

# **Exercise capacity and breathing pattern in patients with chronic obstructive pulmonary disease**

Predictors and longitudinal changes

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## Scientific environment

This doctoral thesis was performed in the period 2011-2015 and the scientific environment was the Bergen Respiratory Research Group, Department of Clinical Science, University of Bergen and Department of Thoracic Medicine, Haukeland University Hospital. This group is led by Professor S. Bakke. The thesis is anchored in the project “Bergen COPD Cohort Study”, which was led by professor Bakke until 2014, and now by Professor Tomas M.L. Eagan.

The work is a collaborative project with Centre for Evidence-Based Practice, Bergen University College, led by Professor Monica Wammen Nortvedt. The Bergen University College funded my PhD position, and I had my office at the Centre for Evidence-Based Practice during the work with this thesis. I was affiliated with the Regional Strategic Research Programme for Health and Social Science funded by the Regional Western Health Authority, led by Professor Nortvedt.

The supervisors during this work have been:

*Einar Thorsen*, physiologist, professor at Department of Clinical Science, University of Bergen.

*Birgitte Espehaug*, statistician, professor at Centre for Evidence-Based Practice, Bergen University College.

*Jon Andrew Hardie*, pulmonologist, professor at Department of Clinical Science, University of Bergen.

*Liv Inger Strand*, physiotherapist, professor at Physiotherapy Research Group, Department of Global Public Health and Primary Care, University of Bergen.

*Rolf Moe-Nilssen*, physiotherapist, professor emeritus at Physiotherapy Research Group, Department of Global Public Health and Primary Care, University of Bergen.

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## Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by expiratory flow limitation. The knowledge about factors contributing to the long-term changes in exercise capacity and breathing pattern in terms of the relationship between tidal volume ( $V_T$ ) and minute ventilation ( $\dot{V}_E$ ) in COPD is scarce. This thesis deals with issues related to long-term changes in exercise capacity and breathing pattern in COPD and potential predictors for the changes. The thesis is based on three studies.

Study I was a 3-years prospective cohort study, including 389 patients with COPD in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II-IV. We examined predictors for the longitudinal change in six-minute walking distance (6MWD). Study II was a cross-sectional study, including 63 COPD patients performing a cardiopulmonary exercise test (CPET) on treadmill. We aimed to study if a quadratic equation ( $V_T = a + b \cdot \dot{V}_E + c \cdot \dot{V}_E^2$ ) could describe the breathing pattern in terms of the relationship between  $\dot{V}_E$  and  $V_T$  during incremental exercise in COPD. Study III was a longitudinal cohort study, where the 63 COPD patients performed two CPETs with a mean time of 4.5 years between the tests. The longitudinal changes in peak oxygen uptake ( $\dot{V}O_{2peak}$ ) and breathing pattern as well as potential explanatory variables of change were examined.

The 6MWD decreased significantly during the observation period in GOLD stage III ( $B = -36$ , 95 % Confidence Interval (CI): -51 to -7,  $p=0.009$ ) and IV ( $B = -79$ , 95 % CI: -125 to -20,  $p=0.007$ ), while patients in GOLD stage II maintained their walking distance. Predictors for the longitudinal change in 6MWD were self-reported hard physical activity and  $FEV_1$ . The fraction of subjects performing hard physical activity at three years was higher in those who had participated in a pulmonary rehabilitation program during the observation period, odds ratio 2.4 (95 % CI 1.4–4.2,  $p=0.001$ ).



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In Study II we found that a quadratic model could describe the relationship between  $\dot{V}_E$  and  $V_T$  in 59 of 63 COPD patients ( $p < 0.05$ ) and the linear coefficient (b) was negatively ( $p = 0.001$ ) and the quadratic coefficient (c) positively ( $p < 0.001$ ) related to  $FEV_1$ .

In Study III,  $\dot{V}O_{2peak}$  and  $FEV_1$  deteriorated significantly during follow-up. The reduction in  $\dot{V}O_{2peak}$  was related to baseline  $\dot{V}O_{2peak}$  ( $p < 0.001$ ), the changes in resting inspiratory capacity (IC) ( $p = 0.005$ ) and  $FEV_1$  ( $p = 0.031$ ), age ( $p = 0.023$ ) and smoking during follow-up ( $p = 0.021$ ). A higher baseline  $\dot{V}O_{2peak}$ , a larger decrease in IC and  $FEV_1$  and higher age were associated with a larger reduction in  $\dot{V}O_{2peak}$ . The quadratic model described the relationship between  $\dot{V}_E$  and  $V_T$  in 61 of 63 patients at CPET1 and at 59 of 63 patients at CPET2. The linear coefficient (b) increased ( $p = 0.007$ ) and the quadratic coefficient decreased significantly ( $p = 0.002$ ) from CPET1 to CPET2. Maximal  $V_T$  was achieved at a lower  $\dot{V}_E$ . The changes in the curve parameters were all related to the change in  $FEV_1$ .

We have concluded that exercise capacity deteriorates over time in COPD, and that the longitudinal change is related to the decline in lung function. Persistent smoking is associated with a larger decline, while high habitual physical activity is associated with a lower decline in exercise capacity. The longitudinal change in breathing pattern is associated with the reduction in lung function. Any relationships between exertional dyspnea and changes in breathing pattern need further studies.

## List of publications

### Paper I

Frisk B, Espehaug B, Hardie JA, Strand LI, Moe-Nilssen R, Eagan TM, Bakke PS, Thorsen E. (2014): Physical activity and longitudinal change in 6-min walk distance in COPD patients. *Respir Med.* Jan;108(1):86-94

### Paper II

Frisk B, Espehaug B, Hardie JA, Strand LI, Moe-Nilssen R, Eagan TM, Bakke PS, Thorsen E. (2014): Airway obstruction, dynamic hyperinflation, and breathing pattern during incremental exercise in COPD patients. *Physiol Rep.* Feb 7;2(2):e00222. Doi: 10: 1002/phy2.222.

### Paper III

Frisk B, Hardie JA, Espehaug B, Strand LI, Moe-Nilssen R, Eagan TM, Bakke PS, Thorsen E. (2015): Peak oxygen uptake and breathing pattern in COPD patients – a four year longitudinal study. Submitted

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## Abbreviations

6MWD	6-min Walk Distance
6MWT	6-min Walk Test
ATS	American Thoracic Society
BCCS	Bergen COPD Cohort Study
B <sub>f</sub>	Breathing frequency
BMI	Body Mass Index
BTPS	Body Temperature Pressure Saturated
CI	Confidence Interval
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardio Pulmonary Exercise Test
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
EELV	End-Expiratory Lung Volume
EILV	End-Inspiratory Lung Volume
ERS	European Respiratory Society
ESWT	Endurance Shuttle Walk Test
FEV <sub>1</sub>	Forced Expiratory Volume in one second
FFMI	Fat Free Mass Index
FMI	Fat Mass Index
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GEE	Generalized Estimating Equations
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Heart Rate
IC	Inspiratory Capacity
IRV	Inspiratory Reserve Volume

ISWT	Incremental Shuttle Walk Test
MCID	Minimal Clinical Important Difference
mMRC	modified Medical Research Council
PaO <sub>2</sub>	Partial pressure of Oxygen in arterial blood
PO <sub>2</sub>	Partial pressure of Oxygen
RV	Residual Volume
SaO <sub>2</sub>	Arterial Oxygen Saturation
SpO <sub>2</sub>	Oxygen Saturation measured with pulse oximetry
SD	Standard Deviation
STPD	Standard Temperature Pressure Dry
SV	Stroke Volume
TLC	Total Lung Capacity
$\dot{V}CO_2$	Carbon Dioxide Production
$\dot{V}_E$	Minute Ventilation
$\dot{V}O_2$	Oxygen Uptake
V <sub>T</sub>	Tidal Volume

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## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by expiratory flow limitation (1), and is a leading cause of mortality and morbidity worldwide (2, 3). The prevalence of the disease is expected to increase in the coming decades (3) and the economic and social burden is substantial and increasing (2, 3). COPD accounts for a significant portion of the costs of health care in high income countries (4, 5) and there is a relationship between the disease severity and the cost of care (1).

Dyspnea is usually the major symptom in patients with COPD, and is defined as “*a subjective experience of breathing discomfort that consists of qualitatively distinct sensation that varies in intensity*” (6). The individual’s sensation of dyspnea is related to the reduction in breathing capacity, which in turn is related to the volume of each breath and breathing frequency (7-9). Dyspnea is frequently the cause of exercise limitation (8, 10-12), leading to inactivity and reduced participation in activities of daily living (13, 14). During the time course of COPD, the disease severity usually progresses with further deterioration of lung function (15, 16) and reduced exercise capacity (17-19).

The knowledge about factors contributing to long-term changes in exercise capacity and ventilatory capacity, including breathing pattern in terms of the relationship between tidal volume and ventilation is scarce in patients with COPD. The objectives of the present thesis were therefore to examine long-term changes in exercise capacity and breathing pattern in patients with COPD and to examine potential predictors for the changes. These questions were addressed in the three studies of the present thesis.



## 1.1 Chronic obstructive pulmonary disease (COPD)

### 1.1.1 Definition

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined COPD in the following way: *“a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients”* (1).

COPD is not curable, and known risk factors for developing the disease are cigarette smoking and occupational and environmental exposures including dusts and chemicals (1).

### 1.1.2 Epidemiology

COPD is today the fourth leading cause of death worldwide (20) and the burden of COPD is expected to increase in the coming decades. In 2030 COPD is predicted to be the third leading cause of death (20). The prevalence of COPD is estimated to be around 9-10 % in the population older than 40 years in the Western world (21), with variations between countries and across different groups within countries (1). In Norway the prevalence is around 7-10 % (22, 23). There are variations in the prevalence estimates due to differences in diagnostic criteria, survey methods, and analytic methods (21). Still COPD may be largely undiagnosed (24-26), because some persons may have major reduction in lung function before they experience that the symptoms are limiting their participation in activities of daily living (1).

### 1.1.3 Diagnosis

COPD is characterized by irreversible airflow limitation with permanently reduced lung function (1). Airflow limitation is assessed with spirometry measuring the forced vital capacity (FVC) which is the total volume of gas that can be expired from total lung capacity (TLC) with maximal effort. Forced expiratory volume in one second ( $FEV_1$ ) is the volume of gas expired in the first second (27).  $FEV_1$  and the  $FEV_1/FVC$  ratio are related to the maximal expiratory flow rates during the forced expiratory manoeuvre, and  $FEV_1$  and  $FEV_1/FVC$  ratio are used to evaluate the severity of airflow limitation (27). COPD is categorized into four stages according to the GOLD-2007 classification (1) (Table 1). The common criterion for all categories is a post bronchodilator  $FEV_1/FVC < 0.70$ , and the severity is increasing with an increasing reduction in  $FEV_1$ .

**Table 1.** The GOLD-2007 classification of COPD

Classification of severity of airflow limitation in COPD (Based on post bronchodilator $FEV_1$ )		
GOLD 1:	Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 \leq 50\%$ predicted
GOLD 4:	Very severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted

GOLD: Global Initiative for Chronic Obstructive Lung Disease;  $FEV_1$ :

Forced Expiratory Volume in one second; FVC: Forced Vital Capacity

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<http://www.goldcopd.org>.

