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CHALLENGES IN PHYSIOLOGICAL ASSESSMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

BY
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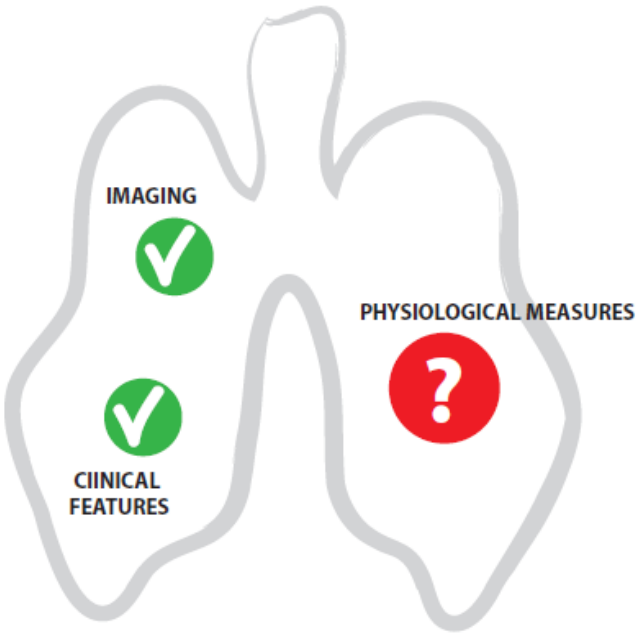

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   The effect of comorbidities on COPD assessment: a pilot study
   International Journal of COPD 2015:10, 429–438

2. Ulla Møller Weinreich, Lars Pilegaard Thomsen, Christina Brock, Dan Stieper Karbing, Stephen Edward Rees
   Diffusion capacity of the lung for carbon monoxide – a potential marker of impaired gas exchange or of systemic deconditioning in Chronic Obstructive Lung Disease?
   Accepted for publication in Chronic Respiratory Diseases

3. Ulla Møller Weinreich, Lars Pilegaard Thomsen, Anita Hansen, Søren Kjærgaard, Peter Wagner, Stephen Edward Rees
   Time to Steady State after Changes in FIO_2 in Patients with COPD
   COPD 2013: 10(4), 405-410

4. Ulla Møller Weinreich, Lars Pilegaard Thomsen, Stephen Edward Rees, Bodil Steen Rasmussen
   The effects of oxygen induced pulmonary vasoconstriction on bedside measurement of pulmonary gas exchange
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Aalborg May 13 2015

Ulla Møller Weinreich

Summary:

In recent years intense research has been carried out in Chronic Obstructive Lung Disease (COPD).The methods for physiological examination and classification of COPD patients have not developed during this period. This PhD thesis investigates the association between the tools used to investigate and characterize COPD as well as the influence of the presence of comorbidities on these associations. Furthermore, it investigates the need for development of new tools to investigate lung function in COPD patients in order to obtain a more detailed knowledge of the character of the disease in the individual.

The Automatic Lung Parameter Estimator (ALPE) has, over the last decades, been developed as a method for measuring pulmonary gas exchange. The method is primarily used in intensive care. In this thesis, the assumptions behind the ALPE method are investigated to elucidate the possibility of future use in COPD patients. ALPE uses oxygen as a tracer gas and the method is based on several assumptions concerning oxygen. ALPE measures oxygen steady state at different levels of inspired oxygen and it is assumed that, in COPD patients as in healthy individuals, oxygen steady state is reached within a few minutes of changes in inspired oxygen. When oxygen is changes stepwise, the saturation of the blood is reduced. It is assumed that the changes in saturation do not cause changes in pulmonary circulation to an extend that has any influence on either the patient's well-being or on the result of the ALPE examination. These assumptions are evaluated in this thesis.

The thesis is based on four studies. The first study investigates the influence of presence of comorbidities on the outcome of currently available measures of disease severity and lung function as well as radiological examinations in COPD patients. The second study investigates the relationship between diffusion capacity of the lung and changes in oxygenation of the blood. In the third study, time to oxygen steady state following changes in inspired oxygen in patients with very severe COPD and chronic respiratory failure was examined. In the fourth study, changes in pulmonary arterial pressure and pulmonary resistance in response to the changes in inspired oxygen were examined in a group of postoperative patients who had undergone cardiac surgery.

The first study indicated that evaluation methods for COPD are influenced by the presence of comorbidities. The second study showed that diffusing capacity was not associated with changes in oxygenation but rather with systemic parameters. These studies indicate that more specific tools for evaluation of COPD patients are needed.

The third study showed that in patients with very severe COPD oxygen steady state occurs 16 minutes after changes in inspired oxygen.

The fourth study showed that the changes in the oxygen saturation as induced by changes in inspired oxygen during the ALPE measurement only results in limited changes in the pulmonary arterial pressure and – resistance and that these changes are immediate reversible when inspired oxygen is returned to baseline.

In conclusion, this thesis shows the present evaluation methods in COPD are very susceptible to the presence of comorbidities. Therefore new tools for physiological examination of COPD patients could be beneficial and that the use of ALPE, with modifications, is a possible future modality in COPD diagnostics and assessment.

Contents

Abbreviations

ALPE: Automatic Lung Parameter Estimator
BMI: Body Mass Index
CAT: COPD Assessment Score
CCQ: Clinical COPD Questionnaire
COPD: Chronic Obstructive Pulmonary Disease
ΔCO_2: end tidal PCO_2 - arterial PCO_2
CT: Computed Tomography
FEV1: Forced Expiratory Volume in the first second
FiO_2: Inspired oxygen fraction
FVC: Forced Vital Capacity
GOLD: Global initiative for chronic Obstructive Lung Disease
HPV: Hypoxic Pulmonary Vasoconstriction
HR-CT: High Resolution Computed Tomography
IC: Inspiratory Capacity
LTOT: Long Term Oxygen Therapy
MIGET: Multiple Inert Gas Elimination Technique
MRC: Medical Research Council Score
mMRC: modified Medical Research Council Score
MPAP: Mean Pulmonary Arterial Pressure
MRI: Magnetic Resonance Imaging
PCO_2: Partial pressure of Carbon Dioxide in the blood
PO_2: Partial pressure of Oxygen in the blood
PVR: Pulmonary Vascular Resistance
SpO_2: Peripheral oxygen saturation
T90: Time to reach 90% of the final value of oxygen steady state
TLC: Total Lung Capacity
$\dot{V}/\dot{Q}$: Ventilation/perfusion

This thesis is based on the following protocols, approved by the Ethical Committee of the Northern Jutland Region: N20090012, N20140019, N20100013, VN2000/170 and VN2002/97. In addition, patients were included in paper II from a feasibility project carried out in the Department of Respiratory Medicine, Aalborg University Hospital. This project was presented to the Ethical Committee of the Northern Jutland Region who found no need for ethical approval of the study.

Chapter 1: Background

1.1 Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by a progressive and irreversible decline in lung function. Different types of physiological assessment are used for diagnosing COPD, to evaluate disease severity, as well as to understand the symptoms of patients with COPD. However, it has been acknowledged that physiological measurements used to assess COPD patients have limitations when demonstrating functional pathophysiology [1]. A tool not previously investigated in COPD, the Automatic Lung Parameter Estimator (ALPE), may be of use for this in the future.

This thesis investigates the adequacy of, and the relationship between, the different assessment tools we have to diagnose, understand and evaluate COPD patients. It includes consideration of comorbidities and investigates the impact they have in the evaluation of COPD. In continuum of this, it questions the need to augment possibilities of investigating pathophysiology of COPD in clinical care. This leads to the question of ALPE as a bedside tool for investigating lung function in COPD. However, before considering this, the assumptions behind its use in clinical care require further evaluation, both in general and for COPD patients in particular.

This first chapter provides information on the impact, complexity and nature of COPD and presents the pathophysiological measurements obtained in COPD patients from the tools at our disposal today. Furthermore, it introduces the clinical assessment tools used to stratify disease severity. Lastly, it discusses the potential pitfalls of combining the information obtained from the different types of assessment used in the evaluation of COPD.

1.2 COPD – mortality and social impact

COPD has become the most important respiratory disease on a global scale. The Global initiative for chronic Obstructive Lung Disease (GOLD) has estimated that 210 million people suffer from COPD worldwide [2], and in Denmark the prevalence of COPD is estimated to 9% in Danes aged above 45 years [3]. Globally, COPD now causes 5% of all deaths and is predicted to increase to 30 % over the next 10 years in low-, middle- and high-income countries [4–6].

The socio-economic expenditure in connection with COPD, both health care-related costs and costs for social benefits, has increased considerably in recent years and is comparable to that of stroke in the western world population [7–9]. Furthermore, the expenditure associated with COPD is larger than the expenditure associated with other chronic diseases, such as heart disease and

cancer [10]. The expenses are primarily associated with the large number of patients who have numerous comorbidities[11].

1.3 COPD and comorbidity

COPD patients are predisposed to comorbidities, with this being an important cause of the increased mortality and morbidity seen in this disease [12,13]. Indeed, the GOLD recommends assessment of comorbidities in all COPD patients [2]. The incidence of comorbidities has been shown to rise with increased dyspnea and disease severity [14]. The high prevalence of comorbidity is likely to be multifactorial, and is associated with age and the excess risk of mortality and morbidity due to tobacco exposure [13,15]. However, even when controlling for common risk factors such as smoking, conditions as cardiac disease and type 2 diabetes, are even more prevalent than should be expected in patients suffering from COPD [16,17]. Thus, it has been suggested that COPD may, to some extent, be part of a metabolic syndrome [18]. The frequent co-existence of COPD, diabetes and heart disease has lead to speculations of a common inflammatory genesis [19,20], and has suggested an inflammatory phenotype of COPD [21]. In patients with concomitant COPD and cardiac disease, both diseases are often under-diagnosed [22], and even when recognized, they remain undertreated [23]. A recent study by Garcia-Olmos et al has found that 90 % of COPD patients in general practice had comorbidities, in average 4 per patient, and a study by Divo et al found 6 comorbidities per patient in tertiary care [16,24]. The prevalence of the 10 most common comorbidities in both studies are presented in Figure 1, which shows that malignancies, ischemic heart disease and anxiety are more prevalent in patients handled in tertiary care. These comorbidities have all been associated with a higher risk of death [16,25] and morbidity [26–30].

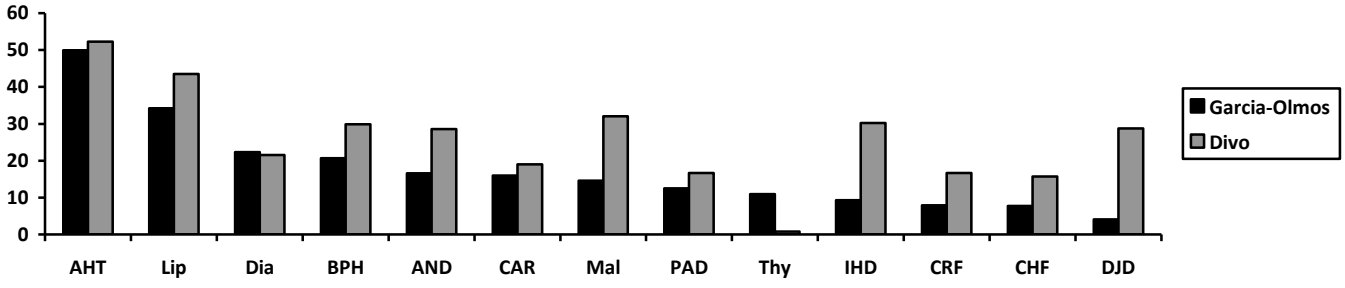

Figure 1: The 10 most common comorbidities in the studies from Garcia-Olmos [24] **and Divo** [16]**. ART = Arterial hypertension, Lip = Hyperlipidemia, Dia = Diabetes, BPH = benign prostatic hypertrophy, AND = Anxiety/Depression, CAR = Cardiac arrhythmia, Mal = Malignant disease, PAD = Peripheral arterial disease, Thy = Thyroid disease, IHD = ischemic heart disease, CRF = Chronic renal failure, CHF = Congestive heart failure, DJD = Degenerative joint disease. In addition, Divo registered obesity in 34 % of patients; this parameter was not included in the figure as it was not included in study by Garcia-Olmos.**

Thus, one could hypothesize that, as patients with more severe COPD are allocated to tertiary centres, the comorbidities in themselves may influence our assessment of COPD severity.

