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Lung function in relation to exercise capacity in health and disease

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Abstract

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Background: Exercise capacity (EC) is widely recognized as a strong and independent predictor of mortality and disease progression in various diseases, including cardiovascular and pulmonary diseases. Furthermore, it is generally accepted that exercise capacity in healthy individuals and in patients suffering from cardiovascular diseases is mainly limited by the maximum cardiac output.

Objectives: This thesis investigated the impact of different lung function indices on EC in healthy individuals, patients with cardiovascular disease (e.g., pulmonary hypertension (PH)) and patients with pulmonary disease (e.g., chronic obstructive pulmonary disease (COPD)).

Methods: The present thesis is based on cross-sectional and longitudinal analyses of patients suffering from COPD, attending pulmonary rehabilitation at Uppsala University Hospital (studies I and II), and healthy men enrolled in the "Oslo ischemia study" (study IV). Study III is a cross-sectional study of patients suffering from PH attending the San Giovanni Battista University Hospital in Turin. EC was assessed using a bicycle ergometer in studies I and IV, with 12-minute walk tests (12MWT) in study II and with 6-minute walk tests (6MWT) in study III. Extensive pulmonary function tests, including diffusing capacity of the lung (DL_{CO}), were performed in studies I-III and dynamic spirometry was used to assess lung function in study IV.

Results: DL_{CO} is more closely linked to decreased levels of EC than airway obstruction in COPD patients. Furthermore, the decline in 12MWT over a 5-year period was mainly explained by deterioration in DL_{CO} in COPD patients. Spirometric parameters indicating airway obstruction significantly related to EC and exercise-induced desaturation in PH patients. A significant, but weak association between lung function parameters and EC was found in healthy subjects and this association is strengthened with increasing age.

Conclusion: DL_{CO} is the strongest predictor of low EC and EC decline in COPD. In PH, airway obstruction is strongly related to reduced 6MWT. Therefore, extensive analysis of lung function, including measurements of diffusing capacity, along with standard assessment of airway obstruction, gives a more comprehensive assessment of the functional exercise capacity in patients suffering from pulmonary hypertension or COPD. Lung function is also significantly linked to EC even in healthy subjects, lacking evident cardiopulmonary diseases.

Keywords: Exercise capacity, Exercise test, Lung function, Spirometry, Diffusion capacity, COPD, Pulmonary hypertension

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*To my mother Parvin,
my wife Anette and
my daughters,
Isabell and Clara.*

List of papers

This thesis is based on the following papers, which are referred by their Roman numerals to in the text.

- I Farkhooy, A., Janson, C., Arnardóttir, RH., Malinovschi, A., Emtner, M., Hedenström, H., (2013) Impaired carbon monoxide diffusing capacity is the strongest predictor of exercise intolerance in COPD. *COPD* 10(2):180-185
- II Farkhooy, A., Janson, C., Arnardóttir, RH., Emtner, M., Hedenström, H., Malinovschi, A., (2015) Impaired carbon monoxide diffusing capacity is the strongest lung function predictor of decline in 12 minute-walking distance in COPD. A 5-year follow-up study. *COPD* 12(3):240-248
- III Farkhooy, A., Bellocchia, M., Hedenström, H., Libertucci, D., Bucca, C., Janson, C., Solidoro, P., Malinovschi, A., (2016) Lung function in relation to six-minute walk test in pulmonary hypertension (*Submitted*)
- IV Farkhooy, A., Bodegård, J., Erikssen, JE., Janson, C., Hedenström, H., Stavem, K., Malinovschi, A., (2016) Longitudinal analysis of the association between lung function and exercise capacity in healthy Norwegian men (*Submitted*)

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Abbreviations

6MWD	6-minute walk distance
12MWD	12-minute walk distance
6MWT	6-minute walk test
12MWT	12-minute walk test
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CWRET	Constant work-rate exercise test
DL _{co}	Diffusing capacity of the lung for carbon monoxide
EC	Exercise capacity
ESWT	Endurance shuttle walk test
GOLD	Global initiative on chronic obstructive lung disease
FEV ₁	Forced expiratory volume in one second
FVC	Forced vital capacity
IC	Inspiratory capacity
IET	Incremental exercise test
ISWT	Incremental shuttle walk test
PEF	Peak expiratory flow
PH	Pulmonary hypertension
RV	Residual volume
SD	Standard deviation
SpO ₂	Peripheral oxygen saturation
TDWT	Time-dependent walk test
TLC	Total lung capacity
VC	Vital capacity

Introduction

Exercise capacity

Historical perspective

The belief that the ability to exercise could mirror the status of health (or disease), and that physical activity in itself prevents disease development, is not new. Hippocrates (460-370 BC), one of the most prominent physicians of the ancient world, wrote two books on such regimens and noted that “All parts of the body, if used in moderation and exercised in labours to which each is accustomed, become thereby healthy and well developed and age slowly; but if they are unused and left idle they become liable to disease, defective in growth and age quickly” (1).

In the world’s first medical encyclopaedia “*The Canon of Medicine*”, Avicenna, the great ancient Persian physician (980-1037 AD), designated exercise (which he called “*Riazat*”) a preventive measure for the progression of, or a cure for, some diseases (2). Examples of the necessity of exercise for good health abound in medical literature throughout history. Francis Fuller stated in the early 1700s in *Medical Gymnastics: A Treatise Concerning the Power of Exercise*: “That the Use of Exercise does conduce very much of the Preservation of Health...is scarce disputed by any; but that it should prove Curative in some particular Distempers” (3).

The modern science of exercise emerging in the 1960s was primarily built on the novel findings of epidemiologists Jeremy Morris and Ralph Paffenbarger, who linked physical inactivity to a variety of chronic diseases (4). The fact that exercise had achieved scientific and medical credibility was further demonstrated in Warren R. Johnson’s large edited volume, *Science and Medicine of Exercise and Sports* (5). Unique to this new exercise research was that it focused on the healthy individuals, as compared with much of the earlier work in physiology and medicine, which looked at sick and diseased patients. The focus was shifted from “curing the disease” to how to keep the healthy in health. In the 1980s, medical professionals and national health institutes began to take a more serious interest in exercise and health, evidenced by numerous publications in mainstream medical journals such as *JAMA* and *The New England Journal of Medicine*. Highly acclaimed studies drew attention to the link

between low physical fitness in healthy individuals and considerably higher all-cause mortality risk (6-8).

Since the late 1990s, measurements of exercise capacity (EC) have emerged as a substantial clinical implement in the multidimensional evaluation of most cardiopulmonary diseases (9-12). In light of this, exercise testing has gained considerable importance in disease assessment and has become a mandatory, if not a primary, outcome measure in most of the recent clinical trials regarding pulmonary hypertension (PH) and chronic obstructive pulmonary disease (COPD) (13, 14).

Cardiopulmonary physiology in exercise

The body's demand for oxygen increases with exercise and the first-line physiological response to this higher demand is an increase in heart rate, breathing rate and breathing depth. Oxygen consumption (VO_2) during exercise is usually described by the Fick principle, which states that oxygen consumption is equal to cardiac output (Q) multiplied by arteriovenous oxygen difference ($\text{C}_a\text{O}_2 - \text{C}_v\text{O}_2$): $\text{VO}_2 = \text{Q} * (\text{C}_a\text{O}_2 - \text{C}_v\text{O}_2)$.

More simply described, the amount of oxygen consumed during exercise is dictated by the quantity of blood distributed by the heart and the working muscle's ability to take up the oxygen within that blood. Thus, it is generally accepted that EC in healthy individuals is principally limited by the maximum cardiac output (15, 16). In contrast, the respiratory system is considered to be oversized in terms of both respiratory volume and diffusing capacity. Therefore, the respiratory system is believed not to be the limiting factor of maximum EC in healthy, non-endurance athletes (17). However, the notion that cardiac function is the only cardiopulmonary limiting factor of maximal EC is an oversimplification; other factors such as diffusion and ventilation limitation are essential to blood oxygenation and might be of importance in disease or healthy aging.

In aging, our maximum EC decreases and there is a physiological decline in lung function parameters (18). However, the age-related decline in EC has customarily been attributed to "geriatric-attained" sarcopenia and/or decreased cardiac output and the possible association between age-related decline of lung function and decline in EC has not been comprehensively studied (19).

Exercise testing

Exercise testing has now become an essential instrument for the accurate quantification of cardiorespiratory fitness and for identifying mechanisms underlying exercise intolerance (20, 21). The currently existing formats of exercise tests, for both laboratory and field use (Table 1), are particularly designed with regard to activities having a significant aerobic prerequisite. However, none of the primary test formats could reasonably be regarded as stressing purely “aerobic” mechanisms; their symptom-limited character also confers varying degrees of anaerobic conditions (22).

Laboratory-based exercise tests

Laboratory-based tests are carried out on either a cycle ergometer or a treadmill. A broad selection of physiological parameters are measured throughout these tests, both during exercise and in recovery phase (20, 21).

Incremental exercise test (IET)

The procedure is standardized through a computer-driven ergometer or treadmill. The conventional practice is to start the procedure at a low workload and to incrementally increase the workload every minute until the tolerable limit is reached within approximately 6-10 minutes. A shorter time span is believed to be more suitable for patients suffering from severe COPD, as maximal workload is highly dependent on the ramp incrementation rate and a longer targeted timeframe may result in a greater possibility of exercise intolerance resulting from leg fatigue rather than from dyspnoea (23, 24). Patients are monitored throughout exercise and up to 6-10 minutes post-exercise.

Constant work-rate exercise test (CWRET)

These tests are usually carried out to assess the changes in exercise tolerability following interventions (pharmacological or training programs), particularly in COPD patients (25), as they can characterize the variations in a patient's exercise tolerance in a single session. The most straightforward approach is to assign a work-rate based on a fixed percentage (typically 75-80 %) of the maximum work-rate achieved previously in an IET (26). The subjects perform exercise to the time-point at which they are unable to maintain the target work-rate, despite encouragement.

Table 1. *Characteristics of different exercise tests.*

Test	Main variables	Facilities	Reference values	Remarks
IET	ECG, BP, BF, HR, IC, EC, SpO ₂ , dyspnoea, leg fatigue and other	Laboratory setting, cardiac monitoring system and pulse oximeter	Available	Relatively expensive, additional measurements are added more easily on bicycle. Metabolic measurements can be added.
CWRET	ECG, BP, BF, HR, IC, TLIM, SpO ₂ , dyspnoea, leg fatigue and other	Laboratory setting, cardiac monitoring systems and pulse oximeter	Patients serve as own reference	Relatively expensive, additional measurements are added more easily on bicycle. Metabolic measurements can be added.
ISWT	Distance, BF, SpO ₂ , dyspnoea, HR and leg fatigue	10 m corridor, pulse oximeter	Available	Audio signal under copyright, walk tests induce more desaturation.
ESWT	TLIM, BF, SpO ₂ , dyspnoea, HR and leg fatigue	10 m corridor, pulse oximeter	Patients serve as own reference	Audio signal under copyright, walk tests induce more desaturation.
TDWT	Distance, BF, SpO ₂ , dyspnoea, HR and leg fatigue	30 m corridor, pulse oximeter	Available for 6MWT	Dependent on encouragement, track length and layout. Walk tests induce more desaturation.

IET: incremental exercise test; CWRET: constant work-rate exercise test; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; TDWT: time-dependent walk test; ECG: electrocardiogram, BP: blood pressure, BF: breathing frequency, HR: heart rate; IC: inspiratory capacity; EC: exercise capacity; SpO₂: arterial oxygen saturation measured by pulse oximetry; TLIM: time to the limit of tolerance; 6MWT: 6-minute walk test.

Field tests

These simplified tests require less technical apparatus and are therefore considerably cheaper to execute. As field tests are also considered to be generally safe (27) and highly repeatable (28), they are increasingly used in routine patient assessment. The most common field tests are the time-dependent walk test (TDWT) (e.g., 6-minute walk test) followed by ISWT and ESWT (29, 30).

Time-dependent walk test (TDWT)

TDWTs aim to assess exercise capacity by measuring the distance walked in a controlled length of time (31). Although the 12-minute walk test (12MWT) has been revealed to be more closely associated with maximal oxygen uptake than walk tests using shorter time intervals (32), the 6-minute walk test (6MWT) has become the most commonly used TDWT, as it is found to be the best compromise between variability and length, while remaining discriminative and repeatable (33, 34). TDWTs measure the distance walked in an indoor 30 m flat corridor, as tracks shorter than 15 m have been shown to reduce the walk distance (35, 36). TDWT results are expressed in meters, and other variables, such as SpO₂, heart rate, dyspnoea and fatigue ratings, are usually also measured.

Incremental shuttle walk test (ISWT)

ISWT is an externally paced incremental walk test (37). Subjects are required to walk around markers on a 10 m course. Audio signals (beeps) stipulate the pace and indicate when the subject is expected to walk around the marker. The walking speed is increased, minute by minute, for a maximum of 12 minutes. Customarily, SpO₂ and heart rate are measured during the test and the subject's performance is defined as the achieved distance.

Endurance shuttle walk test (ESWT)

The ESWT is derived from ISWT (38), in much the same way as CWERT is derived from IET. In ESWT, the same course and audio signal are used as in ISWT. However, a constant walking speed is maintained throughout the procedure. The pace is tailored for the individual patient based upon a previously conducted ISWT (usually 80 % of peak ISWT). Customarily, SpO₂ and heart rate are measured during the test and the subject's performance is expressed in seconds (or meters).