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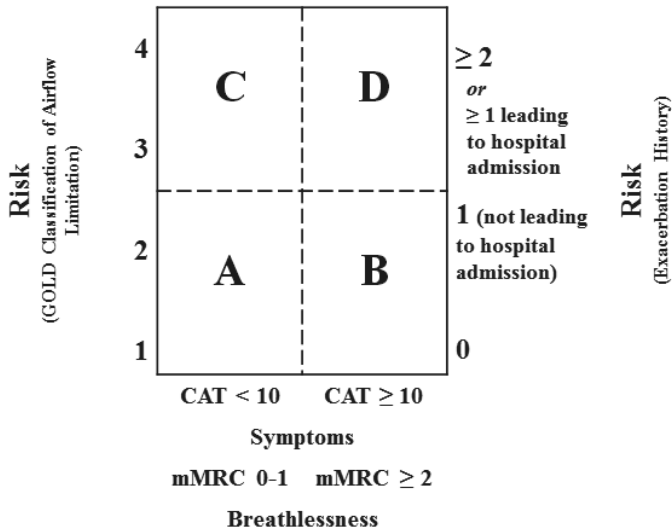
Since the GOLD classification (staging) system was first presented in 2001, the knowledge about COPD and its extrapulmonary features has increased. The original guideline was based on FEV<sub>1</sub>, because at that time, it was believed that the disease severity was tracked by the severity of airflow obstruction in the majority of patients (1). The use of FEV<sub>1</sub>/FVC < 0.7 ratio to define airflow limitation has resulted in more frequent diagnosis of COPD in the elderly (28) and less in adults younger than 45 years (29).

In 2011 the GOLD Scientific committee presented a new approach for clinical grading of COPD (Figure 1) (1). The disease severity was determined by assessing airflow limitation, the impact on the patient's health status, and the frequency of exacerbations and hospital admission. The superiority of the new 2011 GOLD classification compared with the GOLD-2007 classification still needs to be established. In a study by Johannessen et al. (30) a comparison between GOLD- 2011 and GOLD- 2007 in terms of predicting mortality and hospitalization was examined. They concluded that the predictive power between these two did not differ significantly.

Exacerbation of COPD is defined as worsening of the patient's respiratory symptoms beyond normal day to day variation which may lead to a change in medication (31-33). Exacerbations have negative influence on quality of life in the individual patient (32, 34). The recovery time after exacerbations regarding symptoms and lung function can be several weeks, and lung function may show a permanent decline after recovery (35, 36). Exacerbations in COPD are associated with mortality and have high socioeconomic costs (37).

Patients with COPD often have other coexisting diseases (comorbidities) (1). These diseases can either occur independently of COPD or be causally related. Comorbidity can occur regardless of disease severity. The most common comorbidities in COPD are cardiovascular disease, hypertension, osteoporosis, lung cancer, infections (especially respiratory infections), bronchiectasis, anxiety and depression.

The combined COPD assessment (1) including symptom scores, breathlessness, spirometric classification and exacerbation history is illustrated in Figure 1.



**Figure 1.** Assessment of COPD with risk factors according to the GOLD grading system including assessment of symptoms, breathlessness, spirometric classification and exacerbations history.

mMRC: Modified British Medical Research Council; CAT: COPD Assessment Test

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Another multidimensional grading system developed to assess respiratory and systemic expression of COPD is the BODE index, which includes the body-mass index (B), the degree of airflow obstruction (O), dyspnea (D) and exercise capacity (E) measured by the 6-minute walk test (38). The BODE index has been shown to be better than FEV<sub>1</sub> alone to predict risk of death (38).

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### 1.1.4 Management

The management of COPD can be divided into pharmacologic and non-pharmacologic treatment (1). The recommended non-pharmacologic treatment includes smoking cessation, pulmonary rehabilitation, exercise training, physical activity and oxygen therapy (1).

#### *Smoking cessation*

Cigarette smoking is identified as the most common risk factor for COPD, and smoking cessation is the intervention that with greatest significance can influence the natural development of COPD. Pharmacotherapies for smoking cessation are nicotine replacement products that have shown to decrease the long-term abstinence better than placebo (39-41).

The most important intervention for all patients with COPD, who still smoke, regardless of disease severity, should therefore be smoking cessation (1).

#### *Pulmonary rehabilitation*

The definition of pulmonary rehabilitation according to American Thoracic Society (ATS) and European Respiratory Society (ERS) Statement is as follows (14):

*“Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behavior.”*

A pulmonary rehabilitation program includes a combination of education, exercise training and strategies for behavioral change. It is recommended that treatment should

be tailored to the individual patient's need, based on initial and ongoing assessments according to disease severity, comorbidities and complexity (13, 14).

The settings for pulmonary rehabilitation as described in the ATS/ERS Statement (14) can be conducted in inpatient and outpatient settings. Outpatient settings can include outpatient clinics at hospitals, community facilities and physiotherapy clinics.

Inpatient rehabilitation can find place at rehabilitation departments at hospitals, or during inpatient acute care, for example at intensive care units (14). In addition, exercise training can also be provided in the patient's home.

There is no consensus about the optimal duration of pulmonary rehabilitation programs (19). However, longer programs are considered to provide greater gains and benefits, and a minimum of 8 weeks is recommended (42-44). Programs longer than 12 weeks have shown greater benefits than shorter programs (43, 45, 46). The number of sessions per week in a pulmonary rehabilitation program varies, but two or three days per week are common in outpatient settings, while five days per week is common in inpatients settings (47, 48).

### *Exercise training*

Exercise training is considered as the cornerstone in a pulmonary rehabilitation program, but what is the distinction between physical activity and exercise? These terms describe different concepts, but are often used interchangeably. Physical activity is defined as *“any bodily movement produced by skeletal muscles that result in energy expenditure”* (49). Physical activity in daily life can be categorized as household, sports, conditioning, occupational or other activities. Exercise is defined as *“a subset of physical activity that is planned, structured, and repetitive and has a final or an intermediate objective of the improvement or maintenance of physical fitness”* (49).

Exercise training does not improve lung function or gas exchange (50), but improves the function of other body systems so the effect of reduced lung function is

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minimized. Gains from exercise training are increased exercise tolerance, reduced dyspnea and increased health-related quality of life (51). The deconditioned skeletal-muscle function is improved by exercise training as a result of changes in muscle biochemistry; higher work rates can be tolerated without substantial lactic acidosis (52). The sensation of dyspnea is improved after pulmonary rehabilitation, because exercise training and breathing techniques reduce the ventilatory requirement and respiratory rate, prolonging the time for expiration and thereby reducing dynamic hyperinflation (53).

Exercise training in a pulmonary rehabilitation program should, according to the ATS/ERS Statement (14), consist of a combination of endurance and resistance (or strength) training. The endurance training can either be continuous or interval based. Interval training consists of periods with high intensity exercise alternated with periods of low intensity exercise. Interval training may show to result in lower symptom scores (54), but not at the cost of the effects of the training (54-56). However, previous studies have not found any clinically important differences in effect between interval and continuous training regarding exercise capacity, health-related quality of life, and improvements in skeletal muscles (55, 57-62), and these training modalities appear to be equally effective. In symptom-limited patients who are unable to tolerate high-intensity continuous training, interval training is preferred (14).

### *Breathing techniques*

Breathing techniques are often a part of pulmonary rehabilitation program (63) and focus on slowing the respiratory rate, primarily by prolonging the expiration. This can be useful in reducing dyspnea in patients having dynamic hyperinflation (64). Different breathing strategies can be pursed-lips breathing (65), yoga breathing and computer-aided breathing feedback (66). Patients who undergo breathing training have shown an adaptation to a slower and deeper pattern of breathing (66). Pursed-

lips breathing have reduced dyspnea after a walk test (65), and computer-aided breathing feedback has shown reduced dynamic hyperinflation (65).

Decreased anxiety and depression are also demonstrated after pulmonary rehabilitation, and are thought to occur as a consequence of increased exercise capacity, increased activities of daily living and in turn increased experience of mastering (51).

In patients with COPD, the short-term effect of pulmonary rehabilitation has demonstrated a reduction in dyspnea, increased exercise capacity and improved quality of life (13). Without any strategies to maintain benefits after pulmonary rehabilitation, the effects seem to diminish after 6-12 months, with quality of life being better maintained than exercise capacity (67-69).

### *Physical activity*

Daily physical activity is recommended for all patients with COPD (70), however, research evidence that support this recommendation is scarce. Physical inactivity is common in these patients and found to be associated with poor outcomes, independent of the degree of reduced lung function (71). Activity monitors have been developed to measure activity, and are increasingly being included to quantify activity in pulmonary rehabilitation (70).

### *Oxygen therapy*

Long-term oxygen treatment (>15 hours per day) is indicated in patients who have a resting partial pressure of arterial oxygen ( $\text{PaO}_2$ ) below 7.3 kPa or arterial oxygen saturation ( $\text{SaO}_2$ ) values of 88 % or lower with or without hypercapnia. These measurements have to be confirmed twice over a period of three weeks (1). Another indication for long-term oxygen treatment can be  $\text{PaO}_2$  between 7.3 and 8.0 kPa, or



SaO<sub>2</sub> of 88 %, if there is pulmonal hypertension, cardiac failure or polycythemia (1). A decision about this treatment should be based on resting PaO<sub>2</sub> or SaO<sub>2</sub> in stable patients (1).

### *Pharmacologic treatment*

In stable COPD, pharmacologic treatment is used to improve lung function and to reduce symptoms, improve health status, improve exercise tolerance, and reduce the frequency and number of exacerbations (1, 13, 51). The overall goal is to optimize the medical treatment to the individual patient using the GOLD-2011 grading assessment as a guideline (1). However, the existing medications for COPD have not conclusively demonstrated attenuation of the long-term deterioration in lung function (72-75).

## 1.2 Patophysiology and exercise limitation in COPD

The cause of exercise intolerance in patients with COPD is multifactorial and related to disease severity. Contributing factors can be, either alone or in combination, ventilatory constraints, dyspnea, development of dynamic hyperinflation, gas exchange abnormalities, cardiac limitation and peripheral and respiratory muscle dysfunction (76-78).

### 1.2.1 Pathophysiology

COPD is characterized by persistent airway limitation. Maximal expiratory flow rates are determined by airway diameter and compliance of the airway wall (79), and FEV<sub>1</sub> is the integrated sum of maximal expiratory flow rates in the first second (80).

Chronic inflammatory processes contribute to loss of elastic tissue in the lung parenchyma (81). The mechanical support of the airway walls is reduced, increasing the compliance and thereby the airways are more prone to collapse (81, 82).

Furthermore, loss of elastic tissue in the lung parenchyma increases lung compliance and lung elastic recoil is reduced (82). Over time, the destruction of lung parenchyma lead to loss of alveolar surface area and reduced gas exchange capacity (82).

The functional residual capacity (FRC) and closing volume will increase due to reduced lung elastic recoil and increased airway collapsibility (83). Lung hyperinflation is defined as increased FRC or end-expiratory lung volume (EELV) above the normal (83). EELV is the volume air remaining in the lungs after a spontaneous expiration (84, 85). FRC is the equilibrium volume of the lung and chest. FRC and EELV are normally equal with resting breathing, but not with increased ventilatory demands. In normal subjects EELV becomes lower than FRC during exercise (84, 85).

Patients with COPD can have hyperinflated lungs at rest (static hyperinflation) and increasing EELV in response to progressively increasing exercise load and ventilatory demand (dynamic hyperinflation) (86). Hyperinflation in COPD has been shown to contribute to the sensation of dyspnea (87) and morbidity (88). An increased end-inspiratory lung volume (EILV) has been shown to increase the sensation to dyspnea and reduce exercise capacity (10, 89). A critically low inspiratory reserve volume (IRV) defined as a reduction in IRV around 0.5 L or below 10 % of TLC, has also found to be related to increased dyspnea (7, 9).

### **1.2.2 Ventilatory limitation and dynamic hyperinflation**

The minute ventilation ( $\dot{V}_E$ ) is the product of the tidal volume ( $V_T$ ) and the breathing frequency ( $B_f$ ) (90, 91). At a given  $\dot{V}_E$ , the  $V_T$  is lower and the  $B_f$  is higher in patients with COPD compared to healthy subjects, which means that dead space ventilation is

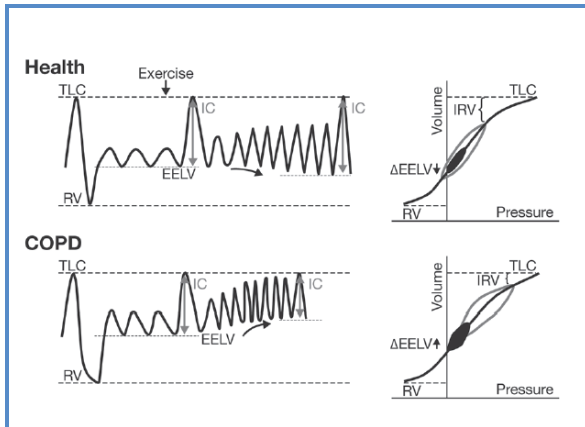
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higher (92). Ventilatory capacity or maximal  $\dot{V}_E$  is related to maximal expiratory flow rates and  $FEV_1$  (92). A breathing reserve less than 15 % is considered as a ventilatory limitation (93).