1.4 COPD: The pathological process

Development of COPD is caused by persistent pulmonary irritation. This affects not only the

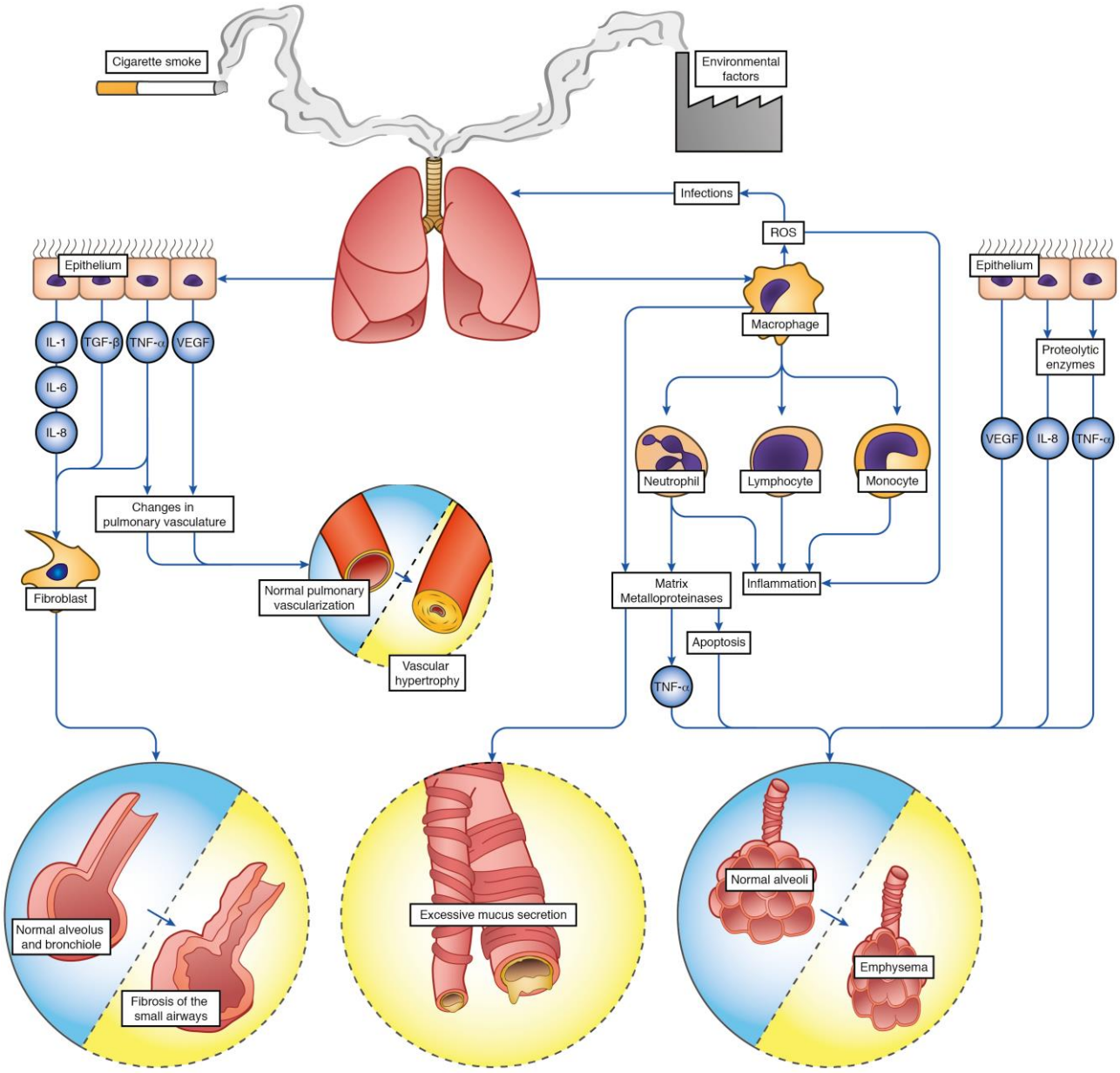

Figure 2: Simplified model of COPD pathology illustrating important pathways resulting in changes in small airways, inflammation causing mucus secretion, development of emphysema and vascular hypertrophy. Transforming growth factor- β (TGF-β), and interleukin (IL) 1, 6 and 8 derives from the epithelium and induces fibrosis in the small airways. Tumour necrosis factor-α (TNF-α) production increase and vascular endothelial growth factor (VEGF) decrease in the epithelium and cause vascular changes. Macrophages stimulate neutrophils and both cause activation of metalloproteinases, which induces development of emphysema. Macrophages also stimulate lymphocytes and monocytes, which, together with neutrophils, cause inflammation. Macrophages also release reactive oxygen species (ROS) which both stimulate inflammation and predispose to infections, which may cause disease progression.

airways, but also the parenchyma and pulmonary vasculature. This leads to complex pathological processes as demonstrated in a simplified model of COPD pathology in Figure 2. As COPD pathology is not the topic of this thesis this will not be described in further detail.

1.5 Assessment of lung function in COPD

Pathological changes lead to changes in pulmonary physiology. In daily clinical practice, lung function measurements allow quantification of the physiological impact of the pathological changes seen in COPD. However, as the pathophysiology of COPD is complex, complementary measures of lung function may be needed to assess different aspects of the disease. The five available assessment tools used in COPD patients will be described here, including their respective strengths and limitations.

1.5.1 Spirometry

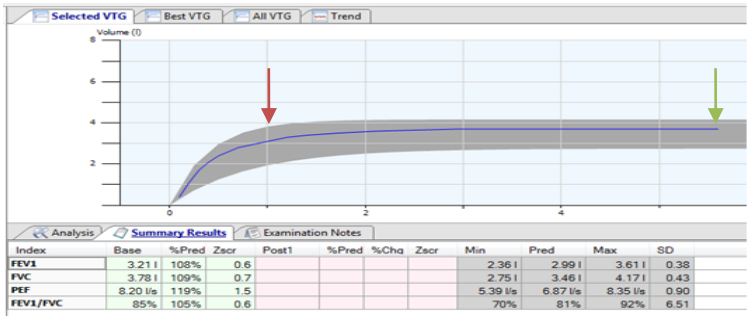

Figure 3: A normal spirometry, volume (L)/time (sec). Red arrow: FEV1, green arrow: FVC

Lung function is primarily measured in COPD using spirometry. Spirometry measurements of airway obstruction are used in determining the diagnosis of COPD [2]. Values of forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and the ratio between these, FEV1/FVC, are obtained from expiratory curves, describing volume/second (Figure 3). A post bronco-dilator value of FEV1/ FVC below 0.7 is diagnostic of COPD, and impairment of FEV1% is commonly used as a description of disease severity [31].

FEV1 is currently used to describe the severity of lung function impairment in COPD, yet to evaluate the results, one has to be critical and ask: What does FEV1 reflect in COPD patients? Older studies have shown that a decline in FEV1 is predictive of mortality in COPD [32]. Furthermore, it has been shown that the number of exacerbations, (further explained in chapter 1.7.2), are associated with decline in FEV1[33]. Moreover, fibrosis, inflammation and luminal secretions in the small airways of COPD patients has also been shown to correlate with FEV1 reduction [34]. As such FEV1 has been the primary assessment tool to evaluate treatment efficacy in COPD [35].

Spirometry may be thought of as a simple procedure but has proved to be difficult to perform, with as many as 40 % of spirometries performed in clinical respiratory laboratories deemed to be not acceptable [36]. A Danish study found that 15 % of all spirometries performed in general practice were inconclusive as the duration of the procedures were too short for FVC to be reached [37]. Moreover, FEV1 only partially reflect patients' self-evaluated dyspnea and general health [38–40]; symptom severity such as cough and sputum production do not to correlate to decline in FEV1 [41,42]; FEV1 does not reflect systemic inflammation, as no association between neutrophils and FEV1 impairment has been shown [43].

As a result the GOLD group has stated that FEV1, as a solitary measure, does not clearly depict disease severity in the individual [2]. Spirometry, therefore, cannot provide us with a complete description of COPD. Additional measurements of the patient's pulmonary pathophysiology may be obtained from other methods such as body plethysmography.

1.5.2 Body plethysmography

In COPD body plethysmography provides additional measures to describe functional and structural aspects of the disease.

The measurements that can be obtained from plethysmography are illustrated in Figure 4. Of these inspiratory capacity (IC) and total lung capacity (TLC) are discussed in further detail below, as these have been shown to be important measures in patients with COPD [44]. Both relate to hyperinflation, which is defined as an increase in operating lung volumes (i.e. shifting lung volumes during work) above resting values. Hyperinflation occurs as a consequence of expiratory flow limitation, caused by increased airway resistance instigated by the diminished lumen of the airway [44]. Dynamic hyperinflation is characterized by dynamic changes in IC alone [45] whereas IC/TLC is a measure of static – or passive - hyperinflation [46]. In COPD, hyperinflation is an independent risk factor of morbidity and mortality [17,47–49].

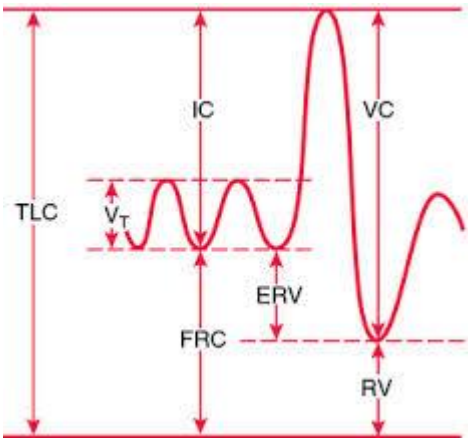

Figure 4: Absolute gas volumes as measured by body plethysmography: TLC, total lung capacity; VT, tidal volume; IC, inspiratory capacity; FRC, functional residual capacity; ERV, expiratory reserve volume; VC, vital capacity; RV, residual volume.

Both IC and IC/TLC alone are strongly associated with dyspnea [46,50] which is consistent with the decrease in dyspnea and IC seen in response to treatment with long-acting muscarinic

antagonists [51,52]. TLC has been shown to increase significantly with disease progression [53]. There has been conflicting results on whether TLC as a isolated measure is predictive of mortality in COPD, with no association between TLC and mortality in COPD in general [54], however an association between TLC and mortality has been suggested in patients with emphysema [47].

The use of body plethysmography has its shortcomings, as it is limited to tertiary care-, and, in some instances, secondary care institutions. This is largely due to the fact that it can only be operated by specially trained healthcare personnel, who need to perform the examinations regularly to secure that standards are kept. This is also the case for diffusing capacity of the lung for carbon monoxide (DLCO), described in the next section.

1.5.3 Diffusing capacity of the lung for carbon monoxide

DLCO measures the transfer of gas from alveolar air to the erythrocytes passing through the pulmonary capillaries. It is a composite measure, which may be influenced by a number of abnormalities of ventilation, perfusion, diffusion, and properties of the blood as demonstrated in Figure 5.

The term "diffusing capacity" is actually misleading; neither is diffusion really measured nor is the obtained value a capacity, but a conductance. The term transfer factor may be used instead; however, diffusion capacity remains the most common term in clinical practice, and is therefore used throughout the thesis.

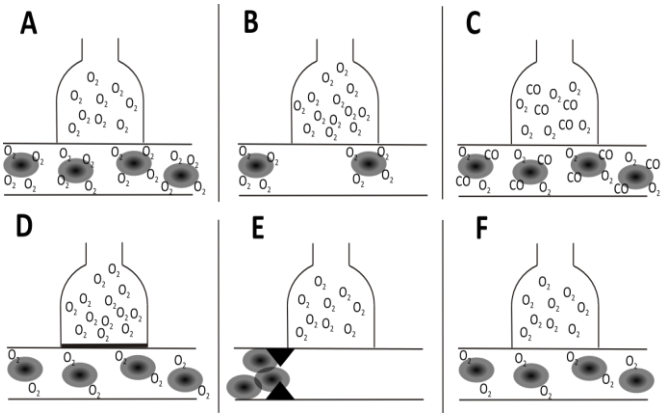

**Figure 5: Reduction in DLCO with A: (no pathology) as reference picture:
B: anemia C: high carboxy-hemoglobin levels D: thickening of the alveolar membrane E: pulmonary vascular disease causing impaired blood flow F: hemoglobinophathy. With permission from** [201]**.**

In COPD, DLCO has been shown to be associated with the degree of emphysema as evaluated by computered tomography (CT) scans [55–57]. Furthermore it has been shown to be associated with dyspnea in COPD [58] and to be predictive of functional decline in COPD [59]. Interestingly, DLCO has also been shown to be associated with body mass index (BMI), both in the general population [60,61] and in COPD patients [62,63]. Additionally, other systemic diseases, frequently seen as comorbidities in COPD, may also influence DLCO. In heart failure impaired DLCO has been seen in several studies, [64–66], even with preserved ejection fraction [67].

Furthermore in COPD patients with comparable FEV1, DLCO been found to be significantly lower in patients with concomitant type 2 diabetes [68,69]. Changes in DLCO in diabetes seem to be independent of heart disease [70]. Taken together, changes in DLCO may be caused by a number of different diseases, including pulmonary disease. The physiological measures used in daily clinical practice such as DLCO are simplified approximations of the underlying complex physiological measures. These are not therefore not able to describe abnormalities of pulmonary gas exchange in detail [71]. The development of the Multiple Inert Gas Elimination Technique (MIGET) by P.D. Wagner and colleagues in the 1970's provided a novel method which overcame these limitations [72].

1.5.4 The Multiple Inert Gas Elimination Technique

MIGET is based on the principle of the relationship between the ventilation/perfusion ratio ($\dot{V}/\dot{Q}$ ratio) and the alveolar and capillary partial pressures of any gas. The method includes intravenous infusion of 6 dissolved inert gasses and calculates pulmonary exchange, using a mathematical model comprised of 50 compartments with different $\dot{V}/\dot{Q}$ ratios. In this way a quantification of the distribution of $\dot{V}/\dot{Q}$ mismatch in the individual patient can be obtained [73].

Using MIGET, it has been shown that $\dot{V}/\dot{Q}$ mismatch is present even in very mild COPD [74,75], and measurement of $\dot{V}/\dot{Q}$ abnormalities could therefore be a help in early diagnosis of the disease. In the 1970's Wagner et al. showed that both areas of high and low $\dot{V}/\dot{Q}$ ratio may be seen in the individual COPD patient and that it is necessary to describe both, to fully understand gas-exchange impairment in COPD [74].Wagner and colleagues divided patients into clinical subgroups based on their $\dot{V}/\dot{Q}$ ratio: patients with predominantly high $\dot{V}/\dot{Q}$ ratios who typically suffered from alveolar wall destruction, and patients with predominantly low $\dot{V}/\dot{Q}$ areas who typically presented with symptoms of severe cough and sputum production [74].

The MIGET provides a detailed description of impairment of pulmonary gas exchange. However, the method is time consuming, costly and requires personnel with high expertise. These factors limit the use of the method in clinical care and in research including large study populations.

However, the MIGET not only quantifies the result of the pathophysiological changes, it also unmasks the underlying pulmonary pathology, which physiologically may help to identify different phenotypes. Today no single clinically available physiological method provides us with this phenotypic classification knowledge. A simple, inexpensive, easy-to-operate alternative measurement could be wished for.