Lung function

Spirometry

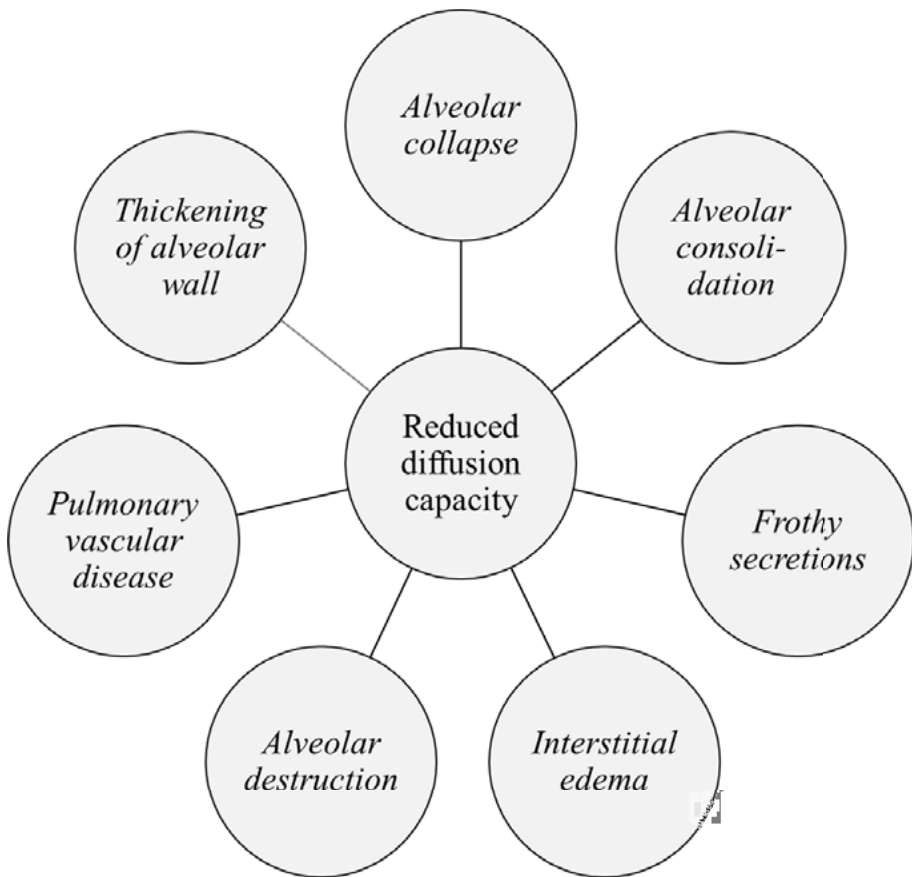
Spirometry is the most commonly used measurement of the pulmonary function, and thus the most important. Simply expressed, by measuring the volume of exhaled air after maximum inspiration, following the standards outlined by international medical organisations (39-41), we are able to assess the integrated mechanical function of the lung and respiratory muscles. The forced vital capacity (FVC), i.e., total amount of air exhaled during a forced breath, the forced expiratory volume in the first second of the exhalation (FEV_1), and the FEV_1/FVC ratio are the major parameters used in evaluating dyspnoea, screening for pulmonary disease, establishing baseline lung function, monitoring effects of therapies and in investigation for occupation-related lung disease.

A disproportionate decrease in FEV_1 as compared with FVC is reflected in the FEV_1/FVC ratio and is the hallmark of any obstructive lung disease. Detection of non-reversible airway obstruction, defined by a FEV_1/FVC ratio lower than 0.7 after bronchodilation, is the imperative measurement in diagnosis of COPD (42). This pathophysiological grouping is not limited to COPD, but also includes other groups of lung diseases such as asthma, acute and chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis and bronchiolitis, which all have airway obstruction as a common disease mechanism (43).

Diffusing capacity of the lung

Measurement of diffusing capacity of the lungs for carbon monoxide (DL_{CO}), also known as transfer factor, is the second most important pulmonary function test, after spirometry (44). Pulmonary gas exchange across the alveolar-capillary membrane provides both quantitative and qualitative assessment of gas transfer in the lungs and a reduced DL_{CO} mirrors diverse limitations (Figure 1), that can be seen in different medical conditions (45). Therefore, DL_{CO} results cannot be used in isolation to “make a diagnosis” and the results should be added to other known medical or physiological parameters, which determine the pre-test probability of the disease under consideration.

Figure 1. Factors associated with reduced diffusing capacity of carbon monoxide

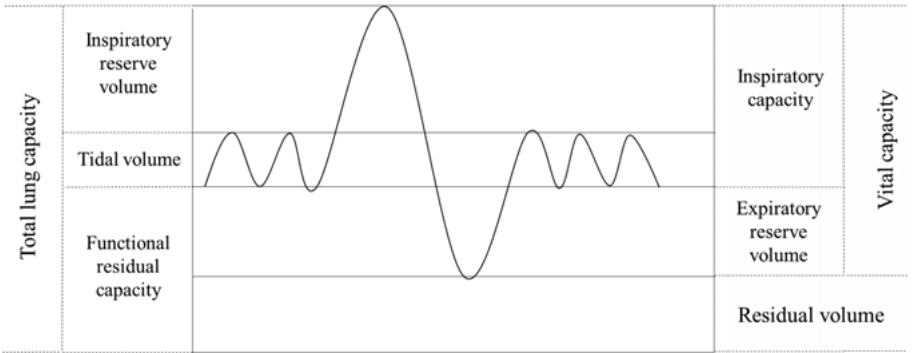


Lung volume determination

By means of standard spirometry it is possible to assess FVC or slow vital capacity. However, it is not possible to use spirometry to assess the residual volume (RV) or capacities including RV, such as total lung capacity (TLC) or functional residual capacity (FRC) (Figure 2). In order for lung volume determination, there are several techniques, such as whole body plethysmography, helium dilution and nitrogen washout, that can be used. This is done in the evaluation of suspected restrictive lung disease and the assessment of hyperinflation, which requires knowledge of the ratio RV/TLC (46). However, measurement of inspiratory capacity (IC) has been shown to be a satisfactory substitute for determination of lung hyperinflation and is more frequently used in evaluation of both static and dynamic hyperinflation. IC is defined by the total amount of air that can be drawn into the lungs after a normal expiration and inversely mirrors FRC.

Measurement of lung volumes might confirm the presence of lung restriction when a reduced FVC is seen upon spirometry. A reduced total lung capacity (TLC) is the hallmark of restrictive lung disease. In presence of obstructive lung disease, static hyperinflation can be verified by demonstrating an elevation of the residual volume (RV) and TLC (47, 48).

Figure 2. Lung volumes and capacities

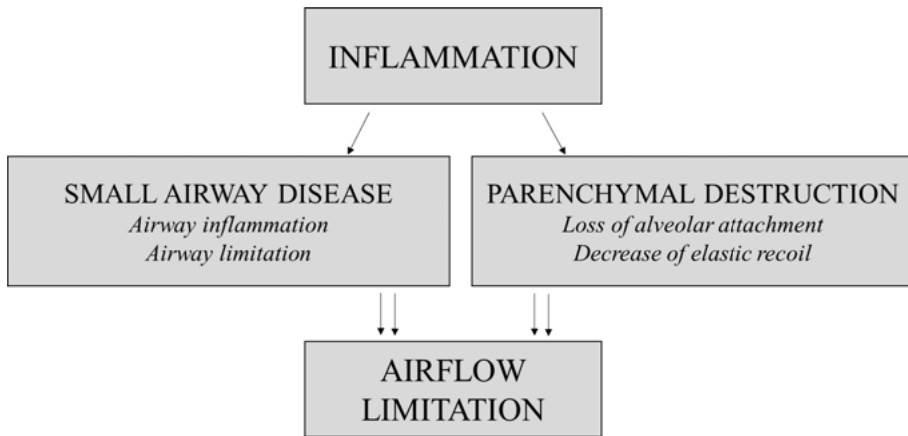


Chronic obstructive pulmonary disease

Definition

COPD ranks among the leading causes of morbidity and mortality worldwide, and is presently the fourth leading cause of death in the world, responsible for over 3 million deaths globally each year (49). COPD presents a global health challenge and is the only leading cause of death with rising mortality and morbidity; it is predicted to be the third cause of death worldwide by the year 2030 (50). The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) with different relative contributions from patient to patient. Inhaled tobacco smoke and other noxious particles, such as smoke from biomass fuels, cause inflammation in the lung, a normal response which appears to be modified in persons developing COPD (51). The chronic inflammation causes structural changes in the lung parenchyma and narrowing of the small airways. Destruction of the lung parenchyma, also through an inflammatory process, leads to loss of alveolar attachment to the small airways and decreases the lung’s elastic recoil. This in turn leads to diminished ability of the small airways to stay open during expiration (Figure 3).

Figure 3. Schematic disease mechanism in COPD



Airflow limitation is best measured through spirometry, which is the most widely available and reproducible test of lung function. To make the COPD diagnosis, a fixed post-bronchodilator FEV_1/FVC ratio of less than 0.7 is required.

The severity of airflow obstruction, measured as decreased FEV_1 , has over the years been the key physiological parameter involved in the categorisation of COPD disease severity, according to Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) (52). FEV_1 is also the traditional lung function parameter used in assessing the disease progression, in addition to defining disease severity. However, disease progression in COPD is characterized not only by progressive airflow limitation, but also by increased hyperinflation, worsening exertional dyspnoea and decline in functional exercise capacity (53). The recent GOLD guidelines (2017) have kept FEV_1 for grading obstruction, but FEV_1 is no longer part of disease severity and exacerbation risk assessment (54).

FEV_1 and COPD

In a landmark study from 1977, Fletcher and Peto reported a relationship between tobacco smoking and accelerated lung function decline in a study of 700 men who were followed for more than two decades (18). Since then, spirometry has become the most widely used non-invasive test of pulmonary function for an overall assessment of lung function and an objective method for following disease progression or improvement and therapeutic response over time (53). The association between FEV_1 measures and prognosis was established more than 20 years ago when Burrows and colleagues revealed that 10-year mortality in COPD patients was directly related to FEV_1 (55). The

study reported that in COPD patients, the risk of death was strongly correlated to the degree of reduced FEV₁, measured at the initial study survey. Longitudinal data, however, revealed overlap in the rate of decline of FEV₁ between COPD patients and control subjects, so that individual values of FEV₁ were not considered to be good predictors of outcome. Moreover, rates of FEV₁ decline vary markedly among individuals with COPD and may change within an individual's lifetime, while "snapshot" spirometric categories ignore differences in disease trajectory (56). Since the original study of Burrows *et al*, several studies have confirmed the statistically significant, but weak relationship between FEV₁ and mortality (57, 58). However, mortality can be more strongly predicted by dyspnoea (59), lung hyperinflation (60), functional status (61), 6-minute walk distance (9), body mass index (57), or mid-thigh cross-sectional area (62) than by FEV₁. Furthermore, impaired exercise ability, which is due to exertional dyspnoea and dominates the patient experience of COPD, correlates poorly with measured airflow limitation (63-65).

In spite of these weak relationships, the disease severity in patients with COPD was to a large extent graded using FEV₁, a single physiological variable, until very recently. To fully appreciate the pervasive effects of COPD requires looking beyond FEV₁, as measures of expiratory flow limitation do not fully express the complexity of COPD and all of its manifestations. This has led to introduction of other evaluation tools assessing the COPD patients such as BODE (**B**ody mass index, **A**irflow **O**bstruction, **D**yspnoea and **E**xercise limitation) and DOSE (**D**yspnoea, **A**irflow **O**bstruction, **S**moking status and **E**xacerbation frequency) indices in order to better predict disease outcome (9, 66). In fact, the newly updated GOLD guidelines take into account both dyspnoea (symptoms) and exacerbation frequency in order to assess disease severity in COPD (42).

DL_{CO} and COPD

DL_{CO} has been validated as the functional respiratory parameter that is most closely related to high resolution computerized tomography attenuation parameters, reflecting the extent of parenchymal destructive changes compatible with emphysema (67, 68). Moreover, greater baseline reduction in DL_{CO} has been found to be a predictor of both faster progression of emphysematous lesions and accelerated decline of FEV₁ in longitudinal studies of COPD (68, 69).

However, a reduced DL_{CO} in COPD does not necessarily reflect only the alveolar-capillary membrane damage subsequent to emphysema (70), but could also be indicative of comorbidity patterns, as increased pressure in the pulmonary circulation (71) or left ventricular heart failure (72) can reduce DL_{CO}.

DL_{CO} itself is only moderately linked to the degree of airway obstruction, probably because of ventilation heterogeneity due to obstruction (73). A number of publications suggest that DL_{CO} is closely linked to impaired exercise capacity, elevated inflammatory biomarkers and arterial oxygen desaturation in patients with COPD (74-76). Furthermore, DL_{CO} has also been reported to be an independent predictor of mortality in COPD patients (77). However, the impact of DL_{CO} on the functional status, measured as walk distance and walk distance changes over time, has been limitedly investigated in COPD patients (76, 77).

Hyperinflation and COPD

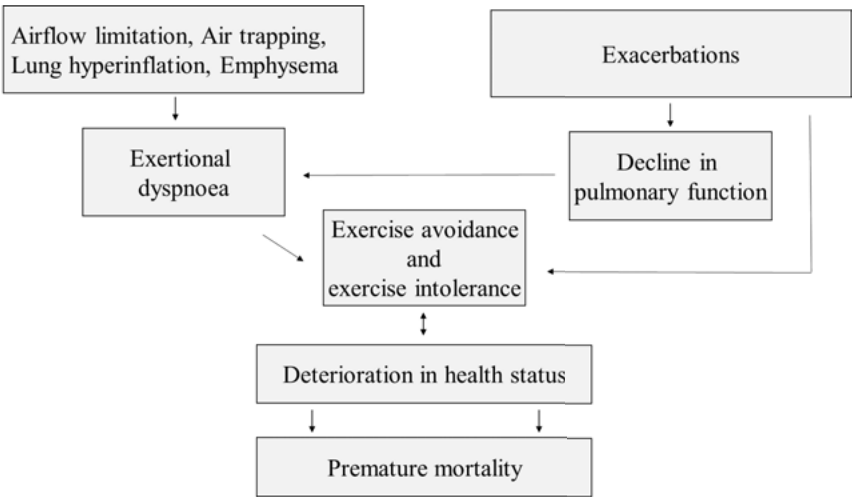
Static lung hyperinflation, defined as an abnormal increase in the volume of air remaining in the lungs at the end of spontaneous expiration, is present in COPD because of the effects of increased lung compliance as a result of the permanently destructive changes of emphysema and expiratory flow limitation. Indices of lung hyperinflation have repeatedly been shown as important predictors of exercise tolerance in patients with COPD. For example, using symptom-limited peak oxygen uptake as the dependent variable, O'Donnell and colleagues (78) found that peak tidal volume emerged as the strongest predictor of exercise tolerance in patients with COPD. Similarly, Diaz and colleagues found that inspiratory capacity (IC) at rest significantly correlated with peak EC in 52 patients with COPD (79). Equally, Puente-Maestu *et al* (80) showed a good correlation between resting IC and EC in patients with severe COPD during constant work-rate exercise. Impaired inspiratory capacity has also been shown to have important clinical consequences in patients with COPD. Cassanova *et al* (60) reported a predictive role for COPD mortality of the inspiratory to total lung capacity ratio or “inspiratory fraction” (IC/TLC). Similarly, in another studies, IC/TLC was shown to be a strong predictor of EC (81) and also had an important influence on cardiac function during exercise in COPD (82).

