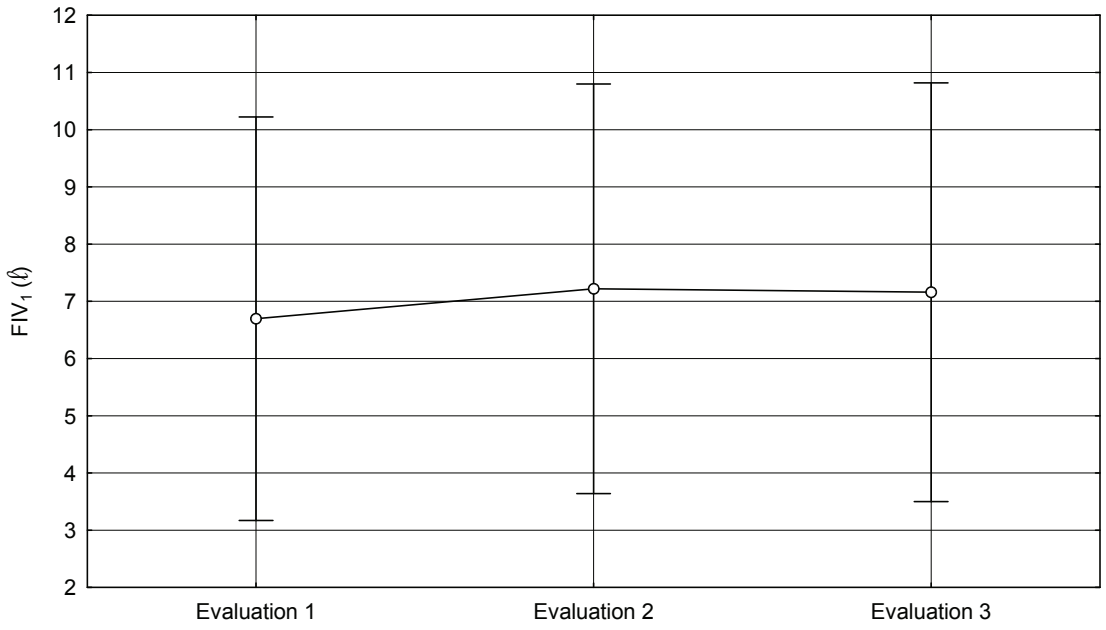

Figure 4.25 An ANOVA graph to illustrate the subjects' differences in mean FIV_1 from the first to the third evaluation.

A repeated measures ANOVA test was used to analyse the subjects' FIV_1's. There was no statistically significant change in the mean FIV_1 from the first to the third evaluation ($p = 0.67$). As seen with FEV_1, once again there was a very wide range in the subjects' scores throughout the evaluations. The mean FIV_1 at the first evaluation was 6.53 ℓ (SD ± 6.06 ℓ; SE ± 1.32 ℓ), which changed to 7.21 ℓ (SD ± 6.06 ℓ; SE ± 1.31 ℓ) at the second evaluation. At the third evaluation, the mean FIV_1 was 7.16 ℓ (SD ± 6.22 ℓ; SE ± 1.66 ℓ).

1.2.5 Physician's Global Evaluation

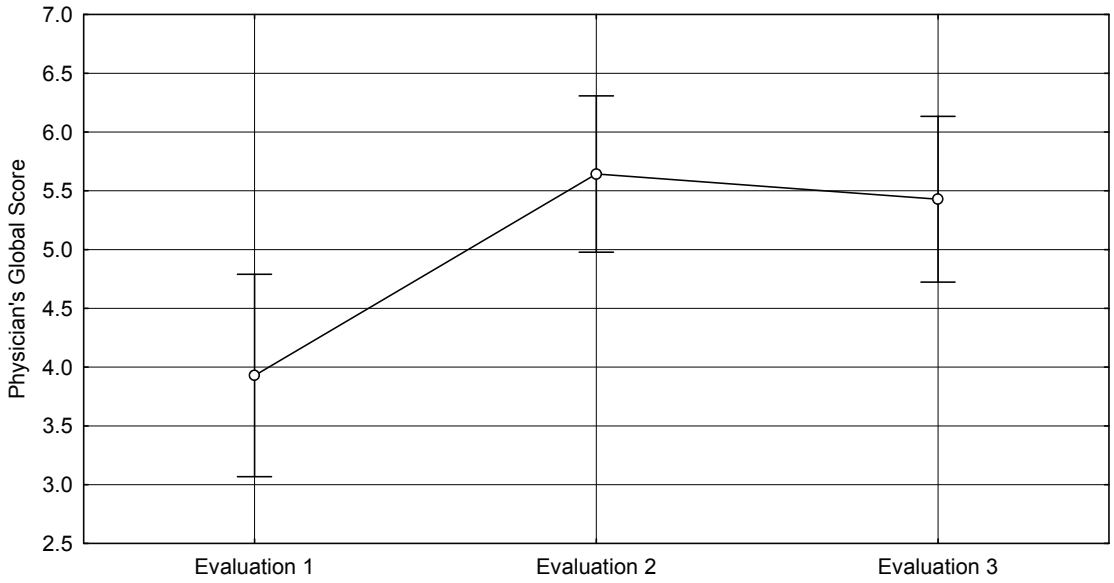

Figure 4.26 An ANOVA graph to illustrate the subjects' differences in mean scores in the physician's global evaluation.

As illustrated in the figure 4.26, there was a statistically significant improvement in the physician's global evaluation of subjects from the first to the second evaluation ($p < 0.0001$). Again there was a decrease in the mean scores from the second to the third evaluation, but this decrease was not statistically significant ($p = 1.00$). The overall improvement from the first to the third evaluation was statistically significant ($p < 0.0001$). The mean score at the first evaluation was 3.93 (SD ± 1.22; SE ± 0.40), which changed to 5.64 (SD ± 1.14; SE ± 0.31) at the second evaluation. At the third evaluation, the mean physician's global score was 5.43 (SD ± 1.34; SE ± 0.33).

1.2.6 Body Mass Index

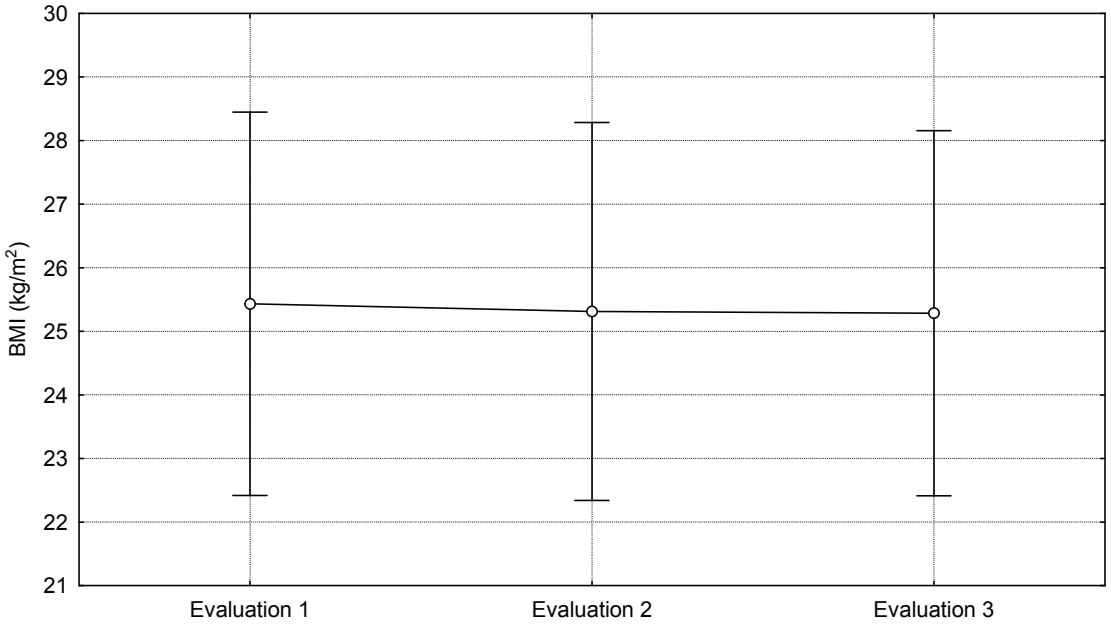

Figure 4.27 An ANOVA graph to illustrate the subjects' differences in mean BMI from the first to the third evaluation.

There was no statistically significant difference in the BMI values of the subjects from the first to the third evaluation ($p = 0.84$). A significant decrease in BMI can be linked to mortality (Gray-Donald *et al.*, 1996). The mean BMI-scores at the first, second and third evaluations was 25.43kg/m^2 (SD ± 4.64kg/m^2; SE ± 1.41kg/m^2), 25.31kg/m^2 (SD ± 4.74kg/m^2; SE ± 1.39kg/m^2) and 25.29kg/m^2 (SD ± 4.58kg/m^2; SE ± 1.35kg/m^2), respectively.

1.2.7 Exacerbations

Exacerbations were assessed through the number of sessions missed due to acute pulmonary infections and through self-reported exacerbations as reported in the SGRQ.

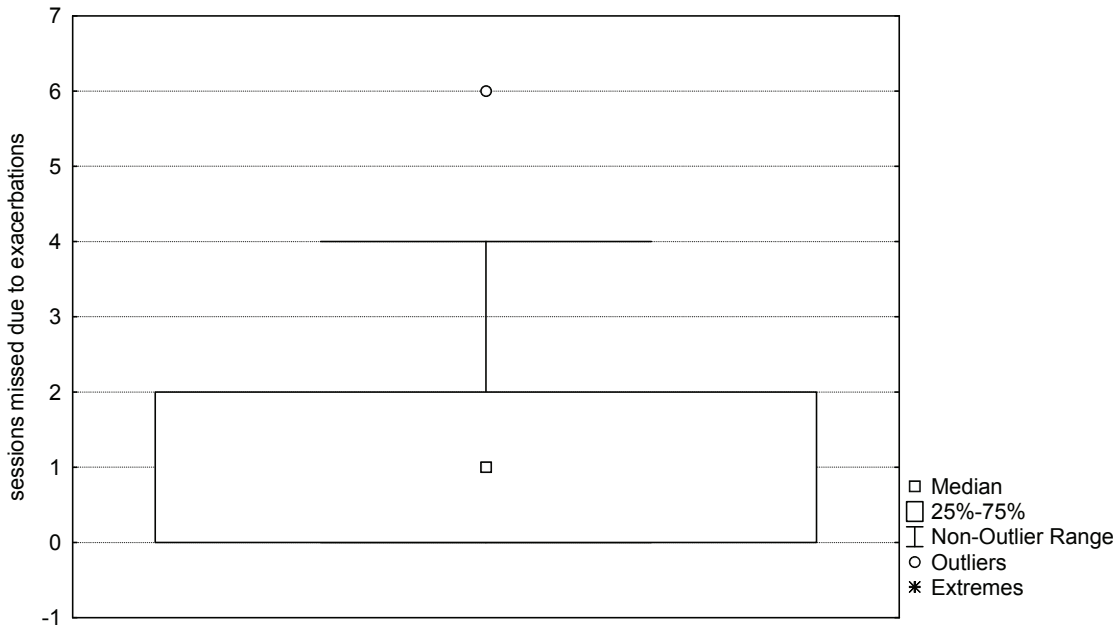

Figure 4.28 A box plot illustrating the exercise sessions missed by subjects due to acute exacerbations.

In the PP, subjects missed an average of 1.33 sessions (SD ± 1.57) due to acute exacerbations. One subject missed a total of six sessions. At the first evaluation the average of self-reported exacerbations was 2.14 (SD ± 1.59), which lowered to 0.62 (SD ± 0.97). This decrease in exacerbations was significantly lower at the second evaluation ($p < 0.001$).

To analyse the data based on the extent of dyspnoea experienced by the subjects at the first evaluation; the group was divided into two, based on their BDI-scores. Subjects who scored less than four on the BDI were in one group and subjects that scored four or more were included in the other. Although the less dyspnoeic group was expected to score better in the other evaluations, none of these analyses delivered significant results (see Appendix M).

The major findings of the PP were that this programme was successful in instigating positive changes in 6MWD, HRQL, dyspnoea and the physician's global evaluation. Furthermore, these positive changes remained significant at the six

month follow-up evaluation. Consistent with previous studies (Bauldoff *et al.*, 2002; Brooks *et al.*, 2002; McArdle *et al.*, 2001:953; Guell *et al.*, 2000; Boueri *et al.*, 2001; Troosters *et al.*, 2000; Benstrup *et al.*, 1997; Strijbos *et al.*, 1996; ATS, 1995a; Celli, 1995; Reardon *et al.*, 1994; Cox *et al.*, 1993; Holden *et al.*, 1990; Busch & McClements, 1988), no significant changes occurred in lung function variables and BMI.

1.3 Correlations

1.3.1 Relationship between FEV_1 and 6MWD

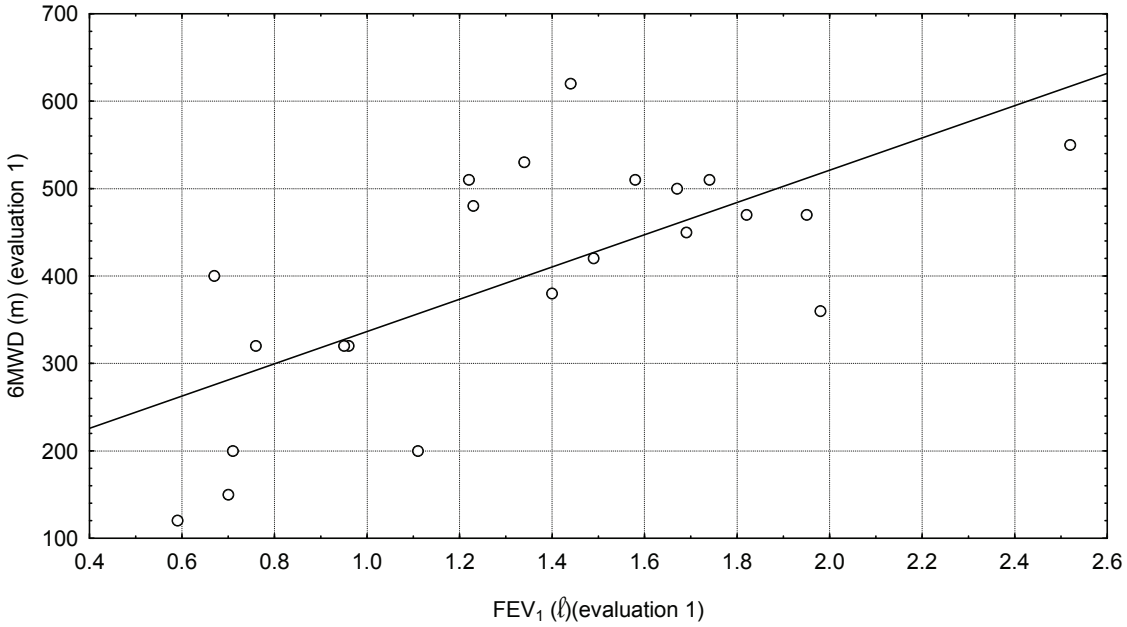

Figure 4.29 A scatter plot illustrating the correlation between 6MWD and FEV_1 at the first evaluation.

Contrary to previous studies (Brooks *et al.*, 2002; Boueri *et al.*, 2001; Benstrup *et al.*, 1997; Jones, 1991; Swinburn *et* al., 1985; McGavin *et al.*, 1976), a strong correlation was found between 6MWD and FEV_1 at the first evaluation ($p < 0.001$).

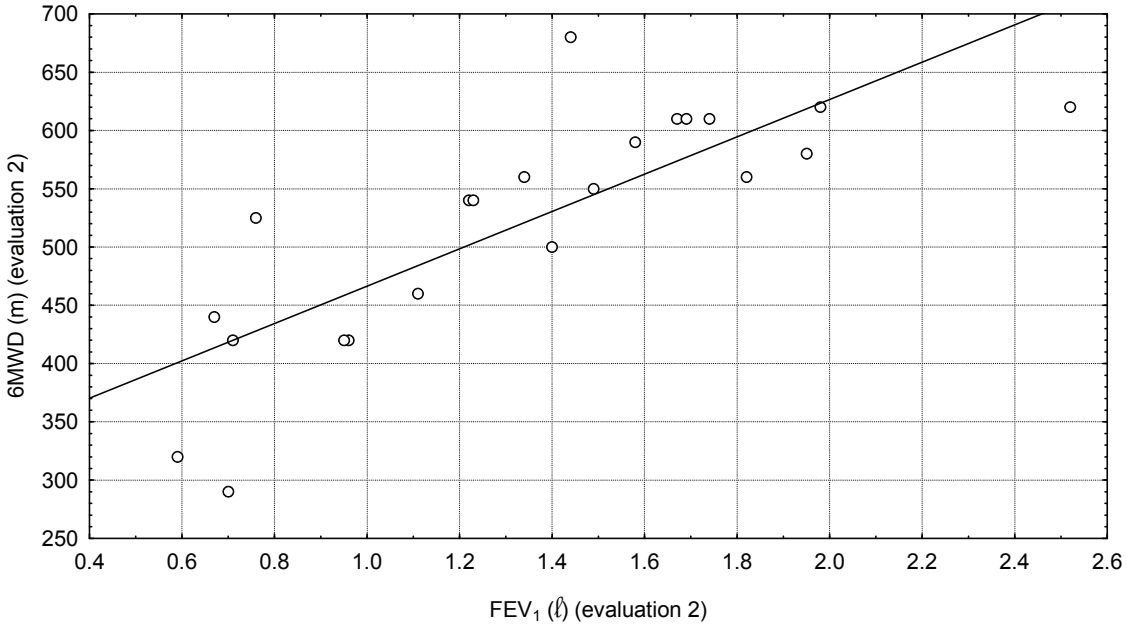

Figure 4.30 A scatter plot illustrating the correlation between 6MWD and FEV_1 at the second evaluation.

Consistent with the first evaluation, there was a very strong correlation between FEV_1 and 6MWD at the second evaluation ($p < 0.0001$).

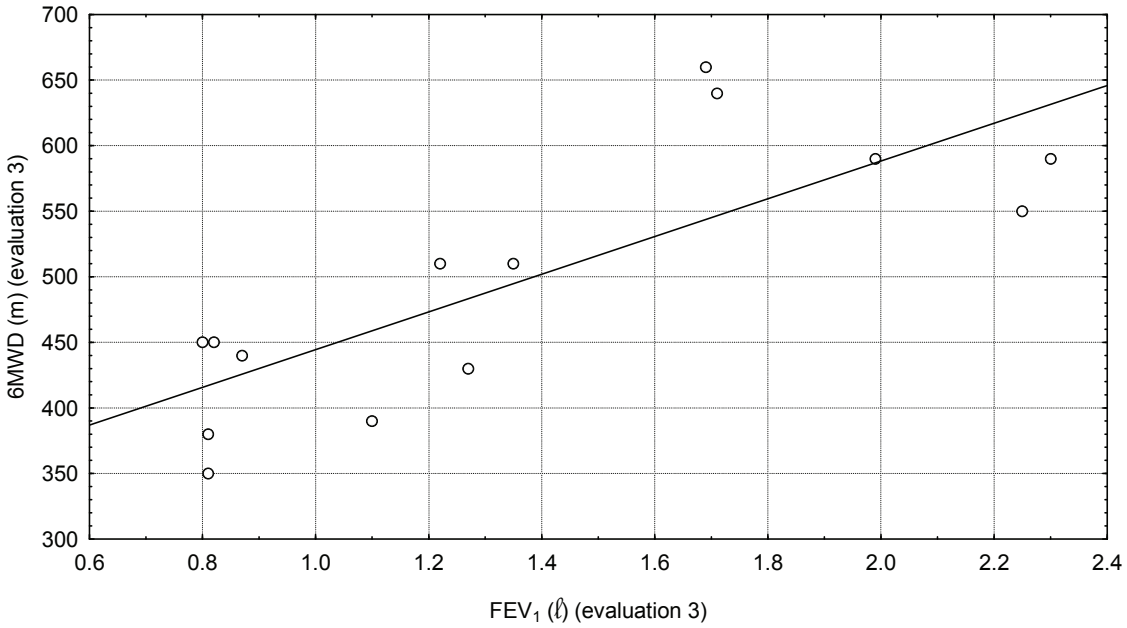

Figure 4.31 A scatter plot illustrating the correlation between 6MWD and FEV_1 at the third evaluation.

As illustrated in figure 4.31, a correlation was found between FEV_1 and 6MWD at the third evaluation. This correlation was the strongest at the second evaluation ($p = 0.000007$) and slightly weaker at the first ($p = 0.0005$) and third evaluations ($p = 0.0007$).

Table 4.10 Correlations calculated that did not deliver any significant results.

Variables	**Evaluation**	**p-value**
6MWT and SGRQ	1	0.06
	2	0.13
Physician's global evaluation and SGRQ	1	0.11
	2	0.19
Physician's global evaluation and BDI	1	0.43
BDI and SGRQ	1	0.42
TDI and SGRQ	2	0.08
6MWT and BDI	1	0.82
6MWT and TDI	2	0.10
Physician's global evaluation and 6MWT	1	0.44
	2	0.09
FEV_1 and SGRQ	1	0.32
	2	0.10
FEV_1 and BMI	2	0.08

Since no significant changes were recorded during the third evaluation for any of the variables, no correlations were calculated between variables of the third evaluation.

2. Modified programme

2.1 Frequency histograms of baseline data

2.1.1 Six minute walk test

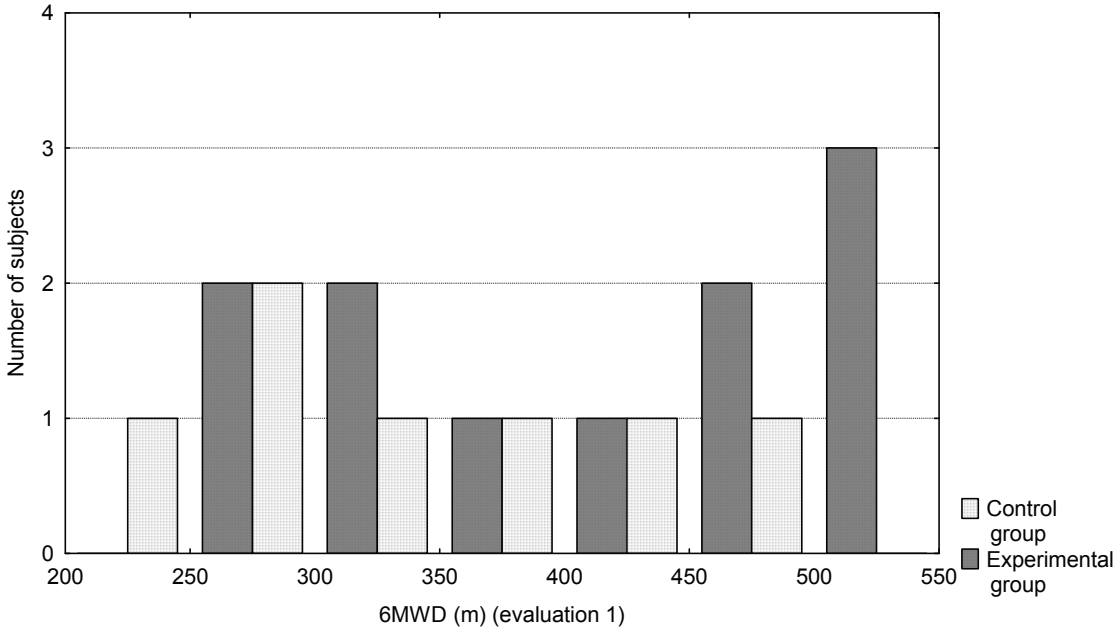

Figure 4.32 A frequency histogram illustrating subjects' 6MWDs at the first evaluation.

There was a wide variation in the baseline 6MWDs of both groups. The shortest distance covered by the experimental group was 280m and the longest distance was 530m. The shortest distance covered by the control group was 220m and the longest distance was 500m.

2.1.2 Baseline dyspnoea index

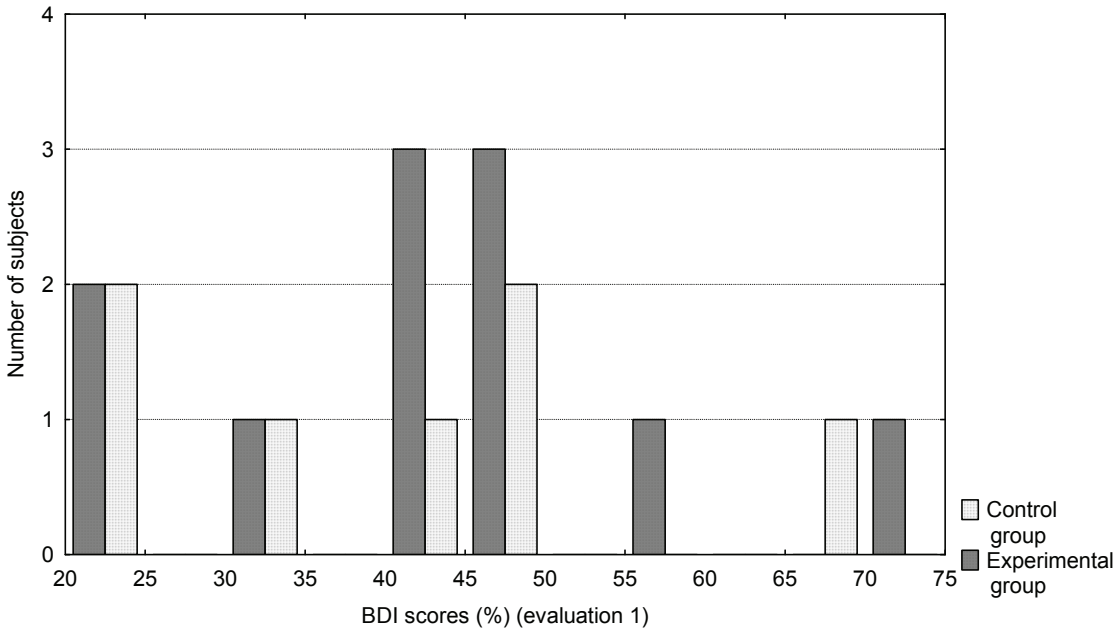

Figure 4.33 A frequency histogram illustrating the subjects' BDI scores at the first evaluation.

BDI scores were converted to a percentage; the lower the score, the more severe the impact of dyspnoea is. The majority of the subjects had scores of less than 50%, or six out of 12. The lowest BDI score recorded for both groups was three out of 12. The highest BDI score recorded for experimental group was nine out of 12 and the highest score recorded for the control group was eight out of 12.

2.1.3 St. George's respiratory questionnaire

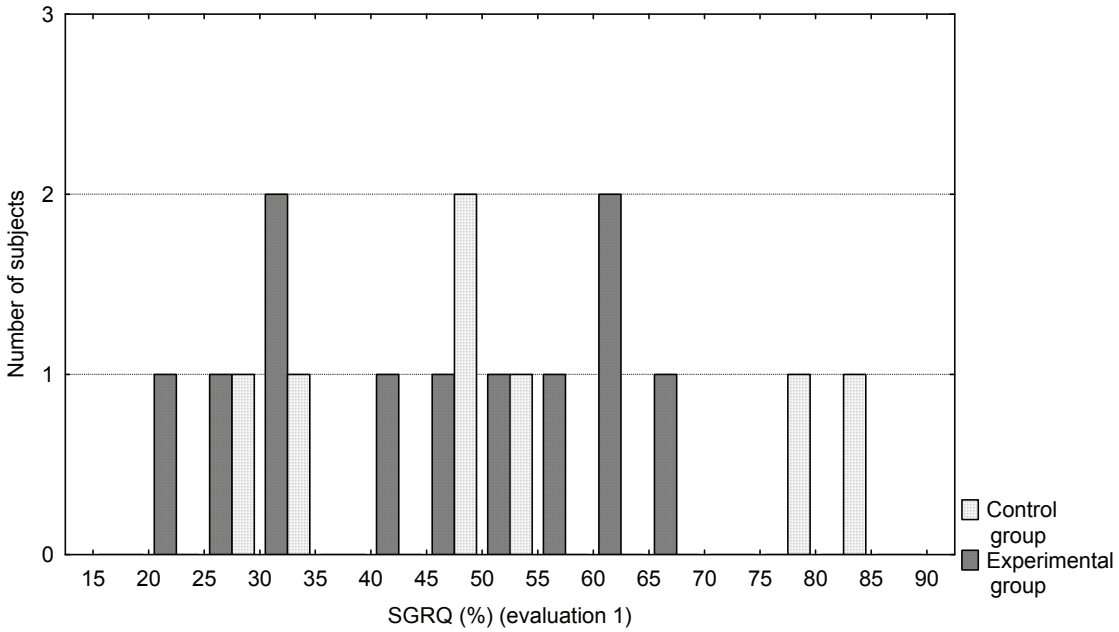

Figure 4.34 A frequency histogram illustrating the subjects' SGRQ scores at the first evaluation.

A high score on the SGRQ represents a severely impaired quality of life, whereas a low score indicates that the impact that the disease has on the subject's quality of life is minimal. The lowest SGRQ score recorded was 21.49 for the experimental group and 29.25 for the control group. The highest SGRQ score recorded was 69.79 for the experimental group and 82.07 for the control group.

2.1.4 Lung function variables

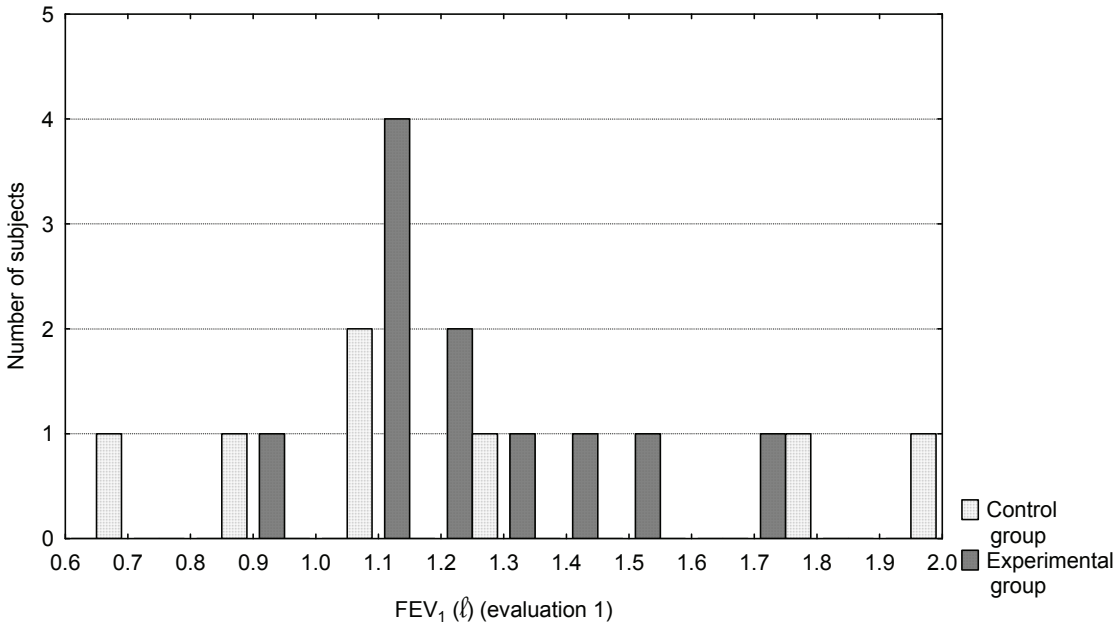

Figure 4.35 A frequency histogram illustrating the subjects' FEV_1's at the first evaluation.

The control group had a wider variation in FEV_1 scores at the first evaluation, compared to the experimental group. The lowest FEV_1 recorded for the experimental and control group was 0.92 ℓ and 0.66 ℓ, respectively. The highest FEV_1 recorded for the experimental and control group was 1.78 ℓ and 1.91 ℓ, respectively.

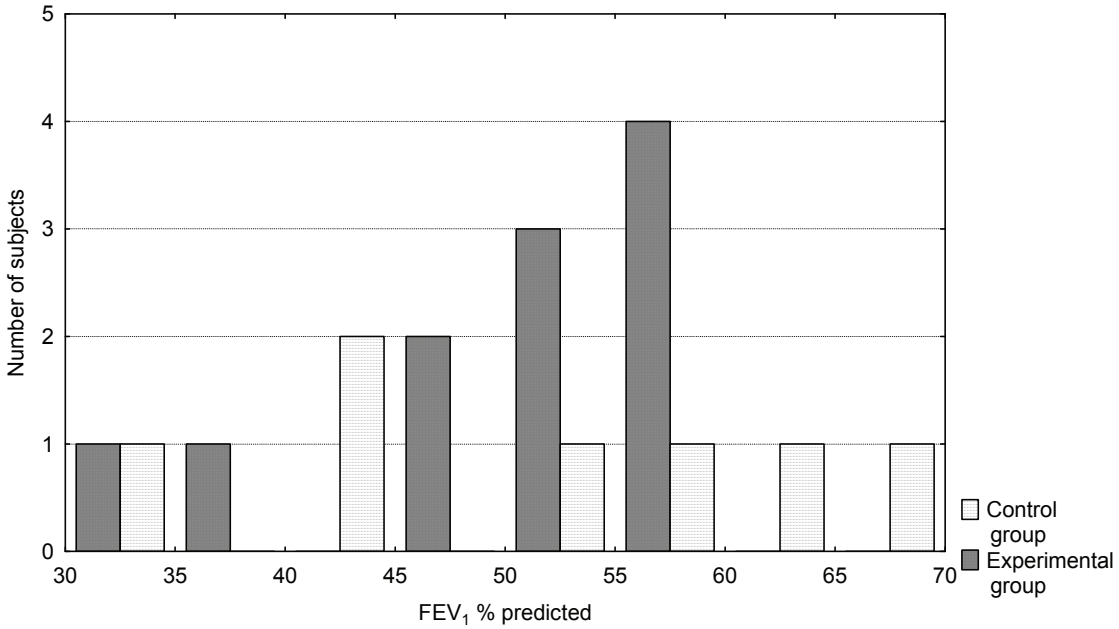

Figure 4.36 A frequency histogram illustrating the subjects' FEV_1 percentage of their predicted values at the first evaluation.