1.6 Computed tomography in COPD

CT-scans are able to illustrate details of both lung parenchyma and the bronchial system, in contrast to conventional two-dimensional chest x-rays. CT-scans are increasingly used in imaging COPD, mainly due to the decreased radiation doses needed for the procedure [76,77]. The use of CT-scans has underlined the complexity and diversity of the pathophysiology of the COPD lung. In COPD, two main features are described in CT scans; 1) emphysema and 2) airways disease. High Resolution CT (HR-CT) has particular advantages in diagnosing and describing the severity of emphysema very accurately [78].

These features may be evaluated either by qualitative and quantitative methods or in combination of the two [79].

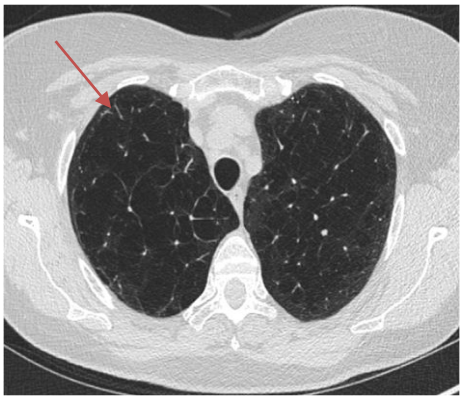

Figure 6: CT scan of patient with centrilobular emphysema (red arrow). Scan from study 1.

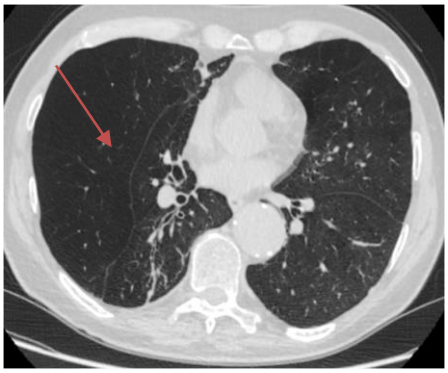

Figure 7: Pan lobular emphysema with the red arrow pointing to the affected lobe. Scan from study 1.

Emphysema: When evaluated from CT-scans, a recognized quantitative method is a threshold technique, the "Density Mask Method", which measures areas of a density <-910 to -950 Hounsfield. This threshold still needs to be finally standardized to the ranges of normal lungs [80]. The Density Mask Method is often used in combination with qualitative interpretation of CT-scans, where various algorithms to support the observer's evaluation exist. In a qualitative evaluation radiologists classically distinguish between three types of emphysema: Centrilobular , panlobular and paraseptal emphysema [81]. Figure 6 shows an example of centrilobular emphysema, which typically emanates from the secondary pulmonary lobule close to the proximal respiratory bronchiole, and is often seen in the upper lobes [77,78]. Figure 7 shows an example of pan lobular emphysema, which may be present in all parts of the lung. It occurs as a result of loss of acini characterized by a diffuse decrease in lung attenuation [83]. Figure 8 shows an example of paraseptal emphysema, which is less common and most often occurs in rows along the pleura in the upper lobes.

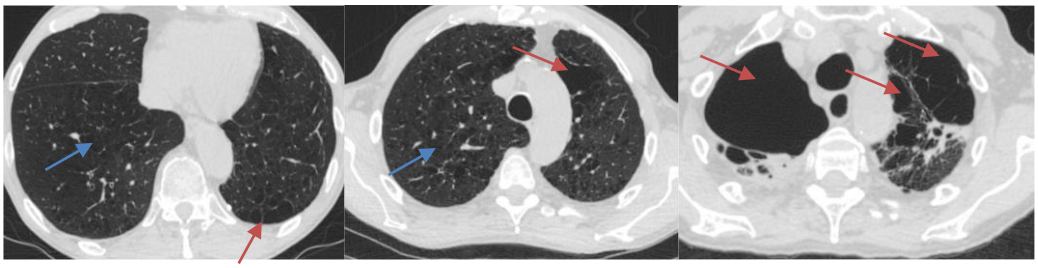

Figure 8: Paraseptal emphysema, with progressive disease severity moving left to right in the figure. Red arrows illustrating the areas of the lung affected with paraseptal emphysema. The blue arrows illustrate areas of concomitant centrilobular emphysema. Scans from study 1.

Paraseptal emphysema does not usually impair lung function unless the disease has progress to a state with large bullae [83].

COPD-patients often present with a combination of the different subtypes, as seen in Figure 8 [83].

Airway disease is not easily interpreted in CT scans. Although bronchial biopsies from patients presenting with cough and sputum reveal bronchial wall thickening and airway inflammation [84], bronchial wall thickening is only visible in 19 % of CT-scans from symptomatic patients with a inter-observer agreement of only 18-28% [85], and a small in-vivo/ex-vivo study showed that only 39% of airways disease was visible in HR-CT [86].

Considered an accurate diagnostic tool the use of CT and HR-CT in COPD has increased considerably in this century, the method described as an [87]. However, the association between CT findings and other measures of COPD has ambiguous. As such, studies investigation the association between CT- and HR-CT findings in COPD versus spirometric measures have shown conflicting results, with no to moderate association found [88–92]. A stronger association is found between CT- and HR-CT findings in COPD and DLCO [58,93]. Furthermore significant associations, although moderate in strength the association have been shown between CT- and clinical manifestations of COPD, such as six minute walking test and dyspnea [58,94,95]. The explanation of these not very convincing results may be related to the challenges of evaluating CT-scans, as described above [76,96]. Moreover, the clinical manifestations associated with COPD are influenced by other parameters than pulmonary changes [97]. However, CT scans may be superior to the traditionally lung function assessment tools in detecting and describing COPD [98], especially in patients presenting emphysematic changes, as these are visible before physiological derangement in lung function [99,100].

Despite the decrease of the radiation dose administered to the patients, the use of CT still poses a risk to the patient. The use of the method is also limited by examination costs and, in some parts of

the world, limited availability [101]. In addition, in the most severely ill COPD patients, a CT scan may be an ordeal, with breath holding while lying flat being very uncomfortable for these patients.

1.7 Patient reported outcomes and assessment of severity in COPD

Individual measurements are rarely sufficient to give the full clinical picture of the COPD patient. As such, in clinical practice, measurements are often used in combination with patient reported outcomes to obtain a more complete assessment of the patient. Valuable information is gained from different patient reported outcomes, as for example the modified Medical Research Council (mMRC) score and the number of exacerbations in the preceding year. A combined risk assessment score has been developed by the GOLD initiative for stratification of COPD patients. To improve readability this has been shortened to the GOLD stratification score throughout the thesis. The GOLD stratification score is a composite measure of lung function and patient reported outcomes, i.e. mMRC and exacerbations in the preceding year. Both the patient reported outcomes and the GOLD stratification score are presented in this section, which also discusses the strengths and limitations of the score.

1.7.1 Dyspnea and the Medical Research Council Score

Patients with COPD experience slowly progressing dyspnea and disability. Traditionally, the impact of dyspnea has been described by the Medical Research Council (MRC) score [102]. The MRC score is based on studies of Welsh coal miners in the Medical Research Council's pneumoconiosis unit in the 1940's. A modified version, the mMRC score, was presented in the late 1980's in order to exclude quantification of potentially healthy individuals during exercise [103]. The score has been shown to describe patients' disability [104,105], with up to 98% inter-observer agreement when repeating questioning [103].

In itself, the mMRC does not quantify breathlessness, but an unexpected level of breathlessness at a given level of activity, which could be described as "inappropriate breathlessness". The mMRC score is one of three suggested symptom scores to be used in the GOLD stratification score; alternative measures are the COPD Assessment Test (CAT) [106], and the clinical COPD Questionnaire (CCQ) [107]. These scores are not described in detail as only the mMRC score was used as symptom score in this thesis.

1.7.2 Exacerbations of COPD

The number of exacerbations varies greatly in COPD-patients and it has been shown that the best predictor for having future exacerbations are exacerbations in the past [108]. One-fourth of COPD

patients are frequent exacerbators, determined as ≥ 2 exacerbations per year [109] and recurrent exacerbations become more frequent with decrease in lung function [108]. Exacerbations of COPD are associated with mortality and morbidity [110–112]. Furthermore, hospitalization due to exacerbation is predictive of future hospitalizations and death [113–116]. With an impact on morbidity and mortality it is evident that exacerbations have massive impact on COPD patients and therefore, not surprisingly, also on patients' quality of life [117]. The number of exacerbations in the preceding year has been included as a risk factor in the GOLD stratification score, described below.

1.7.3 The Global Initiative for COPD

The GOLD initiative was launched in 1997 in collaboration with the National Heart, Lung, and Blood Institute, National Institutes of Health, USA, and the World Health Organization. The aim of GOLD is to supply the clinical community with guidelines for COPD care, created by committees of leading experts from around the world. The initial version of the GOLD guideline was presented in 2001[2] and it undergoes revision every 5 years, with the latest major review having taken place in 2011 [118]. The guideline includes recommendations for disease stratification in terms of assessment of disease severity and for treatment of COPD. The goal of GOLD COPD assessment is to

> "*Determine the severity of the disease, its impact on patient's health status, and the risk of future events (exacerbations, hospital admissions, death) in order to guide therapy.*"

Previously, assessment of COPD severity has been determined alone by spirometric values [119]. Yet, as stated previously by Alvar Agusti, FEV1 alone cannot describe the complexity of the disease [120], nor does airflow limitation capture the heterogeneity of COPD [121]. These and other observations lead to changes in the latest revision of the GOLD recommendations [2], (now no longer called guidelines), where diagnosis by spirometry is augmented with patient reported outcomes, as evaluation of symptoms and future risk of exacerbations, in the final assessment of the patient, using the combined risk assessment score.

1.7.4 The GOLD combined risk assessment score

The GOLD stratification score stratifies patients in four groups, A-D, with group A representing the least severe COPD and D the most severe.

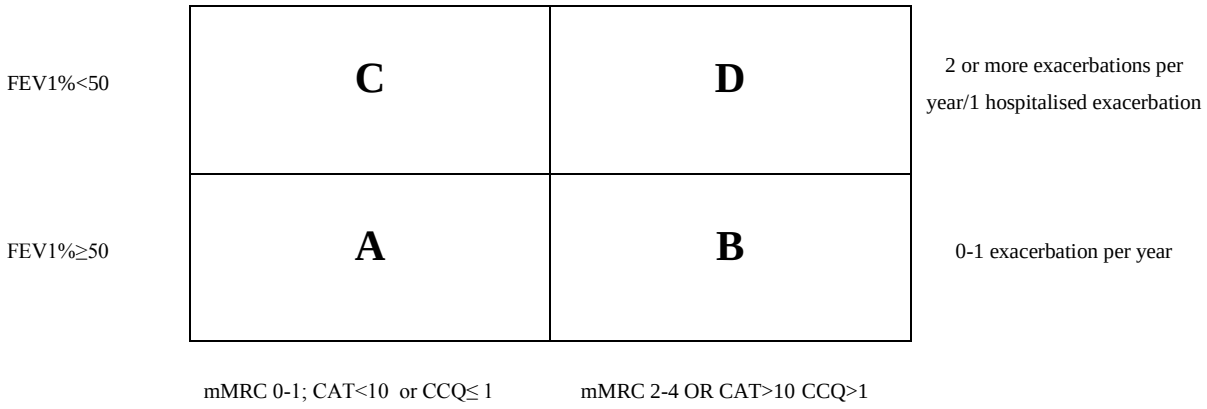

Figure 9: Combined assessment of COPD. Patients are stratified according to symptoms in the right or left column, and, according to lung function and number of exacerbations in the lower or upper row, the most severe result of the two assessments determining the patients' location in the two rows. With permission from the GOLD initiative [2]**.**

Patients are scored according to lung function, evaluated by spirometry; symptom score, in this thesis the mMRC is used, as mentioned above; and the number of exacerbations in the preceding year, using the model in Figure 9.

The present GOLD score has proved better at describing the longitudinal behaviour of COPD than the previous GOLD guidelines; as such the risk of exacerbation and hospitalization increases from group A to D, as does mortality [122]. Perhaps surprisingly, the mortality of patients in group B has been shown to exceed that of patients in group C [122,123]. A possible explanation could be that COPD patients with comorbidities have been shown to be found primarily in groups B and D [123,124]. As such the presence of comorbidities has previously been shown to increase mortality [125]. Furthermore health related quality of life have been shown to decrease from A to D; however similar to the above mentioned group C has been shown to have a better quality of life than group B [126]. Interestingly, the presence of comorbidities has also been shown to negatively influence the quality of life in COPD [28].

The GOLD score illustrated in figure 9 has led to clear improvements in disease stratification. Despite this, there is still several limitations of the GOLD score, for example:

- *Patient evaluation of numbers of exacerbations:* The number of exacerbations either may be under- or over-estimated. Under-estimation can occur due to patients' miss-understanding of the term exacerbation or their recollection of having an exacerbation [127]. Over-estimation could be due to the excessive use of corticosteroids in COPD, used by 70% of patients in both Europe and the US, in contrast to the a use of 20% if patients were treated according to current guidelines [128]. Although corticosteroids have a slight reductive effect on

exacerbations (MD -0.26 exacerbations per patient per year), it concurrently increases the risk of pneumonias (RR 1,56) [129]. Pneumonias may be misclassified as exacerbations by the clinician and therefore influence COPD disease stratification. which are used by

- *comorbidities:* The presence of comorbidities in COPD patients has been shown to increase the risk of exacerbations [130], and in the case of exacerbation, the number of comorbidities has been shown to be associated with increased risk of hospitalization [131]. The presence of comorbidities has also been shown to affect the outcome of the MRC-score. Barr et al. showed that in comparable groups of COPD patients, the mean MRC-score increased with the number of comorbidities, with a median value of 2.3 in patients who suffered from 1-5 comorbidities to a median value of 4.0 in patients with 20-25 comorbidities [13]. This is further supported by a very recent study that comorbidities, no matter which, significantly impair physical activity in COPD independently of airflow limitation [132]. As such comorbidities may influence the stratification of the patient. Even though the GOLD recommendations 2013 recommends to assess CODP patients' comorbidities, it has not previously been considered to which extent they influence the stratification of the patients [2].