Exercise capacity and COPD

The pathophysiological hallmark of chronic obstructive pulmonary disease is expiratory flow limitation, whereas the most common symptom is dyspnoea. Dyspnoea is the primary symptom limiting exercise in patients with more advanced disease, and often leads to avoidance of activity. Decreased exercise capacity in COPD results from several factors, including intrinsic lung disease (airway obstruction, hyperinflation, gas exchange abnormalities), peripheral muscle dysfunction (from systemic inflammation, corticosteroids, hypoxia, deconditioning, and sarcopenia), and other co-morbidities (e.g., heart disease or peripheral vascular disease, osteoporosis, anxiety, and depression). Patients

with COPD commonly cite dyspnoea as the main reason for reducing or stopping exercise, but in a substantial proportion of patients with COPD, the locus of symptom limitation during exercise testing is leg fatigue, not breathlessness (83). Intolerance to exercise is closely linked to impairment and disability and is a stronger predictor of poor quality of life and survival than either spirometry or oxygen saturation, contributing to progressively limited activities of daily living (84). Decrements in exercise capacity often result in reduced ability to perform activities of daily living, and the resulting inactivity and inactive lifestyle may additionally aggravate exercise impairment, a finding which is known as “the COPD vicious circle” (85). However, the relationship between the physiological impairment, as traditionally measured by FEV₁, and dyspnoea and disability in COPD is not straightforward, as described in Figure 4. In this context, 6MWT has proven to be a more useful implement than FEV₁ in assessing health-related quality of life (86), decreased daily activity levels (87), and COPD-dependent mortality (84, 88).

Figure 4. Linkage between exercise avoidance and morbidity in COPD



For most individuals with moderate to severe COPD, even basic daily activities can be demanding and overwhelming. Patients state they are too fatigued at even mild exercise and that any exercise makes them short of breath and very uncomfortable. The relationship between dyspnoea intensity and oxygen consumption during a cardiopulmonary exercise test is notably different between patients with COPD and normal subjects. Several investigations have shown that patients with COPD start to experience dyspnoea at a much lower oxygen consumption level than healthy subjects (47, 89). In this context other lung function impairments, besides airflow limitation, such as static and dynamic hyperinflation or reduced inspiratory capacity, have been suggested to better reflect the pulmonary limitation of exercise ability in COPD (47, 81, 90, 91).

Pulmonary hypertension

Definition and classification

Pulmonary hypertension (PH) is a pathophysiological disorder of the pulmonary circulation and is defined by a resting mean pulmonary arterial pressure above 25 mmHg, as measured by right heart catheterization (92, 93). The clinical classification of PH intends to categorize multiple clinical conditions into five major subtypes based on pathological findings, clinical presentation and therapeutic strategies, and haemodynamic characteristics. The WHO classification divides PH into five major categories: 1) pulmonary arterial hypertension; 2) PH due to left heart disease; 3) PH due to interstitial lung diseases and/or hypoxia; 4) chronic thromboembolic PH; and 5) PH with unclear and/or multifactorial mechanisms (94). A simplified version of the clinical classification is presented in Table 2.

Lung function in pulmonary hypertension

Lung function tests with measurement of DL_{CO} are recommended in the initial diagnostic work-up in patients with PH (95), as they can identify the contribution of the underlying airway or parenchymal pulmonary diseases. On the other hand, neither spirometry nor DL_{CO} measurements are part of the follow-up assessment of PH patients (96).

Though the abnormalities of the cardiovascular system in PH are well described, it is unclear to what extent the respiratory system is affected (97). The abnormal pulmonary vessels could affect the function of their adjacent airways and contribute to symptoms. Contradictory results exist regarding presence of airway obstruction, with studies reporting no differences (98, 99) or a lower ratio of FEV_1/FVC , compared with controls (100, 101). A restrictive pulmonary function pattern can be found in up to 50 % of the PH patients and this is also found in patients with PH due to left heart disease (102). The most consistent lung function limitation in PH is nevertheless an abnormal gas transfer assessed as carbon monoxide diffusing capacity (97, 98, 103, 104), which is found in the large majority of PH patients.

Since PH as a disease may have diverse underlying causes, the reduced DL_{CO} has been attributed to different essential mechanisms, such as ventilation-perfusion mismatch, thickening of the alveolar capillary membrane due to endothelial cell proliferation, reductions in pulmonary capillary blood volume, low cardiac output, hypoxic vasoconstriction and right heart dysfunction. Although reduced DL_{CO} is a common finding in PH, it is not included in the risk stratification protocols of PH patients (105) and the clinical significance of DL_{CO} impairment in PH is less obvious (45, 106).

Exercise testing in pulmonary hypertension

Exertional dyspnoea and exercise intolerance are the major findings in PH, and have been attributed to decreased cardiac output, under-perfused alveoli caused by remodelled small pulmonary arteries, and hyperventilation, as well as respiratory and peripheral muscle dysfunction (107-109). EC has been highlighted in PH as it clearly correlates with survival and functional status (110, 111). As a result, exercise capacity, commonly assessed using the 6-minute walk test (6MWT), has been a mandatory, if not a primary, outcome measure in the majority of the recent clinical trials in PH (112). In the 6MWT, oxygen saturation is measured, and it is known that exercise-induced oxygen desaturation often occurs in patients with pulmonary vascular disease (113). However, the relationship between pulmonary function and exertional desaturation in PH patients is not fully understood (114).

Table 2. *Simplified clinical classification of PH.*

PH category	Subgroups
1. Pulmonary arterial hypertension	1.1 Idiopathic 1.2 Heritable 1.3 Drug-induced 1.4 Associated with connective tissue disorders, HIV infection, portal hypertension, and other
2. Pulmonary hypertension due to left heart disease	2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital cardiomyopathy 2.5 Pulmonary vein stenosis
3. Pulmonary hypertension due to lung disease and/or hypoxia	3.1 Chronic obstructive lung disease 3.2 Interstitial lung disease 3.3 Mixed pulmonary disease 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental lung disease
4. Chronic thromboembolic pulmonary hypertension or other pulmonary artery obstruction	4.1 Chronic pulmonary thrombosis 4.2 Other pulmonary artery obstruction
5. Pulmonary hypertension with unclear or multifactorial mechanism	5.1 Haematological disorders 5.2 Systemic disorders 5.3 Metabolic disorders 5.4 Other

Adapted from Simonneau G et al. J Am Coll Cardiol. 2013.

Aims

The aim of this thesis was to investigate the impact of pulmonary function on exercise capacity in human subjects, both in disease and in health.

More specifically, we aimed to explore which lung function parameters were most closely linked to decline in exercise capacity in healthy subjects, in patients suffering from pulmonary hypertension, and in patients with COPD.

I To determine which lung function parameters are best related to maximal exercise capacity in COPD patients, with and without regard to COPD severity.

II To evaluate both the cross-sectional and longitudinal associations between functional exercise capacity and lung function parameters in a 5-year follow-up study of patients with COPD. Further, to investigate which lung function indices have the greatest predictive value on declining exercise capacity in COPD patients.

III To investigate the relationship of resting pulmonary function including DL_{CO} with exercise capacity and exertional desaturation, assessed through the 6MWT, in patients suffering from PH.

IV To investigate whether lung function indices are associated with peak exercise capacity in middle-aged, healthy subjects at baseline and at 16-year follow-up. Further, to explore the relationship between age-related decline of lung function parameters and decrease of exercise capacity.

Ethics

Studies I and II were approved by the Ethics Committee of Uppsala University (number 01-159) and all participants gave written informed consent.

Study III was reviewed and approved by the “Interaziendale” Ethical Review Board in Turin. All patients gave informed consent.

In 1972, no institutional or regional review board existed in Norway. Hence, no formal institutional approval for the investigation protocol could be obtained for study IV. However, the survey protocol was circulated among prominent physicians at two hospitals in Oslo, who commented on the protocol at an *ad hoc* meeting. All subjects gave their informed consent before inclusion.

Material and methods

Population

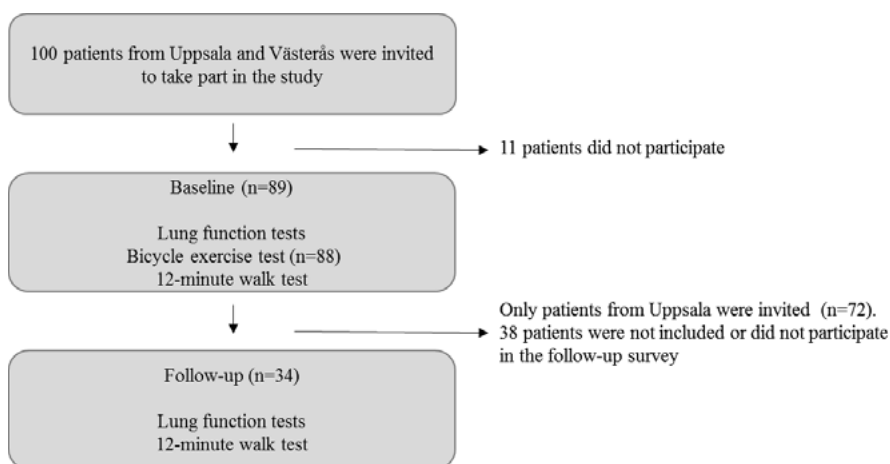
Studies I & II

A total of 100 subjects with moderate to very severe COPD, according to the existing guidelines (115), were invited to take part in study I, when consecutively referred to the Physiotherapy Unit of the Respiratory Department of the University Hospital in Uppsala, Sweden or to the Physiotherapy Unit of the Pulmonary Section at the Central Hospital in Västerås, Sweden (116). All patients fulfilled the following inclusion criteria:

1. FEV_1/FVC ratio < 0.7 after bronchodilation
2. $FEV_1 < 80\%$ predicted
3. Capable of undergoing exercise testing to peak effort
4. Non-acute phase of the disease

Patient characteristics are outlined in Table 3. Eighty-nine patients agreed to participate in the study and one patient declined to perform an exercise test on ergometer cycle as this was perceived as too exhausting (Figure 5).

Figure 5. Flowchart for studies I and II



The patients who were recruited at the Uppsala centre were then invited to take part in the follow-up survey 5 years after the baseline visit ($n = 72$, median follow-up time = 5.2 ± 0.25 years). Thirty-four patients agreed to participate in the follow-up study. Non-participants in the follow-up survey were distributed as following: 21 patients abstained further participation in lung function and/or exercise testing, 14 patients were deceased and 3 patients were not found. Patient demographics are listed in Table 3.

Exclusion criteria included coexisting medical conditions interfering with lung function or exercise testing or the inability to comprehend written or oral instructions. Furthermore, patients with pre-existing cardiac disease, intermittent claudication, musculoskeletal problems and/or signs of cardiac ischemia or cardiac arrhythmia upon exercise testing were excluded from the study.

Table 3. *Patient characteristics and physiological parameters in studies I & II.*

<i>Variables</i>	<i>Study I (n = 88)</i>	<i>Study II (n = 34)</i>	
		Values at baseline	Values at follow-up
Age (y)	64 ± 7	63 ± 8	68 ± 8
Sex (f/m)	64 / 24	22 / 12	-
BMI (kg/m ²)	23.6 ± 4.3	23.3 ± 3.4	23.2 ± 3.5
Smoking (pack years)	40 ± 9	39 ± 9	36 ± 12
Current smoking (y / n)	20 / 68	12 / 22	5 / 29
TLC (L)	6.5 ± 1.4	6.6 ± 1.3	7.1 ± 1.6
TLC (% predicted)	110 ± 20	114 ± 22	119 ± 20
RV (L)	3.5 ± 1.1	3.2 ± 0.9	4.5 ± 1.3
RV (% predicted)	169 ± 59	187 ± 58	198 ± 63
FVC (L)	2.7 ± 0.9	3.0 ± 1.0	2.5 ± 0.9
FVC (% predicted)	73.1 ± 16.2	77.9 ± 16.8	69.4 ± 20.5
FEV ₁ (L)	1.1 ± 0.4	1.2 ± 0.4	1.1 ± 0.4
FEV ₁ (% predicted)	39.2 ± 13.0	40.7 ± 13.0	42.0 ± 13.5
DL _{CO} (mmol/min/kPa)	3.4 ± 1.3	3.8 ± 1.1	3.1 ± 1.4
DL _{CO} (% predicted)	48.3 ± 17.1	50.6 ± 15.7	45.3 ± 19.3
Exercise capacity (W)	63.3 ± 22.4	-	-
12MWD (m)	-	928 ± 193	789 ± 273

Values presented as means ± SD. BMI = body mass index; TLC = total lung capacity; RV = residual volume; FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; DL_{CO} = diffusing capacity of the lung for carbon monoxide; 12MWD: 12-minute walk distance.

Study III

A total of 50 consecutive patients with PH diagnosed according to guidelines (117), visiting the Pulmonary Function Testing Unit of Molinette University Hospital, Turin, Italy, for assessment of pulmonary function and six-minute walk distance during the period 2012–2013, were included in the study. The diagnosis of PH rested upon haemodynamic data attained by right heart catheterization in all patients. All patients displayed a mean pulmonary arterial pressure above 25 mmHg and were subsequently divided into PH subclasses according to guidelines. Patient demographics are shown in Table 4.