The lowest FEV_1 percentage of the predicted value recorded for the experimental and control groups was 32.62% and 32.88%, respectively. The highest FEV_1 percentage of the predicted value recorded for the experimental and control groups was 59.64% and 67.36%, respectively. According to GOLD criteria (see Chapter II), no subjects with mild or very severe COPD were included in this part of the study. In the experimental group, 63.63% of the subjects were classified as having moderate COPD and 36.36% had severe COPD. In the control group, 57.14% of the subjects were classified as having moderate COPD and 42.86% had severe COPD.

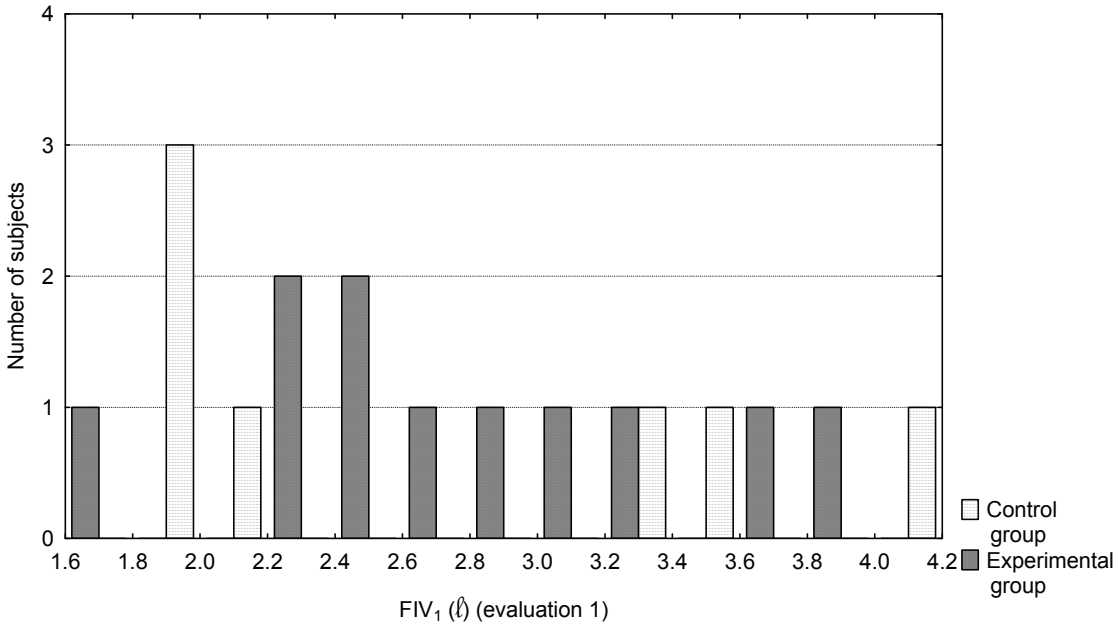

Figure 4.37 A frequency histogram illustrating the subjects FIV_1's at the first evaluation.

There was a wide distribution in the FIV_1 scores of the subjects in both groups. The lowest FIV_1 score recorded for the experimental and control groups at the baseline evaluation was 1.71 ℓ and 1.84 ℓ, respectively. The highest FIV_1 score recorded for the experimental and control groups at the baseline evaluation was 3.85 ℓ and 4.05 ℓ, respectively.

2.1.5 Physician's global evaluation

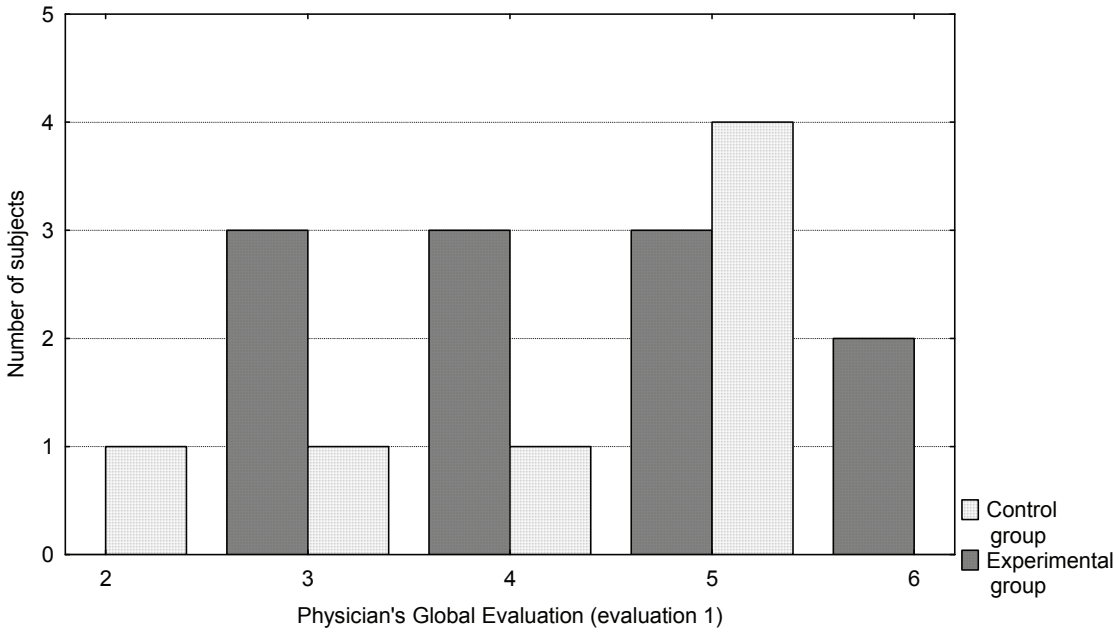

Figure 4.38 A frequency histogram illustrating the physician's global scores of the subjects at the first evaluation.

The lowest physician's global score recorded for the control group was two and for the experimental group the lowest score recorded was three. The highest scores recorded were six for the experimental group and five for the control group.

2.1.6 Body mass index

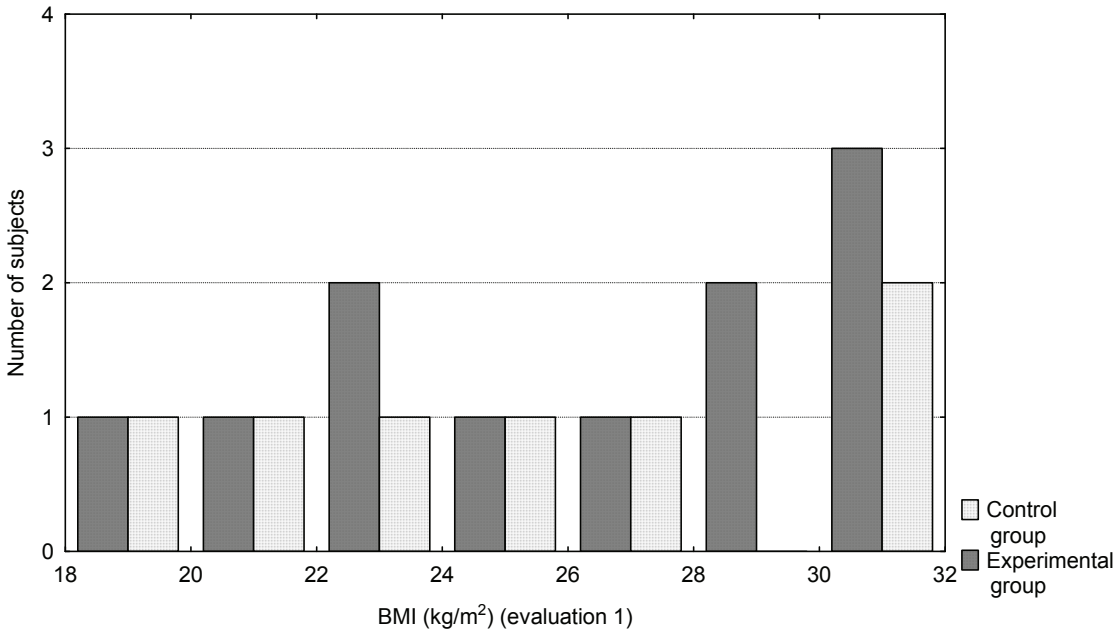

Figure 4.39 A frequency histogram illustrating the subject's BMI's at the first evaluation.

The lowest BMI recorded for the experimental and control group was 18.16 kg/m^2 and 19.92 kg/m^2, respectively. The highest BMI recorded for the experimental and control group was 31.67 kg/m^2 and 31.63 kg/m^2, respectively.

2.2 Changes from the first to the second evaluation

2.2.1 Six minute walk test

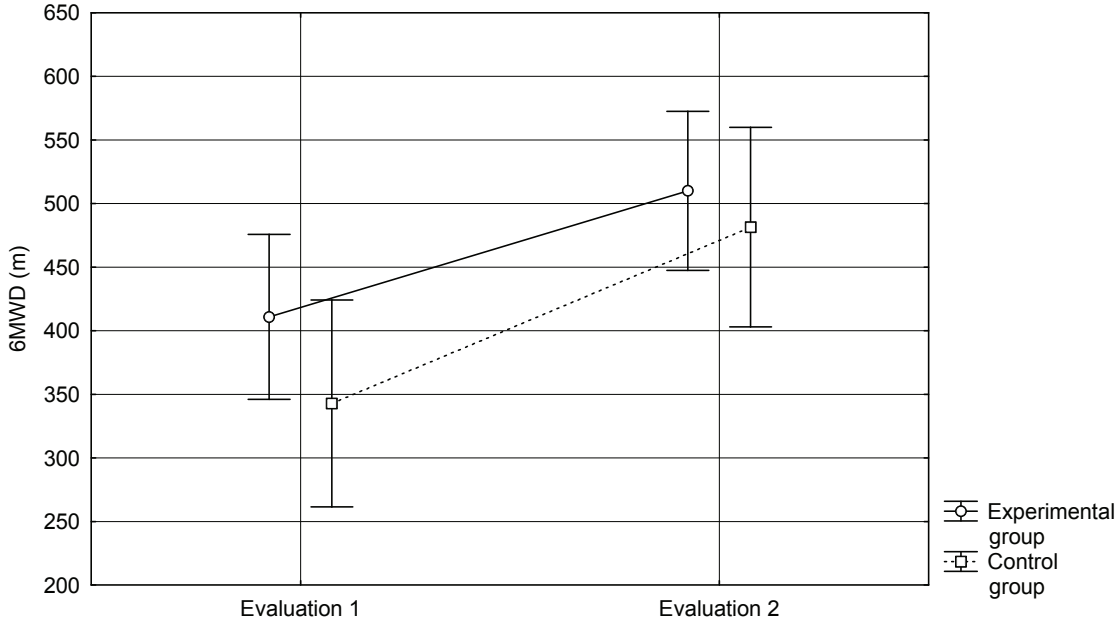

Figure 4.40 An ANOVA graph illustrating the improvement in mean 6MWD of the experimental and control group from the first to the second evaluation.

The mean distances covered by the experimental and control group at the first evaluation was 410.91m (SD ± 101.14m; SE ± 30.60m) and 342.86m (SD ± 101.93m; SE ± 38.36m), respectively. The mean distances covered by the experimental and control group at the second evaluation were 510.00m (SD ± 108.44m; SE ± 29.51m) and 481.43m (SD ± 77.12m; SE ± 36.99m), respectively. Although it seemed as if the control group was more impaired in terms of exercise capacity, there was no statistically significant difference between the mean distances covered at both evaluations ($p = 0.30$). The improvement of both groups from the first to the second evaluation was highly significant ($p < 0.000001$). The mean improvement from the first to the second evaluation for the experimental and control group was 99.09m (SD ± 46.14) and 138.57m (SD ± 88.21m). Both these improvements are higher than the threshold of 54m that is necessary for an

intervention to be significant (Enright *et al.*, 2003; ATS, 1999; Redelmeier *et al.*, 1997; Guyatt *et al.*, 1984).

To confirm repeatability of the 6MWT when conducted by independent supervisors, a second test was included. This 6MWT was performed at the Stellenbosch Biokinetics Centre (SBC), using the same protocol as in the pre-intervention assessment at the physician's practice. The clinical technologist, who administered the 6MWT at the physician's practice, was not informed of the results obtained at the SBC 6MWT. The results obtained in the two 6MWTs are presented in figure 4.41. In figure 4.41, 6MWT 1 refers to the test conducted at the SBC, whereas 6MWT 2 refers to the test conducted at the physician's practice.

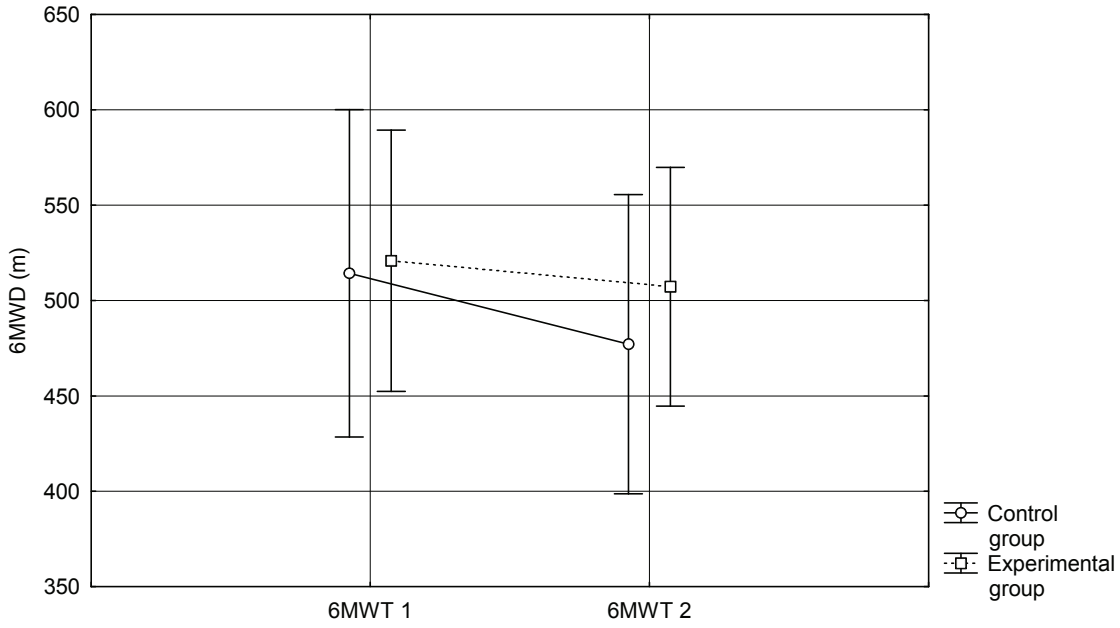

Figure 4.41 An ANOVA graph illustrating the two 6MWTs conducted by independent supervisors.

As illustrated by figure 4.41, there was no statically significant difference in the results obtained in the two 6MWTs of the experimental or control groups ($p = 0.33$).

2.2.2 Baseline and transitional dyspnoea index

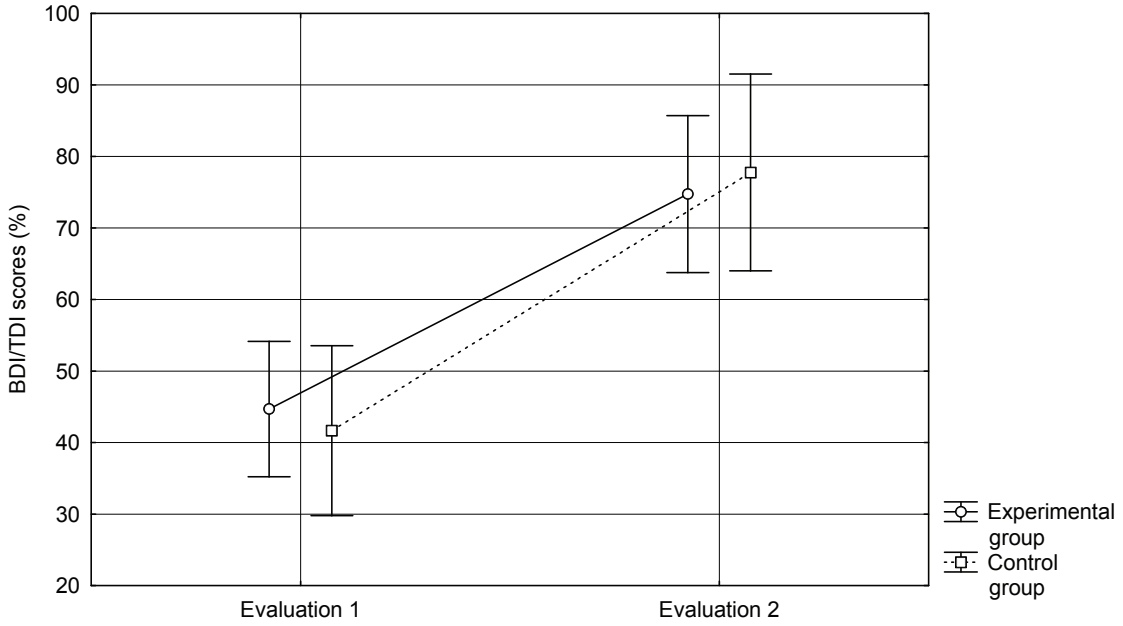

Figure 4.42 An ANOVA graph illustrating the improvement in mean BDI/TDI scores of the experimental and control group from the first to the second evaluation.

The repeated measures ANOVA indicated a significant improvement in BDI/TDI scores of both groups, from the first to the second evaluation ($p < 0.0001$). The mean score for the experimental and control groups at the first evaluation was 44.69% (SD ± 14.56%; SE ± 4.47m) and 41.67% (SD ± 15.22%; SE ± 5.60%), respectively. The mean score for the experimental and control groups at the second evaluation was 74.75% (SD ± 19.30%; SE ± 5.18) and 77.78% (SD ± 12.83%; SE ± 6.49%), respectively. There was no statistically significant difference between the mean scores of the two groups at the first or second evaluation ($p = 0.99$).

2.2.3 St. George's respiratory questionnaire

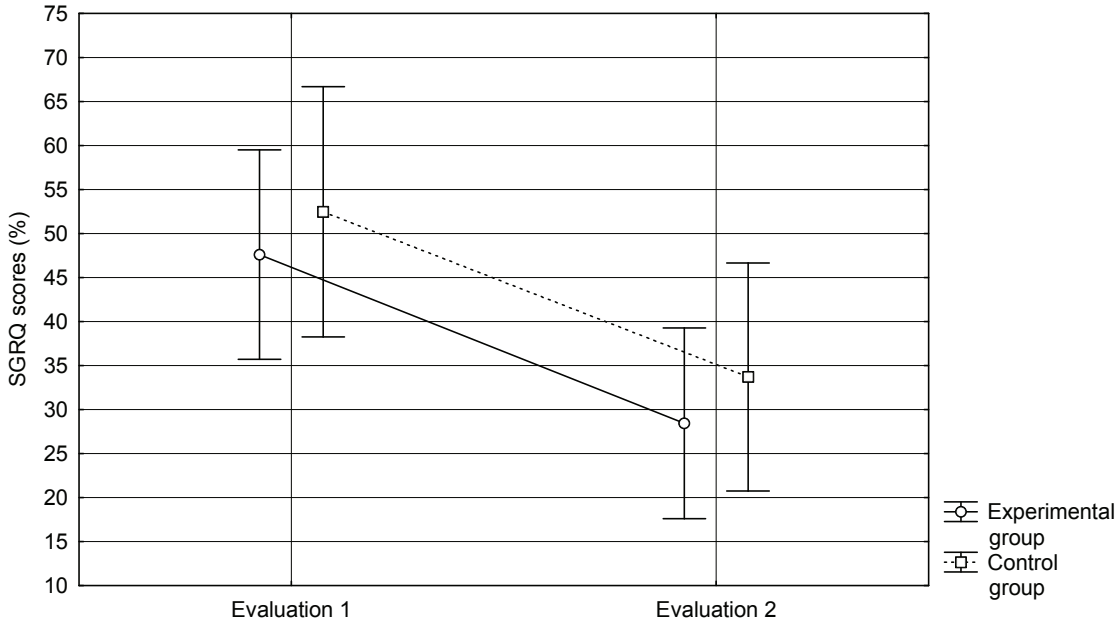

Figure 4.43 An ANOVA graph illustrating the improvement in mean SGRQ scores of the experimental and control group from the first to the second evaluation.

The repeated measures ANOVA indicated a significant improvement in the mean SGRQ scores of both groups, from the first to the second evaluation ($p < 0.001$). The mean score for the experimental and control groups at the first evaluation was 47.60 (SD ± 15.93; SE ± 5.58) and 52.47 (SD ± 19.78; SE ± 6.67), respectively. The mean score for the experimental and control groups at the second evaluation was 28.44 (SD ± 13.10; SE ± 5.08) and 33.71 (SD ± 19.70; SE ± 6.07), respectively. Although there was no statistically significant difference between the mean scores of the two groups at the first or second evaluation ($p = 0.50$), the difference was more than four percent or four units (Jones, 2002) and therefore this difference was clinically significant.

No significant correlation was found between the BDI/TDI and SGRQ for the experimental group at the first ($p = 0.79$) or second evaluation ($p = 0.37$). No

significant correlation was found between the BDI/TDI and SGRQ for the control group at the first (p = 0.11) or second evaluation (p = 0.54).

2.2.4 Lung function variables

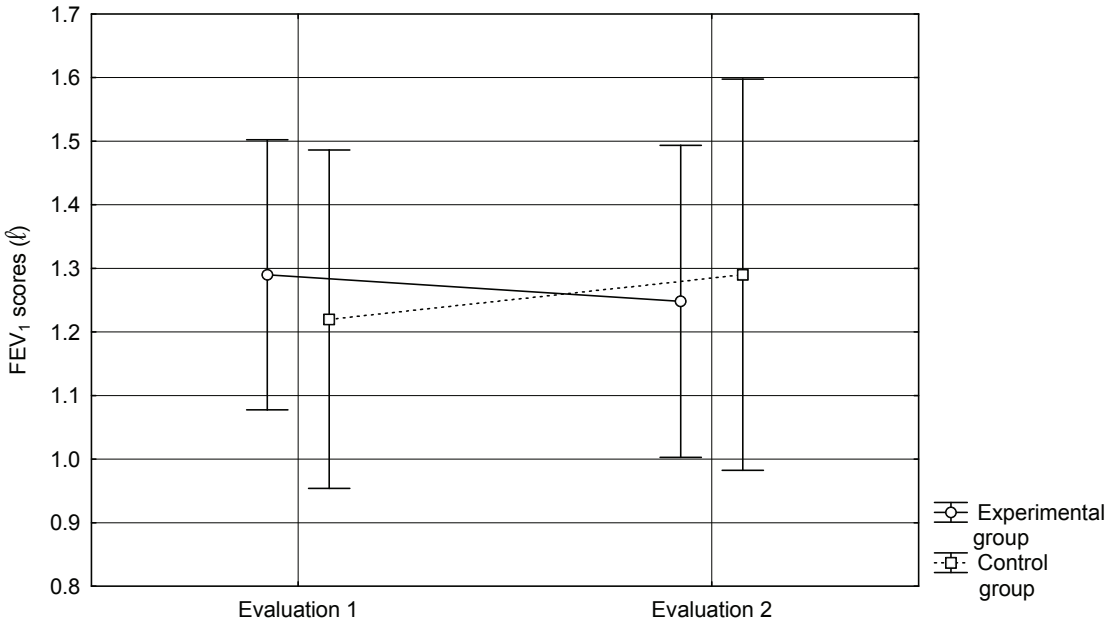

Figure 4.44 An ANOVA graph illustrating the changes in mean FEV_1 scores of the experimental and control group from the first to the second evaluation.

The repeated measures ANOVA indicated that there was no statistically significant difference between the mean FEV_1's of the two groups at both evaluations (p = 0.94). There was also no statistically significant change in the FEV_1 scores of either group from the first to the second evaluation (p = 0.66). The mean FEV_1 for the experimental and control groups at the first evaluation was 1.29 ℓ (SD ± 0.24 ℓ; SE ± 0.10 ℓ) and 1.22 ℓ (SD ± 0.45 ℓ; SE ± 0.13 ℓ), respectively. The mean score for the experimental and control groups at the second evaluation was 1.25 ℓ (SD ± 0.27 ℓ; SE ± 0.12 ℓ) and 1.29 ℓ (SD ± 0.52 ℓ; SE ± 0.15 ℓ), respectively.

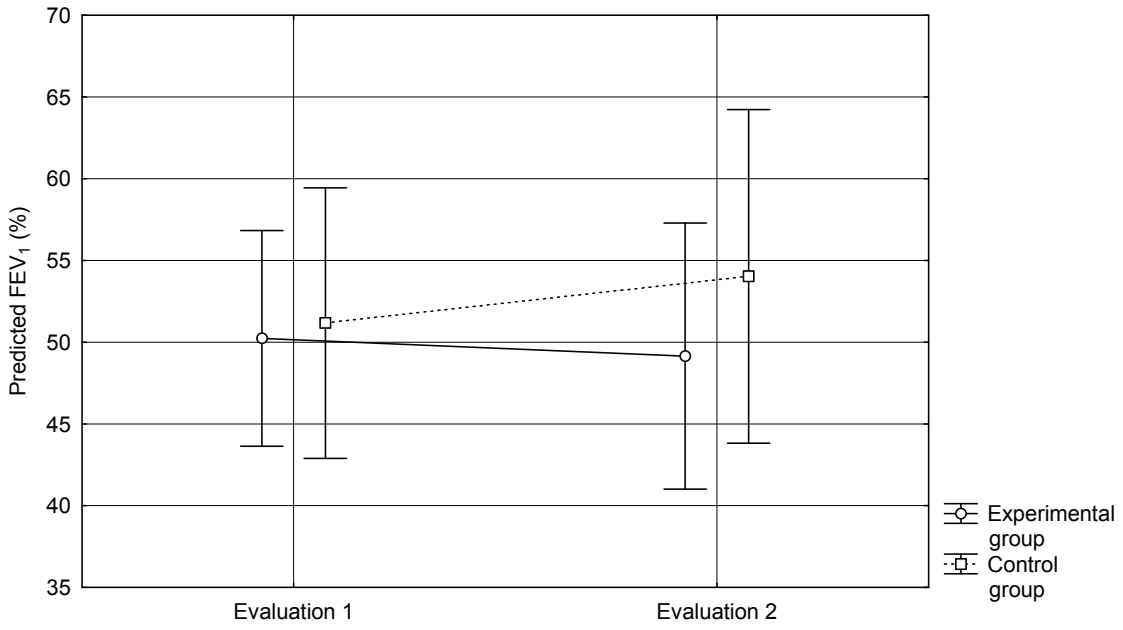

Figure 4.45 An ANOVA graph illustrating the subjects' mean FEV_1 percentage of their predicted values at the first and the second evaluation.

The repeated measures ANOVA indicated that there was no statistically significant difference between the mean predicted FEV_1's of the two groups at both evaluations ($p = 0.60$). There was also no statistically significant change in the predicted FEV_1 scores of either group from the first to the second evaluation ($p = 0.50$). The mean predicted FEV_1 for the experimental and control groups at the first evaluation was 50.24% (SD ± 8.93%; SE ± 3.11%) and 51.17% (SD ± 12.30%; SE ± 3.9%), respectively. The mean prediction for the experimental and control groups at the second evaluation was 49.15% (SD ± 11.01%; SE ± 3.84%) and 54.04% (SD ± 15.18%; SE ± 4.81%), respectively. Although not statistically significant, there was an improvement in the mean predicted percentage FEV_1 of the control group, as indicated by figure 4.45.

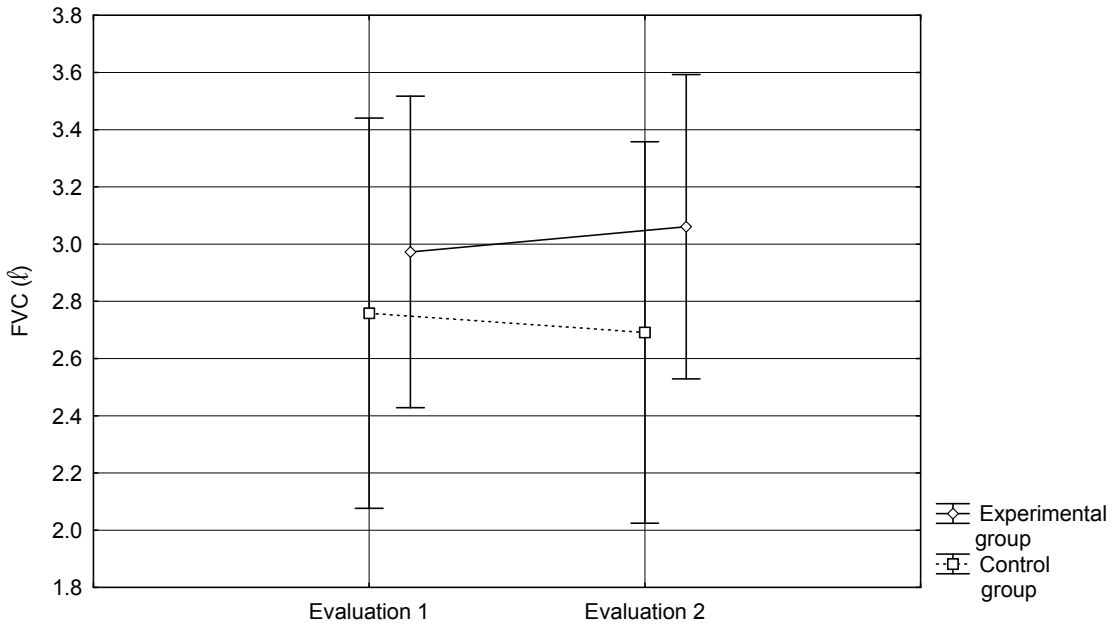

Figure 4.46 An ANOVA graph illustrating the subjects' mean FVC values at the first and the second evaluation.

The repeated measures ANOVA indicated that there was no statistically significant difference between the mean FVC scores of the two groups at both evaluations ($p = 0.71$). There was also no statistically significant change in the FVC scores of either group from the first to the second evaluation ($p = 0.92$). The mean FVC for the experimental and control groups at the first evaluation was 2.97 ℓ (SD ± 0.62 ℓ; SE ± 0.27 ℓ) and 2.76 ℓ (SD ± 0.84 ℓ; SE ± 0.34 ℓ), respectively. The mean score for the experimental and control groups at the second evaluation was 3.06 ℓ (SD ± 0.74 ℓ; SE ± 0.26 ℓ) and 2.69 ℓ (SD ± 0.75 ℓ; SE ± 0.33 ℓ), respectively.

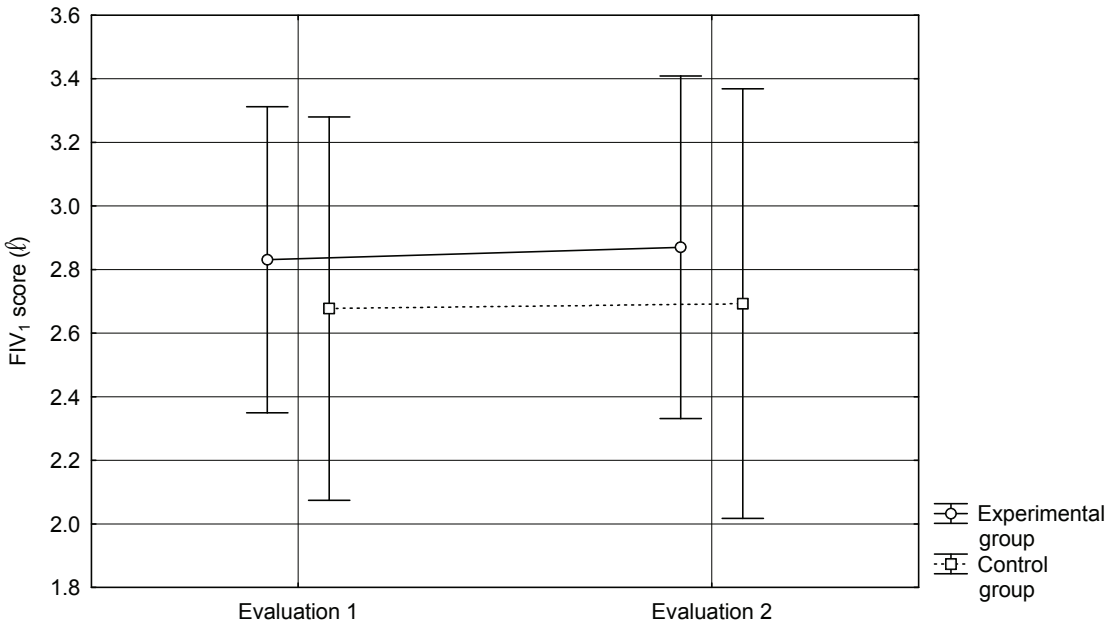

Figure 4.47 An ANOVA graph illustrating the subjects' mean FIV_1 values at the first and the second evaluation.