The maximal  $V_T$  during exercise is typically about 50% of the vital capacity (94). There is a mechanical constraint on the inspiratory side because of the pressure-volume characteristics of the lung and chest wall where the volume gain at some point will be low or minimal with respect to inspiratory effort. On the expiratory side, mechanical constraint on  $V_T$  is the residual volume (RV), but with COPD the time constant of the lung is increased and the drive for the next inspiration may start before expiration is completed. Thus, there is a dynamic constraint on  $V_T$ . The time constant is the product of resistance and compliance, both of which are increased in COPD (95). As a result, EELV increases and breathing takes place at a higher lung volume (dynamic hyperinflation) where both compliance and resistance are lower. The consequences for these compensatory mechanisms is a shorter time constant allowing complete breathing cycles, but it is at the cost of higher work of breathing (95, 96) and the sensation of dyspnea is increased.

In patients with severe COPD, the  $V_T$  during exercise increases quickly and reaches a critically low inspiratory reserve volume (IRV), or the  $V_T$  plateau. This leads to a discrepancy between the effort of the respiratory muscle and the volume displacement achieved (9).

Hyperinflation during exercise is illustrated in Figure 2. (97, 98)



**Figure 2.** Lung volumes and tidal pressure-volume curves during exercise in healthy subjects and in patients with COPD.

EELV: End-Expiratory Lung Volume; IC: Inspiratory Capacity; TLC: Total Lung Capacity; RV: Residual Volume; IRV: Inspiratory Reserve Volume.

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Thomas M., Decramer M., O'Donnell DE. No room to breathe: the importance of lung hyperinflation in COPD. *Prim Care Respir J* 2013; 22(1): 101-111. Official Journal of the Nature Publishing Group.

O'Donnell DE. Hyperinflation, dyspnea, and exercise tolerance in chronic obstructive pulmonary diseases. *Proc Am Thorac Soc.* 2006 Apr;3(2): 180-184. Official Journal of the American Thoracic Society.

### 1.2.3 Gas exchange limitation

The uptake of oxygen is described by the Fick's equation:  $\dot{V}O_2 = \dot{Q} (C_{aO_2} - C_{\bar{v}O_2})$ .  $\dot{V}O_2$  is the oxygen consumption,  $\dot{Q}$  is cardiac output (CO),  $C_{aO_2}$  is the oxygen concentration in arterial blood and  $C_{\bar{v}O_2}$  is the oxygen concentration in the mixed venous blood entering the lungs. The oxygen uptake is proportional with the product of cardiac output and the arteriovenous oxygen difference.

Oxygen is bound to hemoglobin, which is 97.5 % saturated at a partial pressure of oxygen ( $PO_2$ ) of about 13 kPa (99), and an increase in  $PO_2$  beyond 13 kPa increases the oxygen content in arterial blood by increasing the dissolved fraction only, which is

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very low (99). At a lower  $PO_2$ , the oxygen content of blood decreases abruptly about 8 kPa as determined by the oxygen-hemoglobin dissociation curve. The oxygen concentration in arterial blood and pulmonary capillary blood is normally not very different unless the shunt fraction is increased. Gas transfer over the alveolocapillary membrane is by diffusion, and is dependent on the alveolar surface area, thickness of the membrane and the pressure difference of the gas over the membrane (99). In COPD, the number of alveoli is decreased and alveolar volume is increased resulting in a decreased alveolar surface area. The alveolar capillary blood volume is decreased (100). The ventilation – perfusion ratio ( $\dot{V}/\dot{Q}$ ) gives the partial pressures of  $O_2$  and  $CO_2$  in a gas exchange unit. Units with a high  $\dot{V}/\dot{Q}$  ratio will have a high  $PO_2$ , but their contribution to the oxygen content in arterial blood is marginal since hemoglobin is saturated (100). These units contribute to increased alveolar dead space. Units with a low  $\dot{V}/\dot{Q}$  ratio will have a low  $PO_2$ , and may contribute to a substantial reduction in oxygen content in arterial blood (100).

The efficiency of pulmonary gas exchange is judged by the extent of the alveolar-arterial oxygen difference  $P_{(A-a)}O_2$ . Any gas diffusion limitation or  $\dot{V}/\dot{Q}$  mismatch will result in a higher alveolar – arterial  $PO_2$  difference (100). Normally the  $PaO_2$  does not decrease during exercise and  $P_{(A-a)}O_2$  at peak exercise remains low. A  $P_{(A-a)}O_2$  at peak exercise  $>4$  kPa is defined as abnormal (101, 102) and is accompanied by arterial desaturation (103).

Hypoxemia can limit exercise tolerance directly by increasing the pulmonary ventilation through augmenting chemoreceptor output and indirectly by increasing the production of lactic acid (104). During increasingly higher exercise intensity, anaerobic metabolism increases the lactic acid production and contributes to muscle task failure and increased ventilation (104). Supplemental oxygen therapy in patients with COPD, in both hypoxemic and non-hypoxemic patients, has shown to allow for higher exercise intensity. Possible explanations are decreased pulmonary arterial pressure, reduced lactic acid production and reduction in dynamic hyperinflation because of a reduction in respiratory rate (104-109).

### **1.2.4 Cardiac limitation**

CO is the product of heart rate (HR) and stroke volume (SV). HR increases linearly with  $\dot{V}O_2$ , and CO normally increases to a maximum of four to five times resting CO (110). The oxygen pulse is the ratio of  $\dot{V}O_2$  to HR and is oxygen uptake per heartbeat. In fit individuals the oxygen pulse is higher at a given oxygen uptake because of higher SV, and it may be reduced in respiratory patients because of cardiac dysfunction. Maximum HR remains unchanged with fitness, but declines with increasing age, and an increased CO is due to an increment in SV (110). In respiratory patients, the peak HR is often less than predicted value because ventilatory limitation and dyspnea cause an interruption of the exercise before maximal values are reached. The heart rate reserve is usually high in COPD (93).

The cardiovascular system can be affected by chronic lung disease due to increased right ventricular afterload which can result in hypertrophy of the right ventricle and right ventricular failure. Contributing factors to cardiovascular dysfunction during exercise can be hypoxic vasoconstriction (111), increased vascular resistance due to erythrocytosis (112), tachyarrhythmia and elevated right arterial pressure (113).

### **1.2.5 Skeletal muscle dysfunction**

The skeletal muscles consist of two fiber types: type I and II. The type I (or slow-twitch) fibers need a relatively long time to develop peak tension, mostly determined by its myosin-adenosine triphosphates (ATPase) (110). These fibers have high concentrations of oxidative enzymes, high mitochondrial content and high myoglobin concentration. Thus, the type I fibers are resistant to fatigue; the oxidative capacity is high and the glycolytic capacity low. The type II (or fast twitch) muscle fibers have relatively short time to peak tension, and have poor fatigue resistance and oxidative capacity, but have high glycolytic capacity. The type II fibers are classified into type IIa and type IIx. Type IIa fibers have high mitochondrial content and myoglobin

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concentration and have some oxidative capacity, while the mitochondrial content and myoglobin concentration are low in type IIx fibers and there is little oxidative capacity (110).

The recruitment of fiber types depends on the form of exercise. During low-intensity exercise mainly the type I fibers tend to be recruited, while type II fibers are recruited at higher intensity, at or above 70 % to 80 % of maximal aerobic power (114).

Dysfunction of the lower limb muscles is a consequence of COPD and causes limitation in exercise capacity, physical activity, quality of life and morbidity (115-117). Patients with COPD are often deconditioned as a result of inactivity, and muscle atrophy with reduced muscle strength is present. Lower quadriceps strength predicts mortality in COPD (116). The lower limb cross-sectional area and capillarization are reduced, and loss of muscle fiber type I in favour of an increase in type IIx is reported (118-120). Thus, the aerobic muscle metabolism is reduced and production of lactic acidosis for a given exercise work rate increases the ventilatory needs.

### **1.2.6 Respiratory muscle dysfunction**

In patients with COPD the respiratory muscles may be overloaded due to the increased work of breathing. The diaphragm has adapted to the chronic overload and has developed greater resistance to fatigue (121, 122). As a result, the inspiratory muscles in patients with COPD have shown to be capable of generating more pressure as compared to healthy subjects with identical lung volumes (123, 124). However, the respiratory muscles are placed at a mechanical disadvantage and despite the increased ability of the diaphragm to generate force; both inspiratory muscle strength (125) and endurance (126) are compromised. The respiratory muscle dysfunction contributes to hypercapnia (127), dyspnea (128, 129), nocturnal oxygen desaturation (130), and reduced exercise performance (131).

### 1.3 Assessment of exercise capacity

Exercise tolerance (or intolerance) can reflect the level of disability. Exercise tests can be used to measure exercise capacity and can be grouped into diagnostic tests and field tests.

#### *Cardiopulmonary exercise test (CPET)*

The CPET is recommended as the gold standard for evaluating cardiorespiratory fitness in patients with COPD (103). The test is based on the principles that system failure occurs when the cardiovascular system, the pulmonary system and/or the muscles are under stress. CPET can provide an objective measurement of exercise capacity, identify the mechanisms limiting exercise tolerance and evaluate effects of interventions (103). The symptom-limited CPET is an incremental test, and is usually performed on treadmill or cycle-ergometer. To measure the patients' endurance capacity a constant-load cycle or treadmill test can be used instead of incremental CPET. Comparisons between these two tests have indicated that the incremental CPET is suitable to describe system abnormalities, but less suitable than the constant-load endurance test to discriminate improved exercise capacity after interventions (93, 103).

#### *Timed walk tests*

The field tests consist mostly of walk tests like six-minute walk test (6MWT) (132), incremental shuttle walk test (ISWT) (133) and endurance shuttle walk test (ESWT) (134).

6MWT is the most commonly used walk test and the distance walked (6MWD) is the main outcome. Oxygen saturation is measured with pulse oximetry ( $SpO_2$ ), and perception of dyspnea is registered at rest and at the end of the test (135). The



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minimal clinical important difference (MCID) for COPD has been reported to be 54 m (136), while in recently published studies lower MCID values have been reported, varying between 25 to 35 m (137). In a recently published review a MCID of 30 m is suggested (137). A detailed guideline for test performance of the 6MWT was given in 2002 (135), but the knowledge about performing and interpretation of the 6MWT has increased and a new technical standard was published in 2014 (138).

The ISWT (133) and ESWT (134) are externally paced tests performed over a 10 m course. Paced tests are more standardized than 6MWT since the walking speed is set. ISWT is a symptom-limited maximal exercise capacity test; the walking speed is increased during the test until the maximum exercise level is reached. ESWT is a constant walking speed test, and the speed is based on the results from ISWT, and cannot be conducted without first having completed an ISWT.

## 1.4 Longitudinal changes in lung function and exercise capacity

The longitudinal decline in FEV<sub>1</sub> in COPD is higher than normal, but is highly variable. Persistent smoking is the most important predictor for the reduction in FEV<sub>1</sub> with an additional effect of exacerbations (15, 16).

The natural long-term changes in 6MWD in COPD patients, not recruited through a pulmonary rehabilitation program or assessment for surgery, with follow-up times between one and five years, have demonstrated an annual decline that varied between 2 and 40 m per year (17-19, 139).