Table 4. *Patient demographics in study III.*

<i>Variables</i>	<i>All subjects (n = 50)</i>
Sex (f/m)	26 / 24
Age (y)	62.4 ± 11.8
BMI (kg/m ²)	25.5 ± 6.2
Smoking habit	
<i>Never smoker</i>	20 (42 %)
<i>Ex-smoker</i>	4 (8 %)
<i>Current smoker</i>	24 (50 %)
Disease class	
<i>PH class 1</i>	10 (20 %)
<i>PH class 2</i>	27 (54 %)
<i>PH class 3</i>	4 (8 %)
<i>PH class 4</i>	6 (12 %)
<i>PH class 5</i>	3 (6 %)
LTOT	16 (32 %)
OSAS	4 (8 %)
COPD	10 (20 %)
Pulmonary fibrosis	3 (6 %)
Heart disease	33 (69 %)
Diabetes	13 (27 %)
History of cancer	16 (34 %)

Values presented as means ± SD or N (%). BMI = body mass index; PH = pulmonary hypertension; PH class 1 = pulmonary arterial hypertension; PH class 2 = PH due to left heart disease; PH class 3 = PH due to interstitial lung disease and/or hypoxia; PH class 4 = PH due to chronic thromboembolism; PH class 5 = PH with unclear and/or multifactorial mechanisms; LTOT = long-term oxygen therapy; OSAS = obstructive sleep apnoea syndrome; COPD = chronic obstructive pulmonary disease.

Study IV

Study IV is based on data from a cardiovascular observational study, “The Oslo Ischemia Study,” in which men aged 40–59 years were recruited from five companies/governmental institutions in Oslo during the years 1972–1975. Of the 2,341 apparently healthy men who were eligible and invited, 2,014 (86 %) consented to participate. The participants had to be free from known or suspected heart disease, hypertension, diabetes mellitus, malignancy, advanced pulmonary, renal, or liver disease and should have no locomotor activity limitation. Further details about selection procedures and exclusion criteria have been presented elsewhere (118, 119). The subjects underwent a clinical examination survey including questionnaires, assessment of cardiovascular risk factors, a chest x-ray, dynamic spirometry and a symptom-limited exercise test. The survey was repeated in 1989–1990 (120).

Of the 2,014 subjects enrolled at the baseline survey, 391 were excluded due to lack of spirometry or unsatisfactory quality of the lung function test. Furthermore, 605 subjects were excluded as their lung function values at the baseline survey differed from the predicted normal values, as described in greater detail below. The survey was repeated in 1989–1990, and a total of 273 subjects did not participate in the follow-up survey or were not included. The remaining 745 subjects, with lung function and exercise capacity data from both surveys, were included in the current study (Figure 6). The subject characteristics are outlined in Table 5.

Figure 6. Flowchart for study IV

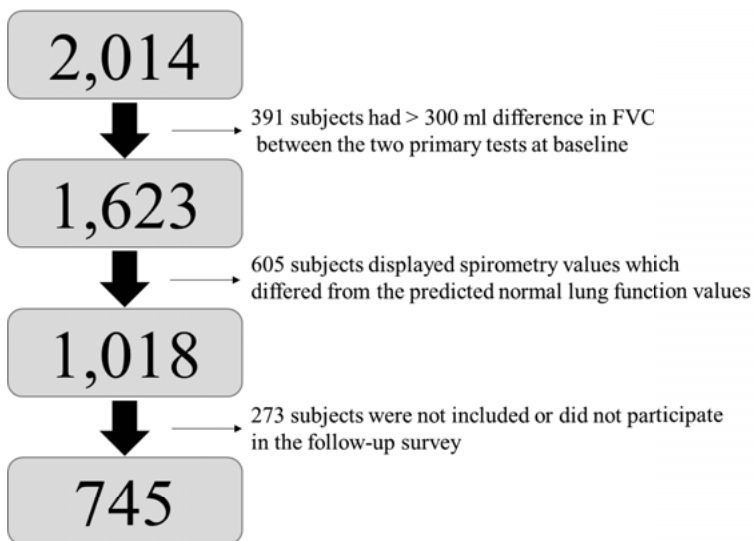


Table 5. *Subject characteristics study IV.*

<i>Variables</i>	<i>Values at base-line (n = 745)</i>
Age (years)	48.5 ± 5.3
Current smoker	245 (34.1 %)
BMI (kg/m ²)	24.6 ± 2.6
Systolic BP (mmHg)	128.8 ± 16.7
Diastolic BP (mmHg)	86.4 ± 10.1
Self-reported physical activity	
<i>No physical activity routine</i>	77 (10.3 %)
<i>Low physical activity routine</i>	548 (73.6 %)
<i>High physical activity routine</i>	120 (16.1 %)

Values presented as means ± SD or N (%). BMI = body mass index; BP = blood pressure.

Exercise tests

Bicycle exercise ECG test

In study I, all patients performed an exercise test on an ergometer cycle (RE 830, Rodby Elektronik AB, Enhörna, Sweden) with continuous cardiac monitoring (Case 8000 Exercise Testing System, GE Medical Systems, Milwaukee, Wisconsin, USA) to a symptom-limited peak work capacity. Patients started pedalling at 20 W and the load was increased by 10 W every minute until exhaustion. Systolic blood pressure, subjective ratings of exhaustion (Borg RPE scale) and perceived exertional dyspnoea (Borg CR-10 scale) were recorded every second minute (121, 122). All parameters were measured before exercise, as well as one, two, four and ten minutes post-exercise. EC was calculated as the highest workload, but the number of seconds the patient endured at the last working load was taken into account as follows (123): $W_{\text{peak}} = W_{\text{last completed workload}} + 10 \text{ W} * (\text{number of seconds endured at the last workload} / 60)$.

In study IV, a different exercise protocol was utilized. The initial workload was 100 W for 6 minutes and then increased by 50 W every 6 minutes. The exercise test was continued until a heart rate of at least 90 % of the maximum predicted heart rate was reached, unless specific symptoms or signs necessitated premature termination. If an individual seemed physically fit despite reaching 90 % of maximum predicted heart rate + 10 beats per minute at the end of one load, he was encouraged to continue as long as possible at the next load, i.e., at most an additional six minutes at a higher load (124). Exercise capacity was assessed as physical fitness, defined as the total bicycle work per

unit of weight and calculated as the sum of work (in Joules) at all workloads divided by bodyweight (in kg) (125).

Twelve-minute walk test

The 12-minute walk tests (12MWT) in study II were performed, as described by McGavin (126), in a 34 m, level corridor. Initially, two tests were performed for practice, and a third served as baseline. In the follow-up survey, only one test was performed. The subjects were asked to cover as much ground as possible in 12 minutes at their own speed and to pause if necessary. To limit bias, no encouragement was given to the subjects and the physiotherapist did not walk alongside them. The subjects were told the time at standard intervals (4, 6, 8, 10 and 11 minutes). Heart rate, PEF, breathing frequency and subjectively perceived symptoms (122) were measured at four time-points: before the walk test, after 6 minutes, directly after completion and five minutes after the performed test. The 12MWT was performed in 84 individuals at baseline and in 34 individuals at the follow-up study after 5 years.

Six-minute walk test

The 6-minute walk tests (6MWT) in study III were conducted in a 30 m flat, straight and enclosed corridor. Walk distance was measured after the subjects had walked as far as possible for 6 min, according to guidelines (127). No encouragement was given to the subjects and the laboratory assistant did not walk alongside them. The subjects were told the time at the start of each minute. Breathing frequency and subjectively perceived symptoms (122) were measured at start and directly after completion of the test. Oxygen saturation and pulse rate were measured before and immediately after the 6MWT using a pulse oximeter with finger sensor. Baseline SpO₂ was obtained while subjects were relaxed and in the sitting position. Exercised-induced oxygen desaturation was defined according to the Royal College of Physicians' guidelines (128) as a minimum of 5 % reduction between arterial oxygen saturation measured by pulse oximetry pre- and post-test.

Lung function testing

Spirometry

In studies I and II, spirometry was performed using a Masterlab Trans Spirometer (Erich Jaeger AG, Würzburg, Germany). The normal values according to Hedenström *et al* (129, 130) were used. All lung function testing was performed by highly experienced technicians in accordance with the standards outlined by ATS/ERS (39-41). Post-bronchodilatory values were used in all patients in study I for all further measurements. In study II, 28 out of 34 individuals performed post-bronchodilatory spirometry at follow-up.

Post-bronchodilatory lung function values were measured 30 minutes after the patients inhaled 5 mg salbutamol and 0.5 mg ipratropium via a nebulizer. All subjects performed all lung function tests at baseline.

In study III, spirometry was performed using a computerized water-sealed Stead-Wells spirometer (Biomedin, Padua, Italy). All lung function testing was performed in accordance with the standards outlined by ATS/ERS (41, 131). Reference values from the European Community for Steel and Coal/ERS were used (46). Pre-bronchodilatory spirometry was used for all subjects, with the exception of the patients with COPD ($n = 10$), where post-bronchodilatory values were used.

In study IV, FVC and FEV_1 were measured with a calibrated Bernstein spirometer at the baseline examination, using a standardized procedure (132). After one trial test, FVC and FEV_1 values were recorded from two successive maximum expiratory manoeuvres, corrected for body temperature and ambient pressure and saturated with water vapour, based on daily room temperature measurements and an assumption of atmospheric pressure of 760 mmHg. Originally, only the mean FEV_1 and FVC values were recorded. To obtain the maximum of the two tests, the original spirograms and recorded values for both manoeuvres were retrieved in 2001 (133). In order to increase the reliability of the data (as the original dataset was obtained before ATS/ERS guidelines existed, and therefore no criteria for standardization were available), only subjects with < 0.3 L difference between the two FVC tests ($n = 1,625$) were included (134). Additionally, only subjects with FEV_1/FVC ratio ≥ 0.7 and a FEV_1 value greater than or equal to 80 % of predicted, according to Norwegian reference values of Langhammer *et al* (135), were included in further calculation, in order to limit the analyses to subjects with normal lung function values. During the follow-up examination, a Vitalograph spirometer was used, with a similar protocol for the procedure. PEF measurements were performed with a Wright's peak flow meter, noting the mean value of the last two out of at least three tests.

Pre-bronchodilatory spirometry was used for all subjects both at baseline and in the follow-up survey, as no bronchodilation was included in the protocol.

DL_{CO} measurements

In studies I and II, DL_{CO} was measured with the single-breath technique using Masterlab Transfer (Erich Jaeger AG, Würzburg, Germany). Pre-bronchodilatory DL_{CO} values, corrected for actual haemoglobin levels, were used in all further analyses. DL_{CO} measurements were performed according to the standards outlined by ATS/ERS (39-41). The normal values according to Hedenström *et al* (129, 130) were used.

In study III, DL_{CO} was measured with the single-breath technique, using the Baires System (Biomedin, Padua, Italy) with a gas mixture of 0.3 % CO, 10 % helium, and balance air. DL_{CO} measurements were performed following the standards outlined by ATS/ERS (41, 131). Reference values from the European Community for Steel and Coal/ERS (46) were used.

Measurements of DL_{CO} were not included in the protocol for study IV.

Lung volumes

In studies I and II, lung volumes were obtained with a Masterlab Body Plethysmograph (Erich Jaeger AG, Würzburg, Germany). The normal values according to Hedenström *et al* (129, 130) were used. The predicted values for inspiratory capacity were obtained by subtracting predicted value for FRC from predicted value for TLC in each specific patient. Lung volume measurements were performed by qualified laboratory specialists according to the standards outlined by ATS/ERS (39, 41, 131).

In study III, lung volumes were obtained by Baires System (Biomedin, Padua, Italy) by means of helium dilution. All lung function testing was performed in accordance with the standards outlined by ATS/ERS (41, 131). Reference values from the European Community for Steel and Coal/ERS were used (46).

Measurements of lung volumes were not included in the protocol for study IV.

Statistical analyses

Statistical analyses in study I were performed using the computer software programs Stata 8.2 (StataCorp, College Station, Texas, USA) and StatView 5.0.1 (SAS Institute Inc.). In studies II, III, and IV, statistical analyses were performed using the STATA 12.1 software program (StataCorp, College Station, Texas, USA).

In study I, the patients were divided into tertiles based on EC (12MWD) and a trend analysis regarding lung function was performed across these groups, with exercise capacity as predictor and lung function parameters as outcomes. Simple linear regression was used to analyse the correlation between different single lung function parameters and EC. A stepwise regression model was used to determine the most important predictors of EC, when using data from spirometry alone or from a combination of spirometry, body plethysmography and DL_{CO} . Simple and multiple linear regression models based on the best predictors of EC from the above model (FEV_1 , IC and DL_{CO}) were used to predict EC in different COPD severity stages. Finally, standardized coefficients for each lung function parameter, which describe their relative contribution to explaining working capacity, were calculated.

In study II, the patients were divided into tertiles based on 12MWD or changes in 12MWD over 5 years ($\Delta 12MWD$) and a trend analysis of lung function was performed across these groups, with lung function parameters as predictors and 12MWD as an outcome. Simple linear regression was used to analyse the correlation between different single lung function parameters and 12MWD and this was presented as the square of the correlation coefficient (r^2). A stepwise regression model, which included lung function parameters demonstrating statistically significant correlation to 12MWD, as well as sex, age, BMI, participating in the pulmonary rehabilitation program and smoking habits, was used to determine the most important lung function predictors of 12MWD. Baseline 12MWD was additionally introduced into the specific model analysing the relation between lung function parameters at baseline and 12MWD at follow-up. Standardized regression coefficients (β) were calculated for the lung function parameters in multiple linear regression models.

In study III, simple linear regression was used to analyse the relation between different single lung function parameters and 6MWD. These relations were tested for consistency in a multiple linear regression model that included sex, age, BMI and smoking habits, in addition to the lung function parameters. The same statistical analyses were performed again, when dichotomization of patients was used with regard to signs of airway obstruction. Finally, stepwise

regression analysis was performed in a model including all lung function parameters, arterial gases, gender, age, smoking habits and BMI, in order to determine the most important predictors of 6MWD.