The repeated measures ANOVA indicated that there was no statistically significant difference between the mean FIV_1 scores of the two groups at both evaluations ($p = 0.67$). There was also no statistically significant change in the FIV_1 scores of either group from the first to the second evaluation ($p = 0.76$). The mean FIV_1 for the experimental and control groups at the first evaluation was 2.83 ℓ (SD ± 0.64 ℓ; SE ± 0.23 ℓ) and 2.68 ℓ (SD ± 0.09 ℓ; SE ± 0.28 ℓ), respectively. The mean score for the experimental and control groups at the second evaluation was 2.87 ℓ (SD ± 0.77 ℓ; SE ± 0.25 ℓ) and 2.69 ℓ (SD ± 0.95 ℓ; SE ± 0.32 ℓ), respectively.

2.2.5 Physician global evaluation

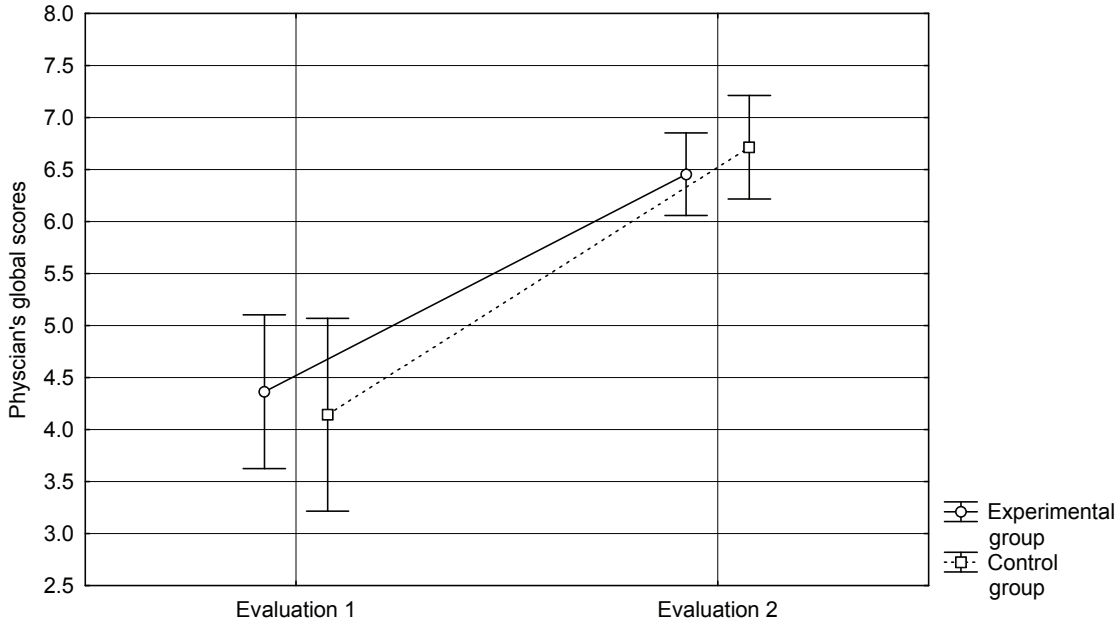

Figure 4.48 An ANOVA graph illustrating the physician's global evaluation for the subjects at the first and second evaluations.

The repeated measures ANOVA indicated a significant improvement in the mean physician's global scores of both groups, from the first to the second evaluation ($p < 0.000001$). The mean score for the experimental and control groups at the first evaluation was 4.36 (SD ± 1.12; SE ± 0.35) and 4.14 (SD ± 1.21; SE ± 0.44), respectively. The mean score for the experimental and control groups at the second evaluation was 6.45 (SD ± 0.52; SE ± 0.19) and 6.71 (SD ± 0.76; SE ± 0.23), respectively. There was no statistically significant difference between the mean scores of the two groups at the first or second evaluation ($p = 0.96$).

2.2.6 Body mass index

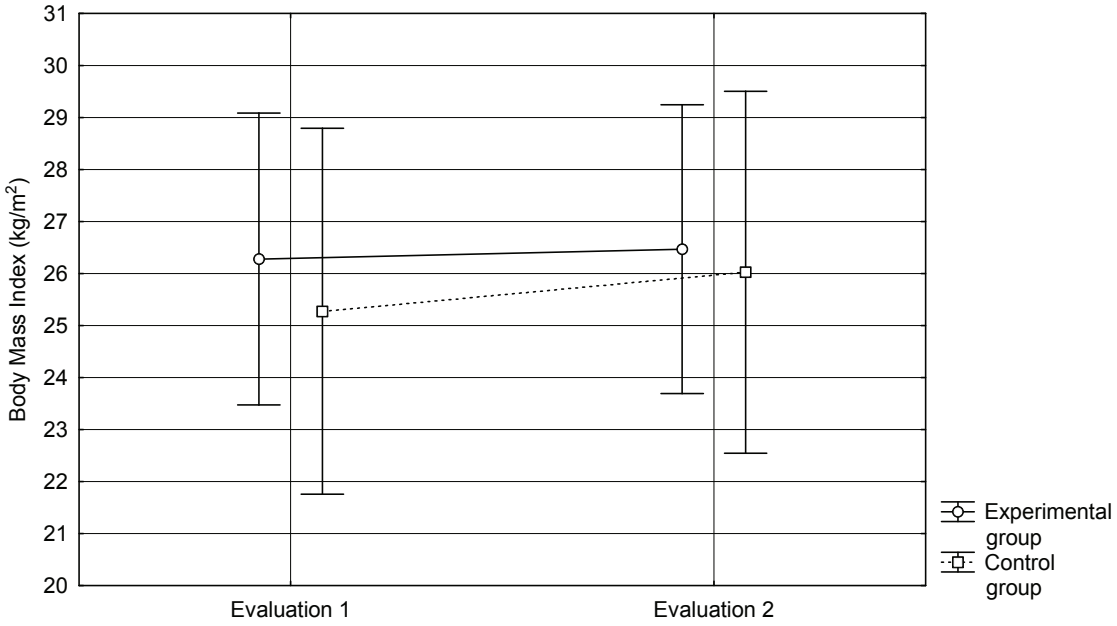

Figure 4.49 An ANOVA graph illustrating the subjects' mean BMI values at the first and second evaluation.

The repeated measures ANOVA indicated that there was no statistically significant difference between the two groups at either evaluation ($p = 0.73$). There was also no statistically significant change in the mean BMI values of the two groups from the first to the second evaluation ($p = 0.23$). The mean BMI for the experimental and control groups at the first evaluation was 26.28 kg/m^2 (SD ± 4.39; SE ± 1.23) and 25.27 kg/m^2 (SD ± 4.39; SE ± 1.66), respectively. The mean BMI for the experimental and control groups at the second evaluation was 26.47 kg/m^2 (SD ± 4.43; SE ± 1.30) and 26.02 kg/m^2 (SD ± 4.19; SE ± 1.64), respectively.

2.2.7 Exacerbations

As in the PP, exacerbations were assessed by the number of sessions missed due to acute exacerbations and by self-reported exacerbations as reported in the SGRQ.

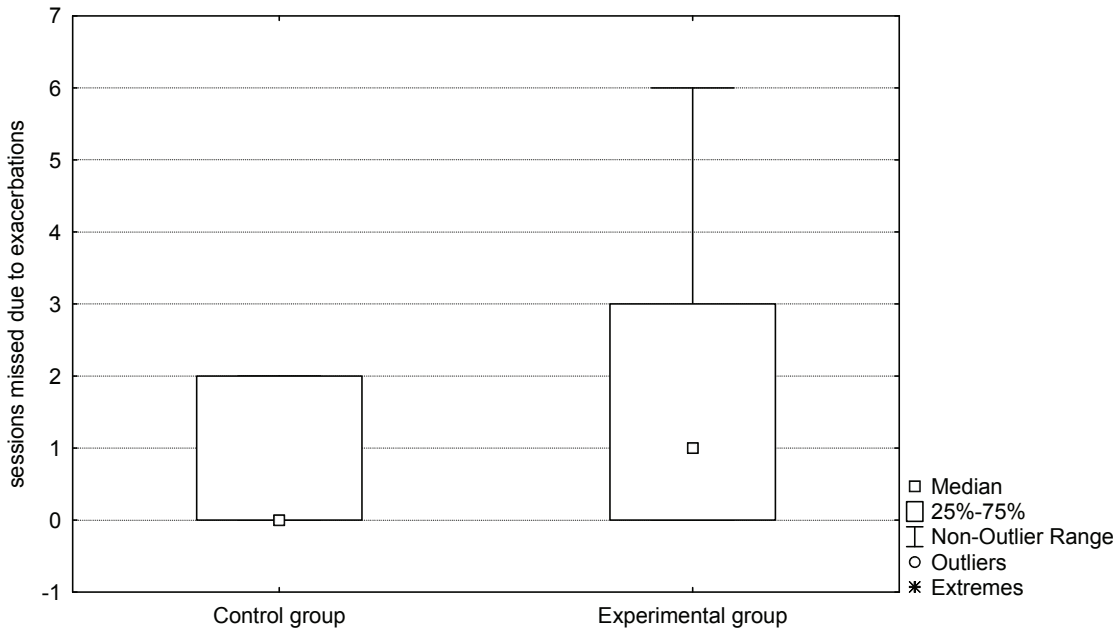

Figure 4.50 A box plot illustrating the exercise sessions missed due to acute exacerbations.

In the MP, acute exacerbations caused the experimental and control group to miss an average of 1.64 (SD ± 2.01) and 0.71 (SD ± 0.95) sessions, respectively. There was no statistically significant difference between the sessions missed by the two groups ($p = 0.28$).

At the baseline evaluation, the experimental and control groups reported an average of 1.87 (SD ± 1.77) and 1.36 (SD ± 1.29) exacerbations, respectively. At the second evaluation the experimental group's average reported exacerbations lowered to 0.18 (SD ± 0.40), while the control group's lowered to 1.29 (SD ± 1.50). This decrease in the number of exacerbations was statistically significant for the experimental group ($p < 0.01$), but not for the control group ($p = 0.41$). There was no statistically significant difference in the number of reported exacerbations by two groups at the first evaluation ($p = 0.50$). However, at the second evaluation the experimental group reported significantly less exacerbations, compared to the control group ($p < 0.05$).

2.3 Correlations

2.3.1 Relationship between FEV_1 and 6MWD

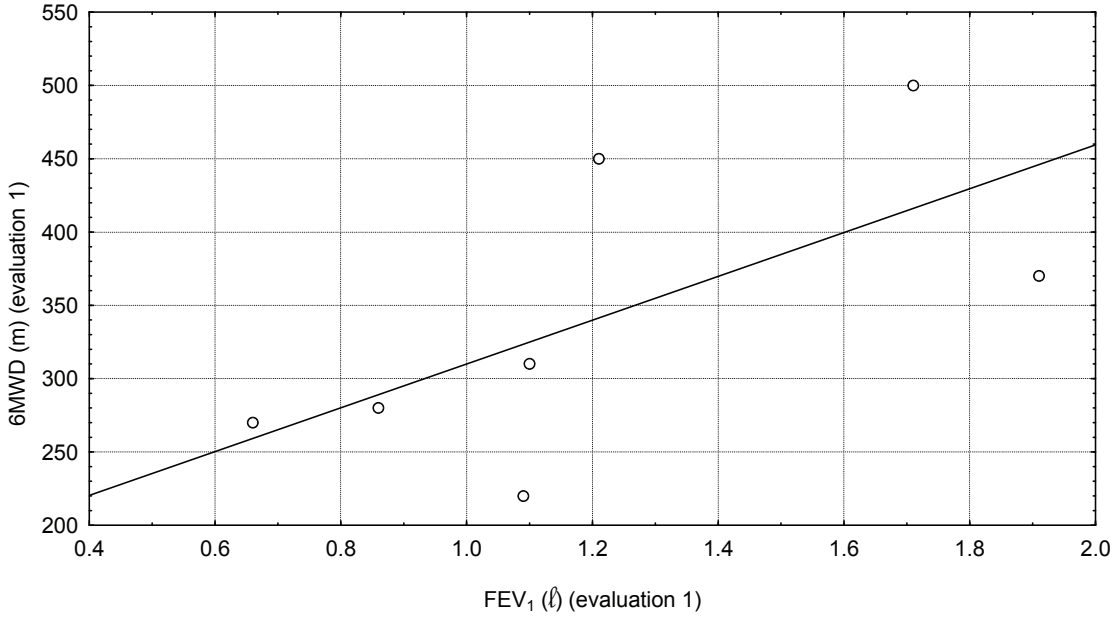

Figure 4.51 A scatter plot illustrating the correlation between the mean 6MWD and mean FEV_1 for the control group at the first evaluation.

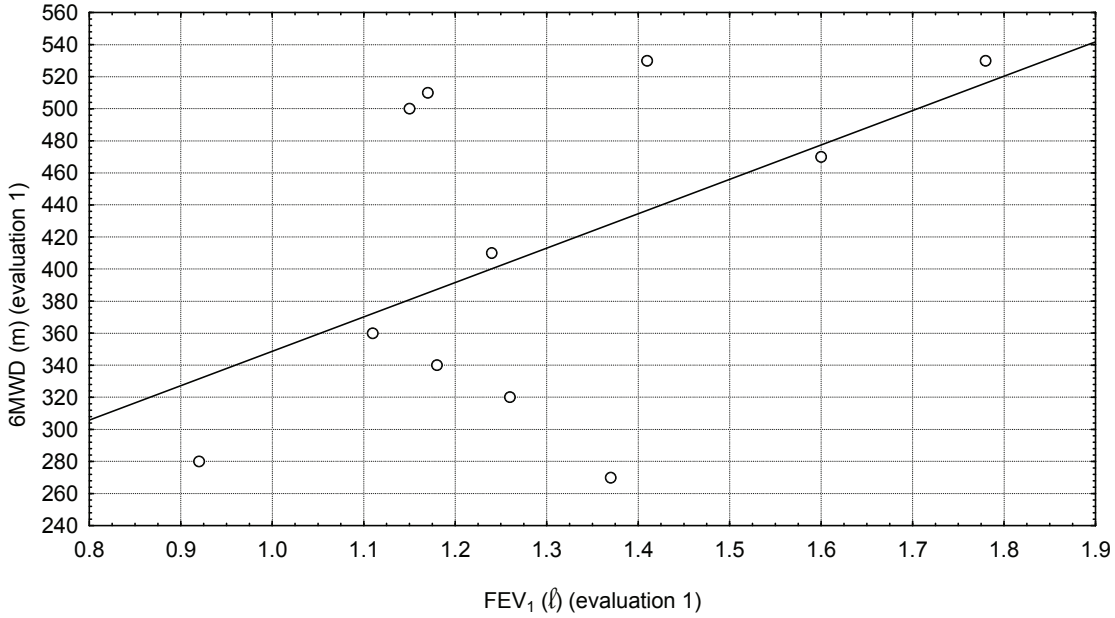

Figure 4.52 A scatter plot illustrating the correlation between the mean 6MWD and mean FEV_1 for the experimental group at the first evaluation.

Although the correlation between 6MWD and FEV_1 was not as strong as in the PP, the correlation between these variables was significant at the 5% level for the experimental and control groups at the first evaluation ($p < 0.05$).

Table 4.11 Correlations calculated that did not deliver any significant results.

Variables	Group	Evaluation	p-value
6MWT and SGRQ	experimental	1	0.57
	experimental	2	0.16
	control	1	0.31
	control	2	0.16
6MWT and BDI/TDI	experimental	1	0.46
	experimental	2	0.85
	control	1	0.82
	control	2	0.91
SGRQ and FEV_1	experimental	1	0.98
	experimental	2	0.96
	control	2	0.12
Physician's global evaluation and SGRQ	experimental	1	0.59
	experimental	2	0.72
Physician's global evaluation and BDI/TDI	experimental	1	0.70
	experimental	2	0.91
	control	2	0.68

Correlations that did not deliver significant results, when comparing the changes in variables from the first to the second evaluation, are presented in Appendix J.

CHAPTER V: DISCUSSION

Primary programme

The PP found that a structured, 12-week exercise programme improves the exercise capacity, quality of life, dyspnoea and a physician's assessment of overall condition in subjects with COPD (as assessed by the 6MWT, SGRQ, BDI/TDI and the physician's global evaluation, respectively). Even though there was a slight decrease in the benefits obtained six months after completion of the intervention programme, this decrease was not statistically significant. This was consistent with previous studies executed in industrialised countries (Cambach *et al*., 1997; Wijkstra *et al.*, 1995; Cox *et al.*, 1993; Vale *et al.*, 1993). This study confirmed that an exercise programme fails to instigate any statistically significant changes in lung function variables and BMI in subjects with COPD. This finding was also consistent with previous authors (Bauldoff *et al.*, 2002; McArdle *et al.*, 2001:953; Guell *et al.*, 2000; Troosters *et al.*, 2000; Bendstrup *et al.*, 1997; Strijbos *et al.*, 1996; ATS, 1995a; Celli, 1995; Reardon *et al.*, 1994; Cox *et al.*, 1993; Holden *et al.*, 1990; Busch & McClements, 1988).

Three subjects included in the PP had very severe COPD, 11 had severe COPD and eight were classified as moderate COPD. There was no statistically significant difference between the results obtained by these two groups ($p > 0.05$). This was consistent with a study by Berry and co-workers (1999). Since such a small number of subjects were classified with severe COPD, the relevance of this finding is questionable. No subjects with mild COPD were included in this study. Although Berry and co-workers (1999) illustrated that the benefits obtained through exercise training do not differ significantly in the different stages (even with mild COPD), previous reports have criticised the inclusion of subjects with mild COPD on the basis that these subjects would be expected to benefit more from exercise training (Albert, 1997). Differentiating between the results obtained by subjects in different stages of COPD, was not one of the key aims of this study, therefore these findings were considered circumstantial.

Contrary to the findings of De Torres and co-workers (2005), there was no statistically significant difference between the 6MWDs achieved by the men and women at all three evaluations. This could be explained by the small number of women included in the PP. Only seven of the subjects included in this group were women.

Modified programme

The MP found that the same benefits in exercise capacity, quality of life, dyspnoea and overall condition could be obtained through a less expensive, adapted exercise programme (as assessed through the 6MWT, SGRQ, BDI/TDI and the physician's global evaluation). Consistent with the PP, no changes in pulmonary function measurements or BMI were observed in the experimental or control group.

In the MP, a significant difference was found between men and women for 6MWD, absolute FEV_1 values and SGRQ scores. The women were more impaired in all these areas ($p < 0.05$). No significant gender differences were found in the percentage predicted FEV_1, BMI, BDI, FIV_1 and the physician's global evaluation. These findings were consistent with the findings by De Torres and co-workers (2005). A difference noted in the findings was that De Torres and co-workers (2005) documented significantly lower BMI-values for the women included in their study.

In the MP, two independent 6MWTs were conducted at the post-intervention assessment. The two tests were conducted within two days of each other, at two different locations, by independent supervisors. An important finding was that there was no statistically significant difference between the results obtained in these two tests. This adds to the validity of the test and indicates that subjects performed at their best. Furthermore, this shows that if supervisors are adequately trained, the 6MWT can successfully be conducted by different supervisors. To my knowledge, it is the first time that the 6MWT has been validated with regards to its

repeatability when conducted by separate supervisors in South Africa. According to the American Thoracic Society (2002), one other study found a mean difference of 7% in 6MWDs when comparing the data of two different testing centres.

Exacerbations

Although not included in the protocol, the impact of exercise training on the frequency of exacerbations and the impact of exacerbations on the outcome measures of the programme were evaluated. As mentioned previously, exacerbations were firstly defined as an increase in pulmonary symptoms that was severe enough to prevent a subject from attending an exercise session. Sessions missed by subjects were carefully documented and these were assessed. Secondly, the subjects' perception of exacerbations was assessed by analysing the number of reported exacerbations in the SGRQ. Subjects reported the number of exacerbations they experienced in the time they were attending the programme. These exacerbations were described as "Over the last 3 months, how many severe or very severe unpleasant attacks of chest trouble have you had?"

Previous studies on the effects of exercise training on the frequency of exacerbations were contradictory. Some studies found that exercise training had no effect on the frequency of exacerbations (Benstrup *et al.*, 1997; Ries *et al.*, 1995), while Guell and co-workers (2000) found a significant decrease. All exacerbations that resulted in subjects missing exercise sessions were thoroughly documented. The value of this data was, however restricted, since data on exacerbations prior to the study was not available for all subjects and exacerbations were defined differently from previous studies. Assessment on possible changes in the frequency of exacerbations had to rely on self-reported incidents in the SGRQ.

1. Primary programme

In the PP, there was a significant decrease in the number of reported exacerbations by the subjects from the first to the second evaluation. Records were not available to assess the number of exacerbations from the second to the third evaluation.

2. Modified programme

An important finding was that the same decrease in the number of exacerbations was observed among the experimental group in the MP. The small number of subjects in the control group could explain why the decrease in exacerbations observed in this group was not statistically significant.

Correlations

1. Primary programme

A significant correlation was found between the FEV_1 and 6MWD in the PP. There was a significant improvement in 6MWD from the first to the third evaluation, but no significant change was noted in the FEV_1 values. The correlation between these variables was the strongest at the second evaluation and weaker at the first and third evaluation.

Various previous studies have found no correlation between FEV_1 and 6MWD (Brooks *et al.*, 2002; Boueri *et al.*, 2001; Benstrup *et al.*, 1997; Jones, 1991; Swinburn *et al*., 1985; McGavin *et al.*, 1976). When comparing the baseline data of the current study with the baseline data of previous studies, this correlation could be attributed to a difference in mean baseline FEV_1 values. The mean baseline FEV_1 of the current study is higher than that of most of the previous studies. The mean FEV_1 value of the study by Brooks and co-workers (2002) was

0.70 ℓ ± 0.03 ℓ, which was significantly lower than the mean FEV_1 (1.31 ℓ ± 0.43 ℓ) of the current study. Detailed information on the baseline values of other studies was not available.

Previous studies have found significant correlations between the number of exacerbations and HRQL (Spencer *et al.*, 2004; Seemungal *et al.*, 1998). Based on this literature, subjects that experienced the most number of exacerbations should score higher (more impaired HRQL) on the SGRQ. This was true in the PP at the first evaluation, but not at the second evaluation.

2. Modified programme

A significant correlation was found between the FEV_1 and 6MWD in the PP. Although the trend was similar in the MP, the correlation was not as strong as in the PP. The fact that the correlation was not as strong in the MP was attributed to the smaller sample size. As in the PP, there was a significant improvement in 6MWD from the first to the second evaluation, but no significant change was noted in the FEV_1 values. In the PP, the correlation between these variables was the strongest at the second evaluation and weaker at the first and third evaluation. In the MP, the correlation between these variables was absent at the second evaluation. The fact that there was no change in the mean FEV_1 of either group, while significant changes were observed in 6MWD, would explain the absence of this correlation at the second evaluation.

The correlation between FEV_1 and 6MWD was inconsistent when analysing the three groups at all the evaluations. Therefore, the conclusion could be made that FEV_1 is not a valuable predictor of functional capacity, as measured by the 6MWT. Furthermore, an improvement in FEV_1 is not essential in the improvement of functional capacity.

According to previous studies (Ketelaars *et al.*, 1996; Curtis *et al.*, 1994), improvements in FEV_1 do not necessarily translate into improvements in quality of life. In the MP, a weak but significant correlation was found between FEV_1 and the SGRQ scores of the control group at the first evaluation. The absence of this correlation at the second evaluation can be explained by the fact that there was no significant change in FEV_1 values, but a highly significant decrease in SGRQ scores and therefore an improvement of HRQL. Consistent with a study by Ketelaars and co-workers (1996), this correlation was not present in the PP, or in the experimental group. Patients with similar FEV_1 values often display a wide range in exercise capabilities and overall health (Maltais *et al.*, 1996b). FEV_1 is therefore not considered a good predictor of HRQL. It could be argued that this correlation could be attributed to the fact that low FEV_1 values are often associated with an increase in exacerbations (Pauwels *et al.*, 2001). The SGRQ has a large component for the assessment of the impact of exacerbations. Therefore, this correlation could be attributed to a relationship between FEV_1 and exacerbations and not HRQL *per se*. However, after assessment of the correlation between FEV_1 and the number of exacerbations, no correlations were found (Appendix J).

According to Gosselink (2002), frequent exacerbations during exercise intervention, would result in a decrease in the effectiveness of exercise training and subsequently reduce improvement in functional capacity. Therefore, it was important to assess the impact of exacerbations on functional capacity. Based on the findings of Gosselink (2002), it would be expected that the subjects that missed the most number of sessions due to exacerbations, would show the smallest improvement in functional capacity. However, no correlations were found between the number of sessions missed due to exacerbations and the improvement in 6MWD (Appendix J).

In the MP, significant correlations were found between the number of exacerbations and HRQL at the first evaluation for the experimental group and at the second evaluation for the control group. These correlations would be

expected, since the number of exacerbations was calculated from the SGRQ. The fact that this correlation was not present at all evaluations could be explained by the fact that the SGRQ includes three sub-categories (Chapter III). Exacerbations contribute to the symptom-category. In the cases where this correlation was absent, it could be concluded that the impact- and activity-components had a greater influence on quality of life compared to symptoms.

Contrary to previous studies (Ketelaars *et al.*, 1996; Okubadejo *et al.*, 1996), the present study found no significant correlations between exercise performance and HRQL. This could possibly be attributed to the small sample size of this study. This was affirmed by the fact that when the results of the subjects in the PP were combined with the results of the control group, a significant correlation was found between 6MWD and SGRQ scores (Appendix K).

Conclusion

In conclusion, the benefits that a structured exercise programme has for patients with COPD have been clearly illustrated by these results. One important benefit that should be emphasised is the improvement in quality of life that was experienced by all subjects included in this study. The interaction between improved quality of life, psychological, physical and social wellbeing, highlights the importance that this holds for these patients. The positive feedback received from all the subjects included in the study, further confirms the important role that an exercise programme could play in the successful management of patients with COPD. The fact that similar results was obtained by a low-cost programme was another important finding. This substantiates the fact that it is possible to make pulmonary rehabilitation accessible to all patients with COPD.

CHAPTER VI: CONCLUSION

Numerous previous studies have focused on the benefits of exercise training on various aspects of COPD. However, most of this research has focused on COPD in industrialised countries. Recently a few studies on COPD in developing countries have emerged. From this limited data, it is obvious that the challenges faced by developing countries are very different from those in industrialised nations. Furthermore, little research exists on exercise training of the COPD patients in a South African setting.

Although the challenges faced by industrialised and developing countries are very different, exercise training of COPD patients in developing countries could prove to be more beneficial. COPD patients in developing countries have to rely more on physical fitness due to the absence of luxuries, such as transport and proper health care. COPD is an incurable disease and therefore, the most important aim of therapy is the enhancement of the remaining life years. Standard medical therapy is however, limited in this regard, due to complex interaction between physiological variables, functional status and quality of life. Therefore, exercise training can enhance the benefits of standard medical therapy and provide the patient with a more comprehensive treatment strategy.

One of the main challenges in South Africa remains the high prevalence of TB and HIV/AIDS. This was illustrated in one subject with severe COPD that developed TB after inclusion in the programme. Both these conditions contribute to the prevalence of COPD and add to the complexity of successful management of the disease process (Diaz *et al.*, 2003; Hnizdo *et al.*, 2000). Although it will always be challenging to keep patients with TB or HIV/AIDS in an exercise routine, these patients should not be excluded from exercise programmes. Exercise programmes can be successfully tailored or adapted to accommodate these patients. This emphasises the importance of individualised programmes.

All subjects included in the study were clinically diagnosed with COPD and conformed to the inclusion and exclusion criteria. Despite this, a large baseline

scatter between subjects was observed for all variables. This highlights the diversity of COPD patients and the complexity of the disease process. An important finding was that despite the large diversity of the study group, all subjects benefited greatly from the intervention programme. This demonstrates that an exercise programme can be successfully implemented in a diverse group of patients and that the benefits that can be obtained remain the same. The diversity of COPD patients further necessitates the individualising of exercise programmes. It is important that exercise programmes should be tailored and adjusted to the specific needs of the patients.

Few previous studies have documented similar improvements in 6MWD. An earlier study (McGavin *et al.*, 1978) suggested that an improvement greater than 30m in the 6MWT could be considered a clinical improvement. Although this benchmark is still used by some studies (Boueri *et al.*, 2001), recently published studies showed that a clinical improvement could only be assumed when a change of 54m or more occurs (Enright *et al.*, 2003; ATS, 1999; Redelmeier *et al.*, 1997; Guyatt *et al.*, 1984). The mean improvements in the current study were 142m (SD ± 69.37m) in the PP, 99.09m (SD ± 46.14) in the experimental group and 138.57 (SD ± 88.21m) in the control group. This indicates that 86.36% of the subjects included in the PP, 81.81% of the subjects in the experimental group and 85.71% of the subjects in the control group had clinically significant improvements in the 6MWT from the first to the second evaluation. Compared to recent literature, this outcome was considerably better than previous studies. A study by Norweg and co-workers (2005) reported a 54m improvement in 6MWD after 15 exercise sessions that consisted mainly of aerobic exercise. Other studies that incorporated both strength and endurance training into their exercise routines failed to achieve a mean improvement of more than 54m in the 6MWT (Boueri *et al.*, 2001; Mador *et al.*, 2004). The primary difference between these studies and the current study was the duration of the intervention programme. Ringbaek and co-workers (2000) found that eight weeks of exercise training is insufficient to obtain a significant change in 6MWD. Another study with a similar design than the current study

reported a mean improvement of 113.1m (SD ± 17.8m) in the 6MWT after 12 weeks of exercise training (Benstrup *et al.*, 1997). The success of the present study suggests that a 12-week exercise programme that focuses on both aerobic and strength training is probably more effective in obtaining health benefits for COPD patients than the studies quoted above. Exercise programmes should also focus on educating COPD patients on safe exercise practices and techniques.

Pulmonary rehabilitation is very limited in South Africa and is currently only available in Stellenbosch and Johannesburg. Current programmes do not allow for training adequate numbers of professionals for pulmonary rehabilitation and is on average not accessible to the broader community. An added benefit of the current study was that various Biokineticists-in-training were trained to assist with the intervention programmes. This enables them to specialise in pulmonary rehabilitation and start their own pulmonary rehabilitation centres once they have finished their training. The networks and co-operation agreements that were established during this study will further contribute to the training of Biokineticists wanting to specialise in pulmonary rehabilitation. This would greatly benefit the accessibility of pulmonary rehabilitation in South Africa.

High costs and specialised equipment are some of the important factors that limit the availability of pulmonary rehabilitation programmes. This study showed that a more cost-effective programme could be successfully implemented with similar benefits than conventional programmes. Feedback received from subjects that followed the modified programme was very positive. Exercising outdoors was effective in eliciting an exercise response and subjects found it to be very enjoyable.

Important to the success of low costs programmes, are comprehensive pre- and post-exercise assessments. These evaluations are important to promote exercise adherence and to identify any co-morbidities that might place an individual at risk during exercise (ATS, 1995a). During a pre-exercise assessment, patients get a

clear understanding of their limitations as well as their capabilities. This assessment is vital in the formulation of clear exercise goals and to individualise exercise prescription (Johnson, 2004). Post-exercise assessments provide an opportunity to evaluate the goals that were set at the pre-assessment and make adjustments where necessary. Furthermore, it provides an opportunity for patients to quantify their progression and evaluate the effectiveness of the exercises, which is essential to exercise adherence (Turner *et al.*, 2004).

Another important factor that has been identified during the present study, is the scientific implementation of exercise programmes. Pulmonary rehabilitation has developed in recent years from an art to a defined medical science (ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, 1997). Scientific implementation is important to maximise the benefits that the patient can obtain. Due to the wide range of physical impairments seen in COPD patients during similar stages of the disease, exercise programmes should be tailored to each individual's capabilities and needs.

An additional factor that contributed to the success of the current programme is the constant individual supervision that the subjects received. Constant supervision is important to ensure that continuous feedback is given, high levels of motivation are maintained and necessary adjustments are made to exercises. These programmes should be supervised by qualified clinicians that are specialised in pulmonary rehabilitation. It is important that patients have confidence in these programmes and in the people that are administering it.

Due to the risk involved when exercising these patients, constant contact with the patient's medical doctor or physician is imperative. Silent ischaemic heart disease can be present in COPD patients, which can be a limiting factor to exercise and an imminent danger if undiagnosed, particularly early in the rehabilitation process. Another factor contributing to the success of the programme is the early identification and treatment of acute chest infections. If there is constant

interaction between the programme supervisors and the patients' doctors or physicians, early identification and treatment of exacerbations is inevitable.

Limitations

The data collection process stretched over a period of more than four years. Despite extensive efforts to recruit subjects for the study, a relatively small number of subjects were included. A major contributing factor, was the fact that the symptoms experienced by these patients fluctuate. Therefore, subjects were primarily recruited during the winter months. Typically, these patients are healthier during the warmer parts of the year and exacerbations are few. In developed countries, COPD is diagnosed earlier and has a higher health status, compared to South Africa. This contributes to the difficulties when studying this population in a developing country. Furthermore, it seems that a considerable portion of this population remains ignorant as to the disease and its impact on quality of life. There is a need in South Africa for education of the broader community on the risk factors, symptoms and treatment of COPD.