The GOLD recommendation suggests treatment dependent on disease severity according to the GOLD score. As discussed above it is not unlikely that patient reported outcomes are influenced by the presence of comorbidities. As such there is a potential risk of assessing the overall morbidity rather than COPD severity when using the GOLD combined risk assessment score, and hence a risk of over, or under, treating COPD.

1.8 Summary: Associations between imaging, clinical and physiological measures in COPD

In recent years, a number of studies have investigated concomitant clinical and radiological features in the endeavour to understand the heterogeneity of COPD. These parameters are often associated with physiological measurements as illustrated in Figure 10A.

Major scientific progress has been made in our understanding of clinical characteristics of COPD and the equipment used for the CT-scans continuously improves in speed and resolution. However, a similar evolution of pathophysiological measurement has not taken place. Therefore, one may speculate: If the easy accessible lung function assessments are insensible to physiological changes,

how can we achieve early disease recognition? If lung function measures do not respond to patient

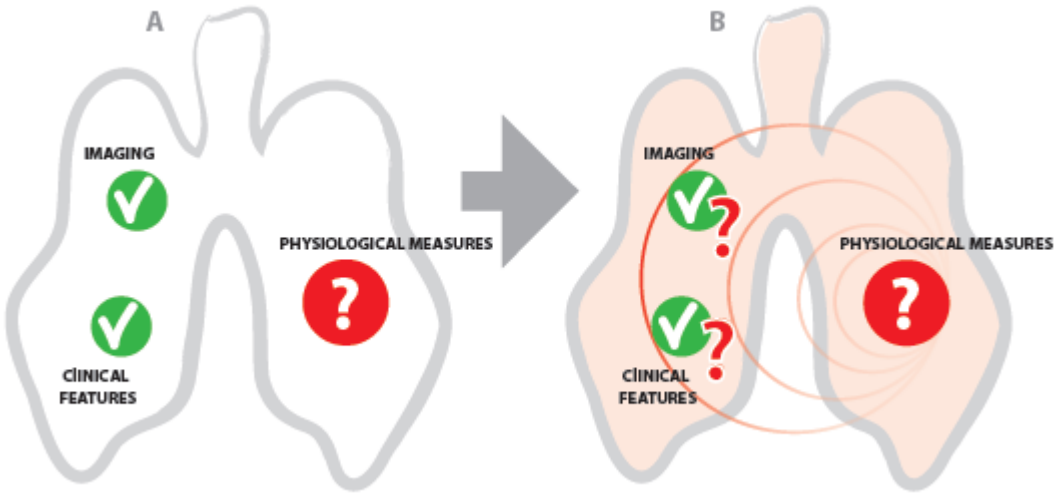

Figure 10: The association between imaging, clinical features and physiological measures in description of lung disease (A). Physiological measures as effect modifiers rather than an associated parameter in relation to imaging and clinical features (B).

reported outcomes how can we quantify disease progression, unmask the reason for disease progression and evaluate treatment? If what is considered pulmonary physiological testing is susceptible to the influence of systemic disease, could it not become an effect modifier rather than an associated parameter in research, as illustrated in Figure 10B [133]? Given that $\dot{V}/\dot{Q}$ mismatch previously has been argued to be a core pathophysiological change in COPD, should we explore the possibilities of other lung function assessments to acknowledge, evaluate and monitor the lung component of the disease?

Chapter 2: Future perspectives in lung function measurements.

2.1 The automatic lung parameter estimator- ALPE

As the available tools in the measurement of lung function have limitations, additional assessment tools should be sought. A possible tool for measuring pulmonary gas exchange is the Automatic Lung Parameter Estimator (ALPE). This method, initially proposed in 2002, uses stepwise changes in inspired oxygen fraction (FiO_2) and measurement of ventilation and arterial oxygenation at steady state for each FiO_2 level, along with a mathematical model representation of gas exchange in the lungs and tissues illustrated in Figure 11. ALPE enables a bedside description of the pulmonary gas exchange properties of the lungs. ALPE has, until recently, primarily been applied in surgical patients during controlled ventilation postoperatively [125,126] and in intensive care patients with acute lung injury or acute respiratory distress syndrome, where the primary cause of abnormal gas exchange is pulmonary shunt and low $\dot{V}/\dot{Q}$ [134–136]. However, observations from these studies indicate that the tool has potential for evaluating spontaneous breathing patients in daily clinical care [137–139].

2.1.1Mathematical model included in the ALPE

The ALPE model, shown in Figure 11, describes pulmonary gas exchange using three compartments; one compartment representing pulmonary shunt, and two ventilated and perfused compartments with uniquely adjustable $\dot{V}/\dot{Q}$ ratios. The model uses three parameters: fs, the fraction of the total cardiac output (Q) not contributing to gas exchange (i.e. pulmonary shunt); f2, the distribution of the remaining Q between the two ventilated and perfused compartments; and fA2, the distribution of total alveolar ventilation ($\dot{V}A$) between these compartments. The three parameters in the model require steady state measurement at different levels of FiO_2. For each level, the patient's response to available oxygen is measured as end tidal oxygen fraction ($FetO_2$) and peripheral oxygen saturation (SpO_2). Aside from these, the inputs for the model are oxygen consumption ($\dot{V}O_2$), obtained from measurement of respiratory gasses, ($FetO_2$ and FiO_2), and respiratory volumes; Q, either obtained by use of invasive or non-invasive techniques or approximated; the acid-base characteristics of blood, which are used to describe the oxygen dissociation curve and the $\dot{V}A$ obtained from frequency, tidal volume, and serial dead space ($\dot{V}_{DS}$). The measurements obtained from the ALPE method are pulmonary shunt, the change in partial pressure of oxygen in the blood (ΔPO_2,); pulmonary shunt is the fraction of the total Q not contributing to gas exchange; ΔPO_2 is the model measure of low $\dot{V}/\dot{Q}$, describing the difference

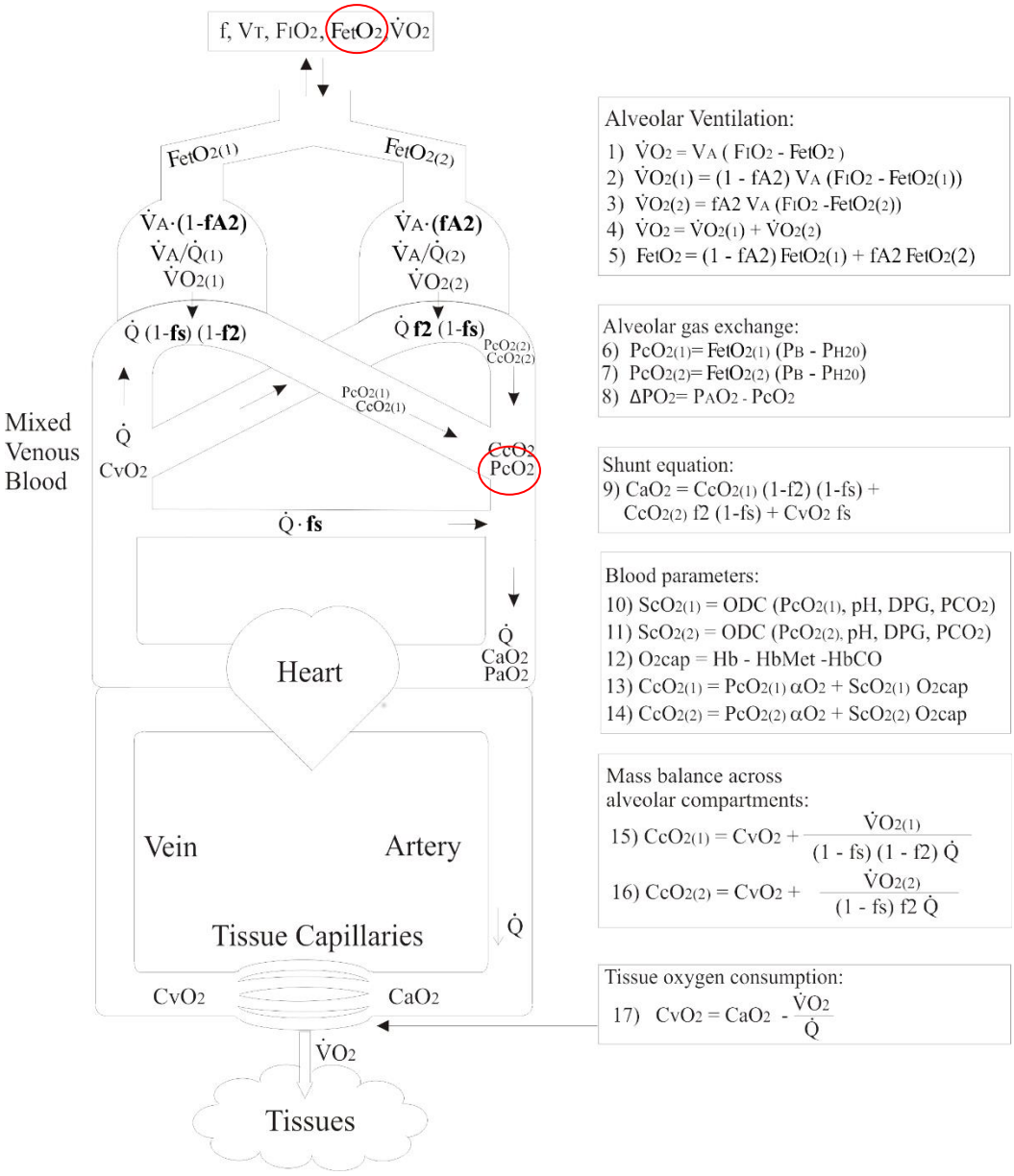

Figure 11: The mathematical model of oxygen transport (from [71] **with permission). The model consist of three compartments, where two are ventilated and perfused representing gas exchange in the lungs, and the third representing pulmonary shunt. The model has three parameters: fs, f2, and fA2; fs: The fraction of the total cardiac output (Q) not contributing to gas exchange (i.e. pulmonary shunt). f2: The distribution of the remaining Q between the two ventilated and perfused compartments. fA2: The distribution of total alveolar ventilation (VA) between these compartments. The equations describe the transport of oxygen at steady state from the a ventilator or air into the tissues: 1-4) oxygen flow into the alveoli and blood (VO_2) in total and addition from each compartment; 5) total expired oxygen fraction (FEO_2); 6-7) Oxygen partial pressure ($PcO_2(1)$, $PcO_2(2)$) in the compartments; 8) drop in O_2 partial pressure from expired gas to capillary blood, marked with red circles; 9) mixed concentration of arterial blood (CaO_2); 10-14) relationship between oxygen partial pressure (PO_2), saturation (SO_2) and concentration (CO_2) in the capillary compartments calculated from the oxygen dissociation curve (ODC) and blood variables; 15-16) concentration of oxygen in the lung capillary compartments ($CcO_2(1)$, $CcO_2(2)$) combining venous concentration (CvO_2) and the increase in oxygen concentration resulting from alveolar equilibration; 17) venous oxygen concentration (CvO_2) combining arterial oxygen concentration (CaO_2) and the drop in oxygen concentration as a result of consumption in the tissues** [137]**.**

between alveolar $FetO_2$ and capillary blood oxygen pressure (PcO_2) leaving the ventilated and perfused compartments, i.e. before mixing with the shunted blood. In Figure 11 these measurements are highlighted (red circles). In the original publication from 2002, ALPE did not include measurement of high $\dot{V}/\dot{Q}$. This addition to the model was first published by Karbing et al. for use in intensive care patients [136].The change in partial pressure of carbon dioxide in the blood (ΔPCO_2) is the model measure of high $\dot{V}/\dot{Q}$, e.g. the difference between the alveolar end tidal and capillary carbon dioxide pressures. The introduction of ΔPCO_2 in ALPE for spontaneous breathing patients has further been investigated in a PhD study carried out simultaneously to this, working on the technical aspects of using ALPE in COPD [140].

2.1.2 Assumptions included in ALPE

The ALPE tool applies changes in FiO_2 to evaluate pulmonary gas exchange. A number of assumptions are included in the model. Some of these have previously been evaluated and some require evaluation if ALPE is to be useful as in COPD. The following text describes these assumptions, and the state of the art in their evaluation.

- *Oxygen steady state:* The ALPE tool describes steady state conditions of oxygen transport, where steady state is defined as minimum variations in $FetO_2$. This has been shown to occur within 2-3 minutes following a step change in FiO_2. A previous study has shown this to be a valid assumption for patients without lung disease [141], but in patients with COPD the time to steady state following changes in oxygenation is considered to be 20-30 minutes[142] based on a 1970's review [85]. However, the criteria for determining oxygen steady state varied substantially between studies, these include 1) the range over which oxygen was changed; 2) the direction in which oxygen was changed, i.e. both an increase (wash in) and a decrease (wash out) of FiO_2; and 3) the definition of the end point for steady state [143–147]. Therefore, a structured study to determine the time to steady state after changes in inspired oxygen in COPD patients is needed. Moreover, monitoring oxygen as therapy to COPD patients in daily clinical care, providing knowledge on when sustainable measurements can be obtained in patients after having changed FiO_2 is also necessary.
- *Hypoxic vasoconstriction*: It is well known that a reduction in alveolar O_2 induces hypoxic vasoconstriction (HPV). HPV has been investigated in numerous studies, which all have investigated the effects of large changes in FiO_2, resulting in large reductions in alveolar oxygen partial pressure [148,149]. HPV caused by changes in FiO_2 may result in adverse changes in pulmonary pressure. As such, significant changes in pulmonary perfusion

distribution may modify V/Q mismatch. Applying the ALPE model, it is assumed that HPV does not occur as the changes in FiO_2 are with a limited range. Despite the large number of studies examining the effects of oxygen changes on HPV, no previous studies have looked at the effect of a small, acute reduction in oxygenation. Neither has the effect on HPV of correcting mild, acute hypoxia been investigated. To evaluate the assumption that no clinically significant HPV occurs during the ALPE procedure these changes need to be investigated.