Studies of longitudinal changes in peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ ), peak ventilatory capacity ( $\dot{V}_{\text{Epeak}}$ ) and breathing pattern are scarce. However, a reduction in  $\dot{V}O_{2\text{peak}}$  in male COPD patients over five years was seen (140). This reduction was related to reduction in maximal tidal volume ( $V_{\text{Tmax}}$ ) and  $\dot{V}_{\text{Epeak}}$ . The decrease in  $\dot{V}O_{2\text{peak}}$  was no

less rapid than the decrease in FEV<sub>1</sub>. We are not aware of any previous studies specifically addressing longitudinal changes in breathing pattern.

## 1.5 Search strategies

Structured literature searches have been done regularly since October 2011. The last search was on February 15<sup>th</sup> 2015. Papers published after this date are not discussed in the thesis. Searches have been performed in Medline, Embase, Cochrane and Ovid, PEDro and SweMED+.

## 2. Objectives

The objectives of this thesis were to characterize the breathing pattern during incremental exercise in patients having COPD and to examine longitudinal changes in exercise capacity and breathing pattern as well as potential predictors for the changes. This was accomplished by three separate studies.

### *Study I*

The aim of this study was to examine predictors for the longitudinal change in the 6MWD. We hypothesized that high habitual physical activity is associated with a lower longitudinal decline in 6MWD, and included self-reported physical activity, lung function, smoking habits, body composition, exacerbations and comorbidity in the analysis.

### *Study II*

The aim of this cross-sectional study was to examine whether a quadratic model could satisfactorily describe the relationship between  $\dot{V}_E$  and  $V_T$  during exercise in COPD patients. The hypothesis was that the curve parameters of the quadratic model which describe the breathing pattern were related to FEV<sub>1</sub>, IRV, and dynamic hyperinflation.

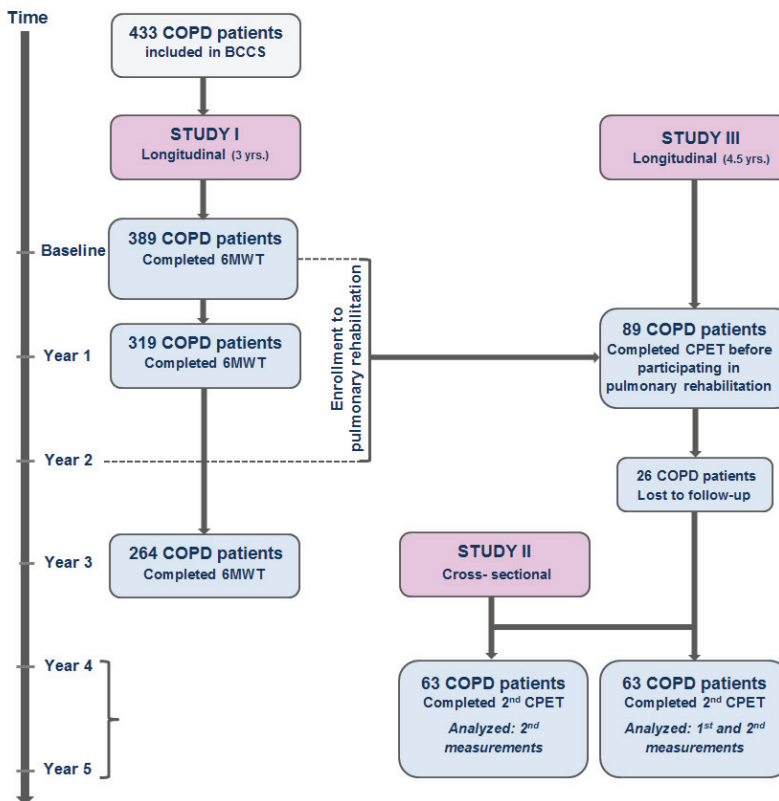
### *Study III*

The aims of this study were to examine changes in exercise and ventilatory capacity and breathing pattern over four years in a group of COPD patients, and to examine the relationship with variables that potentially contribute to explain the changes. We hypothesized that  $\dot{V}O_{2\text{peak}}$  and  $\dot{V}_{E\text{peak}}$  would deteriorate during the observation period, that breathing pattern would be shallower with a lower  $V_{T\text{max}}$ , and that the changes were related to lung hyperinflation and airway obstruction.

### 3. Material and methods

#### 3.1 Design and participants

The three studies were based of patients with COPD. An overview of the study population, timeline and patients included is presented in Figure 3. The patients were recruited from the Bergen COPD Cohort Study (BCCS) (141).



**Figure 3.** An overview of the study population, timeline and patients included in the three studies.

COPD: Chronic Obstructive Pulmonary Disease; BCCS: Bergen COPD Cohort Study; 6MWT: Six-Minute Walk Test; CPET: Cardiopulmonary Exercise Test

The BCCS patients were recruited through outpatient clinics from several hospitals in Western Norway and from three private specialist practices in Bergen, Norway (141). An overview of the study designs, number of patients, gender, baseline age and GOLD stages at baseline for each of the studies are shown in Table 2.

**Table 2.** Overview of designs, participants, gender, age and GOLD- 2007 (1) stages in the three studies

Study	Design	Participants			GOLD 2007 stages at baseline N (%)
		N	Gender Women/men	Age at baseline; mean (SD) year	
I	Cohort study, longitudinal with a three year follow-up	389	153/236	64 (7)	GOLD II: 179 (46) GOLD III: 169 (43) GOLD IV: 41 (11)
II	Cross-sectional study	63	28/35	66 (6)	GOLD II: 32 (51) GOLD III: 23 (36) GOLD IV: 8 (13)
III	Cohort study, longitudinal with a mean 4.5 years follow-up	63	28/35	61 (6)	GOLD II: 34 (54) GOLD III: 26 (41) GOLD IV: 3 (5)

SD: Standard Deviation; GOLD: Global Initiative for Chronic Obstructive Lung Disease

### *Patient inclusion and exclusion criteria in BCCS*

Eligible for inclusion in the BCCS were patients having a clinical diagnosis of COPD in GOLD stage II-IV, smoking history  $\geq 10$  pack years, a post-bronchodilation  $FEV_1/FVC$  ratio  $< 0.7$  and a post-bronchodilation  $FEV_1 < 80\%$  of predicted value according to the Norwegian reference values (22). Exacerbations requiring medical treatment within the last four weeks prior to inclusion led to postponement of the visit. Inflammatory disorders, either self-reported or available from the hospital journal, such as rheumatoid arthritis, systemic lupus erythematosus or other

connective tissue disorders, inflammatory bowel disease and any active cancer in the last five years were causes for exclusion. Common chronic diseases with known inflammatory components such as chronic heart disease, diabetes and hypertension were not causes for exclusion. The inclusion and exclusion criteria in the three studies were the same as in BCCS.

### *Study I*

Of the 433 patients with clinically stable COPD who met for the first visit in BCCS, eleven did not meet the inclusion criteria, five did not want to participate in the study and 28 were disabled. Thus 389 patients performed 6MWT at baseline (2006-2007) and were included and followed for three years in this study (2006-2010). After 1-year 319 (82 %) patients and after 3-years 264 (68 %) patients completed the 6MWT. Of the patients who were lost to follow-up at 1-year, 11 had died and 59 had withdrawn from the study, and at 3-years further 55 patients were lost to follow-up, 10 had died and 45 had withdrawn. The withdrawn patients were deceased or disabled.

### *Study II and III*

Eighty-nine of the BCCS patients participated in a pulmonary rehabilitation program during the first two years of follow-up in 2006-2008. Before start of the rehabilitation program, these patients performed a CPET on treadmill. They were invited to a second CPET in 2011/2012. At that time 26 of the 89 patients were deceased or disabled. The 63 remaining patients performed a second CPET with an intervening time between the tests of mean 4.5 years. The data from the second CPET were used in Study II (cross-sectional) and in Study III (longitudinal) the data from both CPETs were used. In addition to the exclusion criteria in BCCS, patients were excluded from performing the CPETs if the partial pressure of oxygen in blood was less than 8 kPa at rest.

## 3.2 Ethical considerations

The patients were given written and oral information when invited to take part in the BCCS, and informed that participation was entirely voluntary. At any time of the follow-up period they could withdraw from the study without giving any reasons. The BCCS was approved by the Western Norway Regional Committee for Medical and Health Research Ethics (REK 165.08). The recommendations from the Helsinki declaration were followed.

Persons having COPD are struggling with a progressive disease causing comorbidities, loss of exercise capacity, and reduced participation in activities of daily living. During the visits in BCCS the participants performed a lot of tests, and each visit lasted for some hours. It was therefore important to take care of the patients by providing necessary rest between the tests, as well as food and beverages when required.

The first CPET was performed before start of the pulmonary rehabilitation program during the first two years of enrolment in BCCS, and was therefore not synchronized with the visits in BCCS, resulting in a less comprehensive test program compared to the other visits. On the other hand, the second CPET in 2011/2012 was performed at the same time as one of the follow-up in BCCS. We were aware that the total number of tests including the CPET could be strenuous for the patients, and therefore ensured that sufficient rest where included in the test program. At least one hour and maximum two hours before the CPET, the patients were served food. The well-being of the patients was a main concern, and the test was stopped if the patients showed any form of discomfort.

### 3.3 Outcome measures and assessment tools

An overview of the assessments tools used in the three studies is given in Table 3. The 6MWT, the CPET, lung function testing, measurement of dyspnea and self-reported physical activity are presented in more detail.

**Table 3.** Assessment tools used in the three studies

Assessment tool	Study		
	I	II	III
6MWT	x		
CPET		x	x
<i>Spirometry:</i>			
FEV <sub>1</sub>	x	x	x
FVC	x	x	x
Borg dyspnea score	x	x	x
mMRC dyspnea scale	x		
<i>Body composition:</i>			
BMI	x		x
FMI	x		
FFMI	x		
Self-reported physical activity	x		x
Charlson index for comorbidities	x		

6MWT: Six-minute walk test; CPET: Cardiopulmonary Exercise Test; FEV<sub>1</sub>: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; mMRC: modified Medical Research Council; BMI: Body Mass Index; FMI: Fat Mass Index; FFMI: Fat Free Mass Index

#### 3.3.1 Exercise capacity: 6MWT and CPET

##### *6MWT*

The 6MWT is a widely used field test for evaluating functional exercise performance in patients with COPD (14, 103). In Study I all patients in BCCS were assessed with



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6MWT, except those who were disabled. The test was performed according to the ATS guidelines (135) in a 30 m flat, straight enclosed corridor. A trained technician supervised the patients, and the patients were asked not to talk during the test unless they had a problem. According to safety criteria, the test was immediately stopped if the patients had chest pain, intolerable dyspnea, leg cramps, diaphoresis, started staggering and pale or ashen appearance (135). None of the patients were stopped due to adverse events. The 6MWD was used as primary outcome. SpO<sub>2</sub> and HR were measured at the start and at the end of the test using pulse oximetry (NONIN Medical Inc., Plymouth, MN). The Borg dyspnea score (Borg CR10) (142-144) was used to measure the patients level of dyspnea and fatigue at the beginning and at the end of the test. The test was performed once each time, and a practice 6MWT was not done. Of the 389 included patients at baseline, 13 % used supplemental oxygen during the 6MWT, and at one and three years follow-up, 11 of 319 (3 %) and 10 of 264 (4 %) patients, respectively, did so.