The small control group in the MP did limit data analyses. This was unforeseen, since a number of subjects included in the control group withdrew from the study. Due to the randomisation, the study leaders could not supplement this group. If a larger sample size is used in future research, this problem would be counteracted.

The small number of subjects from previously disadvantaged communities could be criticised. Although extensive recruitment campaigns were launched to recruit these individuals, there were a number of unforeseen factors that influenced the inclusion of these subjects, which should be addressed in future research. Typically, patients from previously disadvantaged communities continue working despite severe impairment, which makes it difficult for them to commit to a 12-week programme. Although transportation was provided to patients in the vicinity of Stellenbosch, a number of patients without regular transport came from farms and

areas that were too far to include. Unfavourable housing circumstances contribute to the frequency of exacerbations and the difficulty of exercising continuously. A number of social difficulties were also encountered. Although patients with known drug and alcohol addictions were excluded from the study, some subjects missed sessions due to alcohol misuse. A small number of domestic problems were also encountered, which further contributed to the difficulty of exercise adherence. In one subject new tuberculosis required withdrawal from the programme - another important problem to be faced when COPD rehabilitation is implemented among a population of low socio-economic status.

Despite all these obstacles, the few subjects from previously disadvantaged communities that did finish the study, responded extremely well to the exercise training. This population should definitely be considered for pulmonary rehabilitation and efforts are needed to improve the accessibility of programmes to this population.

Contributing to the importance of pulmonary rehabilitation in previously disadvantaged communities is the fact that many of these patients have to rely on their physical fitness to obtain daily provisions, since proper transport is not always available. Low-cost programmes that are readily accessible can greatly contribute to the inclusion of these patients in structured programmes. This particular programme could easily be used to successfully implement pulmonary rehabilitation programmes in community centres or church halls. In light of the challenges faced in previously disadvantaged communities, programmes should be designed to suit individual needs and must be flexible to accommodate external influences. A programme design that for example, incorporates home-based sessions in addition to supervised sessions, could add to the accessibility and adherence to programmes for patients that continue to work or have other responsibilities. Support of family members proved an obstacle in this study. Therefore, an information session with family members prior to commencing a programme, could further aid adherence.

In the MP, neither the subjects nor the supervisors of the training programmes were blinded towards the group randomisation. Biases could have existed towards a specific programme.

Although patients that require supplemental oxygen were included with great success into the PP, these patients had to be excluded from the MP. This was because of the assumption that supplemental oxygen is not readily available to the broader community, which implies that supplemental oxygen would fall beyond the borders of a cost-effective, community-orientated programme. Therefore, the results of the MP cannot be readily extrapolated to patients with more severe COPD. However, the PP showed that it is important to include severely impaired patients into these programmes. The oxygen apparatuses that were used in the PP were kindly supplied by Vital Aire. This kind of interaction needs to be expanded so that severely impaired patients from previously disadvantaged communities can benefit from pulmonary rehabilitation programmes.

The exercise programme that was followed by the experimental group was designed to be easily implemented into a low-cost setting. A possible limitation to the study design was that the pre- and post-walk tests were done on a treadmill. The decision to perform both the experimental and control group's 6MWTs on a treadmill, were made to ensure that the results obtained from the two groups were comparable. This could have put the experimental group at a disadvantage since the exercise programme did not include treadmill walking. This problem was partly compensated for by including a treadmill walk into the experimental group's training schedule every two weeks. This may however, have influenced the differentiation between the two programmes.

Future research and recommendations

Although it was not objectively measured, the casual observation was made that subjects from previously disadvantaged communities had better functional capabilities compared to other subjects with similar lung function impairment. Due to the small number of subjects from previously disadvantaged communities included in this study, no statistical comparisons could be made. This could be a potentially important opportunity for future research.

The present study focused on making pulmonary rehabilitation more accessible to the broader community. Further research is needed into the role and feasibility of home-based programmes in South Africa and the promotion of exercise adherence.

According to Jindah and co-workers (2006), the lack of consensus around terminology of airway obstruction accounts for a variance of 200% in the estimation of the prevalence of COPD. Research that is concerned with defining the characteristics of COPD is essential to completely understand the impact of this disease (Pauwels *et al.*, 2001). Very little data is available on the prevalence of COPD in South Africa. A comprehensive study into the epidemiology of this disease is vital to fully understand its impact.

Frequent exacerbations are one of the main obstacles to exercise adherence. Functional decline after exacerbations, due to exercise discontinuation, warrants further research into exercise maintenance despite recurring exacerbations (Gosselink, 2002; Foglio *et al.*, 2001).

One other important recommendation would be the inclusion of a mandatory community year for Biokineticists after the completion of their degree, similar to other medical and paramedical professions. This would greatly benefit the implementation of pulmonary rehabilitation in previously disadvantaged

communities, since qualified clinicians would be available to implement these programmes.

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APPENDICES

Appendix A

Borg RPE Scales (Borg, 1982)

Borg RPE scale		Modified Borg RPE scale	
6		0	Nothing at all
7	Very, very light	0.5	Very, very slight (just noticeable)
8		1	Very slight
9	Very light	2	Slight
10		3	Moderate
11	Fairly light	4	Somewhat severe
12		5	Severe
13	Somewhat hard	6	
14		7	Very severe
15	Hard	8	
16		9	Very, very severe (almost maximal)
17	Very hard	10	Maximal
18			
19	Very, very hard		
20			

Instructions for using the Borg RPE scale (ACSM, 2000:79):

> "During the exercise (test) we want you to pay close attention to how hard you feel the exercise work rate is. This feeling should reflect your total amount of exertion and fatigue, combining all sensations and feelings of physical stress, effort, and fatigue."

PULMONARY REHABILITATION PROGRAMME SHEET

	Date													
	BP													
	RHR													
Exercise	**Set/rep**	**Wght**	HR	RPE	HR	RPE	HR	RPE	HR	RPE	HR	RPE	HR	RPE
Treadmill; RPE = 5; (HR 60%-75%max)	10 min													
Stretch H Q C	3 x 15sec													
Hip flexion + knee ext	2 x 15													
Shoulder press	3 x 10													
Squats	3 x 10													
Bicep curls	3 x 10													
Getting up out of chair	3 x 10													
Standing pec push	3 x 10													
Standing hip twists	3 x 10													
Step ups	2 x 10													
Arm swings	2 x 10													
Leg swings	2 x 10													
Treadmill;; RPM = 5; (HR 40%-60%max)	10 min													
	BP													
	RHR													

Appendix B

PULMONARY REHABILITATION PROGRAMME SHEET – ADAPTED MODEL

	Date															
	BP															
	RHR															
Exercise	**Set/rep**	**Wght**	HR	RPE	HR	RPE	HR	RPE	HR	RPE	HR	RPE	HR	RPE	HR	RPE
Walking (flat terrain); RPE = 5; (HR 60%-75%max)	10 min															
Stretch H Q C	3 x 15sec															
Hip flexion + knee ext	2 x 15															
Shoulder press	3 x 10															
Squats	3 x 10															
Bicep curls	3 x 10															
Getting up out of chair	3 x 10															
Standing pec push	3 x 10															
Standing hip twists	3 x 10															
Step ups	2 x 10															
Arm swings	2 x 10															
Leg swings	2 x 10															
Walking (flat terrain); RPM = 5; (HR 40%-60%max)	10 min															
	BP															
	RHR															

Appendix C

Standardised Protocol for the 6MWT (ATS, 2002)

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A “warm-up” period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate.
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer’s instructions to maximize the signal and to minimize motion artefact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

Post-test:

1. Record the post-walk Borg dyspnoea, fatigue levels and ask this: “What, if anything, kept you from walking farther?”
2. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
3. Record the distance covered.
4. Congratulate the patient on good effort and offer a drink of water.

Appendix D

Patient information and consent documents: Primary programme

PATIENT INFORMATION AND CONSENT DOCUMENT

The influence of rehabilitation on the quality of life and exercise capacity of patients with chronic obstructive pulmonary disease (COPD)

You are invited to participate in a research project to determine what the influence of a rehabilitation programme will be on your quality of life and exercise capacity. The evaluations and rehabilitation programme will be monitored and managed by professional individuals.

You are aware that you are suffering from chronic obstructive pulmonary disease (COPD) and that your exercise capacity is impaired. For this reason, you are requested to participate in the study. It is important that you understand the reasons for the study and you are requested to pose appropriate questions to the physician in charge. You are requested to inform your personal practitioner of your participation in the study.

Purpose of the study

The condition known as COPD is an inflammatory process of the airways which is characterised by a wheeze and dyspnoea (shortness of breath). As a result of the impairment of your respiratory function, you have limited exercise capacity and this contributes to weakening of your thigh and chest muscles. The purpose of the rehabilitation programme is to strengthen these muscle groups and thereby improve your exercise tolerance without necessarily improving your lung function.

This process of rehabilitation will take place over a period of 12 weeks and will be scheduled for three days per week. It will be conducted under strict supervision of the professional staff of the Stellenbosch Biokinetics Centre, Stellenbosch University, who will encourage and motivate you to persevere with the programme. The study will be conducted according to international standards for medical research as determined by the ICH guidelines for good clinical practice and the declaration of Helsinki.

All training will take place under personal supervision of one or more honours students and/or biokineticist of the Department of Sport Science (Biokinetics) at the Stellenbosch Biokinetics Centre. If you are symptomatic and in need of therapy your doctor will be requested to put you on standard treatment for at least two weeks before joining the study.

You will remain on your standard medication as prescribed for your lung disease by your clinic or hospital. Smokers will not be excluded, but will be strongly urged throughout the study to abstain.

Permission of the project has been obtained form the Ethics Committee of the Faculty of Health Sciences of the University of Stellenbosch.

Requirements for participation

You will remain under the treatment of your own doctor who will handle incidents of acute exacerbations, hospitalisation and changes to your treatment. You are required to have transport to the Department of Sport Science, Stellenbosch University and will have to be telephonically contactable to be included in the study. Up to 50 patients will participate in the study.

Symptomatic COPD patients who get short of breath while walking on a flat surface or who are even more dyspnoeic will participate. The staging of the disease will be

determined by means of lung function tests, a set of questionnaires and a six minute walk test will be performed. During the walk test you will be encouraged to walk under supervision for as far as you can in a six minute period.

Evaluation: Day 1

You will report by appointment to the consulting rooms of Prof. J.R. Joubert at Rattray Lane 7, Stellenbosch. The consent from will be discussed and you will have the opportunity to pose questions and sign it. A clinical investigation will be conducted after which a standard in- and expiratory lung function test and ECG (heart investigation) will be conducted. Your body length to weight ratio (body mass index) which indicates the severity of your disease will be determined. During the lung function procedure, you will blow into a lung function apparatus. A six minute walk test will then be conducted under supervision of a clinical technologist. During the procedure, your blood oxygen saturation level (saturation) and pulse rate will be monitored. You can conduct the walk test by resting at intervals and you will complete it at your own exercise tempo. Should your blood oxygen saturation become to low during the initial six minute walk test (less than 80%) you will be excluded from the study. At completion of each six minute walk test, your opinion on your degree of exhaustion on a graded Borg scale will be required. Your ability to recover after exercise will be determined by measuring your pulse rate and speed of breathing immediately after, three, five and ten minutes after walking. In the event of you having signs of right heart failure or a combination of left and right heart failure, your doctor will be requested to administer treatment before the rehabilitation process commences. Should you suffer from angina or from uncontrolled hypertension you will be referred to your doctor to be treated accordingly. General advice in connection with the disease, the occurrence of complications, particularly acute exacerbations, as well as when to report to your doctor, will be discussed.

Rehabilitation programme

You will report to the Stellenbosch Biokinetics Centre at Coetzenburg per appointment. The process of rehabilitation will be explained and demonstrated. You will complete the St. Georges Respiratory Questionnaire under supervision, according to which your quality of life and degree of impairment based on history will be determined. You will participate in the rehabilitation programme as an individual. The exercise programme will be conducted on three to five weekdays and will be maintained for 12 weeks. Every session will last for about one hour. Should you indicate that you would not be able to participate uninterrupted to a 12 week period, you will not be included in the study. It is very important that you attend the rehabilitation programme uninterrupted and should you miss more than six appointments, your participation will be terminated. Goals will be set throughout and you will be encouraged to attain them. Should you encounter a temporary exacerbation of your disease, you will not participate in the daily exercise programme and your doctor will be required to do a re-evaluation. The exercise programme will be determined from your own baseline functional ability and you will compete with no one in your group. The exercise programme consists of walking exercises and muscle strengthening with the help of appropriate exercise apparatus. After the 12-week exercise programme, you will receive advice on how to continue with the exercises on your own. The aim of this is to be able to evaluate the patients again six months after the exercise programme has ended, in order to determine how many individuals in the group were able to maintain their fitness level.

Evaluation: Day 2

After completion of the 12-week rehabilitation, the St. Georges Respiratory Questionnaire will be repeated to determine the improvement of your quality of life. You will once again report by appointment to the consulting rooms of Prof. J.R. Joubert. The evaluation that was done initially will be repeated. Your Borg rating

and recovery will once again be determined. Your body mass to length ratio will also be repeated. By this means it will be determined how well you have improved on rehabilitation.

Evaluation: Day 3

You will report again by appointment at the consulting rooms of Prof. J.R. Joubert. The evaluation that was done initially will be repeated. Your Borg rating and recovery will once again be determined. Your body mass to length ratio will also be repeated. By this means, it will be determined how well you have improved on rehabilitation. You will be referred back to your physician who will follow-up on your disease symptoms, acute exacerbations and hospitalisations over the last six months.

Voluntary participation

You should participate voluntary. Should you find it impossible to continue, you may withdraw from the study. In this case, we will request that you attend the final evaluation. Discontinuation of participation will not influence the normal treatment of the disease or an exercise programme which you may choose to follow.

Risks and possible advantages

Weariness after an exercise session and possible stiffness of muscles may be encountered. Risks such as angina incidents, disturbances of heart rhythm or a possibility of myocardial infarctions (heart attack) cannot be excluded. To prevent these complications the exercise programme will be adapted to suit each individual's exercise tolerance, or individuals at risk will be excluded until adequate treatment has been implemented.

Advantages include an improvement of exercise tolerance of every day tasks and more confidence in your own ability to participate in physical activity. An improved quality of life as determined by an objective measurement, the St. George's Respiratory Questionnaire, may also be evident. Decline in the number of acute exacerbations of the disease and days spent in hospital have been shown in a number of studies. You will learn a number of facts relating to your disease and will be given practical advice on daily preventative measures.

Medical supervision will be available during the rehabilitation programme. A doctor will not be physically present, but telephonic contact will be maintained and a doctor will be available within five to ten minutes. Prof. J.R. Joubert can be contacted during working hours (9:00 – 17:00) on (021) 886 7194 or after hours at (021) 887 1785. The Student Health Service's doctors are present in the gymnasium, or are available at (021) 808 3496.

There is no cost involved for the evaluation process or the rehabilitation programme.

Confidentiality

All information will be treated confidentially and you will have the opportunity to review your own results as requested. Your doctor will be kept informed as to the progress of the project and will receive a final report. The results may be reported anonymously, may be presented at national or international level and publications may be forthcoming. Your identity will be treated as confidential at all times and your name will not be associated with the results which may be made public.

Insurance

Insurance cover will not be taken for the study as rehabilitation of COPD patients is accepted as an international procedure. You are requested to inform your own insurance company of your participation in the study.

PATIENT CONSENT DOCUMENT

The information above was provided by ……. (name of relevant person) in English and I understand the language well. I was given an opportunity to ask questions and all the questions were answered to my satisfaction.

No pressure was placed on me to agree to participate and I understand that my participation may be withdrawn at any time without penalisation.

Participation in the project will be at no additional cost to me.

I agree voluntarily to participate in the above mentioned project.

Signed / agreed upon at …… on ……..20….
(place) (date)

…… ……..
Signature of patient Signature of witness

STATEMENT BY OR ON BEHALF OF RESEARCHER(S)

I …….. Declare that I (we):

Explained the information in the document to ……..

Encouraged him/her to at his/her leisure pose questions

This conversation took place in English without an interpreter.

Signed at …… on ……..…20……

(place) (date)

…… ……..…

Signature of Researcher or his representative Signature of witness

(This document was available in English and Afrikaans)

Patient information and consent documents: Modified programme

PATIENT INFORMATION AND CONSENT DOCUMENT

The influence of rehabilitation by two different techniques on the quality of life and functional capacity of patients with chronic obstructive pulmonary disease (COPD)

You are invited to participate in a research project to determine what the influence of rehabilitation by one of two techniques will be on your quality of life and functional ability. The evaluations and rehabilitation programme will be monitored and managed by professional individuals.

You are aware that you are suffering from chronic obstructive pulmonary disease (COPD) and that your exercise capacity is impaired. For this reason, you are requested to participate in the study. It is important that you understand the reasons for the study and you are requested to pose appropriate questions to the physician in charge. You are requested to inform your personal practitioner of your participation in the study.

Purpose of the study

The condition known as COPD is an inflammatory process of the airways which is characterised by a wheeze and dyspnoea (shortness of breath). As a result of the impairment of your respiratory function, you have limited exercise capacity and this contributes to weakening of your thigh and chest muscles. The purpose of the rehabilitation programme is to strengthen these muscle groups and thereby improve your exercise tolerance without necessarily improving your lung function.

This process of rehabilitation will take place over a period of ten weeks and will be scheduled for three days per week. It will be conducted under strict supervision of

the professional staff of the Stellenbosch Biokinetics Centre, Stellenbosch University, who will encourage and motivate you to persevere with the programme. The study will be conducted according to international standards for medical research as determined by the ICH guidelines for good clinical practice and the declaration of Helsinki.

A primary purpose of the study is to determine whether the same degree of fitness can be achieved by training with generally available and cheap methods, such as walking and using sand bags, as with sophisticated gymnasium apparatus. At the end of the study, we may be able to develop an affordable community training programme which could replace the more expensive gymnasium orientated programmes. All training will take place under personal supervision of one or more honours students and/or biokineticist of the Department of Sport Science (Biokinetics) at the Stellenbosch Biokinetics Centre. Individuals will be enlisted voluntarily from predominantly deprived communities by means of the municipal clinics and Stellenbosch Hospital. Patients from the advantaged group will also be allowed to join the study although no recruitment campaign will be launched for this purpose. Individuals will be placed in one of the two exercise groups by random assignment. You will remain in this group for the duration of the study. If your are symptomatic and in need of therapy your doctor will be requested to put you on standard treatment for at least two weeks before joining the study.

You will remain on your standard medication as prescribed for your lung disease by your clinic or hospital. Smokers will not be excluded, but will be strongly urged throughout the study to abstain.

Permission of the project has been obtained form the Ethics Committee of the Faculty of Health Sciences of the University of Stellenbosch.

Requirements for participation

You will remain under the treatment of your own doctor who will handle incidents of acute exacerbations, hospitalisation and changes to your treatment. You will be transported to and from your local clinic or neighbourhood to the Stellenbosch Biokinetics Centre at Coetzenburg at no cost. You will have to be telephonically contactable to be included in the study. Up to 50 patients will participate in the study.

Symptomatic COPD patients who get short of breath while walking on a flat surface or who are even more dyspnoeic, will participate. The staging of the disease will be determined by means of lung function tests, a set of questionnaires and a six minute walk test will be performed. During the walk test, you will be encouraged to walk under supervision for as far as you can in a six minute period.

Pre evaluation

Once your clinic or hospital doctor has identified you, trained nurses from the Embrace Nursing Service will meet you by appointment at your clinic, hospital or home. By means of some questions, a preliminary clinical evaluation and a lung function measurement will be done and they will invite you to attend a first meeting with the rehabilitation team at the rooms of Prof. J.R. Joubert. This does not mean that you have been automatically included, as a second evaluation by means of more sophisticated techniques, has to take place after the procedures have been explained in depth and you have signed an informed consent document. Once this has been done and you fulfil the programme requirements, the study can proceed.

Evaluation: Day 1

You will report by appointment to the consulting rooms of Prof. J.R. Joubert at Rattray Lane 7, Stellenbosch. The consent form will be discussed and you will

have the opportunity to pose questions and sign this form. A clinical investigation will be conducted, after which a standard in- and expiratory lung function test and ECG (heart investigation) will be conducted. Your body length to weight ratio (body mass index) which indicates the severity of your disease, will be determined. During the lung function procedure, you will blow into a lung function apparatus. A six minute walk test will then be conducted under supervision of a clinical technologist. During the procedure, your blood oxygen saturation level (saturation) and pulse rate will be monitored. You can conduct the walk test by resting at intervals and you will complete it at your own exercise tempo. Should your blood oxygen saturation become too low during the initial six minute walk test, (less than 80%) you will be excluded from the study. At completion of each six minute walk test, your opinion on your degree of exhaustion on a graded Borg scale will be required. Your ability to recover after exercise will be determined by measuring your pulse rate and speed of breathing immediately after, three, five and ten minutes after walking. In the event of you having signs of right heart failure or a combination of left and right heart failure your doctor will be requested to administer treatment before the rehabilitation process commences. Should you suffer from angina or from uncontrolled hypertension you will be referred to your doctor to be treated accordingly. General advice in connection with the disease, the occurrence of complications particularly acute exacerbations, as well as when to report to your doctor, will be discussed.

Rehabilitation programme

You will report to the Stellenbosch Biokinetics Centre at Coetzenburg per appointment. The process of rehabilitation will be explained and demonstrated. You will complete the St. Georges Respiratory Questionnaire under supervision, according to which your quality of life and degree of impairment based on history will be determined. You will participate in the rehabilitation programme as an individual. The exercise programme will be conducted on three to five weekdays and will be maintained for a minimum period of eight weeks. Every session will last

for about one hour. Should you indicate that you would not be able to participate uninterrupted to a ten week period, you will not be included in the study. It is very important that you attend the rehabilitation programme uninterrupted and should you miss more than six appointments, your participation will be terminated. Goals will be set throughout and you will be encouraged to attain them. Should you encounter a temporary exacerbation of your disease, you will not participate in the daily exercise programme and your doctor will be required to do a re-evaluation. The exercise programme will be determined from your own baseline functional ability and you will compete with no one in your group. For the gymnasium group the exercise programme consists of walking exercises and muscle strengthening with the help of appropriate exercise apparatus. The community training programme will walk Coetzenburg fields (or indoors if the weather is unfavourable) and do muscle training with light objects such as small sand bags.

Evaluation: Day 2

After completion of the ten week rehabilitation, the St. Georges Respiratory Questionnaire will be repeated to determine the improvement of your quality of life. You will once again report by appointment to the consulting rooms of Prof. J.R. Joubert. The evaluation that was done initially will be repeated. Your Borg rating and recovery will once again be determined. Your body mass to length ratio will also be repeated. By this means, it will be determined how well you have improved on rehabilitation.

Voluntary participation

You should participate voluntary. Should you find it impossible to continue, you may withdraw from the study. In this case, we will request that you attend the final evaluation. Discontinuation of participation will not influence the normal treatment of the disease or an exercise programme which you may choose to follow.

Risks and possible advantages

Weariness after an exercise session and possible stiffness of muscles may be encountered. Risks such as angina incidents, disturbances of heart rhythm or a possibility of myocardial infarctions (heart attack) cannot be excluded. To prevent these complications the exercise programme will be adapted to suit each individual's exercise tolerance, or individuals at risk will be excluded until adequate treatment has been implemented.

Advantages include an improvement of exercise tolerance of every day tasks and more confidence in your own ability to participate in physical activity. An improved quality of life as determined by an objective measurement, the St. George's Respiratory Questionnaire, may also be evident. Decline in the number of acute exacerbations of the disease and days spent in hospital have been shown in a number of studies. You will learn a number of facts relating to your disease and will be given practical advice on daily preventative measures.

Medical supervision will be available during the rehabilitation programme. A doctor will not be physically present, but telephonic contact will be maintained and a doctor will be available within five to ten minutes. Prof. J.R. Joubert can be contacted during working hours (9:00 – 17:00) on (021) 886 7194 or after hours at (021) 887 1785. The Student Health Service doctors are present in the gymnasium, or are available at (021) 808 3496.

There is no cost involved for the evaluation process or the rehabilitation programme. Your transport will be arranged to and from your clinic or neighbourhood by appointment only, at no cost.

Confidentiality

All information will be treated confidentially and you will have the opportunity to review your own results as requested. Your doctor will be kept informed as to the progress of the project and will receive a final report. The results may be reported anonymously, may be presented at national or international level and publications may be forthcoming. Your identity will be treated as confidential at all times and your name will not be associated with the results which may be made public.

Insurance

Insurance cover will not be taken for the study as rehabilitation of COPD patients is accepted as an international procedure. You are requested to inform your own insurance company of your participation in the study.

PATIENT CONSENT DOCUMENT

The information above was provided by ……. (name of relevant person) in English and I understand the language well. I was given an opportunity to ask questions and all the questions were answered to my satisfaction.

No pressure was placed on me to agree to participate and I understand that my participation may be withdrawn at any time without penalisation.

Participation in the project will be at no additional cost to me.

I agree voluntarily to participate in the above mentioned project.

Signed / agreed upon at …… on …….....20….
(place) (date)

…… ……..
Signature of patient Signature of witness

STATEMENT BY OR ON BEHALF OF RESEARCHER(S)

I …….. Declare that I (we):

Explained the information in the document to ……..

Encouraged him/her to at his/her leisure pose questions

This conversation took place in English without an interpreter.

Signed at …… on ……..…20……

(place) (date)

…… ……..…

Signature of Researcher or his representative Signature of witness

(This document was available in English and Afrikaans)

Appendix E

Standard Karvonen Formula (ACSM, 2000:189-190).

$$THR = (HR_{max} - HR_{rest})\ (target\ \%) + HR_{rest}$$

- THR = training heart rate
- HR_{max} = 220 – age
- Target % = required intensity i.e. 75%

Appendix F

The SGRQ: Guide to administration and calculations (Jones, 1991)

What is the St. George's Respiratory Questionnaire?

The St. George's Respiratory Questionnaire (SGRQ) is designed to measure health-related quality of life, which is the impact that chest disease has on daily life and wellbeing. Asthma, chronic bronchitis and emphysema can cause major disturbances to daily life, which vary from person to person regardless of lung function.

How should it be administered?

The questionnaires should be completed in a quiet room and the patient should be sitting at a desk or table. If the spouse had accompanied the patient, try to separate them. It is important that the patient complete the SGRQ themselves, without any advice from their partner.

Explain to the patient why they are completing the questionnaire and how important it is for us to understand how they feel about their illness and the affect it has on their day-to-day lives. The SGRQ is designed as a supervised, self-administered questionnaire. This means that the patients should complete the SGRQ themselves, but someone must be available to give advice if it is needed.

Ask the patient to complete the SGRQ as honestly as they can and stress that there are no right and wrong answers, simply the answer that the patient thinks applies to them best. Explain that they must answer every question and that someone will be close at hand to answer any queries.

Do not let the patients take the SGRQ home to be completed. It is important that it is done in the presence of the investigator and that you can be sure it is answered by the patient alone without the help of his/her family.

What should I do about queries?

Answers to some possible queries are given in the guide to completing the SGRQ; beneath each question. Read through this before seeing the patient. It is worth being prepared.

If the patient asks you to help them answer a question, don't give them an answer. The point of quality of life questionnaires is to get an understanding of how the patient views his/her illness. Simply readdress the question back to them.

Questions may be read out to patients who have difficulty in reading, but the responses must be theirs alone.

What should I do when the SGRQ has been completed?

Once the patient has completed the questionnaire, read through to check that each and every question has been answered. Don't send the patient away before you have done this. If any questions have been left unanswered, point them out to the patient and ask for answers.

If you see an answer that you disagree with, e.g. the patient tick off that he/she coughs a few days a month and you know that they cough more often, do not question its accuracy. By asking the patient "are you sure this is right?" you are more or less telling them that you think it is wrong. Since you are the expert, they may change their answer to agree with you, even though they still may feel that their first answer was right.

Finally, thank the patient for their time and again stress how important and useful this information is.

Calculation method for the SGRQ

Three component scores are calculated: Symptoms; Activity; Impacts. One total score is also calculated. Each questionnaire response has a unique empirical derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in two groups:

i. The weights for all items with a positive response are summed.
ii. The score is calculated by dividing the summed weights by the maximum possible weight for that component and expressing the result as a percentage:

Score = 100 x Summed weights from positive items in that component / Sum of weights for all items in that component

The total score in calculated in similar way:

Score = 100 x Summed weights from positive items in the questionnaire / Sum of weights for all items in the questionnaire

Sum of maximum possible weights for each component and Total (these are the maximum possible weights that could be obtained for the worst possible state of the patient:

Symptoms	662.5
Activity	1209.1
Impacts	2117.8
Total	3989.4

Symptom component

This consists of all the questions in Part I. The weights for Question 1 to 8 are summed. It will be noted that the questionnaire requests a single response to Questions 1 to 7. If multiple responses are given to a question, then averaging the weights for the positive responses for that question is acceptable.

Activity component

This calculated from the summed weights for the positive responses to Section 2 and Section 6 in Part 2 of the questionnaire.

Impacts component

This is calculated from Sections 1, 3, 4, 5 and 7. Again it will be noted from the questionnaire that a single response is required fro the two parts of Section 1 and the last part of Section 7. In the case of multiple responses, the mean weights for any multiple responses to these parts are used.

Total score

The Total score is calculated by summing all the positive responses in the questionnaire and expressing the result as a percentage of weights for all items in the questionnaire.

Handling missing items

It is better not to miss items and any missing items are the fault of the experimenter, not the patient. The following methods are recommended:

Part I

Missed items are treated as if the answer was in the negative.

Part II

Items in Sections 2, 3, 4, 5, 6 and first part of section 7 all require a response of either ‘True’ or ‘False’. If neither box is ticked, the item should be coded as ‘missing’. If this approach is to be used, the scoring program should be written so that when an item is coded as ‘missing’ the weight for that item is subtracted from the total possible weight for the component of the questionnaire and from the Total weight.

This method has been carefully tested and it was found to be a reliable method for up to 10 missed items in Part II of the questionnaire.

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems.

PART 1

Questions about how much chest trouble you have had over the last 3 months. Please tick in <u>one</u> box for each question.

		most days of the week	several days of the week	a few days a week	only with chest infections	not at all
1)	Over the last 3 months I have coughed:	☐	☐	☐	☐	☐
2)	Over the last 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3)	Over the last 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4)	Over the last 3 months, I have attacks of wheezing:	☐	☐	☐	☐	☐

5) Over the last 3 months, how many severe or very severe unpleasant attacks of chest trouble have you had?

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6) How long did the worst attack of chest trouble last? (Go to Question 7 if you had no attacks)

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7) Over the last 3 months, in an average week, how many good days (with little chest trouble) have you had?

- no good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8) If you have wheeze, is it worse in the morning?

- no ☐
- yes ☐

PART 2

SECTION 1

How would you describe your chest conditions? (Please tick in one box only)

	TRUE	FALSE
the most important problem that I have	☐	☐
causes me quite a few problems	☐	☐
causes me a few problems	☐	☐
causes no problems	☐	☐

If you have ever had paid employment, please tick one of these:

	TRUE	FALSE
my chest trouble made me stop my work	☐	☐
my chest trouble interfered with my work or made me change my work	☐	☐
my chest trouble does not affect my work	☐	☐

SECTION 2

Questions about what activities usually make you feel breathless these days. For each item, please tick either true or false as it applies to you.

	TRUE	FALSE
sitting or lying still	☐	☐
getting washed or dressed	☐	☐
walking around the home	☐	☐
walking outside on a level surface	☐	☐
walking up a flight of stairs	☐	☐
walking hills	☐	☐
playing sports or games	☐	☐

SECTION 3

Some more questions about your cough and breathlessness these days. For each item, please tick either true or false as it applies to you.

	TRUE	FALSE
my cough or breathing disturbs my sleep	☐	☐
my cough makes me tired	☐	☐
my cough hurts	☐	☐
I get exhausted easily	☐	☐
I am breathless when I walk	☐	☐
I am breathless when I bend over	☐	☐

SECTION 4

Questions about other effects that your chest trouble may have on you these days. Please tick either true or false as it applies to you.

	TRUE	FALSE
my coughing or breathing is embarrassing in public	☐	☐
my chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

SECTION 5

Questions about your medication. If you are receiving no medication go straight to Section 6. To complete this section, please tick either true or false as it applies to you.

	TRUE	FALSE
my medication does not help me very much	☐	☐
I get embarrassed using my medication	☐	☐
I have unpleasant side effects from my medication	☐	☐
my medication interferes with my life a lot	☐	☐

SECTION 6

These are questions about how your activities might be affected by your breathing. For each question, please tick true if one or more parts apply to you because of your breathing, otherwise tick false.