In study IV, a simple linear regression model was used to analyse the correlation between lung function parameters and variables relating to physical fitness. These relations were tested for consistency at the baseline visit in a multiple linear regression model that included age, weight, height, exercise habits and current smoking, in addition to the lung function parameters. A similar model at the follow-up visit included age (defined as age at start-up + 16 years, the median-follow-up time), weight, and height, in addition to the lung function parameters. The residuals in the regression models were checked for non-normality using plots versus fitted values and dependent variables and found to be normally distributed.

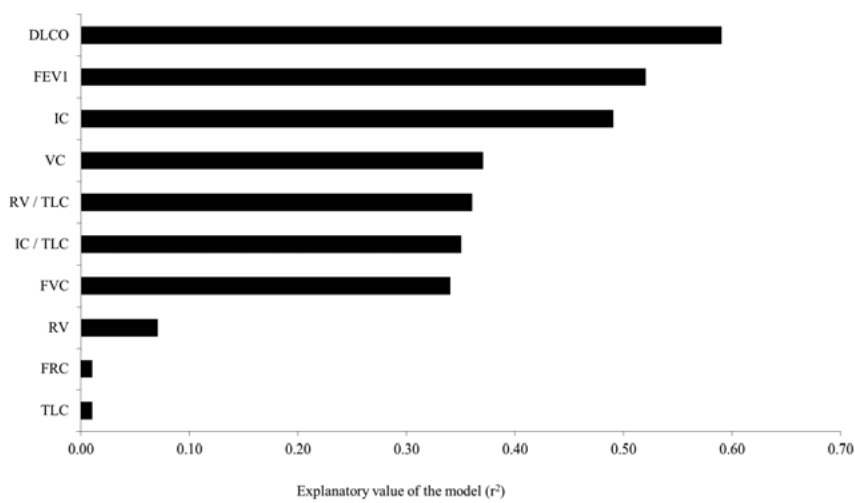
Results

Study I

Spirometry, body plethysmography and DL_{CO} measurements were performed on 88 patients with COPD former GOLD stages II-IV. Exercise capacity was determined in all subjects by symptom-limited, incremental cycle ergometer testing.

A significant trend of increasing DL_{CO} and spirometric values with increasing EC was found. Conversely, a significant trend of decreasing lung volumes with increasing EC was seen. The strongest correlation with EC was found with DL_{CO} , followed by FEV_1 and IC (Figure 7). The majority of the other lung function parameters were significantly related to EC, with the exception of FRC and TLC.

Figure 7. Explanatory value (r^2 values) from simple linear regression models of each of the lung function parameters (absolute values) for the patient's exercise capacity



DL_{CO} = diffusing capacity of the lung; FEV_1 = forced expiratory volume in one second; IC = inspiratory capacity; VC = vital capacity; RV = residual volume; TLC = total lung capacity; FVC = forced vital capacity; FRC = functional residual capacity.

In a stepwise regression analysis where only data from spirometry were used, FEV₁ and IC were the main determinants of EC with an explanatory value of 58 % (Table 6). After adding DL_{CO} data into the model, FEV₁, IC and DL_{CO} were the main determinants of EC with an explanatory value of 72 %. None of the lung volumes obtained by body plethysmography contributed to the explanatory value of the model.

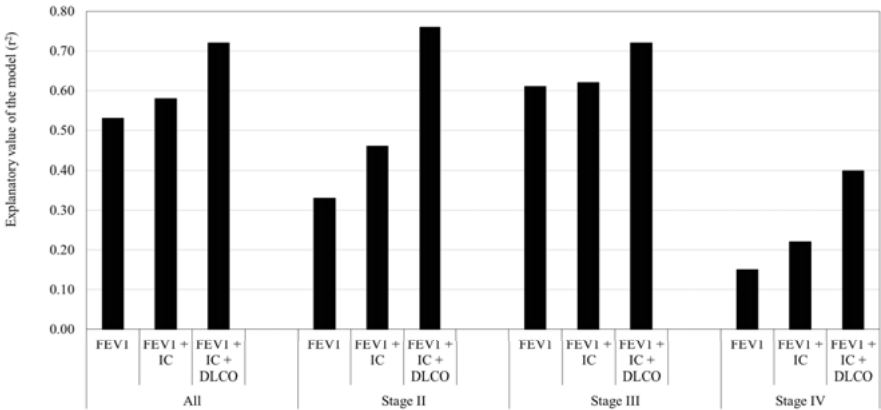
Table 6. Stepwise regression models of determinants of exercise capacity when using data from spirometry alone or from spirometry and diffusing capacity.

	Spirometry	Spirometry + DL _{CO}
FEV ₁	0.45 (0.23, 0.67)	0.26 (0.06, 0.46)
IC	0.36 (0.14, 0.58)	0.22 (0.04, 0.40)
DL _{CO}	-	0.48 (0.34, 0.62)
r ²	0.58	0.72

Absolute values were used in the calculation. The explanatory value of the model is described as adjusted r² values, and each parameter in the model is expressed as a standardized coefficient. FEV₁ = forced expiratory volume in one second; IC = inspiratory capacity; DL_{CO} = diffusing capacity of the lung.

The predictive value of FEV₁ for EC is presented along with the additive information of IC and DL_{CO} in a sub-analysis of the now outdated COPD stages according to GOLD (42) (Figure 8). Overall, DL_{CO} was the most consistent predictor of EC in each individual GOLD stage. The additive information of IC and FEV₁ in GOLD stages II and IV was minor.

Figure 8. The explanatory value of lung function indices for exercise capacity in different COPD stages



Values are presented as r² values from the linear regression model. FEV₁ = forced expiratory volume in one second; IC = inspiratory capacity; DL_{CO} = diffusing capacity of the lung; Stage II = FEV₁ 50-80 % predicted, Stage III = FEV₁ 30-50 % predicted, Stage IV = FEV₁ < 30% predicted.

Study II

Spirometry, body plethysmography and DL_{CO} measurements were performed in patients with moderate to very severe COPD, at baseline survey ($n = 84$) and at follow-up visit ($n = 34$), after approximately five years. Functional exercise capacity was assessed by standardized 12MWT.

At the baseline survey, higher DL_{CO} , FEV_1 , IC, FVC and VC values were associated with increased 12MWD, while having higher RV and RV/TLC was associated with decreased 12MWD (Table 7).

Table 7. Lung function values for all 84 patients at baseline in lower, middle and upper tertiles of 12-minute walk distance. *p* values are presented for trend along different tertiles. A *p* value < 0.05 was considered to be statistically significant.

Variables	* Lower tertile ($n = 28$)	Middle tertile ($n = 28$)	Upper tertile ($n = 28$)	<i>p</i> value
TLC (L)	6.4 ± 1.3	6.4 ± 1.5	6.6 ± 1.5	0.542
IC (L)	1.5 ± 0.4	1.8 ± 0.6	2.0 ± 0.5	< 0.001
IC/TLC (%)	23.4 ± 7.7	28.1 ± 7.4	30.3 ± 8.6	0.002
VC (L)	2.5 ± 0.6	2.8 ± 0.9	3.4 ± 0.9	< 0.001
RV (L)	3.9 ± 1.1	3.6 ± 1.1	3.3 ± 1.2	0.036
RV/TLC (%)	60.3 ± 8.6	55.6 ± 9.4	48.7 ± 9.7	< 0.001
FVC (L)	2.3 ± 0.6	2.5 ± 0.7	3.1 ± 1.0	< 0.001
FEV_1 (L)	0.8 ± 0.2	1.1 ± 0.3	1.3 ± 0.4	< 0.001
DL_{CO} (mmol/min/kPa)	2.9 ± 0.9	3.2 ± 0.9	3.9 ± 1.4	< 0.001

*Lower tertile: < 789 m, middle tertile: $789 - 921$ m, upper tertile > 921 m.

TLC = total lung capacity; IC = inspiratory capacity; VC = vital capacity;

RV = residual volume; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; DL_{CO} = diffusing capacity of the lung.

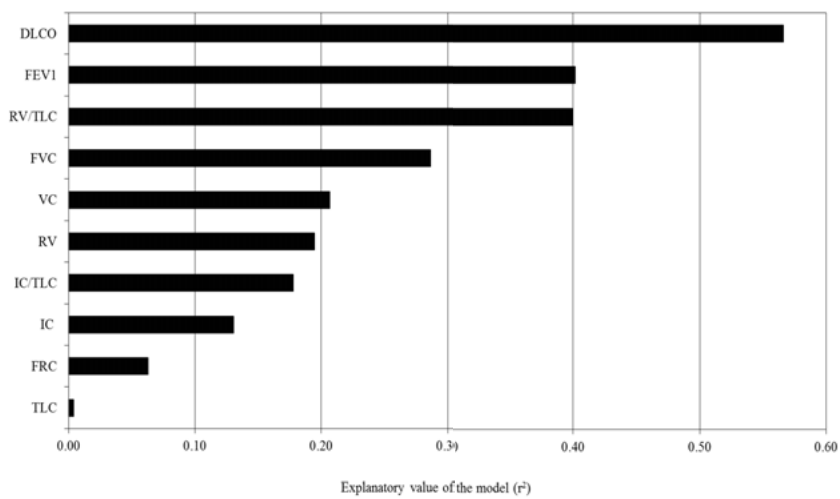
In simple linear regression analysis, the strongest correlation to 12MWD was found with FEV_1 , followed by RV/TLC, IC and DL_{CO} . Other lung function parameters were also significantly associated with 12MWD, with the exception of FRC and TLC.

FEV_1 and DL_{CO} were the main lung function determinants of 12MWD with an explanatory value (r^2) of nearly 40 % in a stepwise regression model which included BMI, sex, age, smoking and completed physical rehabilitation program as shown in Table 8. None of the lung volumes obtained using body plethysmography contributed to the explanatory value of the model.

At the follow-up visits, lower levels of DL_{CO} , FEV_1 , IC, FVC and VC were found compared with in the baseline survey, as was reduced 12MWD. In simple linear regression analysis, the strongest correlation to 12MWD was found with DL_{CO} , followed by FEV_1 and RV/TLC (Figure 9).

Stepwise regression analysis, including sex, BMI, smoking status and completion of pulmonary rehabilitation program, revealed DL_{CO} and RV as the main lung function determinants of 12MWD with an explanatory value of 79 % (Table 8)

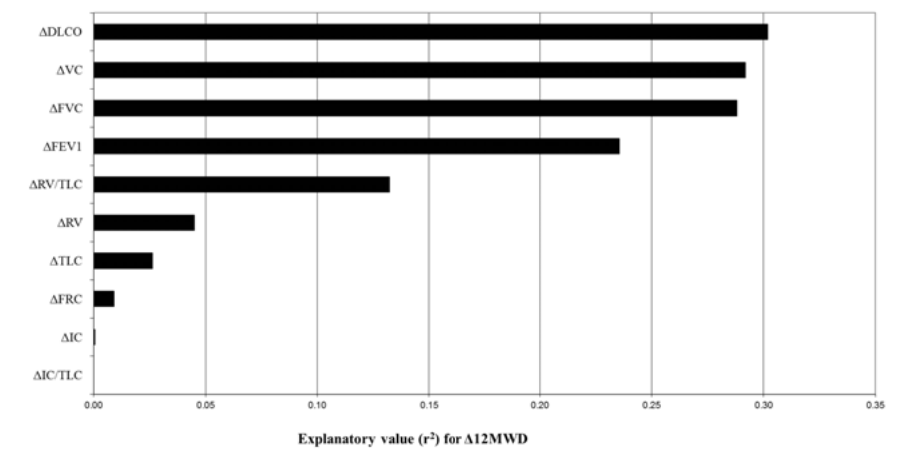
Figure 9. Explanatory value (expressed in r^2 values from simple linear regression models) of the lung function parameters for the patients' EC at the follow-up survey



DL_{CO} = diffusing capacity of the lung; FEV_1 = forced expiratory volume in one second; RV = residual volume; TLC = total lung capacity; FVC = forced vital capacity; VC = vital capacity; IC = inspiratory capacity; FRC = functional residual capacity.

Further, a simple linear regression model was used to determine the impact of declining lung function parameters on the reduced EC. Changes in DL_{CO} (ΔDL_{CO}) appeared to have the strongest correlation with changes in 12MWD ($\Delta 12MWD$), followed by ΔVC , ΔFVC , and ΔFEV_1 (Figure 10).

Figure 10. Explanatory value (expressed in r^2 values from simple linear regression models) of change of lung function parameters for the change in EC at follow-up.



DL_{CO} = diffusing capacity of the lung; VC = vital capacity; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; RV = residual volume; TLC = total lung capacity; FRC = functional residual capacity; IC = inspiratory capacity.

ΔDL_{CO} and ΔFVC were the main predictors of $\Delta 12MWD$ in a stepwise regression analysis including sex, age, smoking, BMI and completed physical rehabilitation program, with an explanatory value of 48 % (Table 8).

Table 8. Stepwise regression models of determinants of 12-minute walk distance. The coefficients in the table are standardized regression coefficients (β) for the respective lung function parameters, with the exception of r^2 , which represents the coefficient of determination of the model (predictive value of the multiple linear regression model including only the lung function parameters presented in the table).