To be able to investigate influences of HPV surrogate measures are needed, as HPV in itself is not easily monitored; therefore, measures of mean pulmonal arterial pressure (MPAP) and pulmonal vascular resistance (PVR) may be used to demonstrate changes.

- *Reference values:* In the traditionally lung function measurements reference values are dependent on a number of variables, as for example age and gender. The mathematical model of ALPE assumes that age, gender and posture do not influence the gas exchange parameters. However, it has only investigated in healthy subjects showing that age and gender does not influence gas exchange, but that posture did influence the shunt fraction [150]. No study in COPD patients exists using ALPE.
- *Reproducibility:* It has been assumed that the ALPE measurement is reproducible. In a test-retest study repeatability was acceptable in healthy subjects [150]. However, studies in COPD patients are needed.

This thesis focuses on two of these assumptions. The present assumption of time to oxygen steady state in COPD differs considerably from the assumption of oxygen steady state in the ALPE algorithm. Therefore, investigation of this assumption seems to be crucial for implementing ALPE as an assessment tool in COPD. Furthermore, the assumption that the ALPE procedure does not cause significant hypoxic vasoconstriction is an assumption, which has not yet been tested. Investigating this before considering further application of the method in COPD is therefore important.

Chapter 3: Hypothesis and aims

3.1 Hypothesis

As highlighted in the previous chapter, obtaining a physiological understanding of the patient with COPD in clinical practice is a challenging process and new tools for evaluation should be sought.

This thesis therefore hypothesises that:

- The combined GOLD risk assessment score is influenced by the presence of comorbidities in COPD patients.
- The current methods to evaluate physiological lung function do not provide the clinician with adequate clinical measure of the pulmonary component in COPD.
- The assumption behind ALPE related to oxygen steady state is valid in COPD patients.
- The ALPE examination does not cause significant hypoxic pulmonary vasoconstriction and does not therefore influence the underlying physiology to a degree that has impact on results.

3.2 Aims

The aims of this thesis are therefore:

1) To investigate the association between the GOLD stratification score and ventilatory parameters, in COPD patients with and without comorbidities (study I).

2) To investigate the clinical association between HR-CT findings, physiological lung parameters and the classification of COPD patients with or without comorbidities, (study I).

3) To investigate the association between DLCO, the GOLD stratification score and ventilatory- or systemic parameters respectively, (study I and II).

4) To elucidate the time to steady state in SpO_2 and PO_2 after changes in FiO_2, both in wash in and wash out in patients with COPD, (study III).

5) To investigate the changes in MPAP and PVR as surrogate measures of HPV as response to changes in FiO_2 (study IV).

Chapter 4: Presentation of studies

4.1 Material

Four studies constitute this thesis. Data was registered and kept according to the legislation of the Danish Data Protection Agency and with approval from the Agency. All patients were informed and signed consent according to the Helsinki Declaration.

4.2 Study I

4.2.1 Study objectives

Study I: This study was a prospective study, investigating the possible influence of comorbidities on the association between the GOLD stratification score and lung function parameters as well as HR-CT findings of emphysema and airway disease in COPD patients.

4.2.2 Study population, inclusion/exclusion criteria

A total of 111 patients were included, of those 106 eligible for the final analysis.

Patients were included based on

- Verified COPD, i.e. post-bronchodilator FEV1/FVC < 70
- Stable state with no exacerbations within 6 weeks prior to examination.

Exclusion criteria were:

- Previous lung surgery
- Other treatment for or suspicion of lung cancer

4.2.3 Methods

Patients were examined with high resolution computered tomography (Discovery CT750HD, General Electric Company, Fairfield, Connecticut, USA) was performed in accordance with the protocol.

Table 1: relevant features of the scan protocol in study 1

Scan type	Rotation time	Thickness/ Image interval	Pitch
Helical scan	0.5 sec	0.625 mm	0.984:1

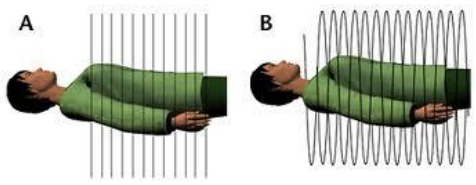

Figure 12: Illustration of an axial CT-scan procedure (A), versus a helical scan procedure (B).

An axial scan, Figure 12A, moving both the scanner and the sleigh at the same time, was performed, to reduce scan time. The features if the scan are sketched in Table 1.

A body plethysmography was performed with MasterScreen® Body *(VIASYS Healthcare GmbH).*and diffusing capacity of the lung for carbon monoxide measured with MasterScreen® PFT *(VIASYS Healthcare GmbH).*

For evaluation of the HR-CT scans the approach of Aziz et al. was chosen in combination with the reference material published by the COPDGene group [96,151]. Three individuals, two radiologists and one pulmonologist, the primary investigator, evaluated the HR-CT scans. The scans were prior to evaluation anonymised by a fourth person, who was not otherwise involved in the project. Evaluation was performed using the PACS solution (McKesson Radiology™), and as such allowed the use of the quantitative tools embedded in this system in combination with qualitative evaluation. Before evaluating the HR-CT scans the doctors received a thorough introduction to the scoring system accompanied by instruction material, which was available to them throughout the evaluation process. The instruction material is available in Appendix 1, although partly in Danish.

4.2.4 Results

A significant association between GOLD stratification score was found, and each of the lung function parameters: FEV1%, IC% IC/TLC and SpO_2 as illustrated in Table 2. These correlation coefficients were weakened when patients were stratified to subgroups according to numbers of comorbidities. When comparing pairs of variables in patients with 0-1 and 2 or more comorbidities, there was a significant difference between GOLD stratification score and FEV1 as well as GOLD stratification score and IC/TLC. Furthermore, there was a significant association between emphysema grade and lung function parameters as FEV1, IC/TLC, SpO_2, (Table 3), as well as between emphysema grade the GOLD stratification score in the total study population (p=0.03). However, when analyzing subgroups, significant association was only seen between emphysema grade and FEV1 in patients with 0-1 comorbidity (p=0.02), as well as emphysema grade and SpO_2 on patients with 2 or more comorbidities, Table 3.

DLCO was associated with both GOLD stratification score (Table 2) and emphysema grade (Table 3). Interestingly, the association between DLCO and both of these were not weakened by the presence of comorbidities.

Unpublished data on correlation analysis between mMRC and lung function parameters showed an effect of comorbidities similar to that seen on the correlation between GOLD stratification and lung function parameters (Table 4). This may not be surprising, as mMRC is part of the GOLD

stratification score; however, mMRC is the patient reported outcome of the score, and could therefore well be influenced by other chronic diseases.

When hierarchical cluster analysis was applied to the dataset comorbidities clustered with the number of exacerbations, the GOLD score and the mMRC score (Figure 12). This further supports the associations presented in table 2.

Table 2: Spearman's correlation analyses of GOLD-score versus FEV1 in percent of expected value, DLCO in percent of expected value, IC in percent of expected value, the ratio between IC and TLC and SpO2

	GOLD score, total study population (n=106)		**GOLD score, patients with 0-1 comorbidity (n=50)**		**GOLD score, patients with 2 or more comorbidities (n=56)**	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
FEV1%	-0.677	<0.001	-0.805	<0.001	-0.543	<0.001
DLCO%	-0.479	<0.001	-0.475	<0.001	-0.496	<0.001
IC%	-0.584	<0.001	-0.670	<0.001	-0.504	<0.001
IC/TLC	-0.554	<0.001	-0.696	<0.001	-0.426	0.001
SpO2	-0.327	0.001	-0.387	0.006	-0.315	0.02

Table 3: Pearson's correlation analyses of emphysema grade versus FEV1 in percent of expected value, DLCO in percent of expected value, IC in percent of expected value, the ratio between IC and TLC and SpO2

	Emphysema grade, Total Study population (n=106)		**Emphysema grade, Patients with 0-1 comorbidity (n=50)**		**Emphysema grade, Patients with 2 or more comorbidities (n=56)**	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
FEV1%	-0.281	0.004	-0.418	0.002	-0.138	0.3
DLCO%	-0.454	<0.001	-0.480	<0.001	-0.454	<0.001
IC%	-0.192	0.05	-0.191	0.2	-0.198	0.2
IC/TLC	-0.192	0.04	-0.258	0.07	-0.149	0.3
SpO_2	-0.331	0.001	-0.255	0.07	-0.398	0.002

Table 4: Spearman's correlation analyses of mMRC-score versus FEV1 in percent of expected value, DLCO in percent of expected value, IC in percent of expected value, the ratio between IC and TLC and SpO_2

	mMRC, Total Study population (n=106)		mMRC, Patients with 0-1 comorbidity (n=50)		mMRC, Patients with 2 or more comorbidities (n=56)	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
FEV1%	-0.494	<0.001	-0.598	<0.001	-0.436	0.01
DLCO%	-0.486	<0.001	-0.498	<0.001	-0.471	<0.001
IC%	-0.421	<0.001	-0.425	0.002	-0.409	0.02
IC/TLC	-0.363	<0.001	-0.471	0.001	-0.280	0.04
SpO2	-0.387	<0.001	-0.368	0.009	-0.405	0.02

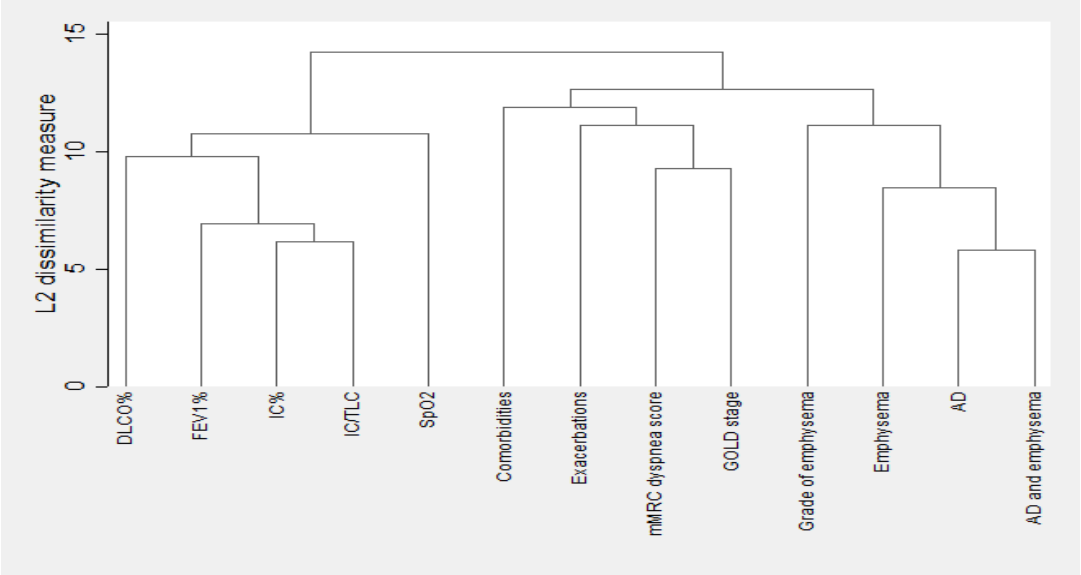

Figure 12: Hierarchical cluster analyses of variables of lung function parameters, number of comorbidities, number of exacerbations, mMRC score and GOLD score as well as grade of emphysema presence of emphysema or airways disease(AD) and both emphysema and airways disease.

4.2.5 Conclusion

Study I investigated two of the hypotheses in this thesis and found that the combined GOLD risk assessment score was influenced by the presence of comorbidities in COPD patients. Furthermore, the current methods to evaluate physiological lung function may not provide the clinician with an adequate clinical measure of the pulmonary component in COPD.

4.3 Study II

4.3.1 Study objectives

This study was a retrospective study investigating whether DLCO is predictive of respiratory impairment in COPD, described by measurements of O_2 and CO_2, and whether DLCO is associated with the GOLD stratification score.

4.3.2 Study population, inclusion/exclusion criteria

Fifty patients were included retrospectively in the second study, all eligible for final analysis. Patients were included based on

- Verified COPD, i.e. post-bronchodilator FEV1/FVC < 70
- Stable state with no exacerbations within 6 weeks prior to examination.

Exclusion criteria were:

- Previous lung surgery.
- Other treatment for or suspicion of lung cancer

4.3.3 Methods

Diffusing capacity of the lung for carbon monoxide measured with MasterScreen® PFT *(VIASYS Healthcare GmbH)*. Furthermore oxygen saturation at FiO_2 = 0.21 and =0.15 was investigated, mediated by ALPE® Essential (Mermaid Care, Nr.Sundby Denmark).

4.3.4 Results

DLCO% was associated to the GOLD stratification score (R^2= 0.42, p<0.001). The regression equation describing this being:

$$DLCO\% = 69 - (10 * GOLD)$$

However, the association found between DLCO% and the GOLD stratification score was strengthened when controlling for BMI, haemoglobin and glucose, (R^2=0.58, p<0.0001), with the multiple regression equation describing the influence of the different components on the diffusion capacity being:

$$DLCO\% = 56 + (-0.6 * GOLD) + (0.6 * BMI) + (1.5 * haemoglobin) - (2 * Glucose).$$

These parameters were chosen by forward selection. The initial analyses also included investigation of the association between DLCO% and smoking status and number of pack years, which were non-significant and did not qualify for inclusion in the multiple regression analysis.

There was a weak but significant association between DLCO% and SpO_2 at room air, (R^2=0.25, p= 0.001) and a significant association between DLCO% and ΔCO_2 (end tidal PCO_2- arterial PCO_2), (R^2=0.16, p= 0.03). Multiple regression analysis showed weak association between DLCO%, SpO_2 at room air, SpO_2 at FiO_2=0.15 and ΔCO_2, (R^2=0.3, p=0.03) with the regression equation describing the influences of the different components as follows:

$$DLCO\% = -277 + (5.5 * SpO_2^{21}) - (2.2 * SpO_2^{15}) - (2.8 * \Delta CO_2).$$

4.3.5 Conclusion

Study II investigated the second hypothesis in this thesis and further supported that the current methods to evaluate physiological lung function do not provide the clinician with an adequate clinical measure of the pulmonary component in COPD.