	TRUE	FALSE
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
jobs such as housework take a long time, or I have to stop for rests	☐	☐
if I walk up one flight of stairs, I have to go slowly or stop	☐	☐
if I hurry or walk fast, I have to stop or slow down	☐	☐
my breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening, such as weeding, dance, play bowls or golf	☐	☐
my breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles an hour, play tennis or swim	☐	☐
my breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

SECTION 7

We would like to know how your chest trouble usually affects your daily life. Please tick either true or false as it applies to you because of your chest trouble. (Remember that true only applies to you if you cannot do something because of your breathing)

	TRUE	FALSE
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

Here is a list of other activities that your chest trouble may prevent you from doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

going out for walks or walking the dog

doing things at home or in the garden

sexual intercourse

going to church, or place of entertainment

going out in bad weather or into smoky rooms

visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you from doing:

_____

_____

_____

Now, would you tick in the box (one only) which you think best describes how your chest affects you:

it does not stop me doing anything I would like to you	☐
it stops me doing one or two things I would like to do	☐
it stops me doing most of the things I would like to do	☐
it stops me doing everything I would like to do	☐

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE. BEFORE YOU FINISH WOULD YOU PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED ALL THE QUESTIONS.

Appendix G

The baseline and transitional indexes (BDI/TDI) (Mahler *et al.*, 1984)

BASELINE DYSPNOEA INDEX

Functional Impairment

_____ Grade 4: No Impairment. Able to carry out usual activities and occupation without shortness of breath.

_____ Grade 3: Slight Impairment. Distinct impairment in at least one activity, but no activities completely abandoned. Reduction in activity at work or in usual activities that seem slight or not clearly caused by shortness of breath.

_____ Grade 2: Moderate Impairment. Patient has changed jobs and/or has abandoned at least one usual activity due to shortness of breath.

_____ Grade 1: Severe Impairment. Patient unable to work or give up most or all customary activities due to shortness of breath.

_____ Grade 0: Very Severe Impairment. Unable to work and has given up most or all customary activities due to shortness of breath.

_____ W: Amount uncertain. Patient is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.

_____ X: Unknown. Information unavailable regarding impairment.

_____ Y: Impaired for reasons other than shortness of breath. For example, musculoskeletal problems or chest pain.

Magnitude of Task

_____ Grade 4: Extraordinary. Becomes short of breath only with extraordinary activity, such as carrying heavy loads on the level, lighter loads uphill, or running. No shortness of breath with ordinary tasks.

_____ Grade 3: Major. Becomes short of breath only with major activities such as walking up a steep hill, climbing more than three flights of stairs or carrying a moderate load on the level.

_____ Grade 2: Moderate. Becomes short of breath with moderate or average tasks, such as walking up a gradual hill, climbing less than three flights of stairs or carrying a light load on the level.

_____ Grade 1: Light. Becomes short of breath with light activities, such as walking on a level surface, washing, standing or shopping

_____ Grade 0: No Task. Becomes short of breath at rest, while sitting, or lying down.

_____ W: Amount Uncertain. Patient has limited exertional capacity due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.

_____ X: Unknown. Information unavailable regarding limitation of magnitude of task.

_____ Y: Impaired for reasons other than shortness of breath. For example, musculoskeletal problems or chest pain.

Magnitude of Effort

_____ Grade 4: Extraordinary. Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.

_____ Grade 3: Major. Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.

_____ Grade 2: Moderate. Becomes short of breath with moderate effort. Tasks performed with occasional pauses and requiring longer to complete than the average person.

_____ Grade 1: Light. Becomes short of breath with little effort. Tasks performed with little effort or more difficult tasks with frequent pauses and requiring 50 to 100 percent longer to complete than the average person might require.

_____ Grade 0: No Effort. Becomes short of breath at rest while sitting, or lying down.

_____ W: Amount Uncertain. Patient has limited exertional capacity due to shortness of breath, but amount cannot be specified. Details not sufficient to allow impairment to be categorised.

_____ X: Unknown. Information unavailable regarding limitation of effort.

_____ Y: Impaired or reasons other than shortness of breath. For example, musculoskeletal problems or chest pain.

WORKSHEET TO BE USED FOR ASSEMENT OF BDI

Dyspnoea recordings:		Date:	Patient's Initials:
	FUNCTIONAL IMPAIRMENT	MAGNITUDE OF TASK	MAGNITUDE OF EFFORT
Job			
Housework, shopping			
Leisure activities, gardening			
Social activities			
Washing, dressing			
At rest			
Any other			
BDI SCORE: 0 - 4	Functional impairment:	Magnitude of task:	Magnitude of effort:

TOTAL: /12

TRANSITIONAL DYSPNOEA INDEX

Change in Functional Impairment

_____ -3: Major Deterioration. Formerly working and has had to stop working and has completely abandoned some of the usual activities due to shortness of breath.

_____ -2: Moderate Deterioration. Formerly working and has had to stop working or has completely abandoned some to the usual activities due to shortness of breath.

_____ -1: Minor Deterioration. Has changed to a lighter job and/or has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.

_____ 0: No Change. No change in functional status due to shortness of breath.

_____ +1: Minor Improvement. Able to return to work at reduced pace or has resumed some customary activities with more vigour than previously due to improvement in shortness of breath.

_____ +2: Moderate Improvement. Able to return to work at former pace and/or able to return to most activities with moderate restriction only.

_____ +3: Major Improvement. Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.

_____ Z: Further impairment for reasons other that shortness of breath. Patient has stopped working, reduced work, or has given up or reduced other activities for other reasons. For example, other medical problems, being "laid off" from work, etc.

Magnitude of Task

_____ -3: Major Deterioration. Has deteriorated two grades or greater from baseline status.

_____ -2: Moderate Deterioration. Has deteriorated at least one grade but less than two grades from baseline.

_____ -1: Minor Deterioration. Has deteriorated less than one grade from baseline. Patient with distinct deterioration within grade, but has not changed grades.

_____ 0: No Change. No change from baseline.

_____ +1: Minor Improvement. Has improved less than one grade from baseline. Patient with distinct improvement within grade, but has not changed grades.

_____ +2: Moderate Improvement. Has improved at least one grade but less than two grades from baseline.

_____ +3: Major Improvement. Has improved two grades or greater from baseline.

_____ Z: Further impairment for reasons other than shortness of breath. Patient has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problems or chest pain.

Magnitude of Effort

_____ -3: Major Deterioration. Severe decrease in effort from baseline to avoid shortness of breath. Activities now take 50 to 100% longer to complete than required at baseline.

_____ -2: Moderate Deterioration. Some decrease in effort to avoid shortness of breath, although not as great as preceding category. There is greater pausing with some activities.

_____ -1: Minor Deterioration. Does not require more pauses to avoid shortness of breath, but does things with distinctly less effort than previously to avoid breathlessness.

_____ 0: No Change. No change in effort to avoid shortness of breath.

_____ +1: Minor Improvement. Able to do things with distinctly greater effort without shortness of breath. For example, may be able to carry out tasks somewhat more rapidly than previously.

_____ +2: Moderate Improvement. Able to do things with fewer pauses and distinctly greater effort without shortness of breath. Improvement is greater than preceding category.

_____ +3: Major Improvement. Able to do things with much greater effort than previously with few, if any, pauses. For example, activities may be performed 50 to 100% more rapidly than at baseline.

_____ Z: Further impairment for reasons other than shortness of breath. Patient has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problems or chest pain.

WORKSHEET TO BE USED FOR ASSEMENT OF TDI

Dyspnoea recordings:		Date:	Patient's Initials:
	FUNCTIONAL IMPAIRMENT	MAGNITUDE OF TASK	MAGNITUDE OF EFFORT
Job			
Housework, shopping			
Leisure activities, gardening			
Social activities			
Washing, dressing			
At rest			
Any other			
BDI SCORE: -3 - +3	Functional impairment:	Magnitude of task:	Magnitude of effort:
			TOTAL: /-9 - +9

Instructions for administration of Baseline and Transitional Dyspnoea Index

The objective of the Baseline and Transitional Dyspnoea Indexes is to measure the severity of breathlessness (sensation of breathlessness, shortness of breath) in symptomatic patients. The Baseline Dyspnoea Index (BDI) measures the severity of dyspnoea at the beginning of a trial and the Transitional Dyspnoea Index (TDI) evaluates changes from this baseline (transition period). The test is applicable to patients with dyspnoea on exertion or at rest, due to respiratory disease. Administration of this index should be undertaken before any lung physiologic measurement on the test day and the interviewer must be blinded to other parameters evaluated for this patient.

The dyspnoea indices were devised such that grading breathlessness could be performed as part of obtaining a history from the patient. The indices include the categories “functional impairment”, “magnitude of task” and “magnitude of effort”, which provoke breathlessness. The interviewer asks specific questions based on the criteria of the various grades of impairment or change in the mentioned categories. This approach was selected instead of a questionnaire answered by the patient himself in order to allow an interviewer with medical training or background to grade breathlessness in a simple and brief encounter.

The BDI and TDI are composed of the three categories mentioned. The BDI includes five grades of severity, from zero (severe) to four (unimpaired) and the categories are summed up to create the focal score (zero to twelve). The TDI ranges from minus three (major deterioration) to plus three (major improvement) including zero score to indicate “no change”. Also for the TDI, the three categories are added to obtain a focal score ranging from minus nine, including zero, to plus nine. Provision is made for circumstances when dyspnoea cannot be rated: In the BDI, score “W” if no/insufficient information exists; or “Y if the patient’s capacity is compromised by factors other than breathlessness. In the TDI, score “Z” if

reduction of activities, effort or functional impairment is caused by reasons other than breathlessness.

An interviewer, who should be experienced in history taking for respiratory disease, administers the test. The interviewer should be a physician, nurse, respiratory therapist, cardiopulmonary technician or have similar qualifications with advanced knowledge or training concerning dyspnoea in respiratory disease. Evaluation and scoring are performed during the interview and need the same level of experience. It is preferred that the same person conducts all evaluations for each patient.

The initial question addressed to the subject should be “Do you experience shortness of breath?” If the subject answers “No”, then the interviewer should ask whether any physical activities cause the subject to experience breathlessness. If the answer to the questions is “Yes”, then additional questions follow to achieve the specific grading. Questions concerning the patient’s shortness of breath should be open-ended and concentrate on how the shortness of breath affects his/her daily life, e.g. the maintenance or upkeep of residence, gardening or shopping. The interviewer should focus on the specific criteria for the severity of breathlessness as specified in the indices and the patient should be rated based on the responses to the questions. The interviewer circles one answer in the index that best describes how the patient’s daily activities are affected by his/her respiratory disease.

The interview process at each visit (baseline and follow-up) should not take longer than five minutes.

At the baseline visit (BDI)

Functional Impairment:

The first component focuses on finding out which type of everyday life functions, at home or in his/her job, the patient is still able to perform. Are there any activities that he/she has had to give up or change due to his/her shortness of breath, compared to the level of activity before the onset of his respiratory disease (e.g. can he/she mow the lawn or do house work, can he/she climb the stairs to the office or apartment as previously, can he/she walk uphill or cycle as previously, can he/she do the shopping, can he/she dress him/herself, can he/she care for the pet?). It is important that the interviewer takes notes of the type of activities and the attached form may serve as an example of a record of the identified events that can be referred to at follow-up visits for the TDI. Circle the grade of impairment in the BDI.

Magnitude of Task:

The second component focuses on the level and extent to which the individual can perform tasks until breathlessness is noticed. Again, it is important to record the level on the form to be able to compare at follow-up visits. Ask which activities make the patient feels breathless (e.g. to what extent can he/she do the daily household chores, can he/she mow 30sqm of lawn or what portion, can he/she cycle on ground level, gentle slopes uphill, moderate slopes uphill, which distance can he/she walk). Provide the examples of the various grades and then circle a grade for magnitude of task.

Magnitude of Effort:

The third component focuses on the level of effort (exertion, vigour) that can be invested to perform the individual tasks. Again allude to individual tasks and define

that effort that makes a patient feel breathless (e.g. shortness of breath only with extraordinary effort when mowing the lawn, or can just be done at normal pace, or can do it very slowly, or needs many pauses, can do house work as rapidly as usual, or takes much longer than previously, or needs many pauses). Again, it is important to take notes of examples of the various grades for the magnitude of effort from the index and circle one.

At Follow-up Visits (TDI)

The TDI measures change from the baseline state in the three categories. The interviewer refers to his records of the individual patient's reported activities that result in breathlessness, the magnitude of the task required to evoke breathlessness and the effort of performance possible. The record sheet and grades from the BDI serve as references and for reminding the interviewer, as well as the patient, of his/her selections before selecting a grade from the TDI. At each follow-up visit, the interviewer refers back to the BDI and his original records and the previous TDI.

Change in Functional Impairment:

Review with the patient his/her functional status and the types of activities performed as recorded at baseline. Ask the patient if there are any changes or modifications in his/her activities since the baseline visit (e.g., has he/she given up or taken up any activities). Select a score from the index based on these changes, or circle zero if unchanged.

Magnitude of Task:

Review the level, i.e. magnitude of the specified activities that cause breathlessness. Ask the patient which level now causes breathlessness and if there is any change from baseline (e.g. can he/she climb less or more flight or

stairs, can he/she walk longer or less, can he/she walk steeper or less steep slopes than recorded at the baseline visit?). Select a grade from the index, considering that a change of plus/minus one should indicate the minimum that can be recognised by the patient, a plus/minus three means a major change and plus/minus two mean any change in-between.

Magnitude of Effort:

Review with the patient the effort (exertion, vigour) he/she was able to perform at baseline with the recorded activities, until he/she experienced breathlessness. Ask the patient how much effort now causes breathlessness and whether there is a change from baseline [e.g. does it take more or less time for certain activities, does he/she need to take less or more pauses and can he perform with more or less effort (exertion, vigour)?]. Circle a grade for change in the index or select zero if there was no change.

Appendix H

Physician's Global Evaluation

It is preferred that the same person conducts all evaluations for the patient. This evaluation MUST be completed prior to pulmonary function testing. It reflects the investigator's assessment of the overall condition of the patient's disease.

Circle only one appropriate response below.

Poor			Fair		Good		Excellent
1	2	3	4	5	6	7	8

Concomitant therapy	
Number and severity of exacerbations	
Severity of cough	
Ability to exercise	
Amount of wheezing, etc. since last visit	

Appendix I

Subjects' demographics

Table 7.12 Demographics of subjects included in the primary programme.

Subject	Age	Gender	Race	Currently smoking	Stage	FEV_1
1	70	male	caucasian	no	severe	0.96
2	70	male	caucasian	no	moderate	1.67
3	78	female	caucasian	no	moderate	0.95
4	70	female	caucasian	yes	moderate	1.22
5	44	male	caucasian	yes	severe	1.74
6	73	female	caucasian	no	moderate	1.82
7	79	female	caucasian	no	very severe	0.59
8	65	male	caucasian	yes	moderate	2.52
9	56	female	caucasian	no	severe	0.71
10	59	female	caucasian	no	very severe	0.76
11	67	male	caucasian	yes	moderate	1.49
12	60	male	black	no	very severe	0.7
13	66	female	caucasian	no	severe	0.67
14	64	male	caucasian	no	severe	1.44
15	61	male	caucasian	no	severe	1.4
16	73	male	caucasian	no	severe	1.11
17	54	male	caucasian	yes	severe	1.58
18	42	male	caucasian	no	severe	1.34
19	63	male	black	no	moderate	1.98
20	47	male	black	no	severe	1.69
21	74	male	caucasian	no	moderate	1.95
22	45	male	caucasian	no	severe	1.23

Table 7.13 Demographics of the experimental group in the modified programme.

Subject	Age	Gender	Race	Currently smoking	Stage	FEV_1
1	74	male	black	no	severe	1.41
2	70	male	caucasian	no	severe	1.18
3	67	male	caucasian	no	moderate	1.78
4	51	female	black	no	moderate	1.15
5	64	female	caucasian	no	moderate	1.11
6	70	female	black	no	moderate	1.26
7	66	female	black	no	moderate	1.37
8	63	male	caucasian	no	moderate	1.6
9	72	male	black	no	severe	1.24
10	60	female	caucasian	no	moderate	1.17
11	68	male	caucasian	no	severe	0.92

Table 7.14 Demographics of the control group in the modified programme.

Subject	Age	Gender	Race	Currently smoking	Stage	FEV_1
1	72	male	caucasian	no	moderate	1.71
2	64	female	black	no	severe	0.66
3	64	female	caucasian	no	severe	0.86
4	65	male	caucasian	no	severe	1.21
5	77	male	caucasian	no	moderate	1.91
6	71	female	caucasian	no	moderate	1.1
7	72	female	caucasian	no	moderate	1.09

Appendix J

Correlations that delivered insignificant results

Primary programme

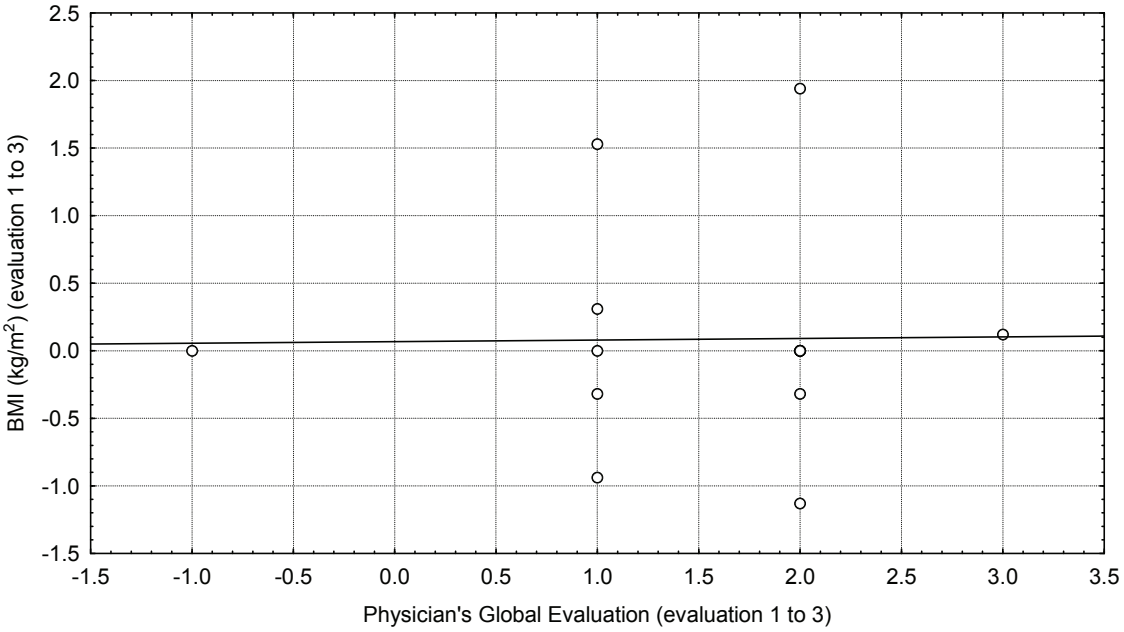

Figure 7.53 A scatter plot illustrating the correlation between the difference in BMI and the physician's global evaluation from the first to the third evaluation.

No significant correlation was found between the difference in BMI and the physician's global evaluation from the first to the third evaluation ($p = 0.96$) in the PP.

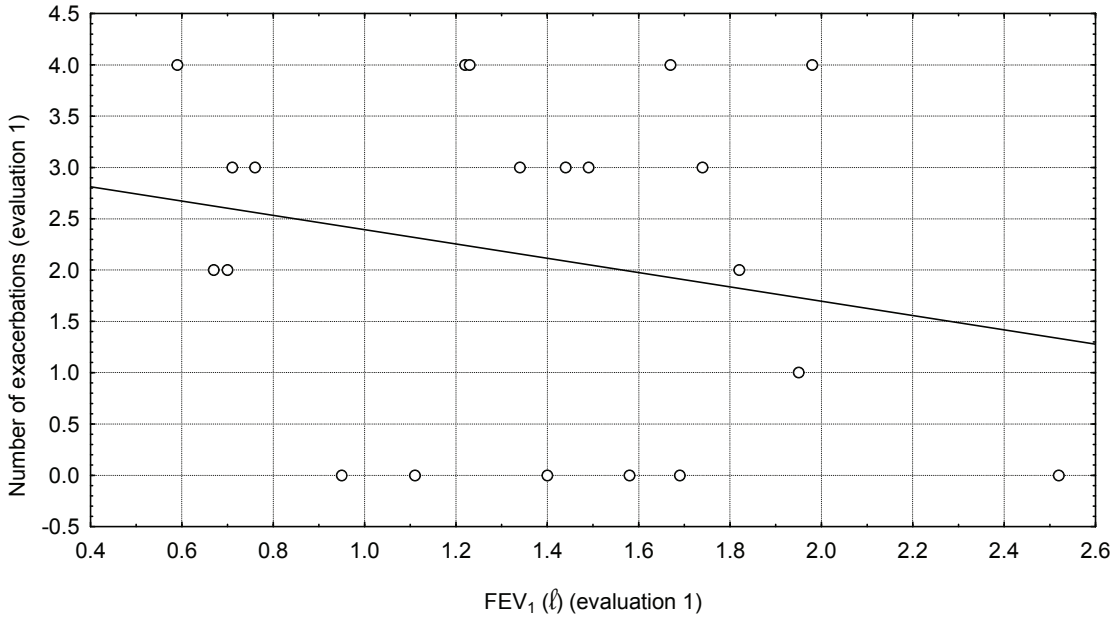

Figure 7.54 A scatter plot illustrating the correlation between the number of exacerbations and FEV_1 at the first evaluation.

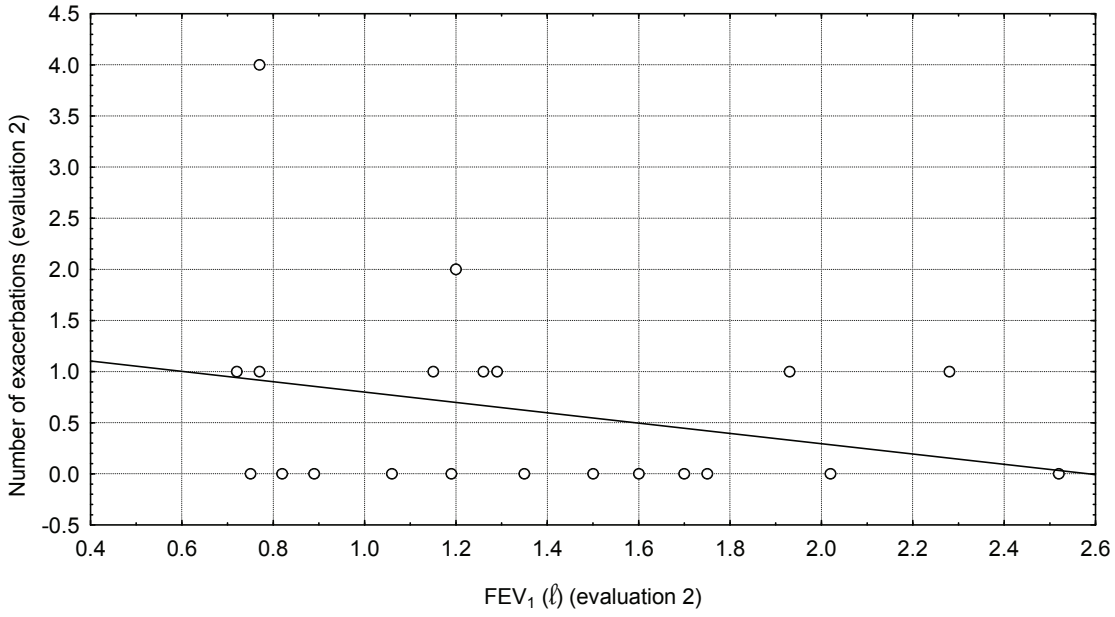

Figure 7.55 A scatter plot illustrating the correlation between the number of exacerbations and FEV_1 at the second evaluation.

No significant correlation was found between the number of exacerbations and FEV_1 values at the first ($p = 0.33$) or second evaluation ($p = 0.23$) in the PP.

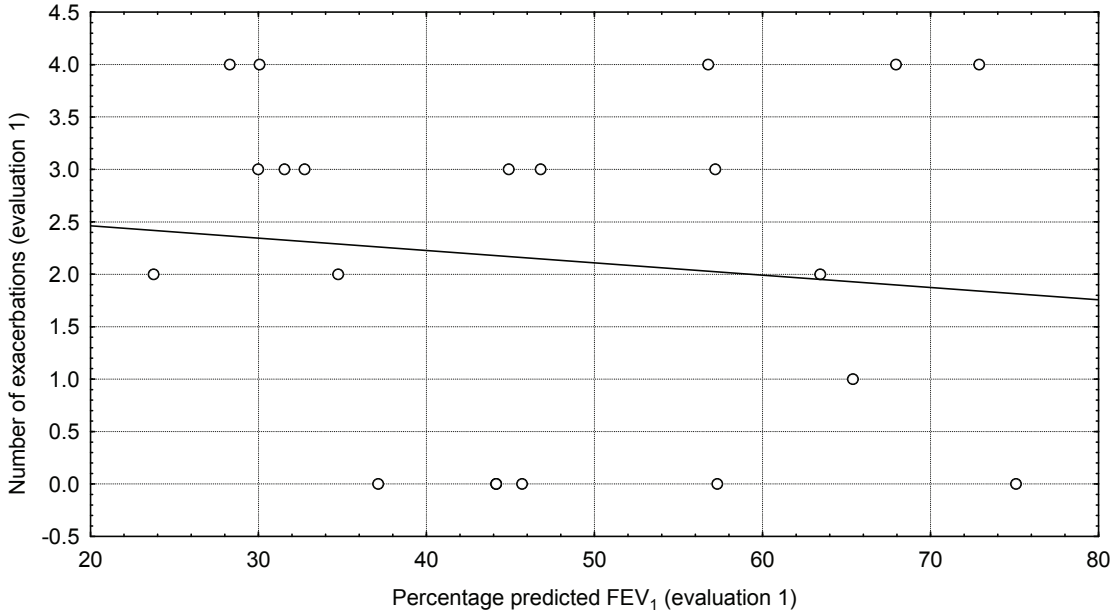

Figure 7.56 A scatter plot illustrating the correlation between the number of exacerbations and the percentage predicted FEV_1 at the first evaluation.

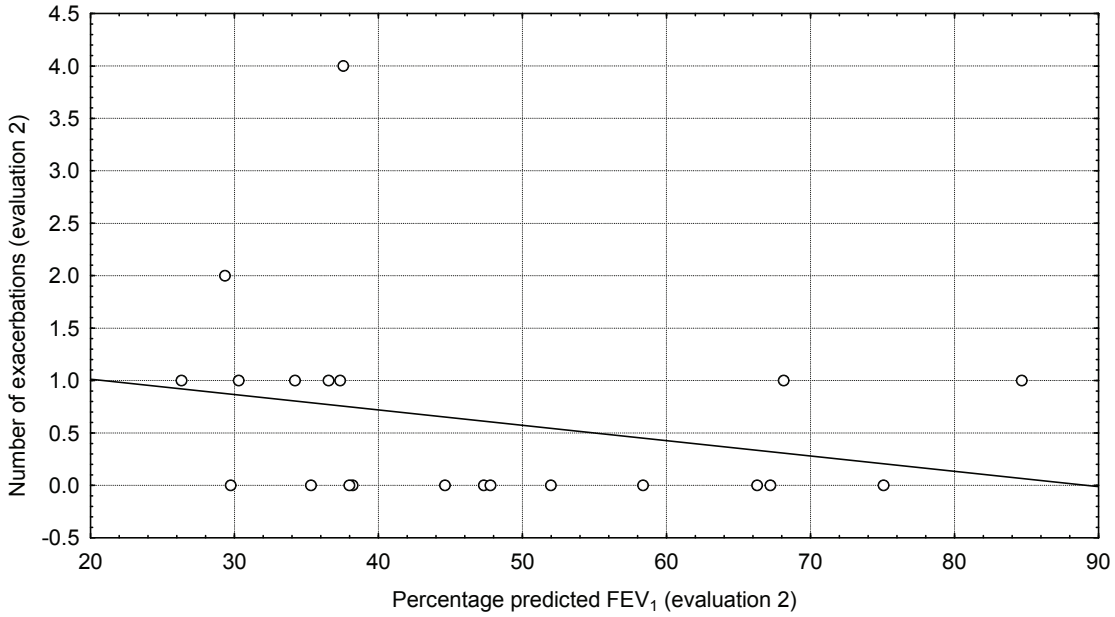

Figure 7.57 A scatter plot illustrating the correlation between the number of exacerbations and the percentage predicted FEV_1 at the second evaluation.

No significant correlation was found between the number of exacerbations and FEV_1 values at the first ($p = 0.62$) or second evaluation ($p = 0.27$) in the PP.

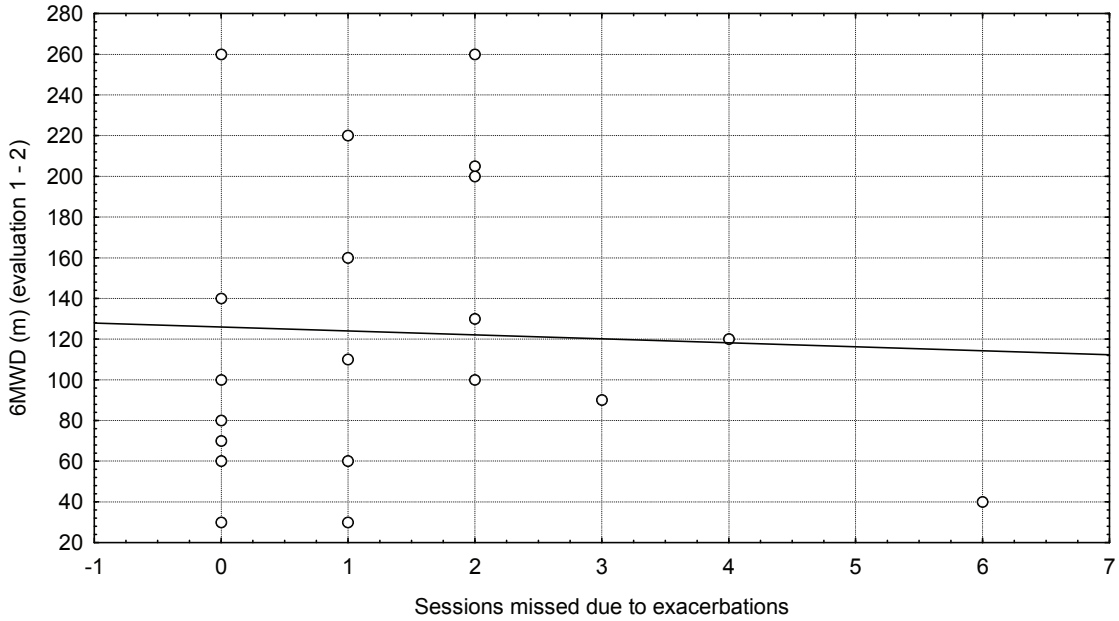

Figure 7.58 A scatter plot illustrating the correlation between the exercise sessions missed due to exacerbations and the change in 6MWD from the first to the second evaluation.

No significant correlation was found between the exercise sessions missed due to exacerbations and the change in 6MWD from the first to the second evaluation in the PP ($p = 0.86$).

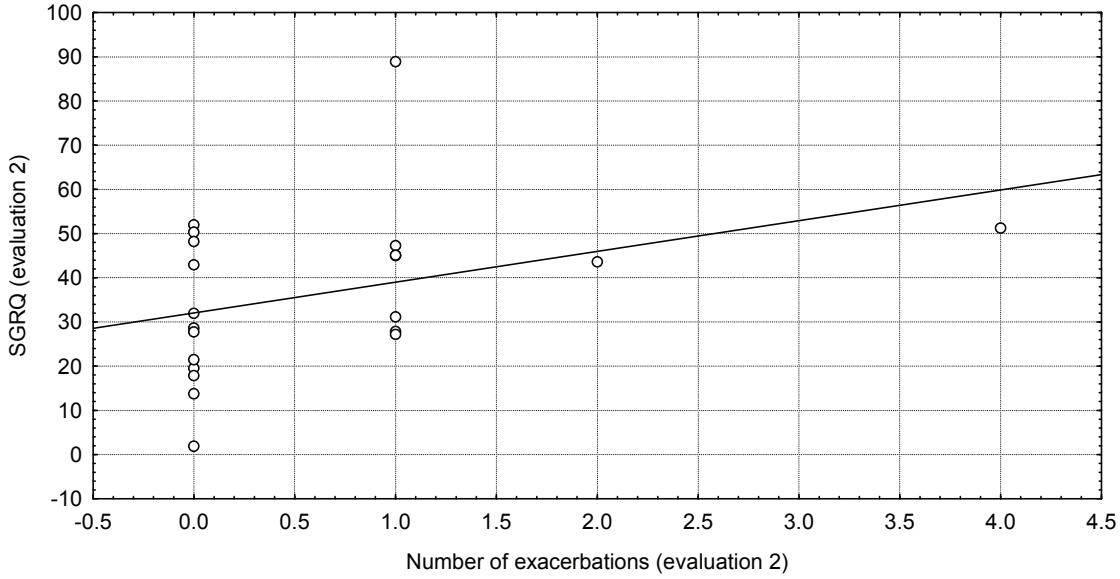

Figure 7.59 A scatter plot illustrating the correlation between the number of exacerbations and SGRQ scores at the second evaluation.

No significant correlation was found between the number of exacerbations and the HRQL as assessed by the SGRQ ($p = 0.01$).