	12MWD, baseline	12MWD, follow-up	Change in 12MWD
FEV_1 at baseline	0.53	-	-
DL_{CO} at baseline	0.12	-	0.51
r^2	0.37	-	0.26
DL_{CO} at follow-up	-	0.60	-
RV at follow-up	-	-0.51	-
r^2	-	0.79	-
Change in DL_{CO}	-	-	0.44
Change in FVC	-	-	0.41
r^2	-	-	0.48

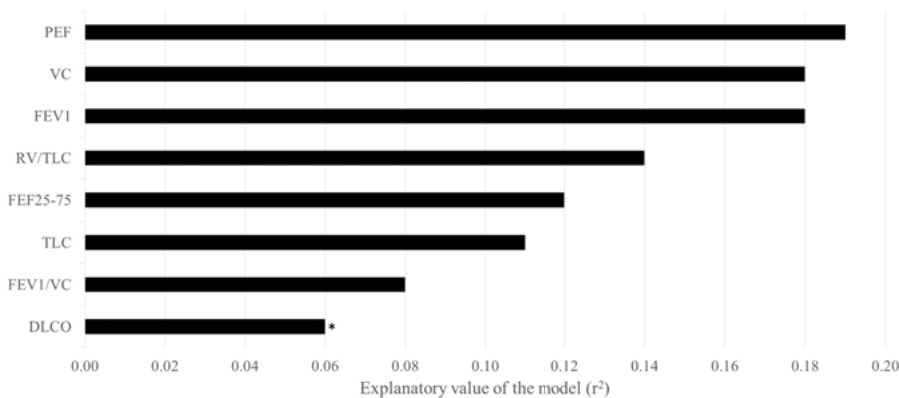
12MWD = 12-minute walk distance; FEV_1 = forced expiratory volume in one second; DL_{CO} = diffusing capacity of the lung; RV = residual volume; FVC = forced vital capacity.

Study III

Fifty consecutive patients with pulmonary hypertension were recruited when referred to Molinette University Hospital in Turin for pulmonary function assessment. The investigation included spirometry, lung volume determination through helium dilution technique and DL_{CO} -measurements. Functional exercise capacity was assessed by standardized 6MWT.

Reduced DL_{CO} was found in 46 patients (92 %), while 5 patients (10 %) showed reduced TLC. A total of 23 patients (46 %) presented signs of airway obstruction, defined as $FEV_1/VC < 0.70$, while 27 patients had decreased FEV_1 and 26 patients had decreased PEF, defined as a value below 80 % of the predicted normal value. The strongest correlation with 6MWD was found for PEF, followed by VC and FEV_1 (Figure 11). DL_{CO} , RV and SpO_2 at rest did not show any association with patient 6MWD. A stepwise regression model containing all PH patients, where all lung function parameters, gender, age, smoking habits and BMI were included, yielded PEF as the sole determinant of 6MWD. A similar stepwise regression analysis, when lung functions were expressed as percent of predicted, revealed FEV_1 (% predicted) as the sole determinant of 6MWD. PEF remained the variable most strongly associated with 6MWD also after adjusting for the aforementioned confounders.

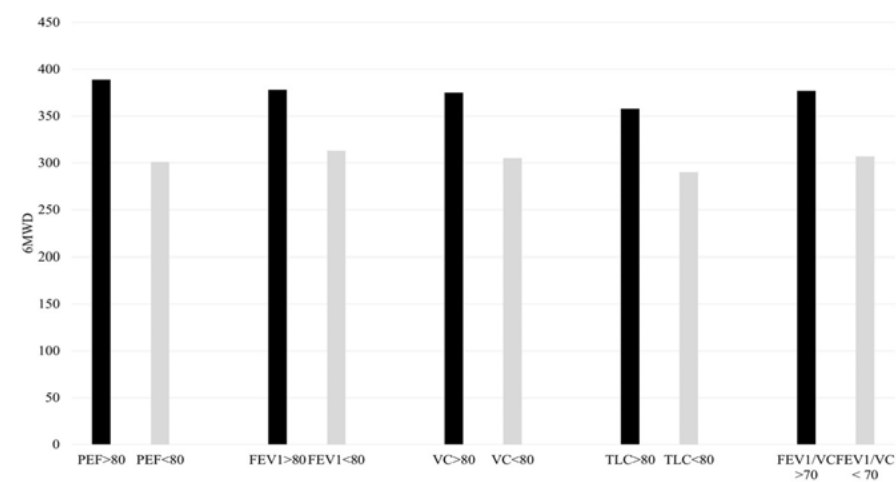
Figure 11. Six-minute walk distance (m) in relation to decreased FEV_1 , PEF and VC (defined as $< 80\%$ of predicted normal value) and FEV_1/VC (defined as < 0.70)



PEF = peak expiratory flow; VC = vital capacity; FEV_1 = forced expiratory volume in one second; RV = residual volume; TLC = total lung capacity; DL_{CO} = diffusing capacity of the lung. * indicates non-significant relation, $p > 0.05$.

In general, decreased lung function indices (< 80 % predicted) were associated with shorter 6MWD, as shown in Figure 12. In a similar pattern, patients with FEV₁/VC ratio lower than 0.7 had a significantly shorter 6MWD than patients without airway obstruction (307 m vs. 377 m, Figure 12).

Figure 12. Six-minute walk distance (m) in relation to decreased FEV₁, PEF and VC (defined as < 80 % of predicted normal value) and FEV₁/VC (defined as < 0.70)



6MWD = Six-minute walk distance; PEF = peak expiratory flow; FEV₁ = forced expiratory volume in one second; VC = vital capacity; TLC = total lung capacity.

Twenty-two patients (44 %) presented exertional desaturation following the 6MWT. Lower levels of resting SpO₂ and FEV₁/VC were the only parameters significantly associated with exercise-induced oxygen desaturation (Table 9). None of the lung volumes obtained through helium dilution technique showed significant correlation with exertional desaturation. Only lower FEV₁/VC ratios (OR 0.9, CI 0.85–0.99, p < 0.05) remained significantly correlated with desaturation also in a logistic regression model adjusted for age, sex, BMI and smoking habits.

Table 9. Values are presented as means (confidence interval) for patients who exhibited exertional desaturation and patients without exertional desaturation. *p* values pertain to the statistical outcomes of the *t*-tests between the groups.

Variables	No desaturation (n = 28)	Desaturation (n = 22)	p value
Baseline SpO ₂	97.1 (96.4–97.9)	94.9 (92.9–96.8)	0.015
FEV ₁ /VC	72.4 (69.3–75.4)	67.1 (62.5–71.6)	0.044
DL _{CO}	13.3 (11.4–15.1)	11.0 (8.9–12.0)	0.090
VC	2.8 (2.5–3.1)	3.1 (2.6–3.6)	0.207
RV	2.1 (1.8–2.3)	2.3 (2.0–2.6)	0.218
TLC	4.9 (4.5–5.4)	5.4 (4.7–6.2)	0.218
PEF	5.2 (4.5–5.8)	5.7 (4.5–6.9)	0.386
FEV ₁	2.0 (1.8–2.2)	2.1 (1.8–2.5)	0.514
RV/TLC	41.9 (38.7–45.2)	43.0 (39.2–46.7)	0.674

SpO₂ = peripheral oxygen saturation; *FEV₁* = forced expiratory volume in one second; *VC* = vital capacity; *DL_{CO}* = diffusing capacity of the lung; *RV* = residual volume; *TLC* = total lung capacity; *PEF* = peak expiratory flow.

Stepwise regression analysis including all lung function parameters and arterial gases, gender, age, smoking habits and BMI, revealed resting oxygen saturation as the main determinant of oxygen desaturation during the 6MWT. In the same model, including only relative values, DL_{CO} (% predicted) was shown to be the main determinant of exertional desaturation.

Study IV

A total of 745 middle-aged men between 40 and 59 years were examined by means of dynamic spirometry and standardized bicycle exercise tests within “The Oslo Ischemia Study.” The baseline survey was carried out for the period of 1972–1975, and the follow-up survey was completed during 1989–1990. Lung function parameters at inclusion and the follow-up survey are presented in Table 10. There were significant decreases of lung function indices, in absolute values, and of physical fitness, between the baseline and follow-up surveys.

Table 10. *Lung function and physical fitness at baseline and follow-up, n = 745.*

	Baseline visit		Follow-up visit		<i>p</i> value*
	<i>Absolute values</i>	<i>% predicted</i>	<i>Absolute values</i>	<i>% predicted</i>	
FEV ₁ (L)	3.8 ± 0.5	95.0 ± 9.8	3.5 ± 0.7	97.5 ± 16.3	< 0.001
FVC (L)	4.7 ± 0.7	95.6 ± 10.1	4.4 ± 0.7	92.8 ± 11.1	< 0.001
PEF (L/min)	558.4 ± 65.5	92.3 ± 10.2	544.7 ± 72.4	90.5 ± 12.0	< 0.001
PF (kJ/kg)	2.1 ± 0.8	-	1.02 ± 0.6	-	< 0.001

* *p* value for paired *t*-test for absolute values. FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow; PF = physical fitness.

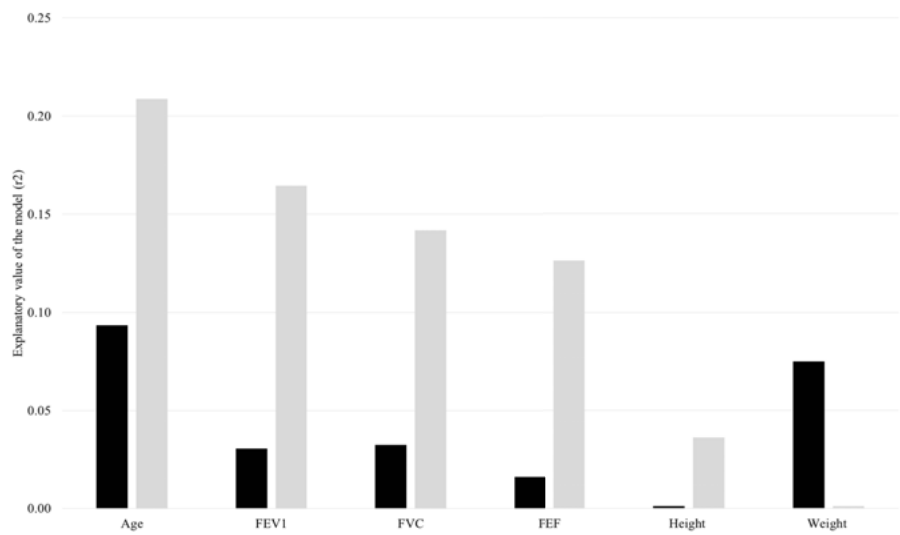
In the follow-up survey, the strongest correlation with physical fitness was found for subject age, followed by FEV₁. Significant associations of higher FEV₁, FVC and PEF with higher physical fitness were found, as was a significant association of lower physical fitness with higher age and weight (Figure 13). All lung function values displayed a higher explanatory value for a subject’s physical fitness at follow-up than at baseline, assessed as regression coefficients in single linear regression models (Table 11).

Table 11. *Regression coefficients (95 % CI) of lung function for physical fitness at baseline and follow-up surveys (n = 745).*

	Baseline survey	Follow-up survey
FEV ₁ (per L)	0.26 (0.16, 0.37)	0.38 (0.32, 0.44)
FVC (per L)	0.22 (0.13, 0.31)	0.30 (0.25, 0.35)
PEF (per 100 L/min)	0.16 (0.07, 0.25)	0.28 (0.23, 0.33)

FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow.

Figure 13. Explanatory value (expressed in r^2 value from a simple linear regression model) of each of the investigated parameters for physical fitness at baseline (black) and follow-up (grey)



FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow.

General discussion

Lung function and exercise capacity in COPD

The major finding of studies I and II was that DL_{CO} emerged as the strongest predictor for exercise capacity in COPD patients. Almost 80 % of the variance of EC in study I could be explained by combining information from DL_{CO} , FEV_1 and IC.

In both studies I and II, a significant association was found between FEV_1 and exercise capacity. Decreased FEV_1 levels mirrored exercise intolerance in different stages of COPD, and FEV_1 could explain about 50 % of the variance of exercise capacity in both studies. These results are in accordance with those of the National Emphysema Treatment Trial where Brown *et al* reported that FEV_1 could explain 66 % of the variance of maximum exercise capacity (136).

IC was the third most important predictor of exercise capacity in both studies I and II (at baseline). This is in accordance with previous studies which have also reported correlations between IC and EC in COPD (137). In study I, including IC in addition to FEV_1 increased the explanatory value of the model by about 10 % and this effect was more prominent in moderate COPD. Surprisingly, adding IC to FEV_1 had no significant impact on predicting EC in patients with more severe COPD. This might be explained by onset of comorbidities associated with COPD. Surprisingly, in study II, IC at follow-up was not related to 12MWD at follow-up. However, in our material no deterioration of IC was found over the 5-year follow-up period. This is in conflict with other study reports which have implied that IC deteriorates in the same manner as FEV_1 in the natural course of COPD (81, 138).

The explanatory value of DL_{CO} for EC in COPD patients was also additive to the explanatory value of spirometry measurements. Furthermore, in study II, we were able to display that the decline of 12MWD over time in COPD subjects could mainly be explained by the decline of DL_{CO} . In these studies, DL_{CO} appeared as a consistent and strong predictor of EC in both cross-sectional and longitudinal study designs (Table 12). These results are in line with the reports of an association between 6MWD and DL_{CO} in the few previous studies available in literature (139-142).

Table 12. *Impact of lung function indices on exercise capacity in COPD.*

	IET Baseline	12MWT Baseline	12MWT Follow-up	Δ 12MWT in relation to Δ lung function indices
1st predictor	DL _{CO}	FEV ₁	DL _{CO}	DL _{CO}
2nd predictor	FEV ₁	RV/TLC	FEV ₁	VC
3rd predictor	IC	IC	RV/TLC	FVC
4th predictor	VC	DL _{CO}	FVC	FEV ₁

12MWT = 12 minute walk test, DL_{CO} = diffusing capacity of the lung; FEV₁ = forced expiratory volume in one second; IET = incremental exercise test; IC = inspiratory capacity; VC = vital capacity; RV = residual volume;

TLC = total lung capacity, FVC = forced vital capacity.

The impact of DL_{CO} on maximal exercise capacity has previously been investigated in a limited way (143, 144). In a study investigating heavy smokers who had not developed COPD, decreased DL_{CO} could explain almost 40 % of the variance of exercise capacity (143). In another study, investigating functional exercise capacity in COPD patients, DL_{CO} was found to be an important predictor of 6MWD, explaining almost 25 % of the walk distance (140).