### *CPET*

The CPET is considered the gold standard for evaluating causes of exercise intolerance in patients with COPD (103). Exercise intolerance in COPD can be due to abnormal oxygen delivery, ventilatory limitation, pulmonary gas exchange abnormalities, muscle metabolic dysfunction, deconditioning and symptoms like dyspnea and leg effort (103). The CPET can also be used for evaluating the effect of interventions for example exercise-based pulmonary rehabilitation, oxygen supplementation and drug therapies. In Study II and III the CPET was used to evaluate exercise capacity and the test was performed on a treadmill under supervisions of experienced technicians (Woodway, model: PPS 55 med Weiss, Weil am Rhein, Germany). The CPET was incremental and the patients walked or ran until they reached their symptom-limited maximum. The exercise protocol was a modified Bruce protocol (145, 146), and started with rest in standing position for 2 minutes. The warm-up phase is lasting for 1 minute with a walking speed of 1.5 km·h<sup>-1</sup>. The

test consists of 20 stages, all lasting for one minute. The first stage in the test is at 1.5 km/h with an inclination of 0 %. In stage 2, the speed is the same as in stage 1 with an inclination of 5 %. From stage 3-5, the speed is increasing with 0.6 km/h and the inclination is 9, 10 and 11 %, respectively. From stage 6-13, the speed increases with 0.6-0.7 km/h and the inclination with 1 %. From stage 13-14, the speed increases with 0.4 km/h, and the inclination increase 1 %. Finally, from stage 15-20, the speed is increasing with 1 km/h each minute and the inclination was the same as in stage 14.

Blood pressure, electrocardiogram (GE healthcare, Cardio Soft EKG, Freiburg, Germany) and pulse oximetry were monitored at rest, continuously during the test and for 3 minutes into the recovery phase. A tight fitting oronasal mask was adjusted to each patient and checked for leaks before starting the exercise. The integrated exercise testing system (Care Fusion, Vmax Spectra 229, Hochberg, Germany), was calibrated every morning and immediately before each test. The  $V_T$ , breathing frequency ( $B_f$ ),  $\dot{V}O_2$ , carbon dioxide production ( $\dot{V}CO_2$ ) and HR were measured on a breath by breath basis and averaged over 20 second intervals.  $\dot{V}_E$  and  $V_T$  were corrected to the body temperature pressure saturated (BTPS) condition, and  $\dot{V}O_2$  and  $\dot{V}CO_2$  to the standard temperature pressure (STPD) condition. The patients graded their level of dyspnea and leg discomfort by the Borg CR10 Scale (142, 143).

In order to measure dynamic hyperinflation during exercise, serial measurements of inspiratory capacity (IC) were performed. IC is the volume air that can be inspired after a normal expiration, and dynamic hyperinflation is described as the decrease in IC from rest to peak exercise (96). A decrease in IC means an increase in EELV of an equal volume (147). Low resting IC reflects severe lung hyperinflation (9).

Measurements of IC were taken at rest, every second minute during exercise and at peak exercise. The change in IC ( $\Delta IC$ ) during each of the CPETs was calculated as IC at rest minus IC at peak exercise.

### 3.3.2 Lung function testing

All lung function measurements were performed by trained study personnel according to ATS/ERS Standardization of Lung Function Testing (148). Spirometry was performed both pre- and post-inhalation of 0.4 mg salbutamol on a Viasys Masterscope (Viasys, Hoechberg, Germany). Spirometer calibration was done before each test with a 3-L calibration syringe. The FEV<sub>1</sub> and FVC were taken as the highest values from at least three satisfactory manoeuvres. Post-bronchodilator FEV<sub>1</sub> was based on Norwegian reference values (22). Spirometry was measured in all the included patients in Study I, II and III.

### 3.3.3 Assessment of dyspnea

We used two different scales to measure dyspnea. The Norwegian version of the Borg CR10 scale (142-144) (Appendix A) was used to measure perceived breathlessness during 6MWT (Study I) and both breathlessness and leg discomfort during the CPET (Study II and III). A comprehensive explanation of the scale was given to the patients, and they either gave verbal response or pointed at the scale to express the self-experienced sensation to dyspnea or leg discomfort.

The second scale that was used was the Norwegian version of the 5-point modified Medical Research Council (mMRC dyspnea scale) (149), which is a standardised self-administered grading system to assess the patient's level of dyspnea in activities of daily life. The mMRC was used in Study I (Appendix B).

### 3.3.4 Self-reported physical activity

To measure physical activity a questionnaire was used with two questions related to spare time physical activity, one for hard and one for light physical activity. The

delineation between the two questions was whether the activity resulted in breathlessness and sweating or not. The response categories for both questions were none, less than 1 hour per week, 1-2 hours per week or 3 or more hours per week. These questions have been tested for validity (150, 151) and were used in a large Norwegian general population study (152). The physical activity questions were used in Study I and III.

### 3.4 Data processing and statistical analyses

#### *Data processing*

The data analyses were performed using IBM SPSS Statistics version 20 and 21 (SPSS Inc. Chicago, Illinois, USA), and are presented in the respective papers. P-values less than 0.05 were considered statistically significant.

#### *Descriptive analyses*

Normally distributed data were presented as mean  $\pm$  standard deviation (SD). Normal distribution was assessed by histogram, Q-Q-plots, and Shapiro Wilks test.

In the three studies, descriptive statistics were used to characterize the study population (mean, SD, median and percent). In Study I and II independent samples t-tests and Persons chi-square tests were used to compare continuous and categorical variables, respectively, across gender. In Study III the independent samples t-test was used to compare the patients who completed one CPET with those who completed two tests.

#### *Regression analyses*

An overview of the regression analyses used in the three studies is shown in Table 4. In the studies, estimated regression coefficients were presented with 95 % confidence intervals (CI).

**Table 4.** An overview over the variables and statistical analyses used in the studies

Study	Variables		Regression analyses
	Outcome	Explanatory	
I	• 6MWD	<ul style="list-style-type: none"> <li>• Age, gender, FEV<sub>1</sub>, FVC, FMI, FFMI, Time, number of exacerbations, pack years, Charlson comorbidity index, self-reported physical activity</li> <li>• Participation in pulmonary rehabilitation, gender, age, FEV<sub>1</sub>, FVC, FMI, FFMI, pack years, exacerbations, Charlson comorbidity index</li> </ul>	<ul style="list-style-type: none"> <li>• Bivariate and multivariate generalized estimating equations regression</li> <li>• Multivariate logistic regression</li> </ul>
	• Self-reported physical activity		
II	• V <sub>T</sub>	• $\dot{V}_E$	• Quadratic regression ( $V_T = a + b \cdot \dot{V}_E + c \cdot \dot{V}_E^2$ )
	• Curve parameters <i>a</i> , <i>b</i> and <i>c</i>	• Age, gender, height, weight, FEV <sub>1</sub> , FVC, IRV, $\Delta IC_{adj}$	• Bivariate and multivariate linear regression
III	• $\Delta \dot{V}_{O_{2peak}}$ or • $\Delta \dot{V}_{Epeak}$	<ul style="list-style-type: none"> <li>• Age, gender, height, baseline <math>\dot{V}_{O_{2peak}}</math> or baseline <math>\dot{V}_{Epeak}</math>, smoking during follow-up, <math>\Delta FEV_1</math>, <math>\Delta FVC</math>, <math>\Delta weight</math>, <math>\Delta IC_{rest}</math>, <math>\Delta IC_{dynamic}</math>, self-reported physical activity, exacerbations and time between the tests</li> </ul>	• Bivariate and multivariate linear regression
	• V <sub>T</sub>		• $\dot{V}_E$
	• The change in the curve parameters <i>a</i> , <i>b</i> and <i>c</i> (CPET2 minus CPET1)	• Age, gender, height, $\Delta weight$ , $\Delta FEV_1$ , $\Delta IRV$ , $\Delta IC_{rest}$ and $\Delta IC_{dynamic}$	• Bivariate and multivariate linear regression

6MWD: Six-Minute Walking Distance; FEV<sub>1</sub>: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; FMI: Fat Mass Index; FFMI: Fat Free Mass Index; V<sub>T</sub>: Tidal volume;  $\dot{V}_E$ : Minute Ventilation; IRV: Inspiratory Reserve Volume; CPET: Cardiopulmonary Exercise Test;  $\Delta IC_{adj}$ : IC at rest minus IC at the end of the CPET adjusted for resting IC;  $\dot{V}_{O_{2peak}}$ : peak oxygen uptake;  $\Delta \dot{V}_{O_{2peak}}$ :  $\dot{V}_{O_{2peak}}$  at CPET2 minus  $\dot{V}_{O_{2peak}}$  at CPET1;  $\Delta \dot{V}_{Epeak}$ :  $\dot{V}_{Epeak}$  at CPET2 minus  $\dot{V}_{Epeak}$  at CPET1;  $\Delta IC_{dynamic}$ : The change in  $\Delta IC$  (IC at rest minus IC at peak exercise) at CPET2 minus  $\Delta IC$  at CPET1.

In Study I generalized estimating equations (GEE) regression analyses with robust standard errors were used to analyze the longitudinal change in 6MWD per year and to identify potential predictors for the change. An unstructured working correlation structure was applied to adjust for within correlation. In Study I logistic regression analyses were applied to assess predictors for physical activity at three years follow-up.

In Study III bivariate and multivariate regression analyses were used to analyze the relationship between longitudinal changes in oxygen uptake or ventilation and the following potential predictors: age, gender, height, baseline  $\dot{V}O_{2\text{peak}}$  or  $\dot{V}_{E\text{peak}}$ , smoking during follow-up,  $\Delta FEV_1$ ,  $\Delta FVC$ ,  $\Delta \text{weight}$ ,  $\Delta IC_{\text{rest}}$  and  $\Delta IC_{\text{dynamic}}$ , self-reported physical activity, exacerbations and time between the tests.

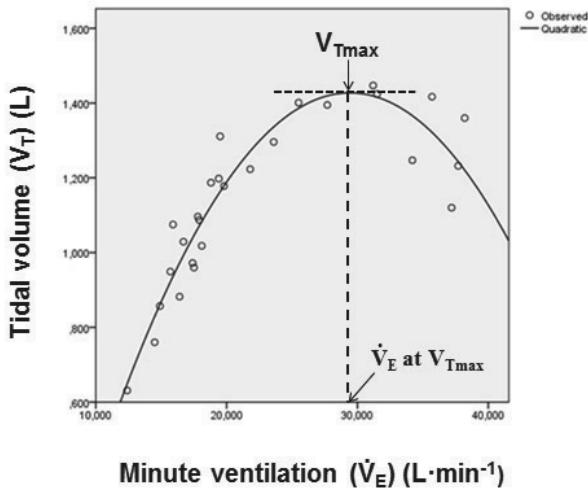
### *Quadratic model*

In Study II and III a quadratic model ( $V_T = a + b \cdot \dot{V}_E + c \cdot \dot{V}_E^2$ ) was used to describe the breathing pattern in terms of the relationship between  $\dot{V}_E$  and  $V_T$  for each individual. Bivariate and multivariate regression analyses were used to analyze the relationship between the curve parameters a, b and c, and possible explanatory variables such as age, gender and height (Study II and III). Additional explanatory variables in Study II were weight,  $FEV_1$ , FVC, IRV and  $\Delta IC_{\text{adj}}$ . (IC in rest minus IC at the end of the CPET adjusted for resting IC), and in study III:  $\Delta \text{weight}$ ,  $\Delta FEV_1$ ,  $\Delta FVC$ ,  $\Delta IC_{\text{rest}}$  and  $\Delta IC_{\text{dynamic}}$ .  $\Delta \text{weight}$ ,  $\Delta FEV_1$ ,  $\Delta FVC$  and  $\Delta IC_{\text{rest}}$  were calculated as the value at CPET2 minus the value CPET1.  $\Delta IC_{\text{dynamic}}$  was calculated as the change in  $\Delta IC$  (IC at rest minus IC at peak exercise) at CPET2 minus  $\Delta IC$  at CPET1.

The  $V_{T\text{max}}$  and  $\dot{V}_E$  at  $V_{T\text{max}}$  were calculated from the individual quadratic relationships. The  $V_{T\text{max}}$  was the point where the first derivative of the quadratic equation was zero (Figure 4);

$$V_T = a + b \cdot \dot{V}_E + c \cdot \dot{V}_E^2$$

$$V_{Tmax} = a + b \cdot (-b/2c) + c \cdot (-b/2c)^2$$



**Figure 4.** The  $\dot{V}_E - V_T$  relationship in one of the patients illustrating the quadratic relationship and the position of  $V_{Tmax}$  and  $\dot{V}_E$  at  $V_{Tmax}$ .