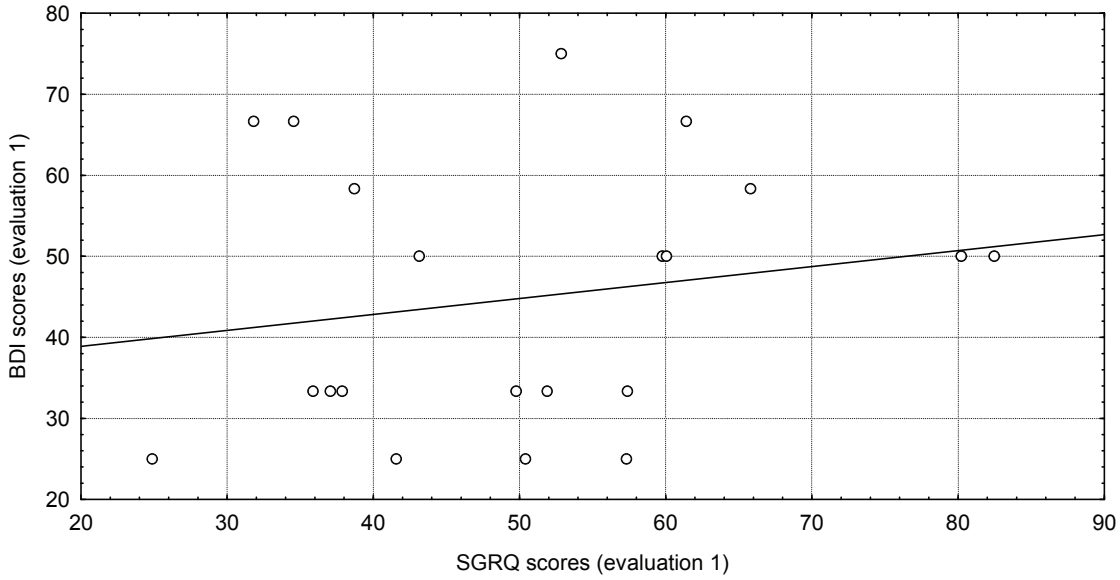

Figure 7.60 A scatter plot illustrating the correlation between the BDI and SGRQ scores at the first evaluation.

No significant correlation was found between the BDI and SGRQ scores at the first evaluation in the PP (p = 0.42).

Modified programme

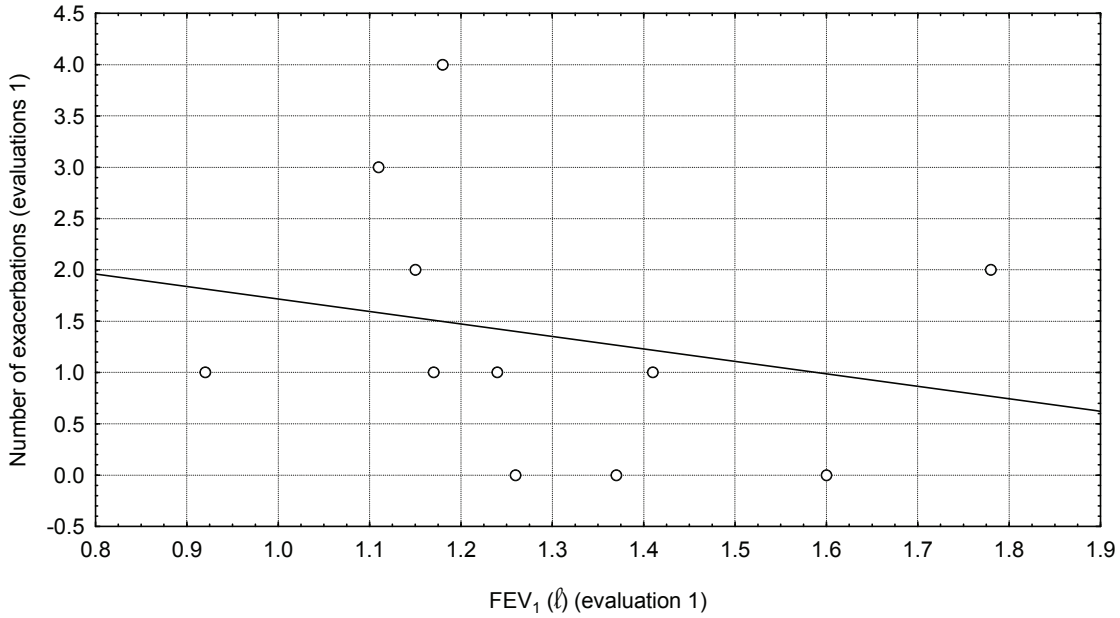

Figure 7.61 A scatter plot illustrating the correlation between the number of exacerbations and FEV_1 at the first evaluation for the experimental group.

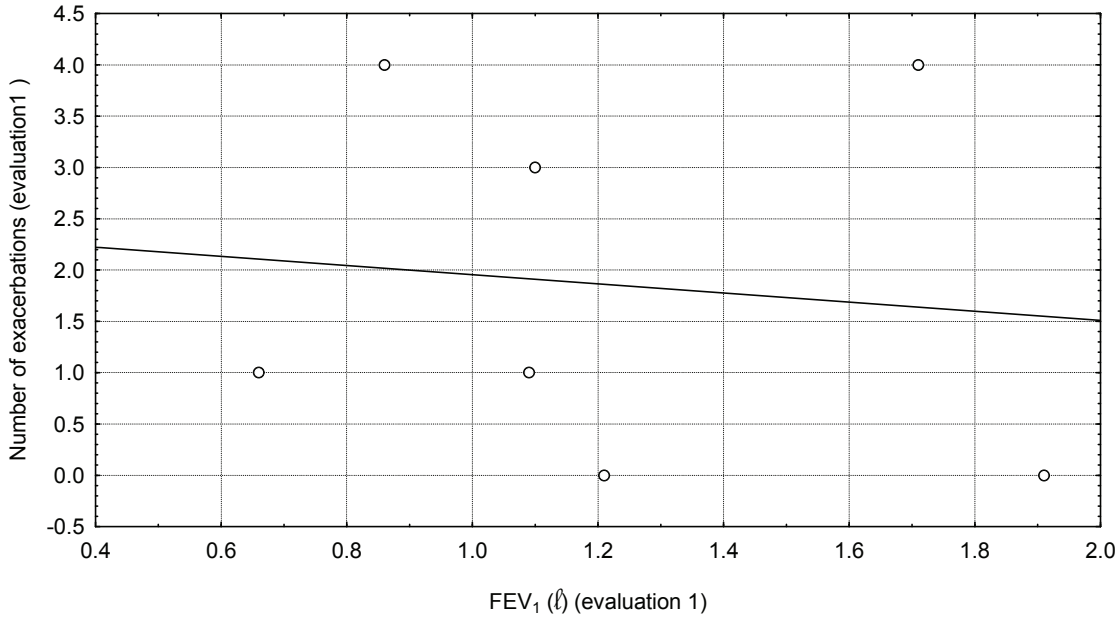

Figure 7.62 A scatter plot illustrating the correlation between the number of exacerbations and FEV_1 at the first evaluation for the control group.

No significant correlations were found between the number of exacerbations and FEV_1 for the experimental ($p = 0.50$) or control group ($p = 0.81$) at the first evaluation.

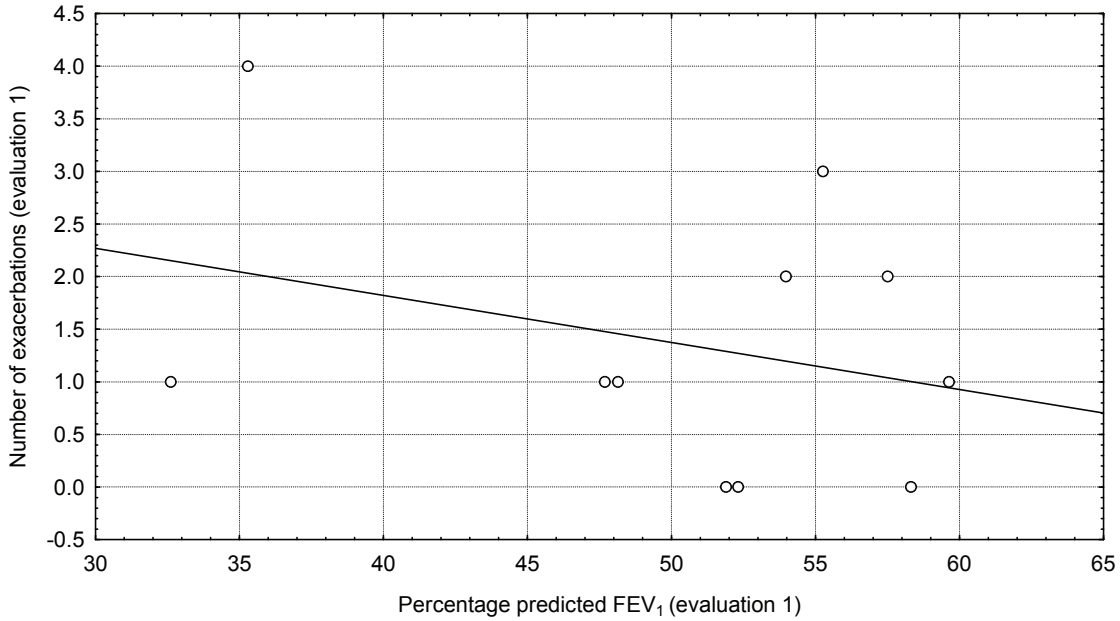

Figure 7.63 A scatter plot illustrating the correlation between the number of exacerbations and the percentage predicted FEV_1 at the first evaluation for the experimental group.

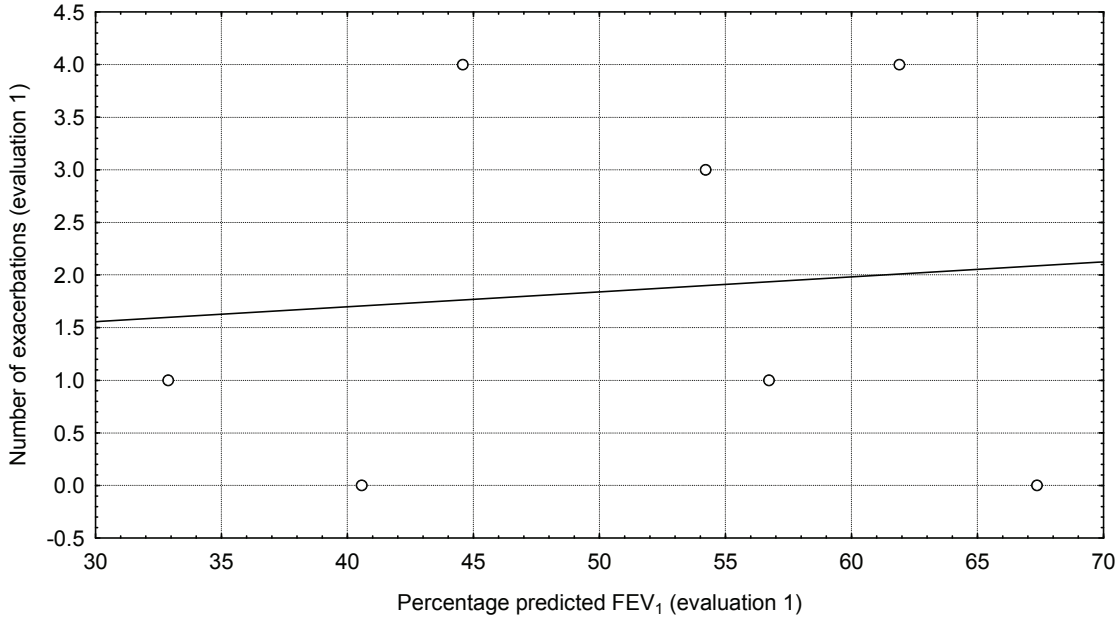

Figure 7.64 A scatter plot illustrating the correlation between the number of exacerbations and the percentage predicted FEV_1 at the first evaluation for the control group.

No significant correlations were found between the number of exacerbations and the percentage predicted FEV_1 at the first evaluation for the experimental ($p = 0.35$) or control group ($p = 0.83$).

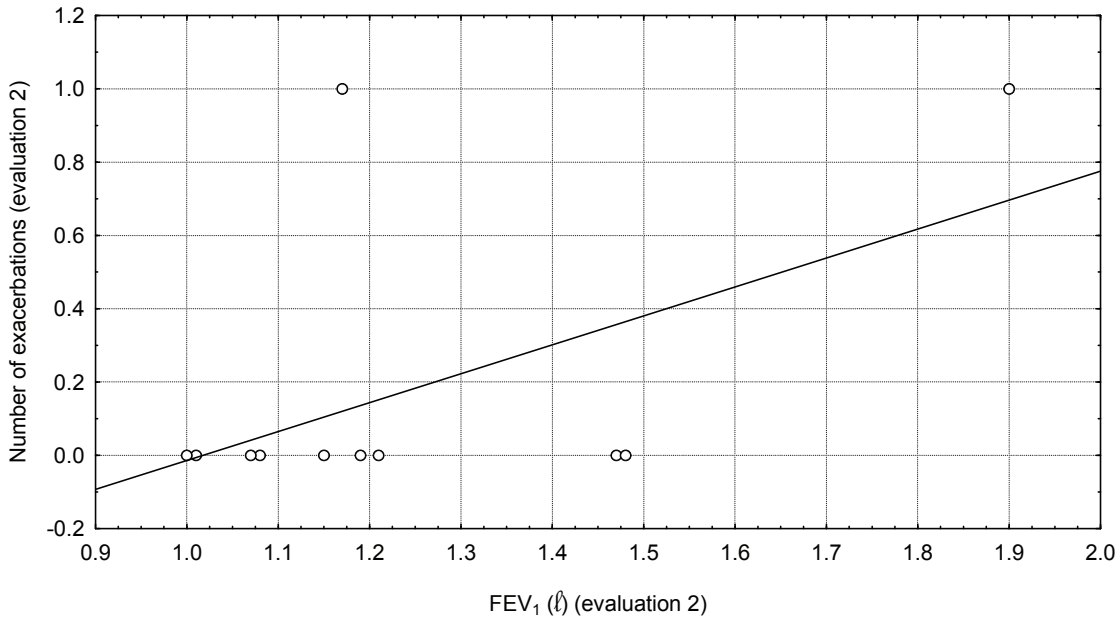

Figure 7.65 A scatter plot illustrating the correlation between the number of exacerbations and FEV_1 at the second evaluation for the experimental group.

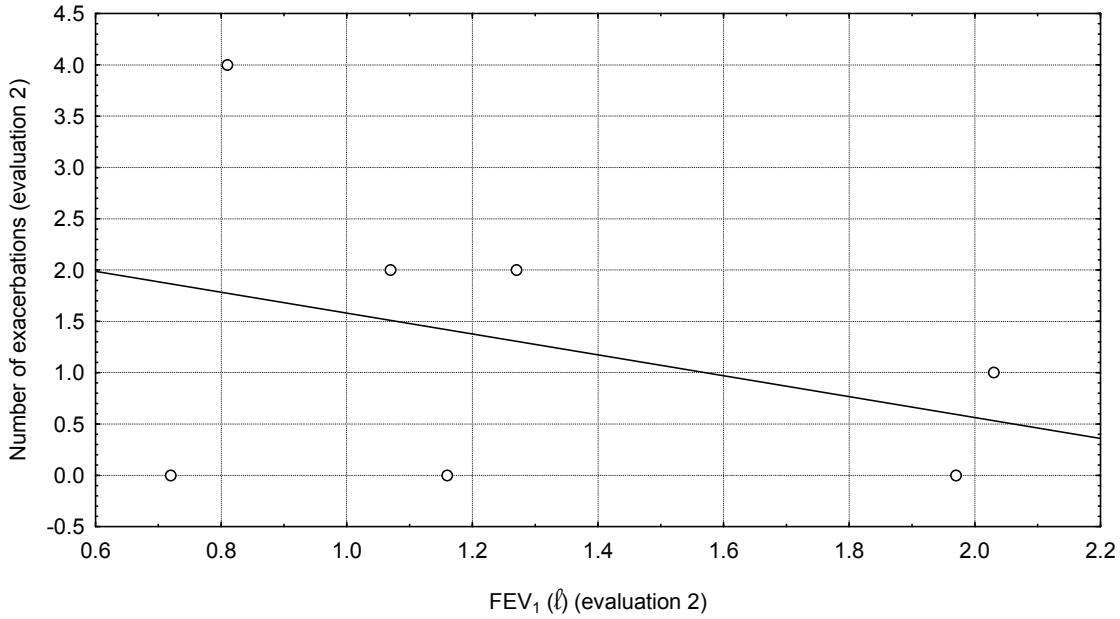

Figure 7.66 A scatter plot illustrating the correlation between the number of exacerbations and FEV_1 at the second evaluation for the control group.

No significant correlations were found between the number of exacerbations and FEV_1 at the second evaluation for the experimental (0.10) or control group ($p = 0.44$).

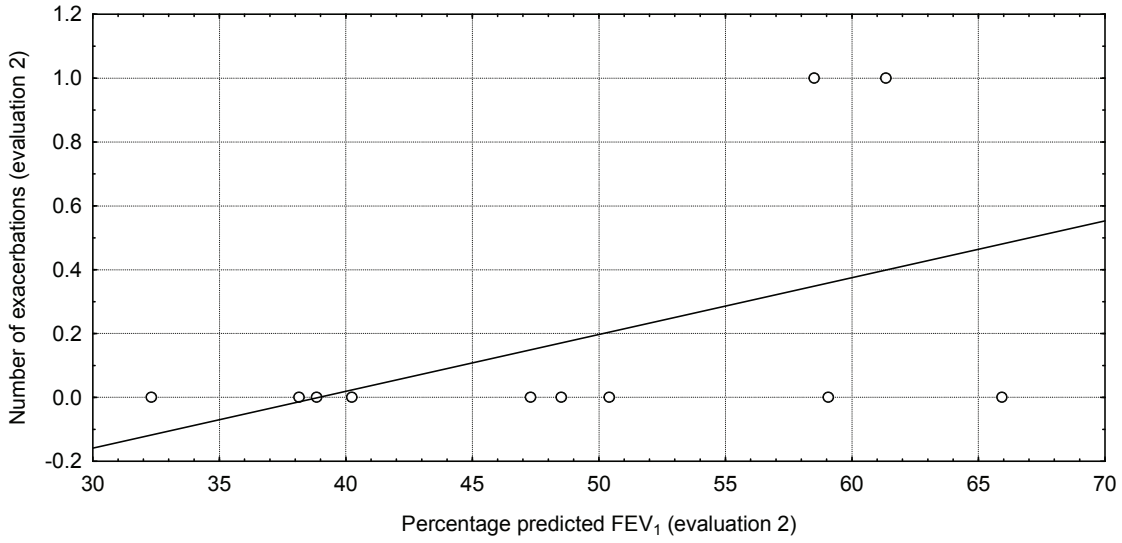

Figure 7.67 A scatter plot illustrating the correlation between the number of exacerbations and the percentage predicted FEV_1 at the second evaluation for the experimental group.

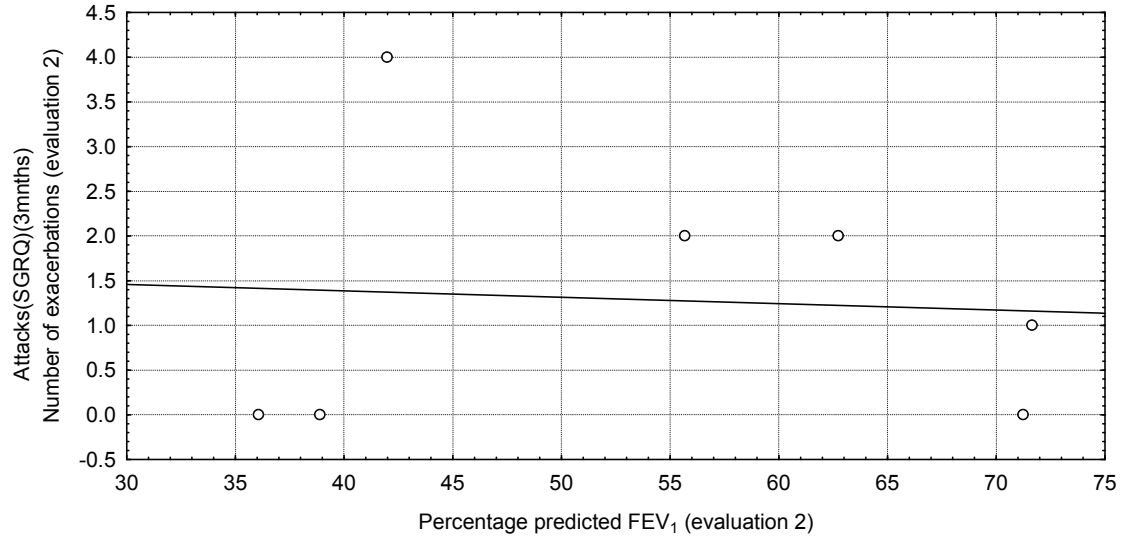

Figure 7.68 A scatter plot illustrating the correlation between the number of exacerbations and the percentage predicted FEV_1 at the second evaluation for the control group.

No significant correlations were found between the number of exacerbations and the percentage predicted FEV_1 at the second evaluation for the experimental ($p = 0.13$) or control group ($p = 0.88$).

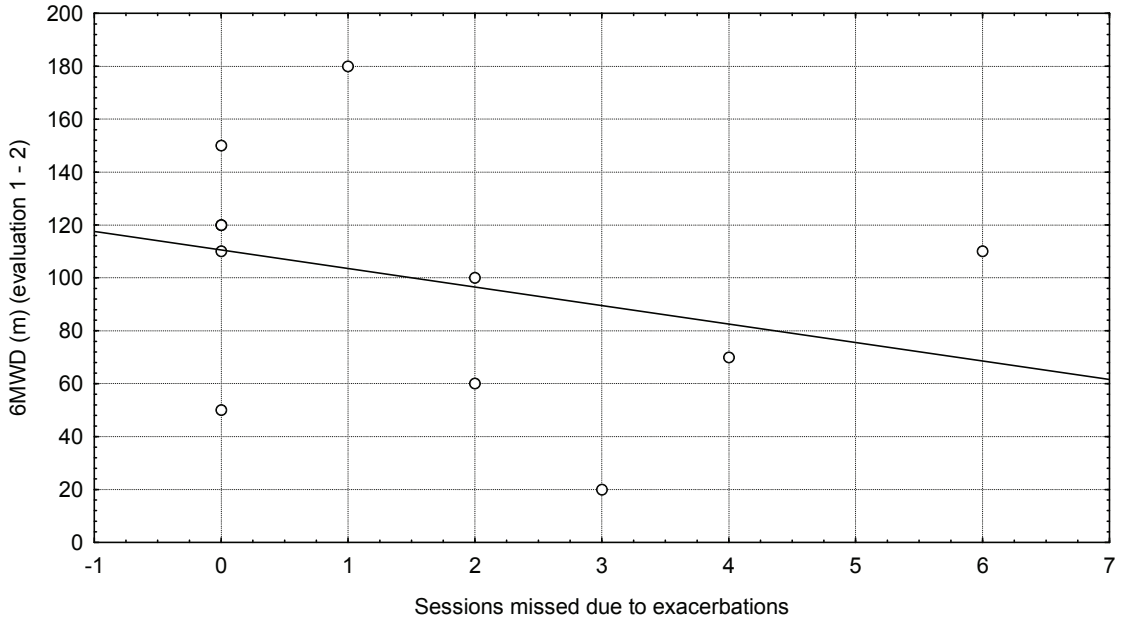

Figure 7.69 A scatter plot illustrating the correlation between the exercise sessions missed due to exacerbations and the change in 6MWD from the first to the second evaluation for the experimental group.

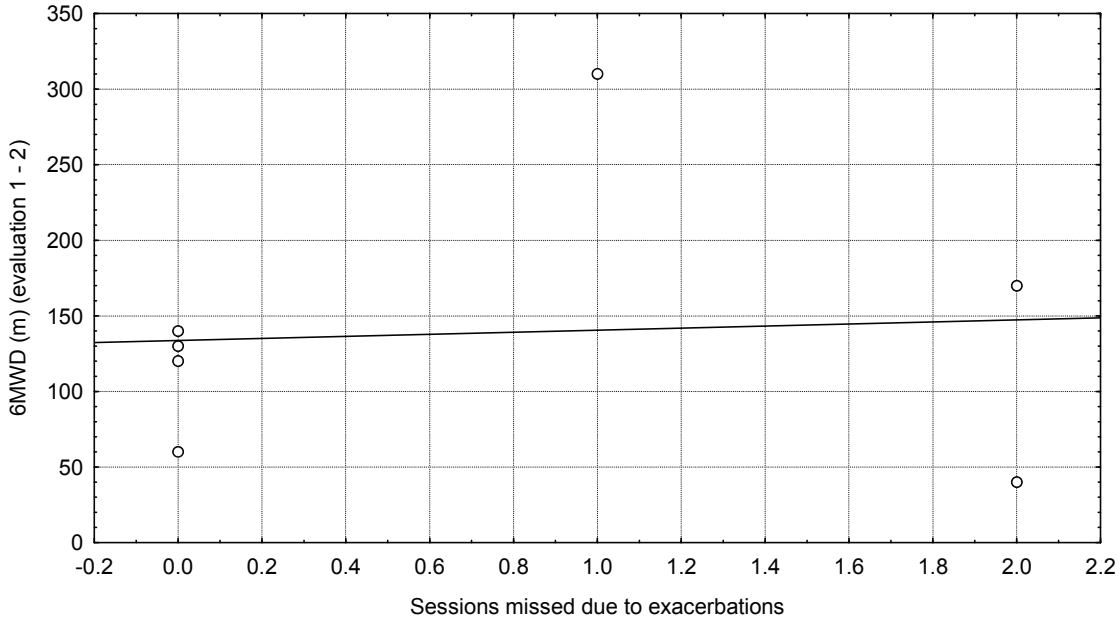

Figure 7.70 A scatter plot illustrating the correlation between the exercise sessions missed due to exacerbations and the change in 6MWDs from the first to the second evaluation for the control group.

No significant correlations were found between the number of exercise sessions missed due to exacerbations and the change in 6MWDs from the first to the second evaluation for the experimental ($p = 0.36$) or control group ($p = 0.87$).

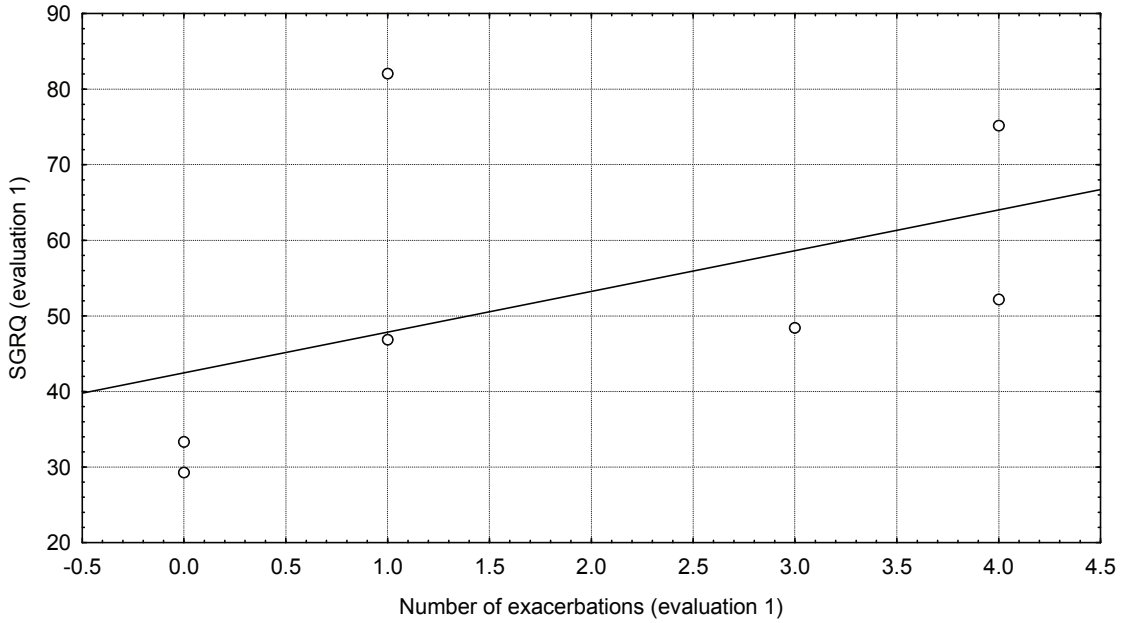

Figure 7.71 A scatter plot illustrating the correlation between the SGRQ scores and the number of exacerbations for the control group at the first evaluation.

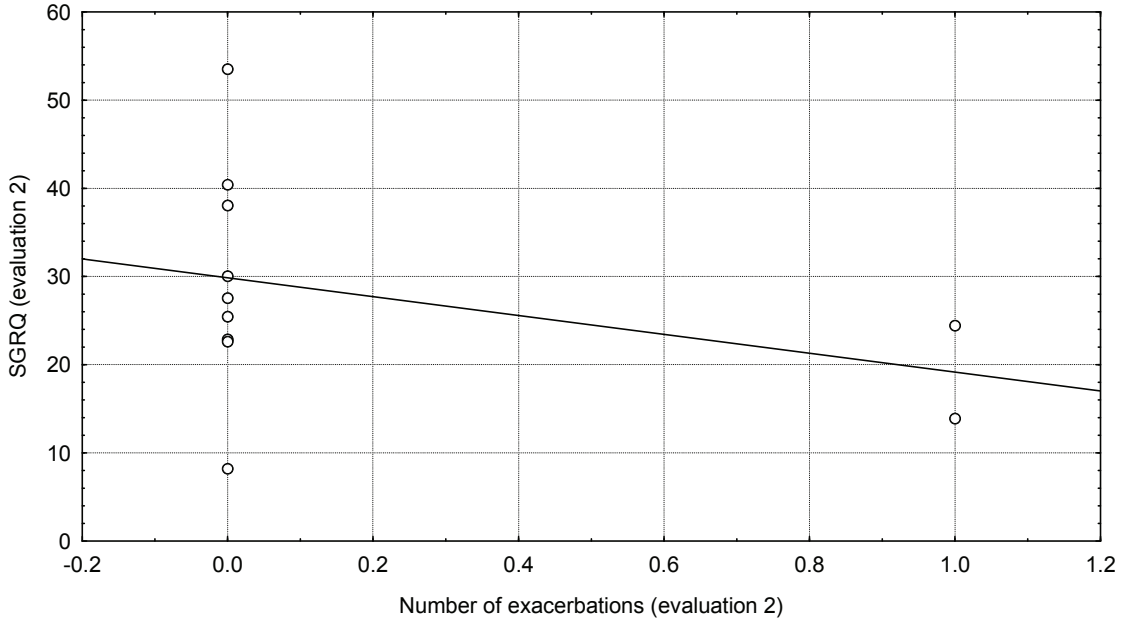

Figure 7.72 A scatter plot illustrating the correlation between the SGRQ scores and the number of exacerbations for the experimental group at the second evaluation.

No significant correlations were found between the number of exacerbations and the SGRQ scores at the first evaluation of the control group ($p = 0.27$) and the second evaluation of the experimental group ($p = 0.30$).

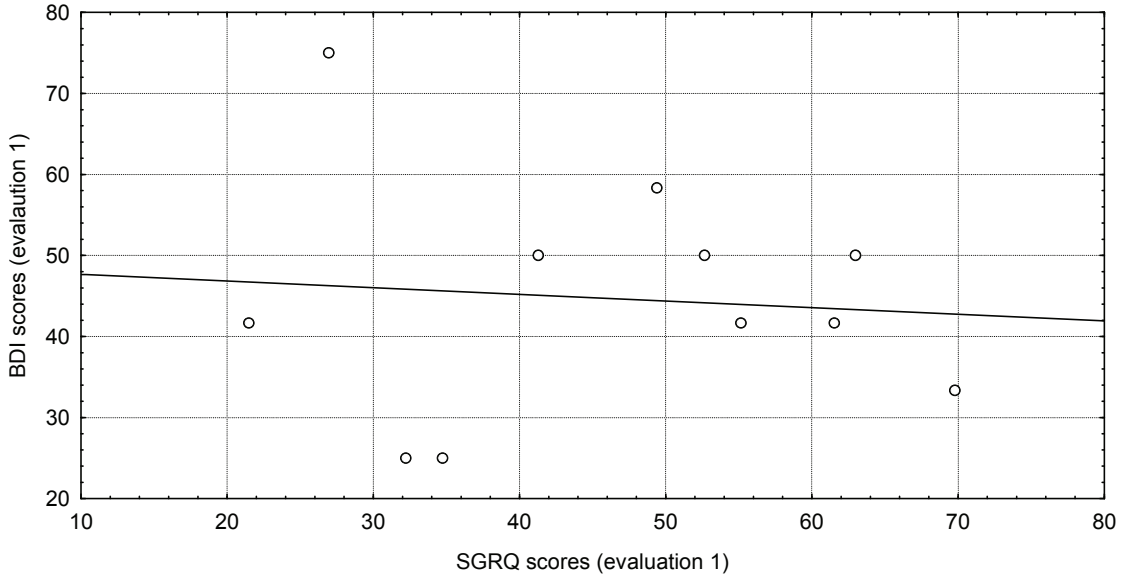

Figure 7.73 A scatter plot illustrating the correlation between the experimental group's BDI and SGRQ scores at the first evaluation.