4.4 Study III

4.4.1 Study objectives

This study was a prospective study, investigating the time to oxygen steady state after decrease as well as increase in inspired oxygen in patients with very severe COPD and chronic respiratory failure.

4.4.2 Study population, inclusion/exclusion criteria

Fourteen patients were included, with 12 eligible for final analysis.

Patients were included based on

- Verified COPD, i.e. post-bronchodilator FEV1/FVC < 70
- Need of treatment with long term oxygen therapy (LTOT), all for more than 1 year prior to inclusion
- Stable state with no exacerbations or major changes in treatment of comorbidities within 6 weeks prior to examination.

Exclusion criteria were:

- Previous lung surgery
- Other treatment for or suspicion of lung cancer

4.4.3 Methods

Wash-out of supplementary oxygen was performed by removing nasal cannula providing 1-4 litres/minute of supplementary oxygen to patients; arterial blood samples were drawn at the time of removal and after 1, 2, 4, 8, 12, 17, 22, 32 and 34 minutes. Oxygen wash-in was performed by reinserting nasal cannula with the prescribed amount of oxygen. Arterial blood samples were drawn as cannula were reinserted and after 1, 2, 4, 8, 12, 17, 22, 32 and 34 minutes. Arterial blood was drawn in PICO50® syringes (Radiometer, Copenhagen, Denmark), and analysed to obtain blood gas- and acid-base status (ABL 835 and 837, Radiometer, Copenhagen, Denmark).

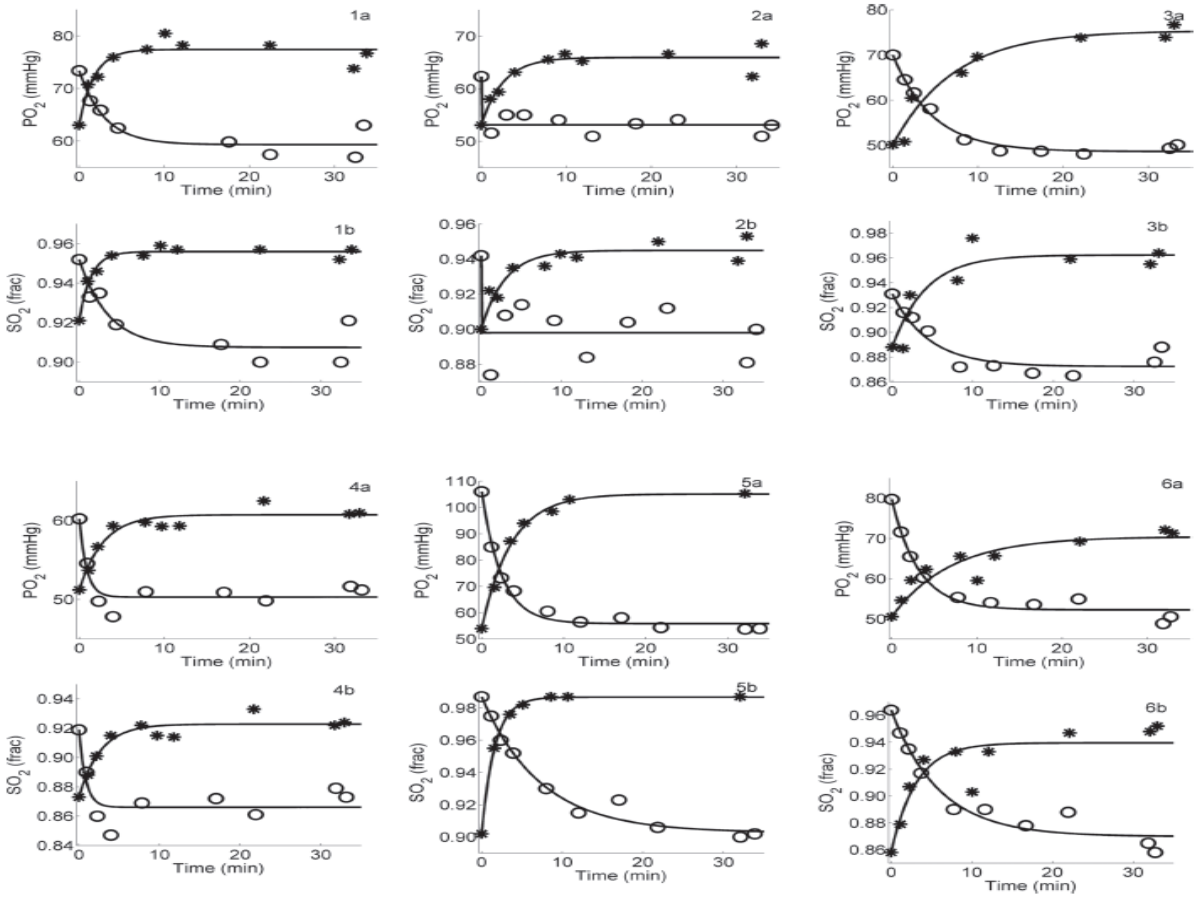

Figure 13: Examples of titration curves for oxygen wash-out over 34 minutes, demonstrating partial pressure, PO_2 (mmHg) and oxygen saturation, SO_2(fraction) in COPD patients in need of LTOT

4.4.4 Results

Oxygen equilibration relevant for clinical interpretation requires 10 minutes following oxygen wash in and 16 minutes following oxygen wash out in patients with COPD in need of LTOT [152]. Examples of titration curves are demonstrated in figure 13.

4.4.5 Conclusion

Study III investigated the third hypothesis of this thesis. As the assumption behind the ALPE is that oxygen steady state is obtained within 2 minutes this assumption proved invalid in COPD patients.

4.5 Study IV

4.5.1 Study objectives

This study was a retrospective study, investigating whether mild hypoxia induced by changes in inspired oxygen causes hypoxic pulmonary vasoconstriction (HPV) and if so, whether these changes are reversed when inspired oxygen is returned to initial values. MPAP and PVR were used as surrogate measures of HPV.

4.5.2 Study population, inclusion/exclusion criteria

In the original protocols, 65 patients were included, with 42 eligible for inclusion in this study. Patients were included based on

- Need of elective coronary artery bypass grafting
- Investigation with the ALPE system 4 hours post-operatively
- Ventricular ejection fraction >0.40

Exclusion criteria were

- Concomitant valve disease, atrial fibrillation or flutter
- Chronic dialysis treatment
- Treatment for lung disease

4.5.3 Methods

Patients in study IV were all monitored with a pulmonary arterial catheter (continuous cardiac output, Edwards Life sciences, Irvine, CA, USA). The catheter was inserted in either the internal jugular vein or the subclavian vein and forwarded through the superior caval vein and into the right atrium. From here, it was further wedged into a medium sized branch of the pulmonary artery in

order to be able to measure the pulmonary artery wedge pressure (PCWP). Besides this procedure, MPAP, cardiac output (CO), central venous pressure and mixed venous saturation was measured. PVR was calculated as

$$(\text{MPAP} - \text{PCWP})/\ \text{CO}*80\ (\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5})$$

4.5.4 Results

In study IV a 4 mmHg increase in MPAP and a 41 $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ increase in PVR was seen in response to a reduction in FiO_2 of 0.20. There was no difference in patients with initial MPAP both above and below/equal to 25 mm Hg, i.e. patients with initially increased or normal pulmonary pressure. The increase in MPAP and PVR was shown to be immediately reversible on returning FiO_2 to baseline or higher values.

Figure 13A illustrates a typical response of MPAP to changes in FiO_2. Figure 13B illustrates a response of PVR to changes in FiO_2 as seen in the majority of patients.

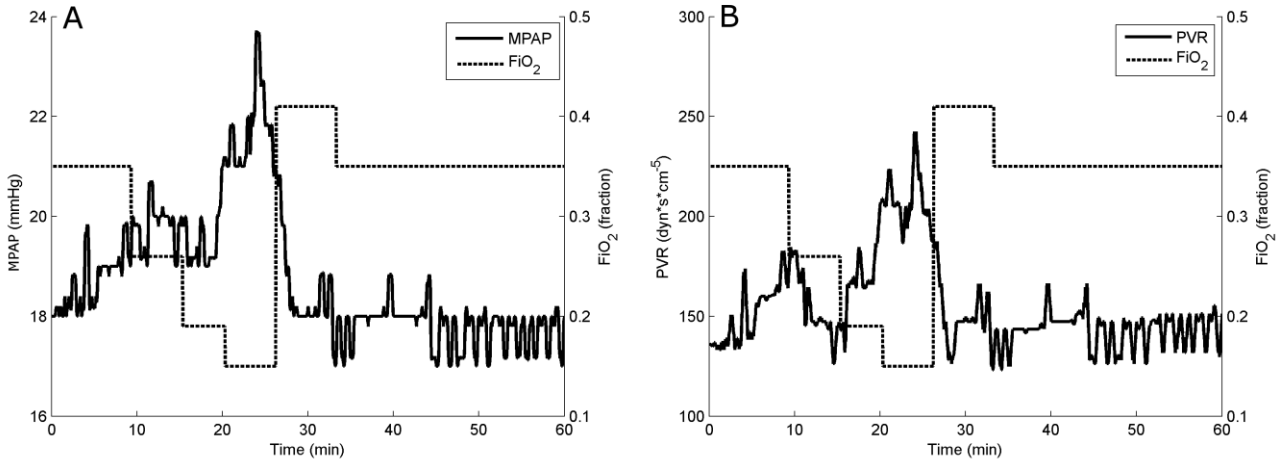

Figure 13: Typical responses in mean pulmonary arterial pressure (MPAP) (A) and pulmonary vascular resistance (PVR) (B) in response to changes in FiO_2

Although the study population for this study was not COPD patients but patients with ischemic heart disease an unpublished sub-analysis was made in patients with a smoking history, demonstrated in table 5 and 6. There was no significant difference in changes in MPAP and PVR in patients with- and without a smoking history.

Table 5: Subgroup analyses in never smokers and former or present smokers (median 35 pack years) of the median pulmonary arterial pressure (MPAP), the variability of MPAP during the study period and the difference between MPAP before decreasing FiO_2 and after having returned FiO_2 to initial or higher values

Median [quartile] (number)	Median MPAP, mm Hg	Variability in MPAP during study period, mm Hg	Difference in MPAP, (mm Hg), initial value – value at FiO_2 increase
Smokers and former smokers (27)	23.0 [21.3-25.5]	4.0 [3.0-5.0]	**0.0 [(-1.0)-0.0]**
Never smokers (12)	**24.3 [22.6-26.3]**	**3.5 [3.0-5.3]**	**0.0 [(-0.25)-1.0]**

Table 6: Subgroup analyses in never smokers and former or present smokers (median 35 pack years) of the pulmonary vascular resistance (PVR), the variability of PVR during the study period and the difference between PVR before decreasing FiO_2 and after having returned FiO_2 to initial or higher values

Median [quartile] (number)	Median PVR, $dyn \cdot s \cdot cm^{-5}$	Variability in PVR during study period, $dyn \cdot s \cdot cm^{-5}$	Difference in PVR, $dyn \cdot s \cdot cm^{-5}$, initial value – value at FiO_2 increase
Smokers and former smokers (27)	**117.6 [86.4-144.0]**	**53.6 [40.8-77.6]**	**1.6 [(-8.8)-15.2]**
Never smokers (12)	**120.8 [101.6-160.0]**	**85.6 [57.6-91.2]**	**(-7.2) [(-16.8)-13.6]**

4.5.5 Conclusion

Study IV studied a general, not yet investigated assumption behind the ALPE model, which was the fourth hypothesis of this thesis. The ALPE examination does influence the underlying physiology but not to a degree, that has impact on results.

Chapter 5: Discussion

In this chapter, the aims of the thesis are discussed in consecutive numbers 1-5. In connection with the aims, the methodological considerations of the papers that investigate the aims are discussed.

5.1 First aim

The first aim was *to investigate the association between the GOLD stratification score and lung function parameters in COPD patients with and without comorbidities*. This was investigated in study I, where the main findings were an association between GOLD score and FEV1%, IC% IC/TLC and SpO_2, which was weakened by the presence of comorbidities. These findings were supported by a significant difference between GOLD score and FEV1 as well as IC/TLC between subgroups with and without numerous comorbidities. The influence of comorbidities on the outcome of the GOLD score is further supported by the clustering between comorbidities and GOLD score in the cluster analysis (study I).

5.1.1 Methodological considerations

Study I was based on two prospective studies with a total of 106 participants. This was a pilot study, reflected by the size of the study population. This may influence whether the study population was representative of COPD patients in general. Given the distribution of comorbidities in this group, compared to previous studies [16,24] it would be reasonable to consider the included patients representative of COPD patients in general. Furthermore, the size of the population may weaken the correlation analyses between subgroups. However, as significant differences are seen in the two key areas, which support the hypothesis, the results are considered valid. Furthermore, these are strongly supported by the hierarchical cluster analysis.

The choice of variables in study I is a matter for discussion. IC and IC/TLC were chosen as measures of hyperinflation. An alternative measure could have been the forced residual capacity. However, IC/TLC is often used to describe static hyperinflation and as such, this measure applied to this study population, which was examined at rest under steady state conditions. A six-minute walking test would possibly have been an interesting measure to evaluate. However, a six-minute walking test elucidates the consequences of pathological changes during exercise, but does not expose the underlying pathology. At rest this can be expressed by SpO_2. Therefore, SpO_2 was chosen in this study population.

The GOLD score is used to stratify COPD patients to treatment regimens worldwide. It is a composite measure that includes evaluation of patients' symptoms that may be done using different

scoring systems. In study I one of the three scoring systems recommended by GOLD was used to evaluate patients' symptoms [2]. The results of this study may therefore not be representative if other scores were used in the GOLD stratification. However other symptom scores such as the COPD assessment score, has been proven to be comparable to the mMRC score [153], and therefore the choice of a single evaluation score appears to be valid.