The findings in studies I and II, that DL_{CO} was the strongest predictor of EC regardless of disease severity, mirror the fact that emphysema is a common finding in COPD (145). As decreased DL_{CO} is associated with conditions of diffuse alveolar-capillary damage, reduced alveolar surface or decreased capillary density (146), it does not necessarily reflect the grade of airflow obstruction in COPD patients. In a study from Shaker *et al*, almost 90 % of patients with COPD, regardless of disease severity, displayed signs of emphysema when evaluated by high resolution CT scan (147). Moreover, in the same study material, it was shown that emphysema could precede airway obstruction (148). There is a body of evidence implying that the magnitude of emphysema is only weakly correlated with the deterioration of FEV₁ and spirometric parameters and could only to some extent predict the degree of emphysema or COPD progression (149). These findings suggest an underestimation of the magnitude of impaired diffusion in COPD patients. In a sub-study of a national emphysema trial, the researchers reported that emphysema was present in all stages of COPD and that deteriorated FEV₁ was not a significant predictor of the severity of emphysema (150).

Change in FEV₁ is frequently a primary endpoint in clinical trials evaluating the efficacy of the treatment and improvement in FEV₁ is seen as a positive result in studies. This is, in fact, self-contradictory, as COPD is perceived as a chronic, non-reversible, obstructive lung disease. In fact, in several major COPD studies investigating the effect of bronchodilators, the rate of decline

of FEV₁ was not affected by therapy (151, 152). Although spirometric assessment is important for the characterization of airflow impairment and improvements following therapy, a broader approach to study endpoints should be employed that includes measures beyond FEV₁. In line with this, more functional parameters, such as walk distance or time performing exercise at a constant workload, have been used as outcomes in more recent pharmacological and longitudinal studies (153, 154). Our study suggests that other lung function parameters, such as DL_{CO} and IC, could be helpful in explaining patient exercise limitations and offer a better characterization of patients.

DL_{CO} measurement, in particular, gave a more comprehensive assessment of the functional exercise capacity at a specific time-point, but also had a prognostic value for deterioration of exercise capacity in patients with COPD. These results support the recent finding on the relation between DL_{CO} and mortality (77), suggesting that DL_{CO} should be assessed in clinical practice more often. For example, DL_{CO} measurements could be used as a complement to routine spirometry to facilitate earlier identification of emphysema or cardiovascular causes of impaired DL_{CO} and exercise capacity in patients with symptoms and exercise intolerance that cannot be explained by the degree of expiratory airflow limitation. Furthermore, DL_{CO} could be used to identify patients with presumably more rapid exercise intolerance/disease development. It seems logical to make efforts for an early detection of patients with a more swift presumed disease progression, in order to intensify therapeutic measures.

In study I, the explanatory value of the lung function parameters for EC was significantly higher in patients in lower disease stages compared to patients with very severe COPD. As far as we know, this relationship has not been reported in other studies. We believe that these results mirror the complexity of COPD in advanced stages. Patients with a heavier disease burden, besides a higher degree of emphysema, are more likely to exhibit systemic effects (155), such as systemic inflammation, right ventricular failure and/or pulmonary hypertension, decreased skeletal muscle function, weight loss and depression, all of which would probably have a strong influence on exercise tolerance.

Furthermore, in study II, DL_{CO} at baseline related to change in 12MWD over time and 12MWD at follow-up, suggesting a prognostic value of DL_{CO} for deterioration of exercise capacity in COPD patients. Additionally, in study II, an increased loss of DL_{CO} had the best predictive value for an increased loss in 12MWD over time, a relationship which no previous studies have investigated. Interestingly, patients in study II did not demonstrate any significant FEV₁ decline during the follow-up period. This might be explained by the fact that the majority of the patients were already ex-smokers and had relatively

low starting FEV₁ values, which can lead to a more modest deterioration of FEV₁ (156). However, there was a significant decline in DL_{CO}, despite smoke cessation, which could be related to progression of emphysema, increased pulmonary vascular pressures and/or increased ventilation heterogeneity.

Even when different measures for evaluating exercise capacity were used in studies I and II, DL_{CO} appeared to be one of the most important predictors of exercise capacity, irrespective of the type of functional assessment. Together with the consistent predictive value both at baseline and follow-up, studies I and II imply that DL_{CO} provides a more comprehensive understanding of COPD patients' cardiopulmonary limitations, which has also been suggested by other investigators (74, 157).

The predictive value of an impaired DL_{CO} for an accelerated deterioration in 12MWD is a novel finding. This, together with the recent reports on the predictive role of diminished DL_{CO} in COPD mortality and exacerbations (77, 158), implies that DL_{CO} should be integrated in the routine evaluation of COPD patients to a greater extent. This could also give relevant clinical information in order to initiate a more integrated approach to the patient's health status and possibly identify other underlying comorbidities, such as heart failure (159). Even if DL_{CO} measurements are still restricted to expensive devices, available only in respiratory physiological laboratories, the appearance of newer, portable devices (160) opens for broader clinical use of DL_{CO} measurements in COPD outpatient clinics (161).

No significant relationship was found between lung volumes obtained by body plethysmography and exercise capacity. Overall, lung volume measurements had low predictive value for EC and did not offer any additional information. This is in line with results from other studies in the field. FEV₁ and DL_{CO} have been shown to be significantly lower in patients experiencing exertional desaturation, whereas lung volumes were not significantly related to exercise-induced desaturation (76, 162).

Lung function and exercise capacity in pulmonary hypertension

The major finding of study III was that airway obstruction was related to exercise capacity in a group of unselected patients with pulmonary hypertension. This significant correlation was consistent for all the different expiratory lung function parameters obtained through dynamic spirometry and after adjustment for patient characteristics. Furthermore, this finding remained in a sub-

analysis of patients with PH secondary to left heart disease, the largest group included in the present material. Diffusing capacity for carbon monoxide was not related to exercise capacity, but was related to oxygen desaturation during exercise. TLC measurements did not provide any additional information in relation to the studied outcomes, while RV/TLC ratio was related to exercise capacity.

No significant association between diffusing capacity for carbon monoxide and walking distance was found in the present material. The diffusing capacity relates inversely to the mean pulmonary arterial pressure and this is in line with results from echocardiography studies, which found no relation between pulmonary arterial pressure and 6MWD (110). Total lung capacity measurements obtained through helium dilution technique did not offer supplementary information. This is in accordance with previous studies, where lung volume measurements offered minimal additional information (163-165). In a study by Armstrong *et al* (163), the authors were unable to show any relationship between peak exercise capacity and lung volumes in patients suffering from interstitial pulmonary disease with or without pulmonary hypertension.

Airway obstruction in PH has previously been studied, with 20–40 % of patients with PH class 1 displaying signs of airway obstruction based on a FEV₁/FVC ratio lower than 70 % (166, 167). Moreover, the association between airway obstruction and exercise capacity could also be seen in patients with PH secondary to left heart failure, patients who are more often regarded to be characterized by a restrictive lung function pattern (168). Additionally, in patients with PH class 2, a relation is found with air trapping assessed through RV/TLC ratio. This might reflect lung congestion causing air trapping through peribronchial cuffs or lung stiffening (169).

As we hypothesised in advance that DL_{CO} would have large impact on exertional desaturation in PH patients, an unexpected significant association was found between FEV₁/VC and exercise-induced desaturation. We assume the fact that the patients were characterized as pulmonary hypertensive, i.e., having reduced diffusing capacity, made airway obstruction more influential in the outcome of 6MWT due to a tendency toward uniformity for DL_{CO} levels. This is actually in line with findings in studies I and II, in which we could demonstrate that in patients suffering from COPD, i.e., airway obstruction, DL_{CO} was more closely linked to reduced walk distance (170). On the other hand, DL_{CO} (% predicted) related to exercise-induced desaturation, which is in line with reported interdependence between pulmonary diffusion and oxygen desaturation during exercise in patients with diffuse systemic sclerosis and interstitial lung disease (171).

No substantial relationship was found between lung volumes obtained through helium dilution technique and outcome parameters in study III. This is in line with results from other studies in the field, in which measurements of lung volumes (172, 173) did not offer any complementary information in distinguishing patients with reduced functional exercise capacity or exercised-induced desaturation.

As field exercise tests in general, and 6MWT in particular, have been shown to be important predictors of mortality in PH and COPD patients, it is important to better understand the correlation between pulmonary limitations and EC in each individual patient (Table 13). Airway obstruction is probably independent of systolic pulmonary pressure in most of the patients suffering from PH. On the other hand, the extent of emphysema in COPD is poorly mirrored by spirometric indices of airway obstruction. This signals an essential need to better characterize the pulmonary function, including both spirometry and DL_{CO} measurements, in the routine assessments of exercise capacity.

Table 13. *Correlation between pulmonary function parameters and EC in COPD and PH in studies I-III.*

Parameter	COPD	PH
DL_{CO}	+++	-
FEV_1	+++	++
FVC or VC	++	++
IC	+++	NA
RV	+	-
TLC	-	-

DL_{CO} = diffusing capacity of the lung; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; VC = vital capacity; IC = inspiratory capacity; RV = residual volume; TLC = total lung capacity; NA = not available.

Lung function and exercise capacity in healthy middle-aged men

In study IV, a significant association was found between lung function indices, obtained through dynamic spirometry, and EC. This association was seen in cross-sectional analyses at both baseline and follow-up surveys. Interestingly, the relation between lung function and EC increased over time. In fact, all three investigated parameters, i.e., FEV_1 , FVC and PEF, behaved in the same manner, although they reflect different aspects. FEV_1 is more closely related

to airway obstruction, FVC to lung volumes and PEF to obstruction and muscular strength (174). However, decline in physical fitness over time was not related to decline in lung function.

In healthy aging, there is a steady deterioration of the dynamic lung volumes. Both FEV₁ and FVC decline with age, and the flow-volume curve may change shape and become more similar to the curve in patients with chronic obstructive lung disease (COPD) (175, 176). The prevalence of dyspnoea increases with age in people not suspected of having lung disease, but most studies investigating the relationship between declining lung function parameters and reduced maximum exercise capacity have been performed on elderly populations and/or with a cross-sectional study design (177-179). To our knowledge, the impact of normal age-related decrease in lung function parameters on maximum exercise capacity in healthy middle-aged and young people has not previously been examined in a longitudinal study. Other studies investigating the impact of aging and exercise capacity have had a cross-sectional study design (180) and/or predominantly examined the relationship between cardiac function and exercise capacity (181). To our knowledge, this is the first longitudinal study investigating the relationship between spirometric parameters and exercise capacity in healthy, middle-aged subjects.

All lung function indices included in study IV correlated significantly with physical fitness at baseline. Given that the healthy respiratory system is oversized, one would expect to observe a relationship between lung function parameters and exercise capacity only when the dimensions of the respiratory system are reduced below a threshold value which represents the lower limit of normal lung function. However, there was a relationship between exercise capacity and lung function in study IV, even at baseline, when the subjects were young, presumed healthy and had a normal lung function. Furthermore, the association between FEV₁ and physical fitness increased with age. However, there was no significant association between the decline in lung function parameters and the decline in exercise capacity in a follow-up period exceeding 15 years. This may partly be related to a loss of lung elastic recoil in aging, which is associated with a reduction in the expiratory boundary of the maximal flow-volume envelope (182).

Dyspnoea and reduced exercise capacity have been shown to be independent predictors of mortality in an otherwise healthy, elderly population, i.e., other than in cardiopulmonary diseases. Argulian *et al* reported that among patients referred for stress testing, a primary symptom of dyspnoea had significantly higher all-cause mortality compared with a primary symptom of chest pain (183). In addition, Berraho *et al* reported that the risk of mortality increases with higher levels of exercise-induced dyspnoea when assessing elderly sub-

jects (> 65 years) over a period of 13 years (184). However, the pathophysiology of disproportionate exercise-induced dyspnoea in elderly who are otherwise healthy is not fully understood. The findings in study IV may contribute to the understanding of the physiology of exercise and determinants of exercise capacity.

Limitations and strengths

It could be argued that different exercise testing modalities were used in this thesis and that they are not comparable. In study I, a modern incremental exercise testing protocol was used, while an outdated protocol (however standard at the time of the study) was used in study IV. Controversy has long existed concerning the optimal exercise protocol. Recent studies have nevertheless confirmed that dyspnoea ratings are similar for any level of ventilation, regardless of the increase in work-rate (185). However, using a more steep incremental protocol may result in underestimation of the maximal exercise capacity (186). Furthermore, while most studies use 6MWT, we assessed the functional exercise capacity by 12MWT test in study II. Even though 6MWT is much more widely used, 12MWT has been shown to be more closely associated with maximal oxygen uptake (32, 187).

One of the limitations of studies I and II is that we used the resting lung function parameters to predict EC, as it is suggested that increasing lung hyperinflation during exercise (dynamic hyperinflation) is more closely related to exercise intolerance and clinical dyspnoea than airflow limitation and static hyperinflation. Another major limitation of study II is the relatively low number of patients that could be re-examined in the follow-up survey. This is, however, an inherent problem with long-term studies in COPD patients (188-190). Considering the observational period of 5 years targeting COPD patients and the fact that our study protocol included exercise testing, the dropout rate is in line with the aforementioned studies.

In the same manner, study III was a single-centre investigation with a relatively low total number of study subjects. This limited the possibilities of performing sub-analyses with regard to type of PH, with the exception of PH class 2, the largest group investigated, where we confirmed the main finding of the study regarding the relation between airway obstruction and exercise capacity. Another limitation of study III is the lack of current data on pulmonary pressure obtained by echocardiographic examination. Although PH is a clinical syndrome with different underlying etiology, the key diagnostic feature is an elevated pulmonary artery pressure. Nevertheless, functional parameters such as 6 min walking distance have shown to have a prognostic significance superior to most standard resting haemodynamic parameters, despite underlying causes of disease (110, 191).

The limitations of study IV included having only male subjects, and a lack of normal values for physical fitness from other populations. In study IV, spirometry was performed according to earlier and less rigorous standards than those used nowadays. The rigorous selection of subjects with normal lung function may be regarded as a strength, as we probably excluded subjects with possible respiratory disease. However, this may have contributed to a lower variability of the lung function variables in the baseline analysis.