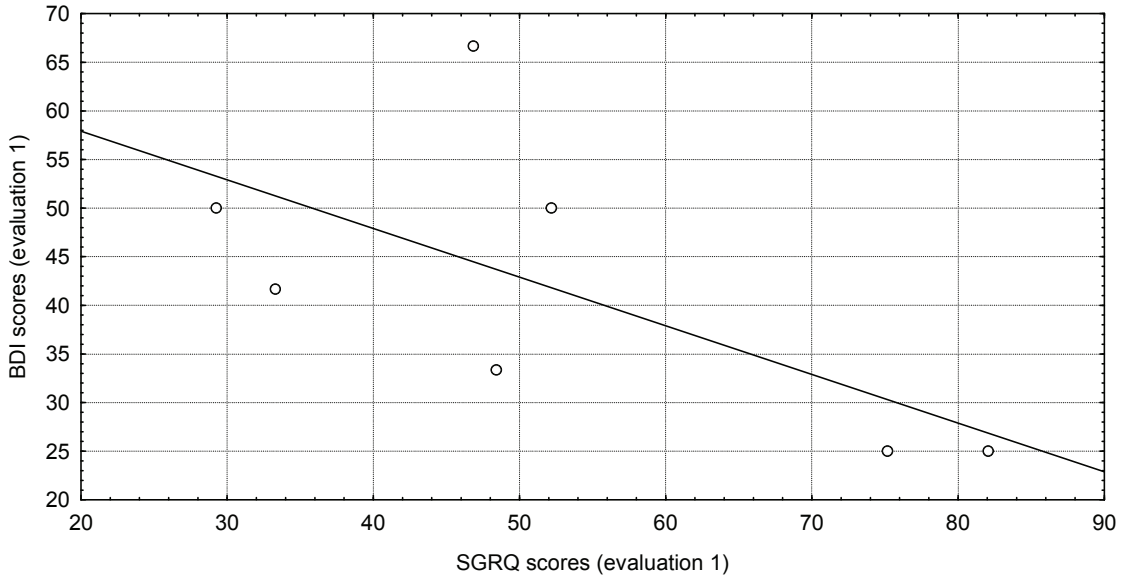

Figure 7.74 A scatter plot illustrating the correlation between the control group's BDI and SGRQ scores at the first evaluation.

No significant correlation was found between the BDI and SGRQ scores for the experimental (p = 0.80) or control group (p = 0.11) at the first evaluation.

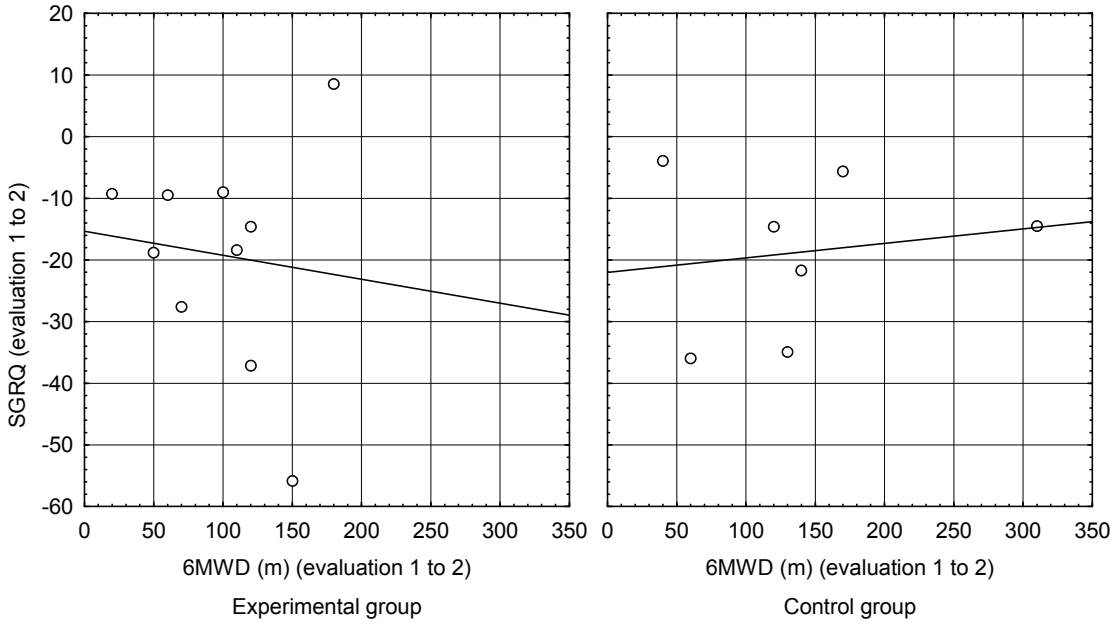

Figure 7.75 Scatter plots illustrating the correlation between the difference in the SGRQ scores and the 6MWDs from the first to the second evaluation for the experimental and control group.

No significant correlation was found between the difference in SGRQ scores and 6MWDs from the first to the second evaluation for the experimental (p = 0.77) or control group (p = 0.73).

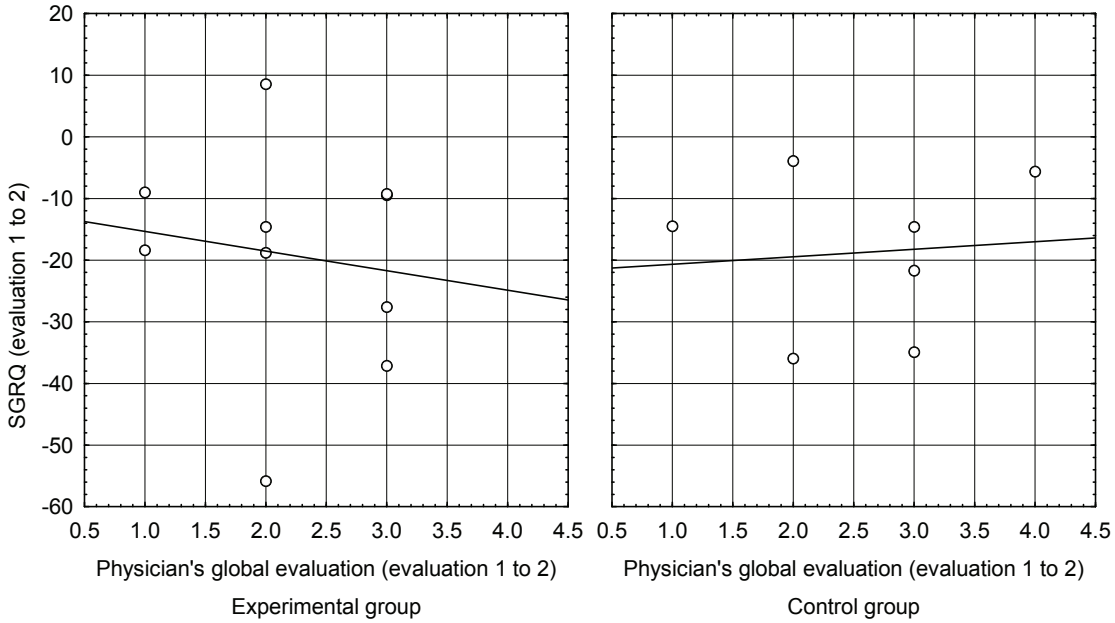

Figure 7.76 Scatter plots illustrating the correlation between the difference in the SGRQ scores and the physician's global evaluation from the first to the second evaluation for the experimental and control group.

No significant correlation was found between the difference in SGRQ scores and the physician's global evaluation from the first to the second evaluation for the experimental ($p = 0.70$) or control group ($p = 0.84$).

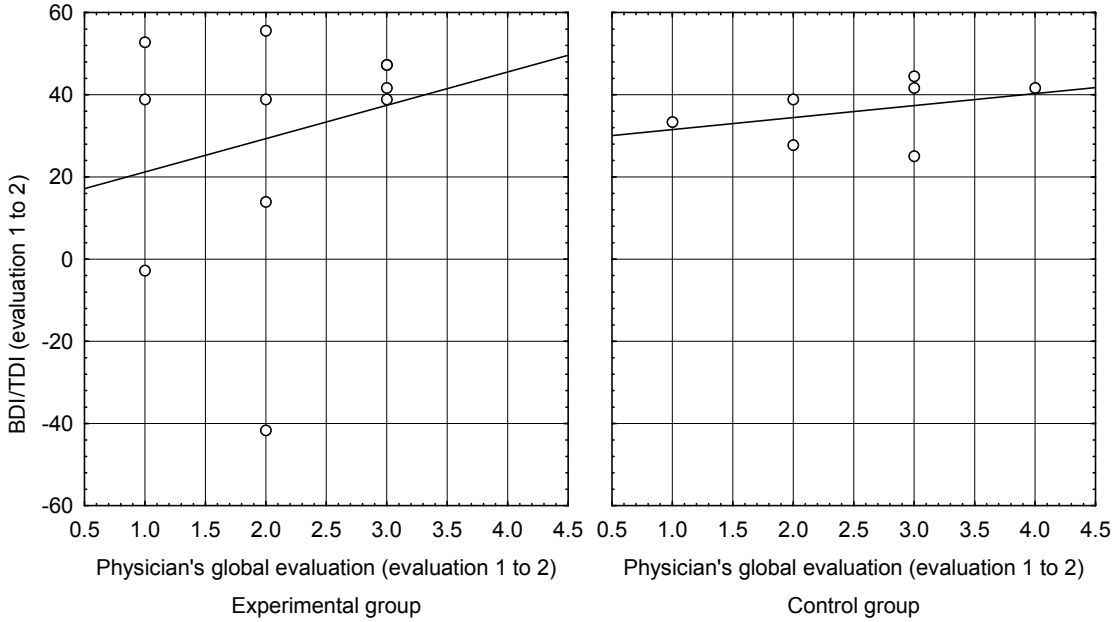

Figure 7.77 Scatter plots illustrating the correlation between the difference in the BDI/TDI scores and the physician's global evaluation from the first to the second evaluation for the experimental and control group.

No significant correlation was found between the difference in BDI/TDI scores and the physician's global evaluation from the first to the second evaluation for the experimental ($p = 0.50$) or control group ($p = 0.40$).

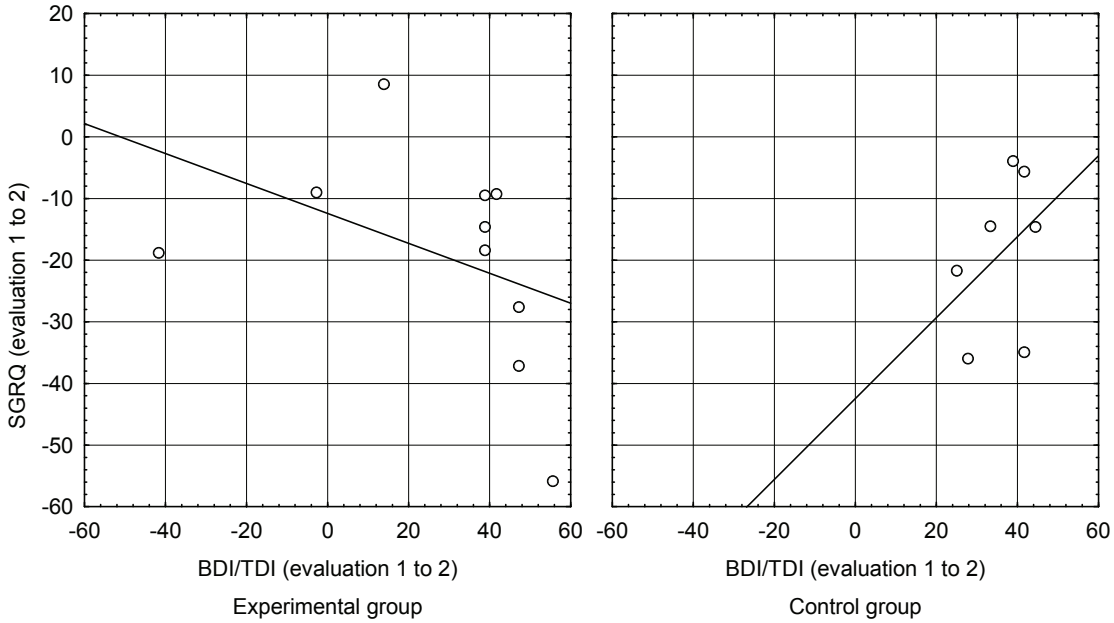

Figure 7.78 Scatter plots illustrating the correlation between the difference in the SGRQ scores and the BDI/TDI scores from the first to the second evaluation for the experimental and control group.

No significant correlation was found between the difference in SGRQ scores and the BDI/TDI scores from the first to the second evaluation for the experimental ($p = 0.24$) or control group ($p = 0.40$).

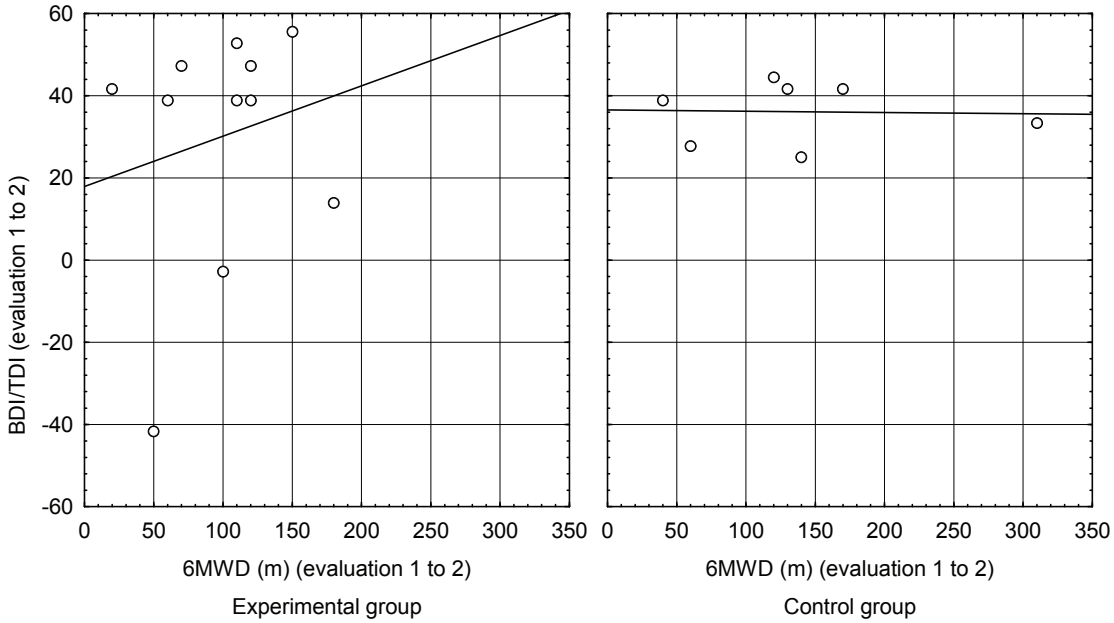

Figure 7.79 Scatter plots illustrating the correlation between the difference in the BDI/TDI scores and the 6MWDs from the first to the second evaluation for the experimental and control group.

No significant correlation was found between the difference in BDI/TDI scores and the 6MWDs from the first to the second evaluation for the experimental ($p = 0.57$) or control group ($p = 0.94$).

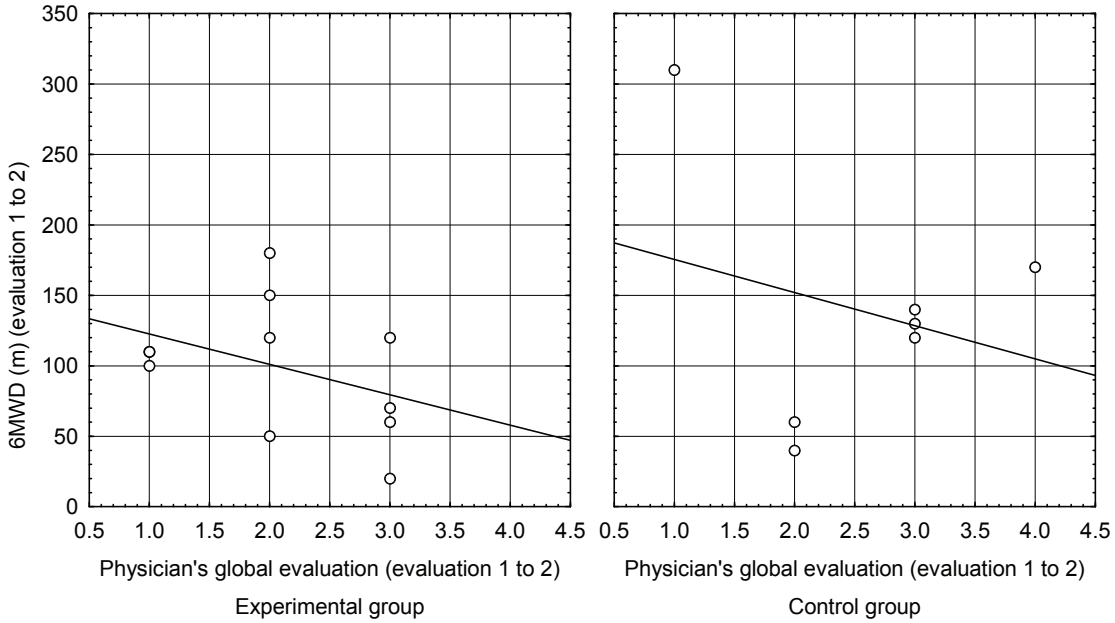

Figure 7.80 Scatter plots illustrating the correlation between the difference in 6MWDs and the physician's global evaluation from the first to the second evaluation for the experimental and control group.

No significant correlation was found between the difference in 6MWDs and the physician's global evaluation from the first to the second evaluation for the experimental ($p = 0.24$) or control group ($p = 0.57$).

Appendix K

Correlations combining results form the primary programme with the results of the control group

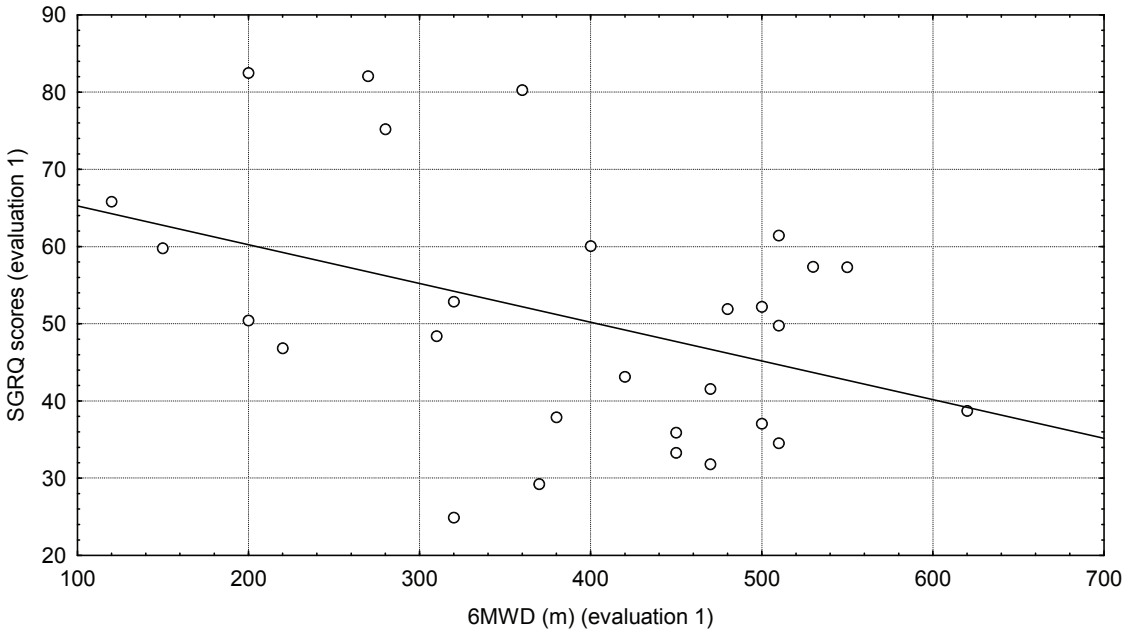

Figure 7.81 A scatter plot illustrating the correlation between the 6MWDs and SGRQ scores of the combined results of the subjects in the PP and control group at the first evaluation.

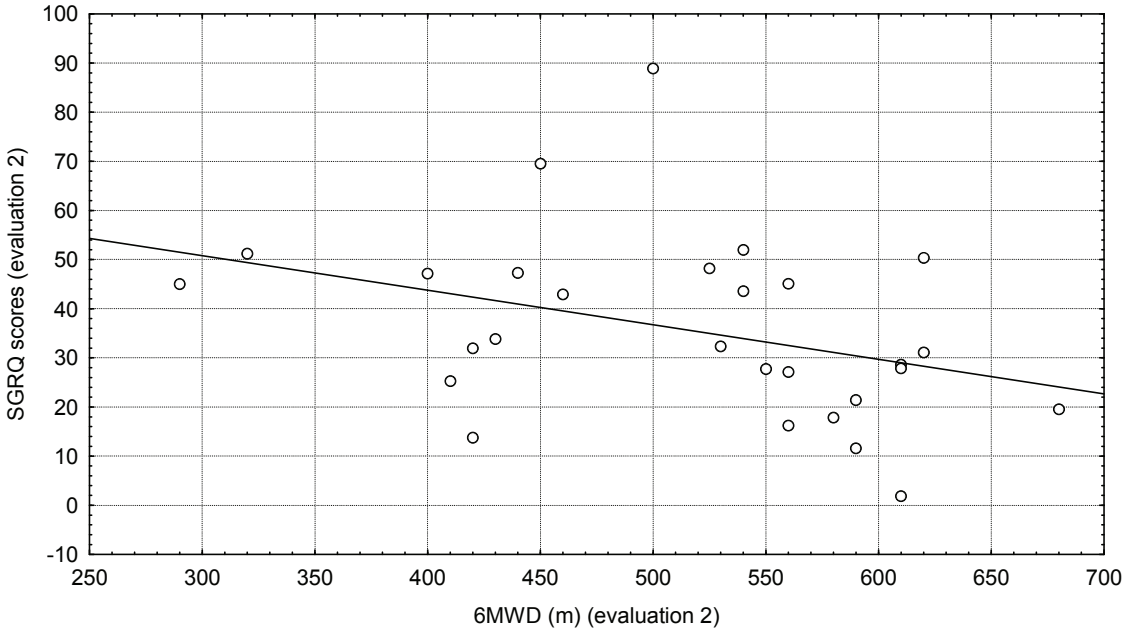

Figure 7.82 A scatter plot illustrating the correlation between the 6MWDs and SGRQ scores of the combined results of the subjects in the PP and control group at the second evaluation.

There was a significant correlation between the combined 6MWDs and SGRQ results of the subjects in the PP and the control group at the first ($p < 0.05$) and second evaluation ($p < 0.05$).

Appendix L

Significant correlations that was considered circumstantial

When calculating the correlations between various variables, some significant correlations were found, but were not consistent throughout the evaluations or different groups. These correlations are presented below, but are considered circumstantial.

Primary programme

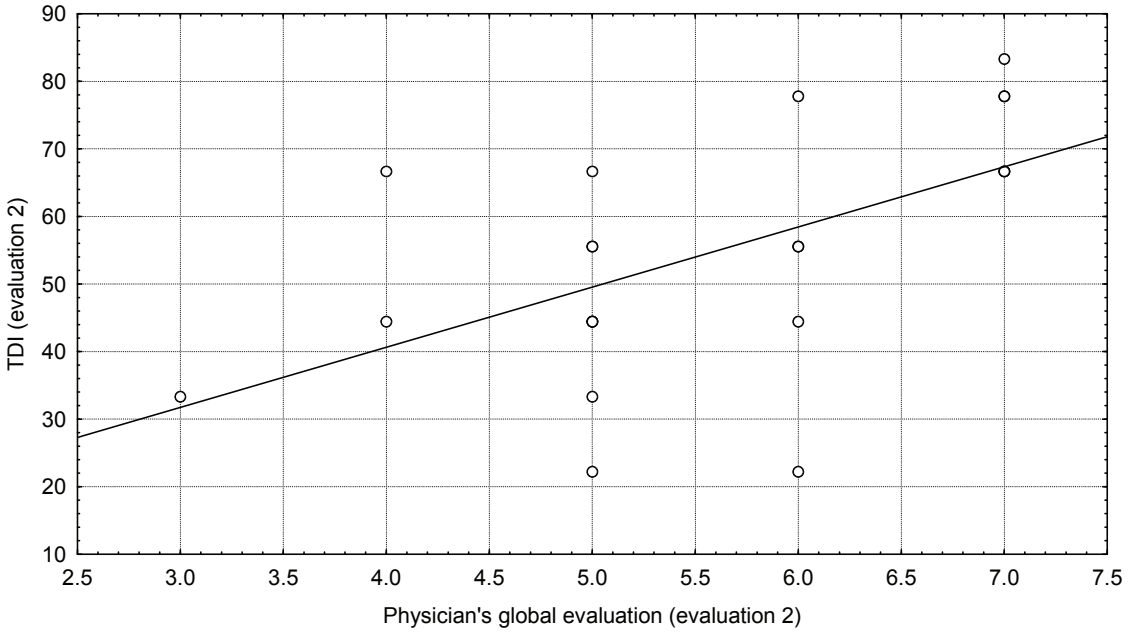

Figure 7.83 A scatter plot illustrating the correlation between TDI and the physician's evaluation at the second evaluation.

A significant correlation was found between the mean TDI and the physician's global scores at the second evaluation ($p < 0.01$). This correlation was not present at the first or third evaluation ($p > 0.05$). In MP, this correlation was only significant in the control group at the first evaluation. Although the assessment of dyspnoea forms part of the physician's global evaluation, other components such as medication, exacerbations, severity of cough and ability to exercise, also form an

integral part of this evaluation. In the cases where this correlation was present, dyspnoea was the primary symptom noted at that stage. Therefore, a correlation would be expected. The absence of this correlation in the other assessments implies that dyspnoea was not the primary concern of the subject at that stage. Dyspnoea is perceived as the most important symptom experienced by COPD patients and receives most of the attention in the treatment of these patients (Franssen, 2003; Gosselink, 2003; Marin *et al*., 2001; ATS, 1999; Carrieri-Kohlman *et al.*, 1996; Lareau *et al*., 1994). This correlation or lack thereof, suggests that the overall wellbeing of COPD patients might be more strongly influenced by factors other than dyspnoea.

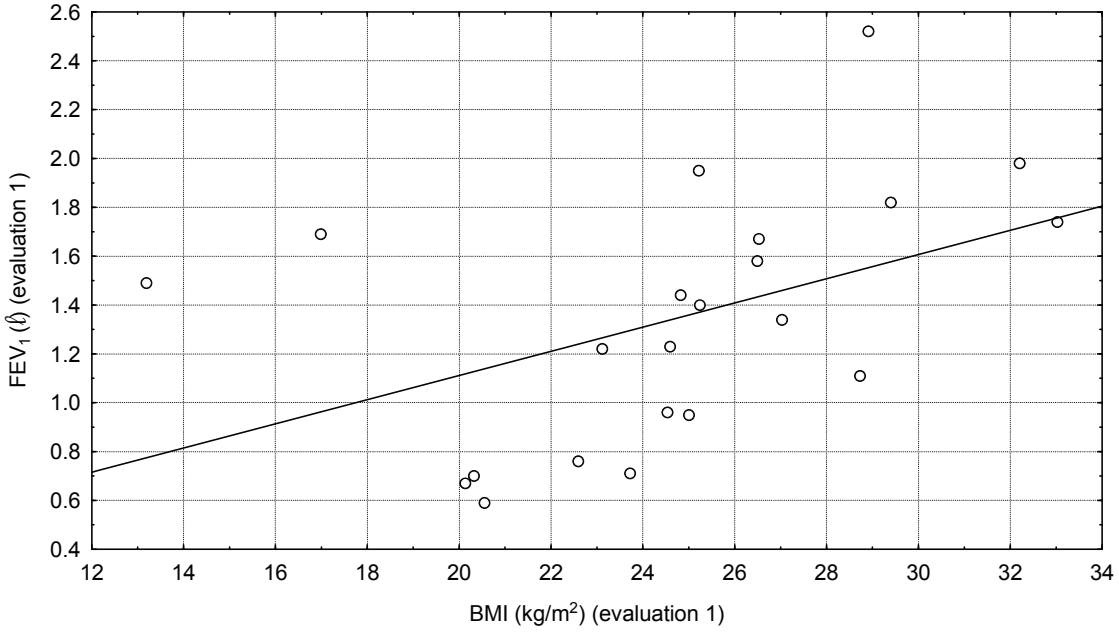

Figure 7.84 A scatter plot illustrating the correlation between the mean BMI and FEV_1 at the first evaluation.

A significant correlation was found between BMI and FEV_1 at the first evaluation ($p < 0.05$). This correlation was not present at the second or third evaluation ($p > 0.05$). This correlation was not present at the second evaluation or in the MP. Although there was not a significant correlation between these variables at the second evaluation, the tendency of the graph is similar to that of the first

evaluation. Even though these variables did not show any significant change from the first to the second evaluation, the similarity between these correlations suggests that the change was sufficient to reduce the correlation at the second evaluation. Due to the fact that height and weight have an effect on FEV_1, a correlation between these two variables would be expected. The absence of this correlation in the MP could be explained by the limitations of BMI (Chapter III).

No significant correlation was found between the mean BMI and SGRQ scores at any of the three evaluations ($p > 0.05$). The lack of correlations found between BMI and other variables could be ascribed to the fact that there was no significant change in the BMI values of the subjects ($p = 0.84$).

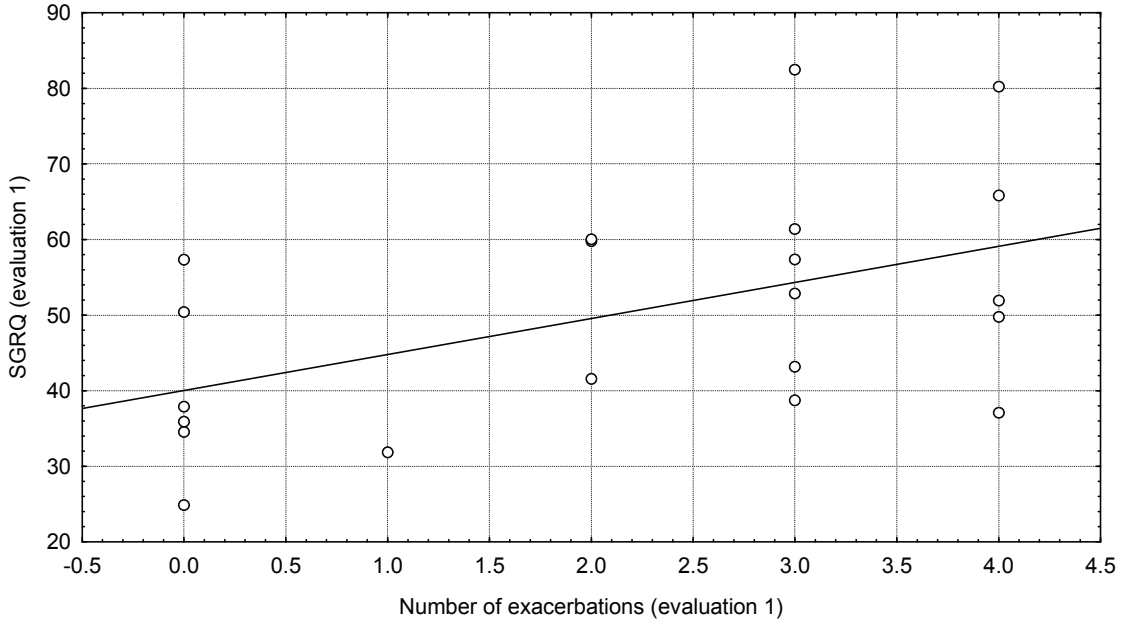

Figure 7.85 A scatter plot illustrating the correlation between the number of exacerbations and the SGRQ scores at the first evaluation.

A significant correlation was found between the number of exacerbations and HRQL as assessed by the SGRQ ($p < 0.05$). This correlation was not present at the second evaluation ($p = 0.10$).

Modified programme

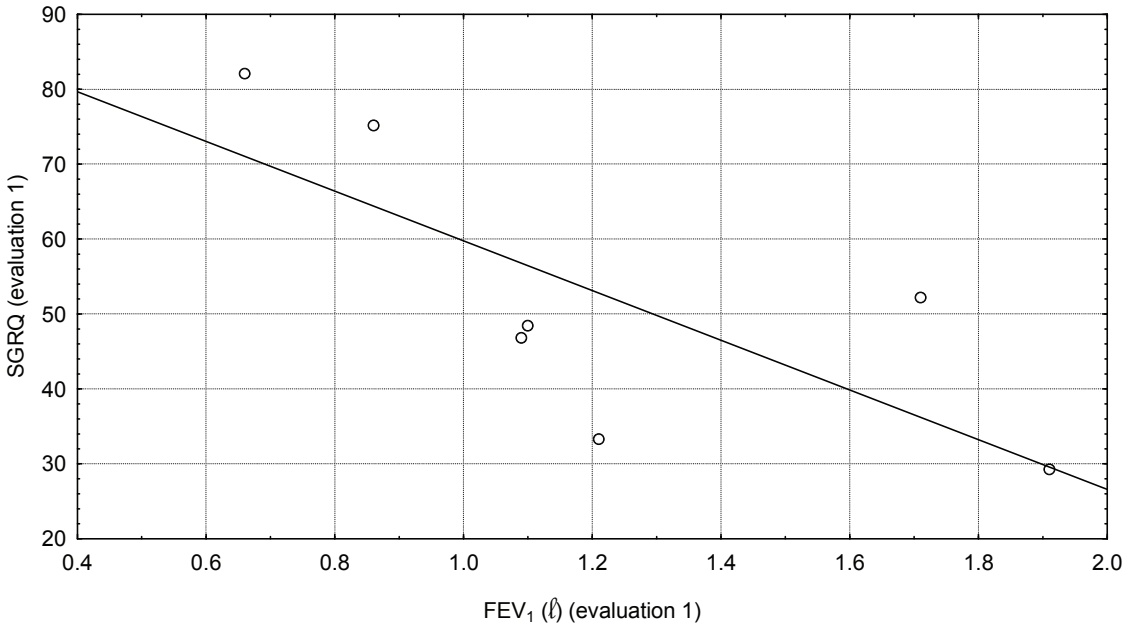

Figure 7.86 A scatter plot illustrating the correlation between the SGRQ and FEV_1 means of the control group at the first evaluation.