#### *Sample size calculation*

Sample size calculation was done prior to study start in BCCS with  $FEV_1$  as the main outcome, and this calculation was basis for the number of patients included in Study I. With a power of 80 % and alpha-level set to 0.05, the study had included enough patients (433 patients) to detect minimal clinical important differences in  $FEV_1$  when the within subject SD was  $200 \text{ mL} \cdot \text{year}^{-1}$  and the SD of the rate of decline in  $FEV_1$  was  $30 \text{ mL} \cdot \text{year}^{-1}$ .

Sample size calculation was also performed for Study II and III to assess whether the available number of observations would render results with acceptable precision (153). With an estimated change in mean  $\dot{V}O_{2peak}$  of 10 %, power of 80 %, alpha of

0.05 and a SD of 20 % the calculations showed that 31 patients had to be included. A change in  $\dot{V}O_{2\text{peak}}$  of 10 % was considered as a clinically important change.



## 4. Summary of results

In this chapter, a condensed summary of the results from Study I, II and III is presented.

### 4.1 Paper I

#### *Physical activity and longitudinal change in 6-min walk distance in patients with COPD*

Frisk B, Espehaug B, Hardie JA, Strand LI, Moe-Nilssen R, Eagan TM, Bakke PS, Thorsen E. *Respir Med.* 2014 Jan;108(1):86-94.

The aim of the study was to examine predictors for the longitudinal change in 6MWD.

The follow-up time was three years with measurements at baseline and at one and three years. Data on 389 patients with COPD were available at baseline, and 319 (82 %) and 264 (68 %) completed the 6MWT at year one and three, respectively. The mean age was  $64 \pm 6$  years, 236 (61 %) were men, and the patients were in GOLD stages II-IV. During the first two years of follow-up, 89 of the 389 patients were enrolled in a 7-week pulmonary rehabilitation program. There were no significant differences in baseline characteristics between the participants in the rehabilitation group and the other participants.

The main findings were that the patients regardless of GOLD stages maintained the 6MWD after one year, while after three years it was significantly decreased in GOLD stage III ( $p=0.009$ ) and IV ( $p=0.007$ ). Baseline predictors for these changes were self-reported hard physical activity and  $FEV_1$ . With a reduced  $FEV_1$  the reduction in 6MWD was higher, and patients who reported that they performed regular hard physical activity had less reduction in 6MWD. The level of physical activity was

higher after three years in patients who had participated in pulmonary rehabilitation during the observation period with an odds ratio of 2.4 (95 % CI 1.4–4.2,  $p = 0.001$ ).

## 4.2 Paper II

### *Airway obstruction, dynamic hyperinflation, and breathing pattern during incremental exercise in patients with COPD*

Frisk B, Espehaug B, Hardie JA, Strand LI, Moe-Nilssen R, Eagan TM, Bakke PS, Thorsen E. *Physiol Rep*. 2014 Feb 7;2(2):e00222. Doi: 10: 1002/phy2.222.

The aim of the study was to examine whether a quadratic model ( $V_T = a + b \cdot \dot{V}_E + c \cdot \dot{V}_E^2$ ) could satisfactorily describe the relationship between  $\dot{V}_E$  and  $V_T$  during exercise in patients with COPD.

In this cross-sectional study, 63 patients, mean age  $66 \pm 6$  years, 35 (56 %) men, performed an incremental exercise test on treadmill. The patients were airflow limited with a  $FEV_1$  of 48 % (SD=15 %) of the predicted value.

The quadratic model could be used to describe the relationship between  $\dot{V}_E$  and  $V_T$  in 59 of the 63 patients. For these patients the p-value of the F-statistic for the quadratic model was  $< 0.05$  and the median  $R^2$  was 0.90 (range 0.40 to 0.98). The remaining four patients were excluded from further analyses, because the goodness of fit was not statistically significant. These patients had a short exercise time and thereby few data available for computing a regression curve.

The multivariate linear regression analyses showed that the linear coefficient (b) was negatively ( $p=0.001$ ) and the quadratic coefficient (c) positively ( $p<0.001$ ) related to  $FEV_1$ . Age, gender, height, weight, FVC, IRV and  $\Delta IC_{adj}$  were not associated with the curve parameters after adjusting for  $FEV_1$ . With a lower  $FEV_1$ , maximal  $V_T$  was lower and achieved at a lower  $\dot{V}_E$ .

In the multivariate regression analyses both  $\dot{V}_{T_{max}}$  and  $\dot{V}_E$  at  $\dot{V}_{T_{max}}$  were related to  $FEV_1$  ( $p < 0.001$ ), but not to age, gender, height, weight, FVC and  $\Delta IC$ .

### 4.3 Paper III

#### *Peak oxygen uptake and breathing pattern in patients with COPD – a four year longitudinal study*

Frisk B, Hardie JA, Espehaug B, Strand LI, Moe-Nilssen R, Eagan TM, Bakke PS, Thorsen E. (2015): Submitted.

The aims of the study were to examine longitudinal changes in  $\dot{V}O_{2peak}$ ,  $\dot{V}_{Epeak}$  and breathing pattern over four years in a group of patients with COPD, and to examine potential predictors of change.

During the first two years of follow-up in BCCS (2006-2008), 89 patients were enrolled in a 7-week pulmonary rehabilitation program. The patients performed a CPET, before start of the rehabilitation program. These patients were invited to a second CPET in 2011-2012. Sixty-three of the 89 patients performed the second CPET. The remaining 26 patients were deceased or disabled. The 63 included patients were in GOLD stages II-IV, the mean age was  $61 \pm 6$  years and 35 (56 %) were males.  $FEV_1$  was  $51 \pm 14$  % of predicted values.

Exercise capacity measured as  $\dot{V}O_{2peak}$  and  $\dot{V}O_{2peak/kg}$  and ventilatory capacity measured as  $\dot{V}_{Epeak}$  deteriorated significantly ( $p < 0.001$ ) during the intervening time of 4.5 years. The reduction in  $\dot{V}O_{2peak}$  was larger with a higher baseline  $\dot{V}O_{2peak}$  ( $p < 0.001$ ) and with a larger reduction in  $\Delta IC_{rest}$  ( $p = 0.002$ ) and  $\Delta FEV_1$  ( $p = 0.031$ ). Smoking and age predicted the change in  $\dot{V}O_{2peak}$  as well. The reduction in  $\dot{V}_{Epeak}$  was larger with a larger reduction in  $\Delta IC_{rest}$  ( $p = 0.005$ ) and  $\Delta FEV_1$  ( $p = 0.031$ ). A higher baseline  $\dot{V}_{Epeak}$  predicted a larger reduction in  $\dot{V}_{Epeak}$  ( $p = 0.002$ ).

The quadratic model was used to describe the relationship between  $\dot{V}_E$  and  $V_T$  at CPET1 and CPET2. At CPET1 the quadratic model could be used in 61 of 63 patients, and in 59 of 63 at the second test. The coefficients in the equations; the estimated constant (a), the linear coefficient (b) and the quadratic coefficient (c) changed significantly from CPET1 to CPET2. The linear coefficient (b) increased ( $p=0.007$ ) and the quadratic coefficient (c) decreased ( $p=0.002$ ). Maximal  $V_T$  was achieved at a lower  $V_E$  at CPET2.  $\Delta FEV_1$  predicted the changes in the curve parameters a ( $p=0.009$ ), b ( $p=0.015$ ) and c ( $p=0.017$ ).

## 5. Discussion

In the first section methodological considerations are discussed, whereas the main objectives of the thesis and results of the three studies are discussed in the second part.

### 5.1 Methodological considerations

#### 5.1.1 Study design and study population

The participants in the studies were subsamples from the BCCS, all diagnosed with COPD. Study I and III were observational longitudinal studies with follow-up times of 3 and 4.5 years, respectively, while Study II was a cross-sectional study. Cohort studies can be categorized as prospective, retrospective or cross-sectional (154). Of these designs, it is only the prospective cohort study that can be characterized as a longitudinal study, and is designed to analyse the longitudinal development of definite characteristics over time (155). The research question addresses whether baseline characteristics can predict the change in an outcome variable, or the change in an outcome variable is associated with the change in one or more possible predictor variables (154). A cohort study comprises persons with a common characteristic, for example regarding exposure or ethnic identity, and can consist of an exposed and an unexposed group. The exposed participants are compared to the unexposed control group in terms of occurrence of the outcome. The main advantage of prospective cohort studies compared to cross-sectional studies is that the change in an outcome variable can be studied over time and analysed with respect to the development in individual explanatory variables (154, 155) An advantage of Study I and III was the longitudinal design with rather long follow-up times of 3 and 4.5 years.

COPD is a progressive disease, and with increased disease severity the loss to follow-up is a natural consequence. The dropout rate of the 389 patients in Study I from

baseline to three years was 32 % and in Study III for the 89 patients at CPET1 with a mean follow-up time of 4.5 years was 29 %. The patients were mainly lost to follow-up because of death or increased disease severity. The dropout rate in Study I was in accordance with previous studies (17, 19, 139), while for Study III the only comparable study had a dropout rate of 51 % (140) being higher than in our study. An advantage with Study I was the large sample size with 6MWD data that allowed for analyses of subgroups, for example to examine the impact of disease severity according to GOLD stages.

Two CPETs were performed in Study III. The CPET aims to measure maximal exercise capacity and is a very exhausting test, where the persons are pushed to their limit of exercise tolerance. In the present study 71 % of patients performed two CPETs over a time interval of 4.5 years. However, a sample size of 63 patients is still small in multivariate linear regression analyses and restricted the number of explanatory variables that could be included in the analyses. The number of explanatory variables included in our multivariate regression analyses was five to seven.

In the BCCS a control group without COPD and a group with COPD were included. The control group did, however, not perform the 6MWT, and since 6MWD was the main outcome variable in Study I, a comparison between the two groups was not possible. The 6MWT has been developed to assess functional capacity targeted at people with at least moderately severe impairment (135). In healthy individuals and in patients with mild COPD the 6MWD is usually biomechanically limited by their maximal walking speed rather than by their ventilatory capacity. Our main focus was on examining the individual COPD patient's longitudinal development in relation to progression of the disease severity, exercise capacity and breathing pattern, and not to examine the relationship or difference in 6MWD change between healthy people and COPD patients.

In Study II a cross-sectional design was used. The data were collected at one point in time. This design is appropriate to describe a phenomenon or an outcome and factors that may be associated with the outcome (154).

### 5.1.2 Internal validity

Internal validity can be defined as the validity of inferences drawn pertaining to the population being studied (154). Two types of errors are of main concern in the study design; systematic error (bias) and random error. Systematic errors have to be dealt with when designing the study and the most common systematic errors are *selection bias*, *information bias* and *confounding*.

#### *Selection bias*

Selection bias can occur in the recruitment process, and from factors influencing the study population (154). There can be a selection bias when the exposure and outcome for the recruited participants in the study differ from the population who theoretically could have been eligible for the study. The BCCS recruited patients through outpatient clinics from several hospitals in Western Norway and from three private specialist practices in Bergen Norway (141). Participation was voluntary, and during the observation period the visits were conducted at the hospital, which meant that the participants had to manage to meet at the hospital. COPD patients are often limited in performing activities of daily living, and the most severely ill patients were supposed not to take part in the study because of reduced functional capacity. In Study I there were few patients with serious disease as represented by GOLD stage IV. Inclusion of seriously ill subjects at baseline will increase the drop-out rate during the observation period. In Study I 11 % of the patients were in GOLD IV at baseline.