Patients were recruited after public announcement at the outpatient clinic at Aalborg University Hospital as well as at local the rehabilitation centre. This approach was chosen to get a broad representation of COPD severity in the study population. However, this recruitment approach includes a risk of selection bias, as these patients all had approached the health care system and therefore showed abilities of self-care. Other types of selection bias may also be present – either, patients with less severe COPD may have the energy to participate in a study – or the most symptomatic patients choose to join in order to be examined thoroughly.Therefore, they may not be representative of the entire population of COPD patients. However, the distribution of COPD severity is very consistent with that found in previous studies [123,154].

5.1.2 Interpretation of results

The significant associations shown in study I are consistent with the results of previous studies [122,155]. Previously, significant associations have been shown between longitudinal changes in the GOLD stratification score and FEV1, SpO_2 and IC, in the ECLIPSE and the UPLIFT studies [122,155].These findings show that the GOLD stratification score is a valid measure of the physiological changes in COPD. However, study I indicated that the association between GOLD stratification score and lung function parameters may be influenced by the presence of comorbidities. The ECLIPSE study is not a population based study and therefore sampling bias cannot be excluded [121]. The UPLIFT study has been criticized for excluding patients with comorbidities [156]. Even though Study I is not a population based study, which would have been ideal, the number of comorbidities in the study population is comparable to the studies from the groups of Garcia-Olmos and Divo, discussed previously in this thesis [16,24]. The findings of study I could therefore indicate that patients with comorbidities should be included in future studies. This should be done to ensure that results could be generalized to the COPD population. Since the presence of comorbidities is important to the classification of the severity of COPD, it may be important to distinguish whether an increased severity is due to worsening pulmonary disease or comorbidities. As discussed below, current clinical tools for measuring changes in pulmonary

pathophysiology have limitations, and in particular the use of FEV1 in the GOLD score. It may therefore be important to consider new, more specific tools.

The GOLD stratification score was implemented to strengthen the evaluation of disease severity in COPD. Prior to the introduction of the GOLD stratification score the assessment of COPD relied heavily on FEV1. However, as stated by the GOLD group, FEV1 is of limited value in evaluation of COPD severity and reflection of symptoms [2]. This was elaborated by the ECLIPSE study group, who concluded that FEV1 does not capture the heterogeneity of the disease [121]. Furthermore, data from the TORCH study showed that the change in quality of life was independent of changes in FEV1 [157]. Therefore, the 2013 interim revision of the GOLD recommendation included the composite measure of patient reported outcomes and FEV1 [2]. Today the GOLD stratification score is the gold standard for evaluation of COPD severity. However, data from study I suggest that the GOLD stratification score seems to be influenced by the presence of comorbidities. This could indicate that the GOLD stratification score may measure morbidity in general rather than COPD severity. If this is the case, one could consider using existing lung function parameters, such as the IC, the IC/TLC and SpO_2, to supplement the existing score, in order to understand the underlying pulmonary pathology.

IC and the ratio IC/TLC are measures of hyperinflation and have been shown to be strongly associated with dyspnea [46,50]. As dyspnea is a central feature of COPD these could be appropriate to include in the evaluation of the patient. However, the measurements require a body plethysmography, which is not easily accessible in primary and secondary care, let alone in developing countries. Moreover, it is expensive equipment dependent on a stable surrounding environment and specialized technical support in order to obtain valid and reproducible results. Furthermore, it requires operation by trained and experienced personnel to obtain valid measurements.

In contrast, SpO_2 is easy to measure, does not require trained personnel, and the equipment for measuring is inexpensive. It is well known that a need for LTOT increases mortality [158,159], but otherwise studies investigating SpO_2 in stable state as a predictor of mortality has shown conflicting results [32,47,159]. However, previous studies have shown low SpO2 to be a risk factor for readmission to hospital after an exacerbation of COPD [160]. In addition, a number of smaller studies have indicated that exertional desaturation is related to a poorer prognosis in COPD. However, different definitions of desaturation and different modes of exercise makes it difficult to compare these studies [161]. Hence, the clinical consequence of decreased SpO_2 in COPD is not fully understood. Moreover, SpO_2 is the result of pathological changes, but does not unmask the

underlying pulmonary pathology; one could dare to say – this may also be the case for GOLD stratification score.

In summary, if COPD patients have comorbidities they may be stratified to a higher stratum than COPD severity would require. This may lead to over treatment of COPD. In contrast, if too much impact is put on the GOLD stratification score, comorbidities could be masked and thereby under-diagnosed. As of today the available tools do not provide the clinician a strong support in distinguishing between pulmonary pathology and comorbidities in COPD, yet there is a need to focus on both. Hence, an easy accessible, inexpensive and easy applicable alternative tool for measuring COPD would be welcomed.

5.2 Second aim

The second aim of this study was *to investigate the clinical association between HR-CT findings, lung function parameters and the GOLD stratification score of COPD patients with or without comorbidities*. This was investigated in study I, where the main findings were a significant association between emphysema grade and lung function parameters as FEV1, IC/TLC, SpO_2, as well as between emphysema grade the GOLD stratification score in the total study population. However, when analyzing subgroups, significant association was only seen between emphysema grade and FEV1 in patients with 0-1 comorbidity, as well as emphysema grade and SpO_2 on patients with 2 or more comorbidities.

5.2.1 Methodological considerations

Methodological issues relating to study I have been discussed in connection with the first aim. However, considerations concerning the choice of method to evaluate the HR-CT scans apply to the third aim of this thesis.

A number of limitations should be considered in connection with evaluation of the CT-scans. As previously discussed in this thesis, it is debatable which choice of method is superior for describing HR-CT scans. In a qualitative approach such as visual scoring, inter-observer variability in the interpretation exists. However, large groups as the COPDGene group and Dirksen and colleagues both consider the inter-observer variability to be acceptable and consider visual scoring a reliable method for interpreting especially emphysema in CT scans [96,162]. The choice of method in relation to describe clinically relevant findings has also been debated previously [151,163] These obstacles have been considered when designing study I. For the analysis performed in study I, the decision as to the selection of the CT-evaluation technique was inspired by two groups, one that has

provided a validated reference material for visual scoring of CT scans and another that has considered the association between radiological and clinical manifestations of the disease [96,151]. Both these considerations were implemented to minimise inter-observer variability and also to accommodate the planned correlation analysis with lung function parameters. Thus, the inter-observer agreement found in study I expresses both the presence of emphysema and airways disease with values comparable and even superior to the results of previous studies [85,96,162]. Furthermore, associations between HR-CT findings and lung function parameters were seen in study I. These observations concerning the choice of method should be carried forward to future studies.

5.2.2 Interpretation of results

Previous studies have shown a significant association between emphysema grade and FEV1 [57,164], which is consistent with the findings of study I. An association between emphysema and hyperinflation has also been shown previously [57], which is consistent with the association between emphysema and IC/TLC shown in study I. Moreover, a negative association between emphysema grade and SpO_2 shown by Fujimoto et al. [165] is also similar to that shown in study I. A single paper from the COPDGene group has shown greater extent of emphysema and more gas trapping in higher GOLD strata than in lower GOLD strata [166], which is also consistent with the findings in study I. These findings suggest that the study population might be generalised to represent other COPD populations.

When analysing subgroups, study I showed a significant association between emphysema grade and FEV1 in patients with 0-1 comorbidities but no association when analysing patients with 2 or more comorbidities. Literature is sparse on the influence of comorbidities on the association between emphysema and lung function parameters, but a single study showed no association between FEV1 and emphysema in heart disease [167]. One could suspect that the association of lung function parameters would be independent of the influence of comorbidities, but in general, this does not seem to be the case when considering the results from study I. A possible explanation could be that systemic inflammation in patients with numerous comorbidities has an impact on either the degree of emphysema or the outcome of lung function parameters, but further studies are required to test this postulate.

Surprisingly, a rather strong association was seen in paper 1 between emphysema grade and SpO_2 in patients with numerous comorbidities, whereas no association was seen in patients with 0-1 comorbidity. To this author's knowledge, this has not been described previously. One could

speculate whether SpO_2 reduction is a result of impaired pulmonary perfusion and that this impairment may be reinforced by the presence of comorbidities. However, this would be a subject for future research, as described in chapter 5.

Finally the subgroup analysis in study I showed a significant association between emphysema grade and GOLD stratification score in patients with 0-1 comorbidity but no association in patients with 2 or more comorbidities. This thesis has suggested that the GOLD stratification score demonstrates overall morbidity in COPD patients. As COPD causes major morbidity, as shown by many authors, [168] the association in the subgroup with 0-1 comorbidity was not unexpected. The fact that there is no association between emphysema grade and GOLD stratification score in patients with numerous comorbidities may support further the hypothesis that the GOLD stratification score does not relate specifically to lung disease

In summary, two messages with possible clinical implications can be concluded from the results of study I. 1) both emphysema or lung function parameters could be influenced by the presence of comorbidities. This should be investigated further in future as it may influence our evaluation of these patients. This is further discussed in chapter 5. 2) a decrease in SpO_2 may be a result of the impairment of pulmonary perfusion, which forces us to consider more than the broncho-alveolar system when we as clinicians evaluate respiratory insufficiency. However, this also needs to be investigated further in future studies.

5.3 Third aim

The third aim *was to investigate the association between DLCO, the GOLD stratification score and ventilatory- or systemic parameters respectively*. This was investigated in study I and II, where the main findings were a significant association between the GOLD stratification score and DLCO. Furthermore, study I indicated that the association between the GOLD stratification score and DLCO was not influenced by the presence of comorbidities. In addition, study II showed weak association between DLCO and respiratory parameters as the outcome of changes in FiO_2 and differences in arterial and end-expiratory CO_2, in contrast to a strong association between DLCO and systemic parameters.

5.3.1 Methodological considerations

Both results from study I and II are included in the discussion of the second aim. As the methodology of study I is discussed above, this section will focus on considerations concerning study II.

Study II was a retrospective study based on patients from a protocolled study as well as patients from a feasibility project carried out in the department. As such, this limited the size of the study population. Furthermore, there were a number of missing values, which could not be obtained retrospectively. Moreover, being retrospective, the study could not be designed to investigate the message from the systemic parameters thoroughly, i.e. glucose levels as well as BMI were within normal ranges in the study population. As such, future study should be designed to consider the impact of systemic parameters, as described in chapter 5.

5.3.2 Interpretation of results

DLCO is a very interesting measure in pulmonary physiology, thought to describe the diffusion properties of the lungs. However, it has previously been demonstrated that the primary problem associated with gas exchange in COPD is not diffusion limitation [169]. Instead, the primary problem is $\dot{V}/\dot{Q}$ mismatch, with heterogeneous distribution of both areas of high, i.e. areas with impaired perfusion, and low, i.e. impaired ventilation, $\dot{V}/\dot{Q}$ ratios are seen in the lung [74,169]. In study II a weak association is seen between DLCO and SpO_2 measured at $FiO_2 = 0.21$, as well as other markers of respiratory disease, such as SpO_2 measured at $FiO_2 = 0.15$ and ΔCO_2, are not associated with DLCO. This is consistent with physiological knowledge about $\dot{V}/\dot{Q}$ mismatch, described above.

Previously an association has been shown between emphysema grade and DLCO [57], which is also consistent with the findings in study I. Furthermore, DLCO has been associated with dyspnea in COPD [59,170,171] and an association between DLCO and mMRC was also seen in unpublished data from study II. Interestingly, DLCO has also been associated with dyspnea in heart disease [171] and, in a single study, in diabetes patients [172]. However, several authors have found a faster longitudinal decline in DLCO in diabetes patients compared to otherwise comparable non-smoking non-diabetics [172], explained by development of micro-angiopathy in the diabetic lung. In study II systemic markers as glucose level and BMI were associated with DLCO when performing multiple regression analysis. Therefore, it is interesting to speculate whether DLCO might be a good descriptor of systemic deconditioning instead of a descriptor of pulmonary gas exchange. The

speculation may seem irrational, given that DLCO is measured by inhalation. However, the explanation could be as follows: If DLCO was to be an adequate representation of $\dot{V}/\dot{Q}$ abnormalities it would need to describe changes in ventilation and perfusion sufficiently. The standard method for measuring DLCO involves breath holding at maximal inspiration. This means that the amount of CO diffused is more likely to reflect maximal inspiratory volume than the individual's normal ventilation. Indeed, it could be postulated that maximal inspiration may increase gas volume in all regions of the lung, potentially normalizing low $\dot{V}/\dot{Q}$ regions and increasing gas exchange abnormality in regions with high $\dot{V}/\dot{Q}$. In contrast, the amount of CO diffused may be highly affected by changes in perfusion and blood hemoglobin-concentration, as previously reported by other authors [75,173]. As pulmonary perfusion changes are seen in systemic diseases as diabetes [172,174], chronic heart failure [175]as well as in COPD [176,177], this could lead to the thought that DLCO may reflect systemic changes, without correlating with oxygen and carbon dioxide levels.

In summary, we may need to re-consider what DLCO measures and how to use it. It is noteworthy to find one measure very closely associated to a composite measure as the GOLD stratification score. If the GOLD stratification score reflects the overall morbidity of the COPD patient, DLCO may be an objective measure of systemic deconditioning in COPD, which allows us to monitor the deterioration of the COPD patient over time. However, it is important to note that abnormal values of DLCO are not only present in patients with COPD but in patients with high morbidity in general.

DLCO has in clinical care been used to evaluate the gas-transfer abilities of the lung. If DLCO is not specific to the lung, this leaves us with another challenge; how do we measure gas exchange in COPD? A new tool to meet this challenge would be welcomed.

5.4 Fourth aim

The fourth aim of this thesis was *to elucidate the time to steady state in SpO_2 and PO_2 after changes in FiO_2, both for oxygen wash in and wash out in patients with COPD*. This was investigated in study III, where the main results were that oxygen equilibration relevant for clinical interpretation required 10 minutes following oxygen wash in and 16 minutes following oxygen wash out in patients with COPD in need of LTOT treatment.