A weak, but significant correlation was found between the control group's mean SGRQ scores and FEV_1 at the first evaluation ($p = 0.05$). This correlation was not present at the control group's second evaluation ($p = 0.12$). No correlation was found between these variables in the experimental group at the first ($p = 0.98$) or second evaluation ($p = 0.96$).

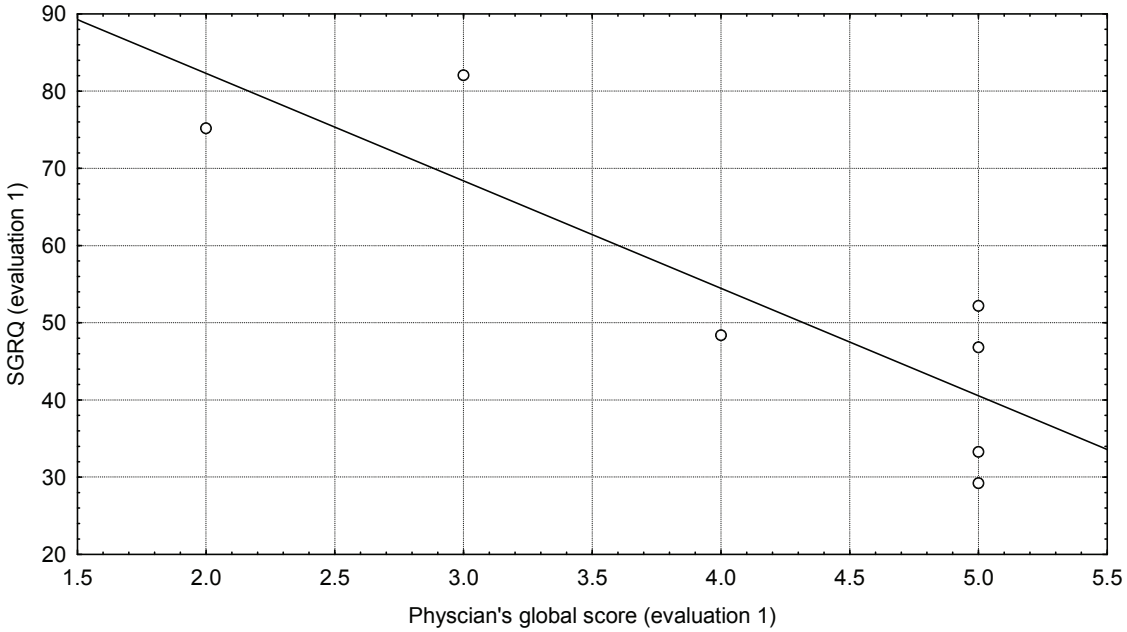

Figure 7.87 A scatter plot illustrating the correlation between the physician's global evaluation and the SGRQ of the control group at the baseline evaluation.

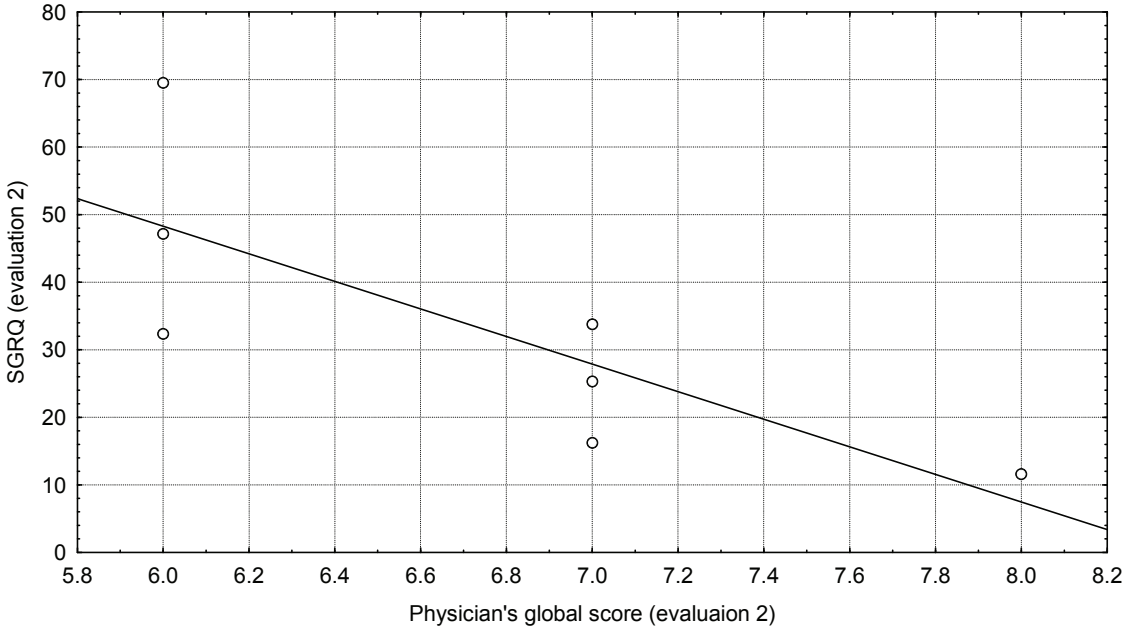

Figure 7.88 A scatter plot illustrating the correlation between the physician's global evaluation and SGRQ of the control group at the second evaluation.

A significant correlation was found between the physician's global evaluation and the SGRQ of the control group at the first ($p < 0.01$) and second evaluation ($p < 0.05$). No significant correlation was found between these values of the experimental group at the first ($p = 0.59$) or second evaluation ($p = 0.72$).

In the MP, a significant correlation was found between the SGRQ and the physician's global evaluation for the control group. A high score on the physician's global evaluation indicates a good overall condition of the patient, whereas a high score in the SGRQ indicates poor quality of life. Therefore, a negative correlation would be expected between these variables. However, this correlation was not present in the PP or experimental group. This indicates that an encouraging physician's evaluation does not necessarily translate into quality of life benefits. Although the physician's evaluation is of vital importance when treating COPD patients, this affirms the importance of the patient's own subjective perception of his/her disease.

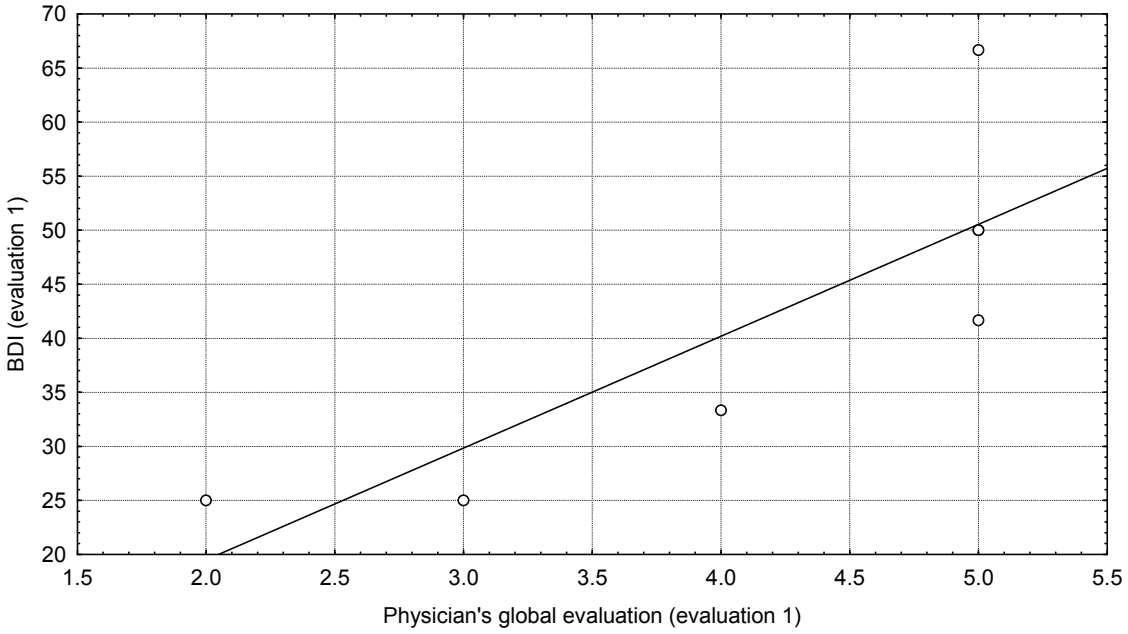

Figure 7.89 A scatter plot illustrating the correlation between the mean BDI and physician's global scores for the control group at the first evaluation.

A correlation was found between the mean BDI scores and the physician's global evaluation for the control group at the first evaluation ($p < 0.05$). No correlation was found for this group at the second evaluation ($p = 0.68$). No correlation between these variables was present for the experimental group at the first ($p = 0.70$) or second evaluation ($p = 0.91$).

No significant correlation was found between the physician's global evaluation and the 6MWT for the experimental group at the first ($p = 0.83$) or second evaluation ($p = 0.70$). No significant correlation was found between the physician's global evaluation and the 6MWT for the control group at the first ($p = 0.26$) or second evaluation ($p = 0.26$).

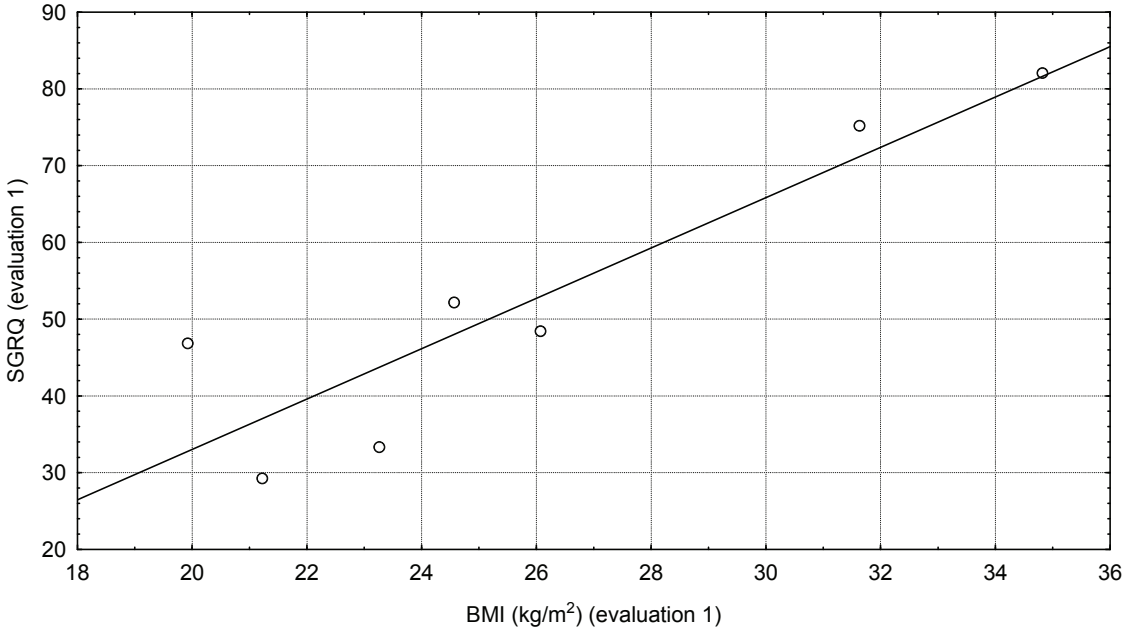

Figure 7.90 A scatter plot illustrating the correlation between the mean BMI and SGRQ scores of the control group at the first evaluation.

A significant correlation was found between the mean BMI and SGRQ scores of the control group at the first evaluation ($p < 0.01$). This correlation was not present at the second evaluation ($p = 0.20$). No correlation was found between these

variables for the experimental group at the first ($p = 0.11$) or second evaluation ($p = 0.19$).

Shoup and co-workers (1997) found that bodyweight has a direct effect on HRQL. According to these authors, underweight as well as overweight patients would have an impaired HRQL. This study did find a correlation between BMI and SGRQ scores for the control group at the first evaluation. However, this correlation was not present in the PP, or with the experimental group. The absence of this correlation could be attributed to the fact that there was no significant change in BMI from the first to the second evaluations. Furthermore, BMI has several limitations (as discussed in Chapter III), which would also influence possible correlations. Contrary to additional findings of Shoup and co-workers (1997), the present study found no correlations between SGRQ and BDI (Appendix J).

No significant correlation was found between the mean BMI and FEV_1 scores of the control group at the first ($p = 0.08$) or second ($p = 0.44$). No significant correlation was found between the mean BMI and FEV_1 scores of the experimental group at the first ($p = 0.61$) or second evaluation ($p = 0.30$).

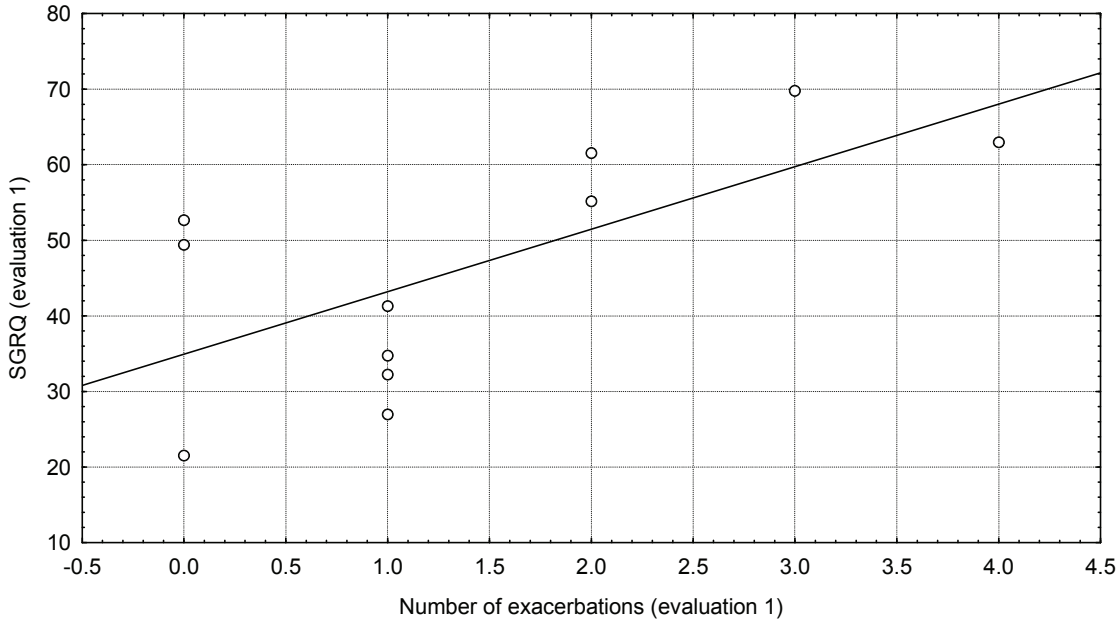

Figure 7.91 A scatter plot illustrating the correlation between the number of exacerbations and SGRQ scores of the experimental group at the first evaluation.

There was a significant correlation between the number of exacerbations and HRQL, as assessed by the SGRQ of the experimental group at the first evaluation ($p < 0.05$). This correlation was not present at the second evaluation of the experimental group ($p = 0.30$).

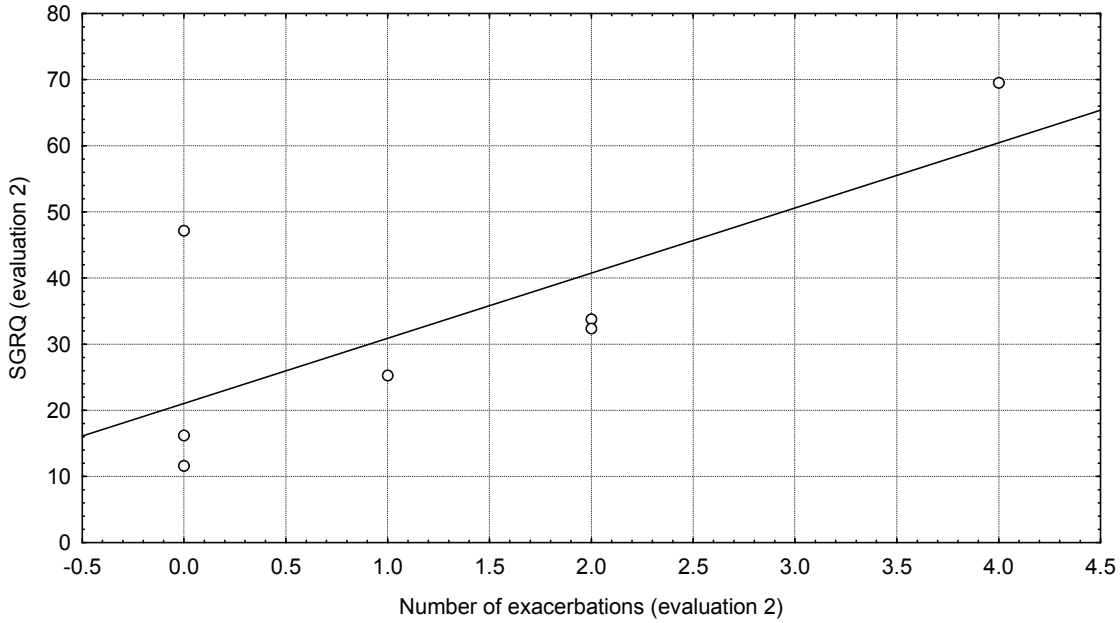

Figure 7.92 A scatter plot illustrating the correlation between the number of exacerbations and the SGRQ scores for the control group at the second evaluation.

There was a weak, but significant correlation between the number of exacerbations and HRQL, as assessed by the SGRQ of the control group at the second evaluation ($p = 0.05$). This correlation was not present at the first evaluation of the control group ($p = 0.27$).

Appendix M

Analyses of variables based on BDI-score

Primary programme

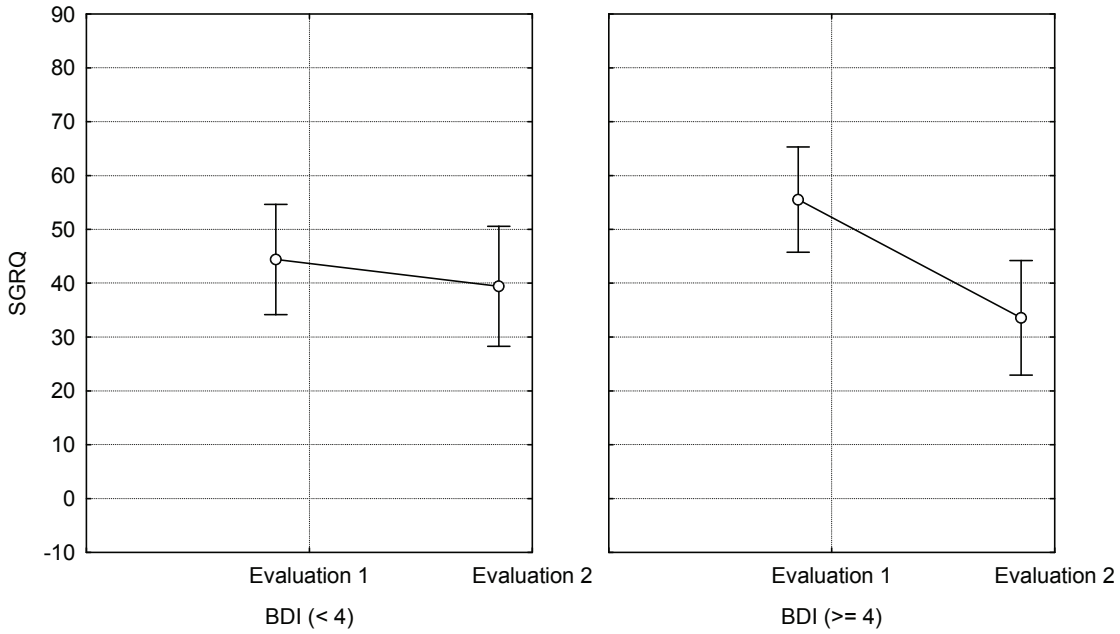

Figure 7.93 ANOVA graphs to illustrate the SGRQ-scores of the subjects when divided based on their BDI-scores.

Although figure 4.93 gives the impression that that subjects that were in the group that was less dyspnoeic had a greater improvement in SGRQ-scores, there was no statistically significant difference between the SGRQ-scores of the subjects in the two BDI groups ($p > 0.05$).

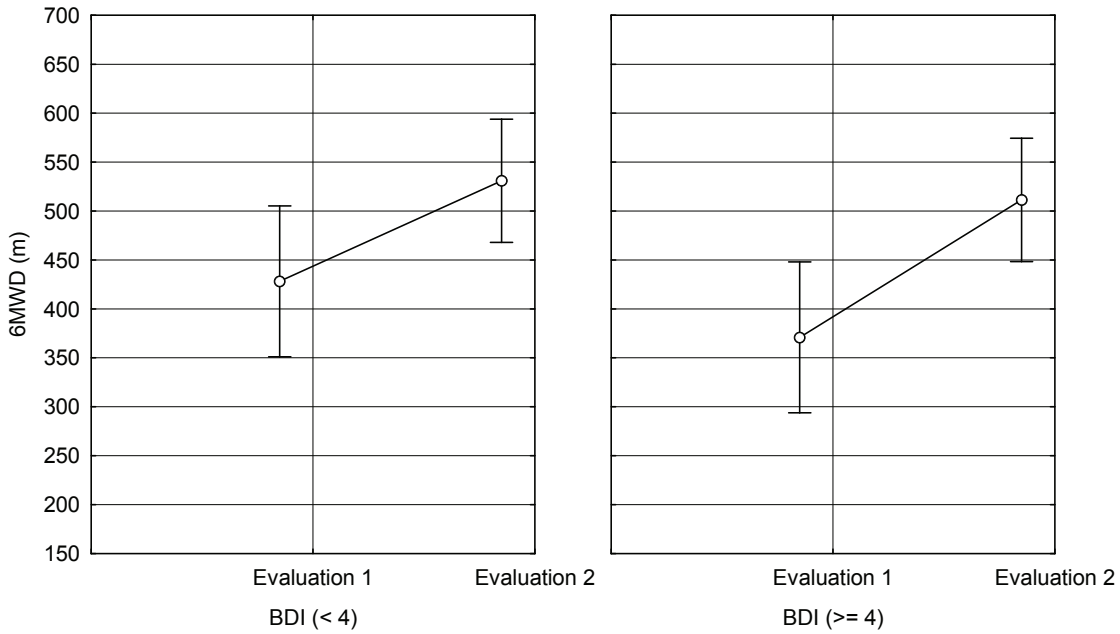

Figure 7.94 ANOVA graphs to illustrate the 6MWD of the subjects when divided based on their BDI-scores.

As illustrated in figure 7.94, there was no statistically significant difference between the 6MWD of the two groups at any of the two evaluations ($p > 0.05$).

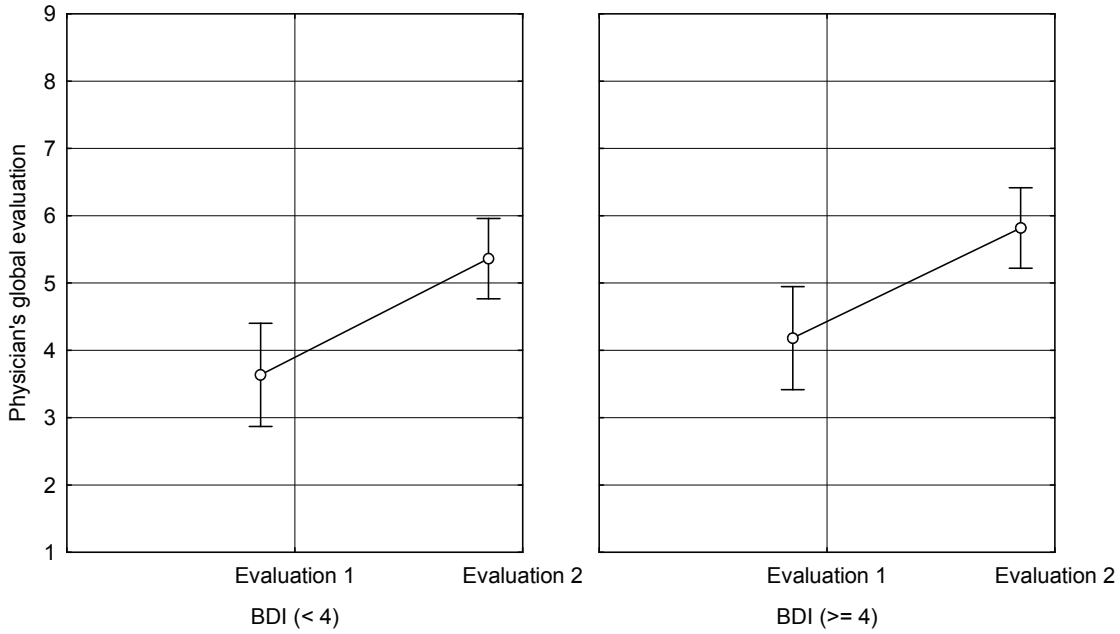

Figure 7.95 ANOVA graphs to illustrate the 6MWD of the subjects when divided based on their BDI-scores.

As illustrated in figure 7.95, there was no statistically significant difference between the physician's global evaluations of the two groups at any of the two evaluations ($p > 0.05$).

Modified programme

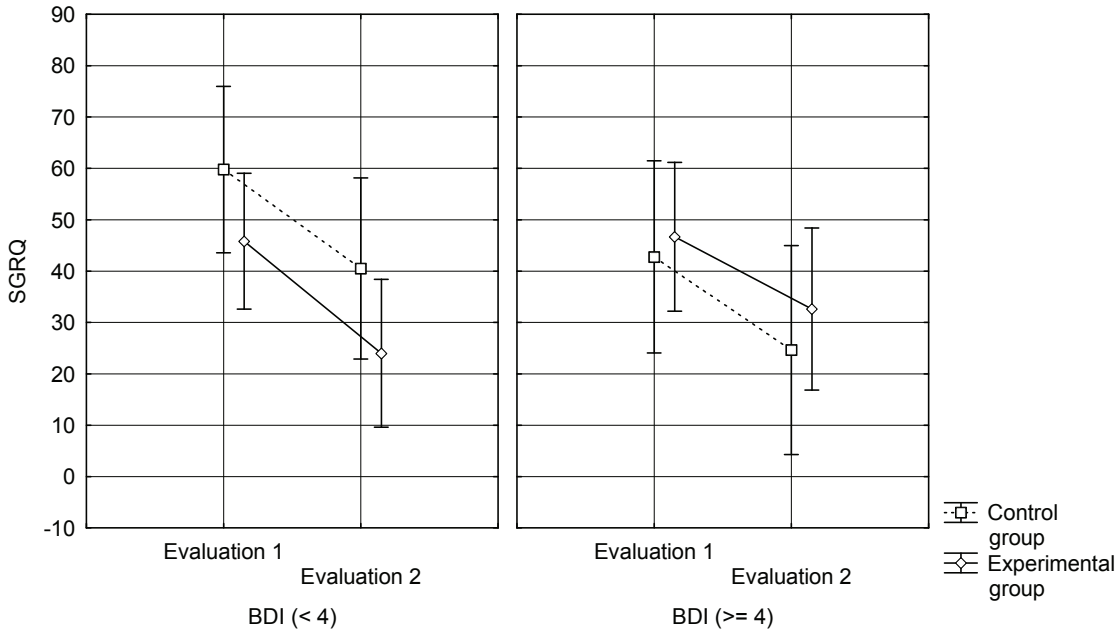

Figure 7.96 ANOVA graphs to illustrate the SGRQ of the subjects when divided based on their BDI-scores.

As illustrated in figure 7.96, there was no statistically significant difference between the SGRQ-scores of the two groups at any of the two evaluations ($p > 0.05$).

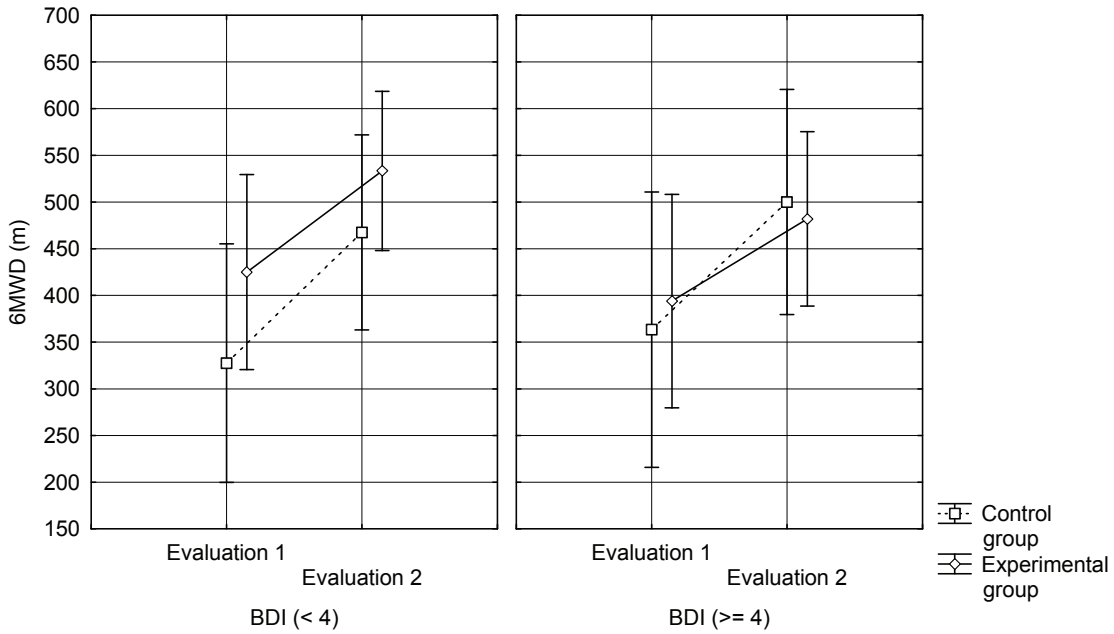

Figure 7.97 ANOVA graphs to illustrate the 6MWD of the subjects when divided based on their BDI-scores.

As illustrated in figure 7.97, there was no statistically significant difference between the 6MWD of the two groups at any of the two evaluations ($p > 0.05$).

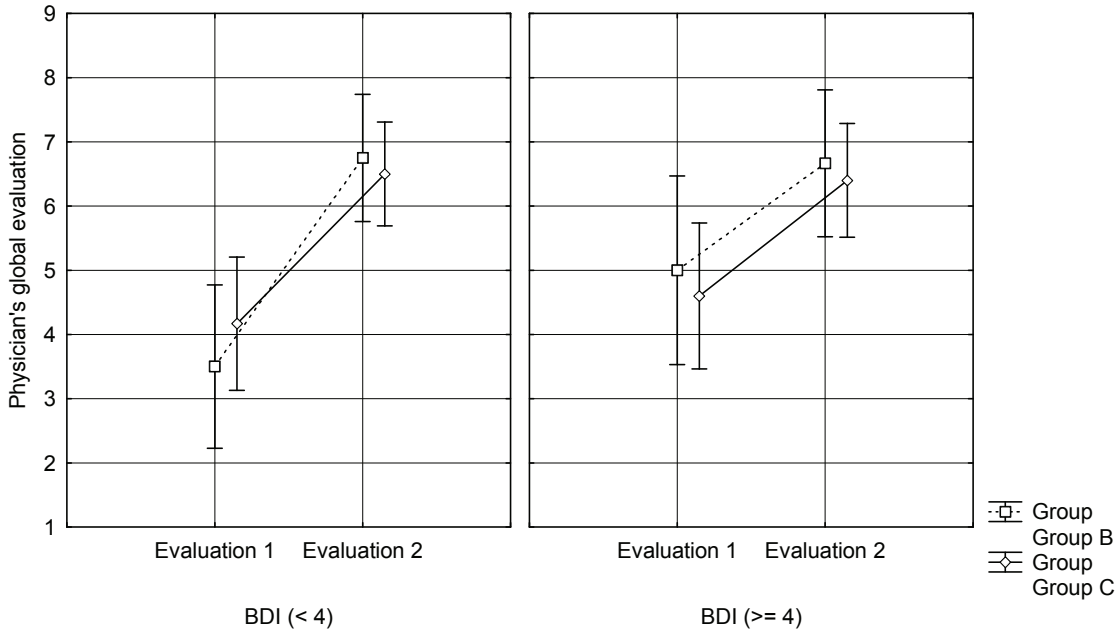

Figure 7.98 ANOVA graphs to illustrate the physician's global evaluations of the subjects when divided based on their BDI-scores.

As illustrated in figure 7.98, there was no statistically significant difference between the physician's global evaluations of the two groups at any of the two evaluations ($p > 0.05$).