We assume that the sample assessed at baseline in Study I was representative for the common COPD population, except those with mild disease in GOLD stage I. In Study II and III the recruited patients were a subsample of those included in Study I. They had participated in pulmonary rehabilitation during the first two years of follow-up in BCCS and could therefore have been biased to have higher functional capacity than the common COPD population. However, when comparing the patients included in Study I there were no significant differences in baseline characteristics between those who participated in pulmonary rehabilitation and the non-participants. According to GOLD stages 49 % of the 63 patients in Study II and 46 % in Study III were in GOLD stages III and IV. The distribution of the patients with respect to disease severity was thus almost the same as in Study I. However, only three of the 63 patients who performed the first CPET were in GOLD stage IV, and at the second CPET eight were in GOLD stage IV. It is therefore likely that the most severely ill patients were not represented.

### *Information bias*

Information bias can result from measurement errors or misclassification (154). If the variable is measured on a categorical scale and the study subject is placed in an incorrect category this leads to misclassification. It is conceivable that participants could have been misdiagnosed with COPD, but at baseline visit in the BCCS the participants went through extensive examinations, and a possible misclassification should then have been detected.

The studies are based on information and measurements collected prospectively, and recall bias could therefore be minimized. In study I and III a self-reported questionnaire about physical activity level was used. The patients should report habitual physical activity for an average week, and there can be a possibility for occurrence of recall bias. It seems more likely that the reported activity level was biased by an overestimation, and thereby a misclassification of patients regarding



activity level could occur. Another possible misclassification for all three studies could be that the smokers underreported their smoking habits and thereby influenced the calculation of pack years. The smoking habits were registered by the physician at each visit, not by questionnaire. In BCCS a detailed registration about smoking habits were done at baseline and at follow-up; whether the subjects were ex- or current smoker as well as the total smoking load. It is demonstrated that the more detailed information registered on smoking habits, the less bias (154). If smoking is due to an underreporting in our sample, this could have led to an underestimation of the effect of smoking.

### *Confounding*

Confounding can be defined as the confusion or mixing of effects (154). A confounder is a third variable, an unobserved exposure, that is associated with the exposure and the outcome variable, and can act as a cause or a proxy for the outcome (154).

Three methods are described to prevent confounding (154). The first concerns randomization to an experimental or a control group, but in cohort studies, randomization is not applicable. The second method is matching, which is an effective way to prevent confounding in cohort studies. The third method concerning restriction, involves selecting subjects for a study in which all have the same or almost the same value for a variable that otherwise could be a confounding factor. Tobacco smoking is the primary cause for COPD, and if we had included never smokers as well as smokers in the study, smoking could be a confounder. Therefore, one of the inclusion criteria in BCCS was that all participants had a smoking history of  $\geq 10$  pack years. There are statistical methods that adjust for possible confounding like stratification, regression, matching, standardization, propensity score analyses, and inverse probability weighting. We have used regression analyses to adjust for potential confounders.

### *Random error*

Random error can be described as the variability in data that cannot easily be explained (154). The main sources of random errors are lack of precision in the measurements (low repeatability), and insufficient sample size. One way of dealing with the latter is to include a large sample size. The precision of estimation can thereby be improved.

Study I has a relatively large sample size, and the precision of the estimate for the change in 6MWD from baseline to three years, given by the CI was -34 to -12 m. For Study II and III sample size calculation was done prior to study start. The calculation was based on a coefficient of variation in  $\dot{V}O_{2\text{peak}}$  of 5 %, and a clinically significant difference of 10 %. With statistical power of 80 %, alpha of 0.05, and a SD of 20 %, 31 patients were then sufficient. However, even though enough patients were included according to the sample size calculation, the estimation process can be comparatively more precise with a larger study sample. Less precision and more random error occurs in small samples.

### 5.1.3 External validity

External validity refers to the generalizability of the results from the study population to the target population (154). This implies that the study population must be a representative subsample of the target population. The target population for the three studies was the common COPD population in Norway.

Roughly 10 % of the Norwegian population lives in Hordaland County where the participants in BCCS were recruited from. The adult sex and age composition of the inhabitants in Hordaland is very similar to the overall Norwegian population (156). Approximately 10 % of the Norwegian population and the inhabitants in Hordaland have been diagnosed with COPD. It is therefore reasonable to believe that the COPD

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population in Hordaland do not differ from the COPD population in the rest of the country.

Participation in BCCS was voluntary, and since the visits at baseline and at follow-up were performed at the hospital, it is likely that most severely ill patients did not accept to be included. The distribution according to GOLD stages confirmed this. The majority of patients were in GOLD stages II and III, while only a few were in GOLD stage IV. However, when performing longitudinal studies with COPD patients, recruiting the most severely ill patients will always be a problem.

#### 5.1.4 Reliability

The reliability of an instrument is the degree of consistency in which the instrument measures what it is supposed to measure (157). The less variation an instrument produces in repeated measurements of a characteristic, the higher its reliability.

In the three studies the 6MWT (Study I) and CPET (Study II and III) were used to measure exercise capacity. The relationship between 6MWD and  $\dot{V}O_{2peak}$  (measured on a progressive incremental CPET) has shown to be moderate to strong, with correlation coefficients ranging from 0.4 to 0.8 (158-166).

The 6MWT is a well-established self-paced test of walking capacity, with 6MWD as the primary outcome (135). The 6MWD is shown to be a reliable measure, with intra class correlation coefficient ranging from 0.72 to 0.99 (167-172). It is recommended to perform two 6MWTs to reduce the learning effect which is a bias in 6MWD (137). The mean distance between two repeated 6MWD in COPD has been reported to be between 24-29 meters (170). Because of limited resources, the 6MWT in Study I was only performed once at each visit. It is possible that a learning effect could hide a natural decline in 6MWD, especially since the patients were shown to increase their 6MWD from baseline to one year, but it is less likely that the learning effect could have lasted for three years.

The CPET was performed on a treadmill and a maximal incremental protocol, the modified Bruce protocol (145, 146), was used. The protocol is standardised and integrated in the exercise testing system. Treadmill exercise testing has some advantages compared to cycle ergometer. For most individuals, treadmill walking is a more familiar activity than cycling. Walking (or running) on a treadmill requires a larger muscle mass and more work against gravity than cycling and leads to a greater stress on the organ systems (93). The maximal  $\dot{V}O_2$  is reported to be 5-10 % higher on treadmill than cycle ergometer (173-176). This may be important for athletes, but less important for COPD patients, unless the  $\dot{V}O_{2peak}$  is critically low, influencing the ability to perform daily activities. More important is to consider if the CPET is used to evaluate an effect of any intervention. Then the same exercise modality has to be used.

To ensure reproducibility of the CPETs, it is important to reduce factors that may contribute to the variability in measures, like patient motivation, patient instructions, time of the day, testing procedures, equipment/calibration errors, change in use of medication and changes in the underlying disease process. The integrated testing system that we used, was calibrated every morning and immediately before each test. At every CPET, one physician and one technician (physiotherapist or bioengineer) were responsible that the test was performed according to the standardised procedure. During the test, the physician monitored the patients while the technician was responsible for the patients' well-being as well as pushing them to their limit of exercise tolerance, and in addition performing measurements of dyspnea and IC during the tests. The IC procedure was done as described by O'Donnell and Webb (96). However, the methodology of measuring IC during exercise has been developed on cycle ergometer. As far as we know reliability testing of IC during treadmill testing has not been done. Whether the cut-off point to define dynamic hyperinflation as a reduction in IC of 0.4L (84) is the same on treadmill as on cycling is unknown.

### 5.1.5 Statistical methods

The statistical methods used in the three studies are described in chapter 3.3. In this chapter the methods used to analyse the longitudinal data in study I and III will be discussed.

In Study I GEE regression analyses were used to analyse the longitudinal development of 6MWD and to identify potential predictors for the change. An advantage with this method is that all available data are included in the analyses, without summarizing the longitudinal development of each individual into one value. Study I had three longitudinal measurements, and patients were lost to follow-up at one and three years. To avoid that subjects were excluded from the analyses without having a complete dataset, GEE provides an approach for analysing repeated measurements.

Instead of using GEE to account for correlated outcome measures, a mixed effects model (multilevel model, random coefficient model) could have been used (155). This method is also dealing with the missing data like GEE; meaning that all available data can be included in the analyses. Hubbard et al. (177), however, argue that the GEE approach is more useful.

In Study III we also analysed longitudinal data. The measurements were only performed twice, and since we had no missing data the relationship between the changes in the outcome variables and associations with the changes in potential predictor variables could be analysed by using multivariate linear regression analyses. To account for a possible regression to the mean effect we included the baseline value of the outcome variable in the regression model.

## 5.2 Discussion of the main results

The overall aims of the thesis were to characterize the breathing pattern during incremental exercise in patients having COPD and to examine longitudinal changes in exercise capacity and breathing pattern, as well as potential predictors for the changes.

### 5.2.1 Longitudinal changes in exercise capacity

In Study I and III the longitudinal changes in exercise capacity were examined, and the main outcomes were 6MWD in Study I and  $\dot{V}O_{2\text{peak}}$  in Study III. The 6MWD decreased significantly from baseline to three years, but the decrease was only evident for patients in GOLD stages III and IV, with 36 m (95 % CI:-51 to -7) and 79 m (95 % CI:-125 to -20) respectively. These reductions are higher than the 30 m which is considered as the minimal clinically important change for 6MWD (137), taking measurement error into consideration. Patients in GOLD stage II maintained the walking distance during the follow-up. In healthy subjects and in patients with milder COPD, the maximal walking speed during the 6MWT may be biomechanically limited and not limited by ventilatory capacity. Since only one 6MWT was performed at each visit, a learning effect could have hidden a natural decline in 6MWD during the first year, but it is unlikely that the effect could last for three years. Our findings were consistent with both Casanova et al. (17) and Spruit et al. (19) who demonstrated that 6MWD declined over time, but was only significant in patients with severe airflow limitation. The patients in our study were a subsample in the ECLIPSE study. The finding that the results were consistent with those of Spruit et al. (19) was therefore not surprising. In the study of Kapella et al. (139) the 6MWD was demonstrated to be stable during a follow-up time over three years, maybe because patients with significant comorbidities were excluded from the study and 80 % of the study sample was smoke free during the study period.

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The  $\dot{V}O_{2\text{peak}}$  deteriorated significantly for the total group during the 4.5 years of follow-up with a mean decline of 50 (SD=68)  $\text{mL}\cdot\text{min}^{-1}\cdot\text{yr}^{-1}$ . To our knowledge there is only one previous study that has examined the natural longitudinal changes in exercise capacity and using  $\dot{V}O_{2\text{peak}}$  as main outcome (140). The follow-up time in this study was 5 years with repeated measurements every 6 months. The annual decline in  $\dot{V}O_{2\text{peak}}$  was 32 (SD=60)  $\text{mL}\cdot\text{min}^{-1}\cdot\text{yr}^{-1}$ , which is slightly lower compared to our results. We performed only two measurements compared with Oga's 11 (140). With only two measurements we were not able to identify short term variability in the changes of  $\dot{V}O_{2\text{peak}}$  during the observation period. In the study of Oga et al. (140) the decline in  $\dot{V}O_{2\text{peak}}$  was shown to be almost linear during the first 2.5 years of follow-up, while in the next 2.5 years an increased variability was demonstrated at each of the visits. The lowest values of  $\dot{V}O_{2\text{peak}}$  were measured after 2.5 and 4 years. These variable changes would not have been detected without the repeated measurements every 6 months.

In Study I a total of three measurements of 6MWD were done. In the GEE regression analyses the variable "time" was modelled as both a continuous and as a categorical variable (baseline, year 1 and year 3). The results from the first alternative did not identify that the 6MWD actually increased from baseline to 1-year, and thereafter decreased. The results only demonstrated a decrease in 6MWD from baseline to three years. When analysing the data with "time" as a categorical variable an increase in 6MWD from baseline to 1-year, and a decrease between year 1 and 3 were demonstrated.