5.4.1 Methodological consideration

Study III was a prospective study on a small group of patients. The size of the study population is therefore a limitation to this study. However, despite some inter-personal variation, steady state in both oxygen partial pressure and oxygen saturation in consecutive tests was seen in the entire study population suggesting that the results are valid. The study participants were all very severely ill COPD patients with chronic respiratory failure in need of LTOT; none of the patients were alive at the time the study was published. Therefore, the results may not be generalized to the COPD population. However, by choosing the most severely ill patients for the study population, the results could be thought of as "worst case scenario" meaning that more healthy patients are likely to reach oxygen steady state at least as fast as the study population.

Patients were all stable at the time of inclusion. Therefore, the results of this study may not be applicable in COPD patients with exacerbations.

The choice of end point in study III is a matter for discussion. Previous studies have used either return to exact steady state or the time to reach 90% of the final value (T90). Moreover, T90 suffers from the fact that it is variable in the same individual, dependent on the increment of the oxygen step. Reaching both of these endpoints is time consuming and the results do not have any relevance for clinical decision-making. For clinical interpretation study III suggests that reaching within 1% of the final oxygen saturation is adequate.

Patients were invited by public announcement in the outpatient clinic at Aalborg University Hospital. Nevertheless, they were all well known to the author and chose to participate despite no financial compensation, the enormous physical effort it took them to get to the investigation site and risk of discomfort due to hypoxia that the study imposed on them. Therefore, there may be both a selection bias and a case of excessive compliance in this study. However, as blood gasses are very objective measures this is unlikely to influence the time to steady state of oxygen in these patients.

5.4.2 Interpretation of results

Oxygen steady state is obtained within 2 to 3 minutes of changing FiO_2 in healthy individuals [178]. The "American Thoracic Society/European Respiratory Society standards for diagnosing and treatment of COPD" contains recommendations for monitoring oxygen during an exacerbation of COPD. In this standard the authors recommend to monitor PaO_2 with 1-2 hours intervals [179]. Until now, recommendations for monitoring oxygen changes in COPD are based upon a review published by Woolf in the 1970'ies. This paper concluded that 30 minutes should be waited before measuring PaO_2 after changes in FiO_2 [142]. However, since the studies cited by this review were

not easily comparable this conclusion could be questioned. The studies included all assess changes in FIO_2, and monitor the subsequent changes in oxygenation in arterial blood in COPD patients. However, the variables chosen to describe the response to oxygen changes were not consistent, with either PaO_2 [143,144], or SpO_2 [147] used to evaluate steady state. Studies did not investigate both decrease (oxygen wash out) and increase (oxygen wash in) in FiO_2. As such, studies in spontaneously breathing patients only considered oxygen wash out [143,144,146,147] and a single study in mechanically ventilated patients only considered oxygen wash in [145]. Moreover, previous studies used different sampling times. Only one study measured PaO_2 frequently enough in the early phase to elucidate the fast dynamics of oxygen changes [144]. Furthermore, the end point for the oxygen change were analyzed in different ways for different studies, with some using return to baseline [143,144], and others T90 [145,146]. Finally, none of the studies were performed within ranges of FiO_2 relevant for daily clinical practice, with studies typically changing FiO_2 from room air (21%) to 100%. In contrast, study III 1) measures both wash out and wash in of oxygen, 2) measures both SpO_2 and PaO_2 and with sample times that allow description of the fast dynamics of oxygen immediately after changing FiO_2 and 3) operates within a clinically relevant range of FiO_2. This serves two purposes: To make the study relevant for clinical practice and to challenge the assumption behind the ALPE method.

In daily clinical practice the findings of study III mirror clinical observation of the COPD patients in need of LTOT, as steady state is obtained within a quarter of an hour opposing the half an hour suggested by Woolf. If this finding can be generalized to the entire COPD population this may change the monitoring procedure in patients in LTOT treatment in the future.

Based on studies in healthy individuals it has been assumed that oxygen steady state is obtained within few minutes during the ALPE measurement [180]. However, study III shows that steady state was obtained after a maximum of 16 minutes in COPD patients. Hence, the assumption behind the ALPE method is not met in these patients. One could therefore argue that the ALPE system should not be used in COPD; new, alternative methods, as the micropore membrane inlet mass spectrometry exists for MIGET [181], which facilitates the procedure. However, it is still a complex and time-consuming procedure compared to ALPE. Even though the ALPE method needs revision before the system is clinically applicable in COPD patients it could potentially be useful due to its simplicity in daily clinical care. The revision has been approached by a new algorithm which evaluate patients' breath-by-breath changes in respiratory and blood oxygenation [182,183]. This algorithm, presented in a recent PhD study [140], has proved promising as an alternative to the need for oxygen steady state in the ALPE method.

In summary, the assumption behind the ALPE that oxygen steady state is obtained within a few minutes does not apply for patients with very severe COPD and therefore needs reconsideration if the method is to be considered in the assessment of lung function in COPD en future.

5.5 Fifth aim

The fifth aim of this thesis was *to investigate the changes in MPAP and PVR, as surrogate measures of HPV, in response to changes in FiO_2.* This was investigated in Study IV, where the main results were a 4 mmHg increase in MPAP and a 41 dyn·s·cm^{-5} increase in PVR in response to a reduction in FiO_2 of 0.20. The increase in MPAP and PVR was shown to be immediately reversible on returning FiO_2 to baseline or higher values.

5.5.1 Methodological considerations

Study IV was a retrospective study on a highly selected study population. As such, this limited the number of participants in the study. Furthermore, there were a number of missing values, which could not be obtained retrospectively. Moreover, it would have been desirable if information on the pulmonary condition of this population had been available. In the original study design patients with signs of severe lung disease were excluded, but given substantial tobacco consumption and the similarity in symptoms between ischemic heart disease and COPD, it is not unlikely that a number of the study participants suffered from both. As such a spirometry measurement, data on mMRC-score and exacerbations would have been helpful to diagnose and stratify COPD. These, along with preoperative values of PCO_2 would have been of interest to elucidate the possible risk of respiratory failure.

This highly selected patient group may not be representative of all critically ill patients, not least spontaneously breathing patients where it has been suggested that mechanisms of HPV differ from those in mechanically ventilated patients [184]. However, this patient group remains very interesting. All study patients had undergone cardiac surgery 4 hours prior to the examination, which induces cardiac stunning; furthermore, they were all treated with beta blockers and paced. As such, one would expect the cardiac response to remain unaltered and to rise only if peripheral ischemia occurs. This provides a unique opportunity to study the isolated effect of changes in oxygenation on the pulmonary circulation.

The use of MPAP and PVR as surrogate measures of HPV have been used by many previous authors [148,185]. This is due to measurement of HPV being very difficult and virtually impossible in vivo. Changes in MPAP as an evaluation of HPV have therefore been used since Euler et al.

recognized an increase in MPAP without concomitant increase in right atrial pressure in response to hypoxia, and hereby started what could be called “modern observations of HPV in vivo” [149]. Only shortly after this Borst et al presented a method to measure PVR, which is now often used to supplement MPAP in elucidating HPV [186]. As such, MPAP and PVR can be considered valid surrogate measures of HPV.

5.5.2 Interpretation of results

Both in healthy persons and patients with chronic heart failure, coronary heart disease and in chronic obstructive lung disease, MPAP has been shown to rise 13-21 mmHg during mild, clinically advantageous exercise [187–190]. The finding in study IV of an increase in MPAP of 4 mmHg can therefore be considered small. Similarly, in the clinical setting, PVR is expected to increase 50-300% in response to HPV [185]. In comparison to these observations, the change in PVR of 35% in study IV is small. However, in contrast to patients in a clinical setting, the cardiac response of the study participants was virtually eliminated and therefore only a HPV response was seen. Another explanation could be that only mild hypoxia was induced on the study population in study IV and therefore only very mild HPV occurs.

In previous studies, larger changes in oxygenation have been carried out. Hambreus-Johnsen et al. showed, that when switching from ventilating both lungs at FiO_2 = 1.00 to ventilating one lung at 1.00 and the other at 0.12, the blood flow to the hypoxic lung decreased only 5% [191]. Furthermore Marshall et al. simulated only small changes in pulmonary shunt when varying FiO_2 within a range of 0.3 to 1.0 [192,193]. As oxygen changes were considerably larger in these studies compared to that of study IV, the minor change in MPAP and PVR were not surprising.

In study IV both MPAP and PVR return to baseline values in response to restoring oxygenation. This probably indicates that only minor vasodilatation occurs. Literature on the effect of hyperoxia have shown conflicting results, with some showing signs of vasodilatation [194,195], other showing no change [194,196,197] and some even advocating risk of vasoconstriction [198–200]. Fineman et al., when changing oxygenation from room air to 100%, indicated that vasodilatation does not occur in healthy individuals, but does occur in patients with pulmonary disease [194]. A possible explanation is that in healthy individuals, breathing room air, there is no HPV in contrast to patients with pulmonary disease. In line with this the minor vasodilatation seen in study IV can only be seen when patients have had preceding HPV. Only a group of 5 patients with severe anemia (Hemoglobin ≤5 mmol/l) did not return either MPAP or PVR to baseline after oxygenation was restored. This could advocate that caution should be taken when performing the ALPE procedure on

patients with severe anemia; however, further studies are needed to investigate the effect of mild hypoxia in patients with anemia.

In summary, the relatively small changes in MPAP and PVR seen in this study indicate that only mild HPV occurs in response to mild hypoxia induced in the patients during an ALPE procedure. From a clinical perspective, knowledge about a mild increase in MPAP and PVR and not least that correcting mild hypoxia has an acute positive effect on MPAP and PVR may be of use to the anesthesiologist. An example of this could be in intensive care, where the anesthesiologist often changes FiO_2 in mechanically ventilated patients. In terms of the ALPE procedure, the results of study IV may assure us that the use of small changes in inspiratory oxygen, probably do not affect the pulmonary circulation to a degree that has major impact on the results of the measurement.

Chapter 6: Conclusion and future perspective

This thesis has elucidated the challenges in physiological assessments of COPD. It indicates that methods for both evaluation of pulmonary pathophysiology and evaluation of COPD severity are susceptible to the presence of comorbidities. Furthermore, it suggests a need of supplementary tools to measure lung function with simple techniques, which are possible to carry out at the bedside. Moreover, it has investigated two essential assumptions behind a tool, which possibly could be of use in COPD; the ALPE. One of these assumptions, the assumption that oxygen steady state could be achieved in 2-3 minutes, showed that modifications to the ALPE method were needed if the tool should be used in COPD; another assumption, that HPV does not affect the outcome of the measurement, is most likely to be a reasonable approximation. However, the thesis has also posed a number of questions that remain unanswered and therefore a number of interesting issues requiring further investigation.

6.1 The GOLD combined assessment score – COPD severity or Risk Assessment?

The results of study I indicate that the GOLD combined risk assessment score is sensitive to patients' morbidity. As study I was a pilot study, further investigation should include a larger sample size to strengthen the statistical power. Future studies should also include measures of dynamic hyperinflation and a six-minute walking test, with these used to evaluate whether the pulmonary component of the disease is more pronounced in activity compared to rest.

6.2 Pulmonary perfusion and COPD

Study I and II of this thesis found that DLCO was associated with the GOLD stratification score. This indicates that DLCO could be used to monitor disease in COPD. However, the interesting question is – what does DLCO really measure in COPD? Both study I and study II suggest that pulmonary perfusion may relate to clinical findings in COPD; study II even speculates that DLCO may be a measure of pulmonary perfusion. The measurement of pulmonary perfusion has, in recent years, become more readily available, not least due to the availability of Magnetic Resonance Imaging (MRI). It may therefore be a useful measurement in investigating whether pulmonary perfusion has an impact on patients reported outcomes such as dyspnea, as suggested by unpublished data from study I. Pulmonary perfusion may also be interesting when investigating the interaction between different pathological findings, as illustrated in Figure 10. However, a number

of questions about the influence of pulmonary perfusion in COPD remain to be answered. These include: Questions about perfusion changes in relation to phenotypic presentations of COPD; longitudinal changes in perfusion; the influence of perfusion changes on morbidity and mortality in COPD and the influence on perfusion changes on the outcome of lung function measurements. Furthermore, an interesting question is whether pulmonary perfusion changes are reflected systemically, i.e. in peripheral muscles, heart and brain.

To pursue these questions, collaboration has been established between the author of this thesis and colleagues with interest in respiration and imaging at Aalborg University Hospital, along with an international collaboration with an Imaging Centre with experience in MRI-imaging of pulmonary perfusion.

6.3 ALPE in relation to COPD-patients.

Study III has shown that modifications were needed for ALPE to be used in COPD. ALPE essential can therefore, in its present form, not be applied directly in the diagnostic process or monitoring of COPD patients.

Study IV included a study population of patients with coronary heart disease. To secure that the findings are valid in COPD, a study on COPD patients should be carried out.

Even though the knowledge of $\dot{V}/\dot{Q}$ mismatch in COPD patients dates back to the 1970's there has never been any approach to apply this knowledge into daily clinical practice. This may be understandable as the measure is difficult to obtain. If the use of this measurement is within reach, we need to relate $\dot{V}/\dot{Q}$ mismatch to define i.e. when $\dot{V}/\dot{Q}$ mismatch is mild, moderate and severe and to relate it to clinical features as dyspnea, desaturation etc., well known in COPD patients.

Study I of this study suggest that lung function parameters may be influenced by the presence of comorbidities. The question is whether this also applies to the ALPE method. As such, the question is to which extent the ALPE method is beneficial for further understanding and increasing diagnostic specificity in COPD? Large scale studies would be needed to elucidate this and the cost-benefit of introducing a new method in the diagnostic procedure.

With modifications the ALPE method, it might be a step forward towards an easily applicable method, which not only provides information on pathological changes, but also allows the unmasking of the underlying pulmonary pathology.

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