The strength of studies I and II is the standardized methodology with all the lung function and exercise testing parameters gathered by the same skilled research assistants in a clinical physiology laboratory setting. A selection bias cannot be excluded with regard to the dominance of women in our material. This probably reflects the fact that women are referred for physical training to a greater extent than men. This preponderance of female subjects in our material adds more knowledge on peak EC in women with COPD; many previous studies concerning exercise ability in COPD patients have included mostly men (192). The strength of study III is the availability of extensive lung function characterization. Another strength of study III consisted of the study design, in which we aimed to investigate the possible weight of pulmonary function on a prognostic test, i.e., 6MWT, in patients suffering from PH, regardless of disease category. Study IV included a large number of participants with a follow-up period extending over 15 years, in the first longitudinal study, to our knowledge, examining the relationship between lung function and exercise capacity in healthy subjects.

Future research

As the results of this thesis suggest that deterioration of exercise capacity in COPD is closely linked to reduced DL_{CO} , future research should focus on understanding the mechanism behind this association. Reduced DL_{CO} may be related to several common comorbidities in COPD, besides emphysema. Including high resolution computed tomography and echocardiography in future research protocols may more accurately reveal the causation behind the declining diffusing capacity. Furthermore, generalization of the results should be done with caution, due to the limited number of subjects in study II, and further investigation is necessary to test the consistency of our results.

Our results also imply a predictive value of impaired DL_{CO} for an accelerated deterioration in functional exercise capacity in COPD. Investigating a much larger group of COPD patients in a routine clinical setting with newly introduced office-based DL_{CO} instruments might better reveal the predictive value of impaired DL_{CO} for COPD mortality and exacerbations.

In this thesis, a significant relationship between EC and airway obstruction in PH was found. Further research in larger groups of patients, allowing sub-analysis of different PH categories, is needed to validate these results. Including cardiopulmonary exercise testing in future research protocols would allow further distinguishing between ventilatory and circulatory limitation of EC in PH. Furthermore, including measurements of DL_{CO} from portable DL_{CO} instruments in routine clinical assessments of a larger patient cohort could better reveal the predictive value of impaired DL_{CO} for mortality and disease progression in PH.

The results of this thesis suggests a weak, but significant, association between lung function indices and exercise capacity in middle-aged, healthy men. Further research, including a more representative cohort of the general population, is needed to confirm these results. Furthermore, a more extensive characterization of the pulmonary function, including DL_{CO} and flow-volume curves, will allow a closer determination of the relationship between pulmonary function and EC in healthy subjects.

Conclusions and clinical implications

- I. Impaired diffusing capacity of the lung is the strongest predictor of reduced exercise capacity in COPD, regardless of the disease severity or the assessment method used. DL_{CO} measurements, along with the standard assessment of airway obstruction, give a more comprehensive view of the functional exercise capacity in patients with COPD at a specific time-point, and also have a prognostic value for deterioration of exercise capacity.
- II. Airway obstruction is an important predictor of walk distance and exercise-induced desaturation in patients suffering from pulmonary hypertension, regardless of disease category. As functional exercise capacity is shown to be an important predictor of mortality in pulmonary hypertension, it is vital to better understand the factors involved in exercise limitation of the individual patient. This signals a need to better characterize lung function in patients with pulmonary hypertension, involving both spirometry and measurements of diffusing capacity in the routine clinical assessment.
- III. Measurements of lung volumes do not offer any additional information on the patient's exercise capacity, neither in COPD nor in pulmonary hypertension.
- IV. Exercise capacity in healthy subjects is not exclusively restricted by cardiac function. Pulmonary function is significantly associated with exercise capacity and this association seems to become stronger with aging, suggesting a larger role for lung function to limit exercise capacity in elderly subjects. However, the decline in physical fitness over time was not related to the decline in lung function.

Summary in Swedish - sammanfattning på svenska

Redan i antikens Grekland såg man kopplingen mellan försämrad ansträngningsförmåga och olika sjukdomstillstånd (Hippokrates ca 400 f.Kr.). Den funktionella ansträngningsförmågan, som mäts genom en rad olika metoder såsom gångtest och arbetsprov, har varit föremål för omfattande forskningsaktivitet under det senaste årtiondet. I flera uppmärksammade studier har man kunnat påvisa en klar relation mellan nedsatt fysisk prestationsförmåga och ökad mortalitet hos friska försökspersoner. Vidare har man i flertalet välrenommerade studier på senare tid kunnat klarlägga betydelsen av fysisk ansträngningsförmåga som en mycket stark prognostisk faktor vid olika sjukdomstillstånd.

Syftet med denna avhandling var att undersöka lungfunktionens betydelse för den fysiska ansträngningsförmågan, dels hos friska försökspersoner, dels hos patienter som hade drabbats av kronisk obstruktiv lungsjukdom (KOL) eller förhöjt blodtryck i lungkretsloppet, d.v.s. pulmonell hypertension (PH).

Sambandet mellan ansträngningsförmåga och lungfunktion vid KOL

KOL kännetecknas av symptom som andfäddhet, fr.a. på grund av kronisk luftvägsobstruktivitet, som försämrar patienternas ansträngningsförmåga, något som i sin tur leder till nedsatt förmåga att utföra dagliga aktiviteter och därmed försämrad livskvalitet. Den kroniska obstruktiviteten är irreversibel i den bemärkelsen att patienterna aldrig kommer att återfå normal lungfunktion. Traditionellt mäts obstruktiviteten genom volymen utandad luft under den första sekunden av en forcerad utandning (FEV_1).

Med tanke på att obstruktiviteten är det mest framträdande patologiska kännetecknet hos KOL-patienter har lungfunktionsundersökningar spelat en central roll i diagnostisering och stadiindelning av dessa patienter. Spirometriundersökning är idag basen i utredningen av KOL och påvisad obstruktivitet är obligat vid diagnossättning.

I ett försök att belysa olika lungfunktionsparametrars inverkan på patienternas prestationsförmåga genomförde vi en tvärsnittsstudie samt en uppföljningsstudie på närmare 90 konsekutiva KOL-patienter (Studier I och II) som var

remitterade för lungrehabilitering till sjukgymnastikenheten på lungkliniken vid Akademiska sjukhuset i Uppsala eller centrallasarettet i Västerås. Patienterna fick bl.a. genomgå fullständig lungfunktionsundersökning, inklusive mätning av lungornas diffusionskapacitet (DL_{CO}), 12 minuters gångtest samt arbetsprov på ergometercykel, innan rehabiliteringsstart. Efter ca 5 år fick patienterna återigen genomgå gångtest samt fullständig lungfunktionsundersökning.

I våra studier kunde vi konstatera att DL_{CO} hade det starkaste sambandet med patienternas arbetsförmåga. Vidare fann vi att ett lågt DL_{CO} -värde vid start hade det starkaste prognostiska värdet och kunde predicera försämrad fysisk prestationsförmåga vid uppföljningsstudien, efter ca 5 år. Dessutom fann vi att försämringen av DL_{CO} över tid hade det starkaste sambandet med försämringen av prestationsförmågan över tid.

Våra studier (I och II) antyder att det är otillräckligt att enbart undersöka graden av lungfunktionsnedsättning, mätt genom FEV_1 , i den kliniska bedömningen av patienter som lider av KOL. Genom att lägga till mätningar av DL_{CO} kunde vi förutse försämrad arbetsförmåga med en större noggrannhet. Vid en diskrepans mellan graden av nedsatt FEV_1 och patienternas funktionella arbetskapacitet kan tilläggs-mätning av diffusionskapaciteten ge värdefull klinisk information.

Sambandet mellan ansträngningsförmåga och lungfunktion vid pulmonell hypertension

Med PH menas ett förhöjt blodtryck i lungornas pulsådror. Många olika tillstånd, såsom hjärtsvikt, kronisk syrebrist, kronisk lungemboli och vissa reumatiska sjukdomar kan orsaka förhöjt blodtryck i lungkretsloppet. Gemen-samt för dessa tillstånd är att de leder till att blodets passage genom lungkär-len försämras, vilket i sin tur påverkar hjärt- och lungfunktionen. Det mest fram-trädande symptomen vid PH är ansträngningsutlöst andfåddhet och kondi-tionsförsämring, vilka kan innebära stora hinder i vardagen för de patienter som drabbas. Med tanke på ovan är undersökning av den funktionella arbets-kapaciteten, fr.a. med hjälp av gångtester, en central del i utredningen och uppföljningen av patienter med PH.

Förutom fysiska funktionsmätningar och kardiovaskulära undersökningar in-går extensiv lungfunktionsundersökning, inklusive DL_{CO} -mätning, i den initi-ala utredningen. Sänkt diffusionskapacitet är det mest förekommande lung-funktionsfyndet vid PH. Däremot föreligger en del motstridiga forskningsre-sultat avseende förekomst av luftvägsobstruktion, och betydelsen av sänkt DL_{CO} eller obstruktivitet vid PH är inte helt utredd.

I studie III försökte vi klarlägga olika lungfunktionsparametrars inverkan på patienternas prestationsförmåga i en oselektad patientgrupp där alla hade påvisats ha förhöjt blodtryck i lungkretsloppet. Femtio konsekutiva patienter med diagnostiserad PH som var remitterade för lungfunktionsutredning till lungfysiologiska enheten vid Molinette universitetssjukhus i Turin rekryterades till studien. Patienterna fick, förutom fullständig lungfunktionsundersökning inklusive DL_{CO} , även genomgå ett standardiserat 6 minuters gångtest.

I vår studie kunde vi konstatera att låg DL_{CO} var det vanligaste lungfunktionsfyndet i studiematerialet och att 92 % av patienterna uppvisade försämrad diffusionskapacitet. Å andra sidan kunde vi fastställa tecken på luftvägsobstruktion hos ca hälften av patienterna (46 %). Generellt uppvisade patienter med luftvägsobstruktion försämrad gångsträcka, och olika lungfunktionsmått förenliga med obstruktivitet, såsom FEV_1 , visade signifikanta samband med gångsträckan. Totalt 44 % av patienterna visade också försämrad syresättning av blodet i samband med ansträngning, s.k. desaturation. Luftvägsobstruktivitet var det enda lungfunktionsmättet som var signifikant korrelerat med ansträngningsutlöst desaturation.

Vår studie (III) visar att förekomsten av luftvägsobstruktion är ett vanligt fynd hos patienter som har drabbats av PH. Vidare visar luftvägsobstruktiviteten signifikanta samband med försämrad gångsträcka och arbetsinducerad desaturation. Eftersom försämrad gångsträcka är ett betydelsefullt kliniskt fynd som vägleder fortsatt handläggning kan lungfunktionsundersökningar i samband med kliniska bedömningar vara värdefulla för att bedöma patienternas funktionsbegränsningar.

Sambandet mellan ansträngningsförmåga och lungfunktion hos friska försökspersoner

Sedan 1990-talet har utvärderingen av den fysiska prestationsförmågan fått allt större betydelse vid den kliniska evalueringen av de flesta hjärt-lungsjukdomarna. Hos friska personer har man dock traditionellt angett hjärtfunktionen som den begränsande faktorn vid ansträngning. Å andra sidan har lungfunktionen ansetts vara överdimensionerad, både när det gäller lungvolym och diffusionskapacitet, och har inte betraktats som en begränsande faktor för den fysiska prestationsförmågan.

Vid normalt åldrande märks en försämring av den fysiska prestationsförmågan. Samtidigt föreligger en fysiologisk försämring av lungfunktionen. Den försämrade arbetsförmågan vid stigande ålder har dock hänförts till det åldersbetingat nedsatta muskel- och/eller hjärtfunktionen. Relationen mellan den fysiologiska försvagningen av lungfunktionen och arbetsförmågan har inte varit föremål för genomgripande studier.

I studie IV försökte vi undersöka lungfunktionens inverkan på prestationsförmågan i en uppföljningsstudie av friska försökspersoner. Mellan 1972 och 1975 deltog 2 014 friska medelålders norska män (40-59 år) i ”Oslo Ischemia Study”. Studien, som syftade till att kartlägga kardiovaskulära riskfaktorer, omfattade förutom arbetsprov även enklare lungfunktionsundersökning. Studien upprepades efter en uppföljningstid på ca 16 år, d.v.s. 1989 – 1990. Efter rigorös genomgång av studiematerialet valdes 745 försökspersoner med normal lungfunktion ut, då de ansågs ha god kvalitet på lungfunktionsundersökningen, även med dagens standard mätt.

Som förväntat sågs en fysiologisk försämring av både lungfunktionen och prestationsförmågan med stigande ålder. Alla lungfunktionsparametrar som ingick i studien visade ett signifikant, om än svagt, samband med prestationsförmågan vid både baslinje- och uppföljningsstudien. Detta samband förstärktes betydligt vid uppföljningsstudien, där t.ex. FEV₁ uppvisade ett flerfaldigt högre förklaringsvärde avseende prestationsförmågan. Däremot kunde vi inte fastslå ett statistiskt signifikant samband mellan nedgången av arbetsförmågan och försämringen av lungfunktionen över tid.

Resultaten i delstudie IV antyder ett samband mellan lungfunktionen och den fysiska prestationsförmågan. Vidare indikerar resultaten att lungfunktionen spelar större roll avseende den nedsatta arbetsförmågan hos den åldrande befolkningen.

Sammanfattningsvis påverkas den fysiska prestationsförmågan av lungfunktionen vid både hälsa och sjukdom. I de sjukdomstillstånd där mätning av arbetsförmågan ingår i den kliniska utvärderingen, såsom KOL och PH, är det lämpligt att inkludera en mer omfattande lungfunktionsundersökning, inklusive DL_{CO}, för att bättre kunna kartlägga orsakerna till den nedsatta prestationsförmågan. Vidare tycks lungfunktionen ha ett större samband till prestationsförmågan än man tidigare har trott. Lungfunktionens betydelse för arbetsförmågan tycks öka hos den åldrande populationen, även utan påvisad hjärt- eller lungsjukdom.

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