In Study I, the findings demonstrated that level of habitual physical activity and  $FEV_1$  at baseline predicted the longitudinal changes in 6MWD. Those who reported performing hard physical activity at baseline demonstrated a positive influence on the longitudinal change in 6MWD. An additional finding was that the level of physical activity was higher at three years follow-up in patients who had participated in a pulmonary rehabilitation program during the observation period. These findings indicates that performing hard physical activity in terms of being breathless and

sweating, influences the long term changes in 6MWD, independent of participation in pulmonary rehabilitation or not. The results indicate that hard physical activity is important to maintain functional exercise capacity.

There was a difference in activity level at 3 years follow-up between participants and non-participants in pulmonary rehabilitation. Previous studies evaluating the effect of pulmonary rehabilitation on physical activity have shown inconsistent results. Some demonstrated effect of pulmonary rehabilitation on physical activity (45, 178), whereas some failed to do so (179-181). In the studies showing negative effects, the lack of improvement in physical activity was observed despite an increased exercise capacity and quality of life. Physical activity was measured with devices as step counters (pedometers) and activity monitors (accelerometers). These instruments have been validated for use in COPD. Some sources of error might, however, have influenced the results in these studies such as; underestimating of the steps during walking at low speed and inaccurate estimation of energy expenditure especially during low speed walking (70).

A methodological problem with self-reported questionnaire is recall bias, and sometimes overestimation. There are limitations with the existing physical activity assessment tools both self-reported and monitors that seem to influence the accuracy of the registrations, which can lead to inconsistent results (70).

In Study III physical activity was not assessed synchronized with the second CPET, which is a limitation. We assumed that the physical activity level measured at 3 years follow-up in Study I was not substantially changed at CPET2 one year later. On this basis we did not find that the change in  $\dot{V}O_{2peak}$  was related to habitual physical activity.

In Study I we demonstrated that  $FEV_1$  at baseline predicted the longitudinal change in 6MWD over 3 years. In Study III we found that the change in  $\dot{V}O_{2peak}$  was associated with the change in  $FEV_1$  over a period of 4.5 years. The association between 6MWD and  $\dot{V}O_{2peak}$  on a progressive incremental CPET has been shown to be only moderate



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to strong (158-166). Ventilatory capacity is reduced in COPD and is related to maximal expiratory flow rates. At some point during the disease progression ventilatory capacity will be the limiting factor for exercise capacity. Therefore it is reasonable to find an association between  $FEV_1$  and exercise capacity measured as 6MWD and  $\dot{V}O_{2peak}$ . However, it is important to keep in mind that exercise capacity cannot be predicted from physiological variables measured at rest, like  $FEV_1$  (103). A person's exercise capacity level can only be determined by actually measuring it.

In Study III we also found that the change in  $\dot{V}O_{2peak}$  was related to the change in IC at rest which is a measure of resting lung hyperinflation. Lung hyperinflation is said to occur when TLC is greater than 120 % of the predicted value and/or when EELV and RV are above 120 to 130 % of the normal predicted value (182). We are not aware of any studies having described the longitudinal changes in TLC in COPD patients. A limitation with our study was that TLC was not measured, thus it is possible that the increase in static hyperinflation is underestimated. Our results demonstrated a decrease in IC at rest from CPET1 to CPET2, and we can only conclude that a relationship between the change in IC at rest and the change in  $\dot{V}O_{2peak}$  was found. We did not find that the change in  $\dot{V}O_{2peak}$  was related to the change in dynamic hyperinflation. Dynamic hyperinflation remained unchanged between the two CPETs. TLC is expected to remain unaltered or slightly increased during incremental exercise (183-185). However without knowledge about the longitudinal change in TLC, changes in dynamic hyperinflation may have been obscured.

### 5.2.2 Breathing pattern during incremental exercise

In Study II we demonstrated that a quadratic model could satisfactorily describe the breathing pattern in terms of the relationship between  $\dot{V}_E$  and  $V_T$  during progressive incremental exercise in most COPD patients.

The relationship between  $\dot{V}_E$  and  $V_T$  during incremental exercise has been characterized by three phases (91). In the first phase, the relationship between  $\dot{V}_E$  and  $V_T$  is linear. In the second phase the increase in  $\dot{V}_E$  is mostly caused by an increase in the  $B_f$  and with only a smaller increase in  $V_T$ , while in the third phase, the increase in  $\dot{V}_E$  is caused by an increase in  $B_f$  only. At the end of this phase a fall in  $V_T$  can be demonstrated. Various methods have been used to characterize the individual  $\dot{V}_E$ - $V_T$  relationship during exercise. The Hey plot (90) describes the slope and intercept in the first part of the response up to a  $V_T$  equal to about half of the vital capacity. Cotes has proposed a maximal  $V_T$  and  $V_T$  at a  $\dot{V}_E$  of  $30 \text{ L} \cdot \text{min}^{-1}$  ( $V_{T30}$ ) (94). Neder et al. (186) has described the breathing pattern including  $V_T$  at predefined fractions of peak  $\dot{V}_E$  in healthy subjects. The maximal  $V_T$  or the plateau of  $V_T$  and the inflection point are described by O'Donnell et al. (9). The inflection point is thought to represent a mechanical limit, and after this point a further increase in  $\dot{V}_E$  can only be accomplished by an increase in  $B_f$ .

There are a limitations with the Hey plot (90),  $V_{T30}$  and  $V_{Tmax}$  (94) and the  $V_T$  at a given fractions of peak  $\dot{V}_E$  (186) in that all the observed data are not included in the analyses. The  $V_{T30}$  (94) requires that a ventilation of minimum  $30 \text{ L} \cdot \text{min}^{-1}$  is achieved. In COPD patients, a maximal  $\dot{V}_E$  below this value may occur, and the method will thereby not be applicable for these patients.

As described by O'Donnell et al. (9) the inflection point is determined “by eye” by two or three persons independently of each other. If less experienced observers are determining the inflection point, it can influence the accuracy and can be biased by increased variability between the observers. When we examined our exercise data, it was not obvious to see where an inflection point occurred. In a quadratic model which is analysed mathematically, the curve parameter  $c$  in the equation will be related to a “perceived” inflection point as it describes the “sharpness” of the curvature, and the  $V_{Tmax}$  can be calculated by derivation of the equation. By using this method determination of the physiological parameters will not be influenced by intra-and/or inter observer reliability. Another consideration is that during an incremental exercise

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test, there will be a gradual transition between the phases described by Gallagher et al. (91), and determining a cut-off point where the change from one phase to the other takes place, is not readily defined. Therefore different choice of cut-off point may affect the characteristics of each phase.

We performed the CPET on treadmill, while in the previous studies that have described the breathing pattern cycle ergometry was used. The breathing pattern has been demonstrated to be different in treadmill exercise as compared with cycle exercise in healthy young subjects (187). The increase in  $V_T$  with increasing  $\dot{V}_E$  was steeper with cycling compared to running, but the  $V_{Tmax}$  was not different between the two modes of exercise. When the absolute value of the quadratic curve parameter  $c$  is increased, as with cycle compared to treadmill exercise, the inflection point may be easier to define. Since we only performed the CPETs on treadmill, our data cannot enlarge upon this issue. Further research is needed.

In Study II we found that the curve parameters in the quadratic equation were related to  $FEV_1$ . With a lower  $FEV_1$ , the maximal  $V_T$  was lower and achieved at a lower  $\dot{V}_E$ . In COPD incomplete expiration leads to accumulation of gas in the lung, and the breathing will take place at a lung volume where the time constant allows complete respiratory breathing cycles. The airway obstruction, expressed by  $FEV_1$ , is determined by airway diameter, gas density and compliance of the airway wall (79). The time constant is the product of resistance and compliance, and  $FEV_1$  is related to both. A relationship between the curve parameters and  $FEV_1$  was therefore not surprising.

In Study III we examined the longitudinal changes in breathing pattern in terms of the relationship between  $\dot{V}_E$  and  $V_T$ . The breathing pattern changed towards a lower  $V_{Tmax}$  and a lower  $V_T$  at a given  $\dot{V}_E$ . Since  $\dot{V}_{Emax}$  and  $\dot{V}O_{2peak}$  deteriorated during the follow-up, a reduced  $V_{Tmax}$  was expected. The changes in the curve parameters were related to the change in  $FEV_1$ .

### 5.2.3 Implications

The results are consistent with previous studies demonstrating that exercise capacity deteriorates over time in patients with COPD and that the decrease in exercise capacity is related to the decrease in lung function. The deleterious effect of persistent smoking on exercise was also demonstrated. Optimal treatment to improve lung function and smoking cessation programs are established corner stones in the treatment of COPD. Our results support the importance of exercise training and physical activity in maintaining exercise capacity. Exercise training is an important part of all pulmonary rehabilitation programs, but the availability of such programs for the patients is still limited and dependent on the priorities of the health authorities. It is established that participation in a rehabilitation program improves exercise capacity, but less is known about the long-term effects of such programs and established guidelines for follow up is lacking.

With respect to the description of breathing pattern with a quadratic equation, there are still many unknowns. Breathing pattern is different with different modes of exercise, but how breathing pattern relates to dyspnea is largely unknown. So far, our description of breathing pattern with a quadratic equation may provide a tool for further studies on these matters.

## 6. Conclusions

- Exercise capacity for patients in GOLD stage II was maintained when measured as 6MWD over 3 years, but was significantly reduced for patients in GOLD stages III and IV. The level of habitual physical activity and  $FEV_1$  were predictors for the longitudinal change in functional capacity.
- The level of physical activity was higher after three years in subjects who had participated in a pulmonary rehabilitation program during the observation period.
- A curvilinear model provides a method to describe a nonlinear breathing pattern during incremental exercise in most COPD patients. The breathing pattern was related to  $FEV_1$ .
- Exercise capacity measured as  $\dot{V}O_{2peak}$  deteriorated significantly over 4.5 years. The reduction was related to an increase in lung hyperinflation and a reduction in  $FEV_1$  along with persistent smoking in the observation period.
- The longitudinal changes in breathing pattern demonstrated a change towards a lower  $V_{Tmax}$  and a lower  $V_T$  at a given  $\dot{V}_E$ , and the reduction in  $FEV_1$  predicted these changes.

## 7. Perspectives

This thesis has highlighted some aspects regarding longitudinal changes in exercise capacity and breathing pattern in patients with COPD. There are, however, still questions to be answered.

Suggestions for further research:

- To perform reliability testing of the IC measurements when the CPET is performed on treadmill.
- To study the longitudinal development of TLC.
- To compare the curvilinear model with determination of the inflection point in treadmill and cycle ergometer in the same patients, cross-sectionally and longitudinal.
- To examine longitudinal changes and associations between  $\dot{V}O_{2\text{peak}}$  and 6MWD when the measurements are performed synchronized in a general COPD cohort.
- To examine the relationship between perceived dyspnea and breathing pattern with treadmill and cycle exercise.

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# APPENDIX

## Appendix A

The Borg CR10 scale, adapted from (142-144)

0	Nothing at all	"No I"	0	Ingenting	"Ingen I"
0,3			0,3		
0,5	Extremely weak	Just noticeable	0,5	Ekstremt svak	Knapt merkbar
0,7			0,7		
1	Very weak		1	Svært svak	
1,5			1,5		
2	Weak	Light	2	Svak	Lett
2,5			2,5		
3	Moderate		3	Moderat	
4			4		
5	Strong	Heavy	5	Sterk	Tung
6			6		
7	Very strong		7	Svært sterk	
8			8		
9			9		
10	Extremely strong	"Strongest I"	10	Ektremt sterk	"Sterkeste I"
11			11		
∞			∞		
•	Absolute maximum	Highest possible	•	Absolutt maksimum	Høyest mulig

## Appendix B

The modified Medical Research Council (MRC) Dyspnea Scale (mMRC).

Adapted from (149)

- 0 Breathless only with strenuous exercise.
- 1 Short of breath when hurrying or walking up a slight hill.
- 2 Walks slower than most people of the same age on the level of breathlessness, or have to stop for breath when walking at own pace on the level.
- 3 Stops for breath after walking about 100 m or after a few minutes on the level.
- 4 Too breathlessness to leave the house or breathless when dressing or undressing.

