Flying with chronic obstructive pulmonary disease

Prevalence of symptoms, pre-flight assessment and in-flight supplemental oxygen

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Acknowledgements

The present work was performed from 2008 to 2012, and was carried out at Glittreklinikken LHL Helse, a pulmonary rehabilitation hospital owned by the Norwegian Association of Heart and Lung Patients (LHL), and Department of Pulmonary Medicine, Oslo University Hospital Ullevål. We have also been cooperating with the Institute of Aviation Medicine, Oslo (Paper IV) and the Department of Thoracic Medicine, Haukeland University Hospital, Bergen (Paper I). The work has been funded by grants from the Norwegian ExtraFoundation for Health and Rehabilitation (ExtraStiftelsen), the Norwegian Association of Heart and Lung Patients (LHL), Glittreklinikken, Haukeland University Hospital, by a grant for Best Abstracts in Rehabilitation and Chronic Care, European Respiratory Society 2010, and by a grant for Best Paper 2012 in Lung Medicine, Norwegian Association of Lung Medicine.

First of all I wish to express my most sincere gratitude to my two supervisors. Professor Dr. med. Ole Henning Skjønsberg, Department of Pulmonary Medicine, Oslo University Hospital Ullevål has been my main supervisor. I am impressed over your clear and clinical thinking and I have learned a lot from your constructive and critical feedback. Dr. philos. Morten Ryg, Glittreklinikken has been my co-supervisor and closest collaborator these years and your unlimited patience, constructive criticism and encouragement have been invaluable for me. The present work has been entirely dependent on your enormous knowledge, experience and never ending optimism as well as teaching skills; thanks to both of you.

I also wish to express my sincere gratitude to all my co-authors. The current work had not been possible without Dr. med Carl Christian Christensen, Glittreklinikken. You introduced me and included me into scientific work and especially air travel medicine. You are the true senior in the field of air travel medicine, and your clinical experience, enormous knowledge and a never-ending source of new ideas has been invaluable. Dr. PhD. Aina Akerø, Department of Pulmonary Medicine, Oslo University Hospital Ullevål is thanked for her contribution in all papers, for clear and constructive feedback, and for a significant contribution to the thesis as the first author of Paper IV. I wish to express my gratitude to Dr. med Jon A. Hardie, Dr. med. Tomas M.L. Eagan and Professor Dr. med. Per S. Bakke, Haukeland University Hospital, who invited us to cooperate with the study presented in Paper I. You showed true positive interest, collected the data and supported me in the analyses of large data files. Dr. Jan Ove Owe, Institute of Aviation Medicine, is thanked for his
participation when planning and collecting data to Paper IV. Your knowledge in aviation medicine and high altitude physiology is outstanding. I also would like to thank Professor Leiv Sandvik, Oslo University Hospital, for statistical support and valuable advice about methodology. Thanks for everything I learned from all of you!

I also wish to express my sincere gratitude to the past director of Glittreklinikken, Dr. Olav Kåre Refvem. You established research at Glittreklinikken and made it possible for me to first carry out a Master of Science and then embark on a doctoral project. I am also indebted to my past and present superior, Dr. Anne Norlund and Dr. PhD. Siri Skumlien. You have organised and made it possible for me to include patients in the studies and encouraged me all along the way. I also appreciated having a part time employment at our Laboratory for Respiratory Physiology, making it possible for me to be “up to date” with current procedures.

Special thanks go to my colleagues at Glittreklinikken. I can not mention everyone, but thanks for making Glittreklinikken a fantastic place to work at and for making me want to go to work every single day! I must, however, mention some of you. Dr. PhD. Aina Kjensli has been my closest PhD “sparring partner” and friend, and I really have enjoyed and learned a lot from our frequent discussions. My colleagues at the Laboratory, Grethe Dahle, Liv Karin Vesteng, Christine G Karlsen, Jan Inge Krog, Turid Vestli and Mona Lisa Digernes have all supported me and participated in the collecting of data; I am truly grateful for your goodwill! In addition to Glittreklinikken, these projects have relied on the effort, experience and loyalty of many employees at Department of Thoracic Medicine, Haukeland University Hospital, the Institute of Aviation Medicine, and Department of Pulmonary Medicine, Oslo University Hospital Ullevål.

I am also grateful to all patients who have participated in the studies. You all enthusiastically volunteered to the projects and shared your air travel experiences. Your feedbacks after successful journeys have encouraged me to believe that this work was worth doing!

Not least, thanks to friends who have been there for me during my busy “PhD-life”. Among other things, looking forward to our mountain walking trips and participating in our reading circle, inspiring me to read more and luckily other literature than the medical has been a nice recreation.
Finally, special thanks go to my dear family for all their support and love. I want to thank my parents and my sister for their kindness and for always believing in me. And last, but not least, I am endless grateful to my dear husband Lars and our great sons, Erik and Ola for all their patience and support; understanding that this work was very important to me!

Oslo, December 2012

Anne Edvardsen
Summary

The reduced pressure in the aircraft cabin may cause significant hypoxaemia in patients with chronic lung disease. This thesis deals with issues related to chronic obstructive pulmonary disease (COPD) and air travel.

Four papers are included in this thesis. Paper I is a cross-sectional study on air travel habits and prevalence of in-flight symptoms in patients with COPD and a non-COPD reference group. In Paper II we constructed and validated a pre-flight evaluation algorithm for patients with COPD based on sea-level arterial oxygen saturation by pulse oximetry at rest and during exercise. Paper III is an observational study on associations between in-flight respiratory symptoms and simulated in-flight arterial oxygen pressure in patients with COPD. In Paper IV we performed a randomised cross-over study to 1) to study methods of pre-flight titration of supplemental oxygen, and 2) to study the effect of various oxygen equipment at altitude.

More than fifty per cent of the patients in a general COPD cohort and 86% of the subjects in a non-COPD group had travelled by air within a two year period. Symptoms during air travel were experienced more frequently in the COPD group than the non-COPD group; 25% of the patients with COPD versus 9% in the non-COPD group had hypoxia-related symptoms. Approximately one fifth of the COPD patients experienced in-flight respiratory symptoms, and occurrence of respiratory symptoms was strongly associated with pre-flight score on the Modified Medical Research Council Dyspnoea score (mMRC).

International guidelines recommend that severe in-flight hypoxaemia should be corrected with supplemental oxygen. Simple and reliable methods for predicting the need for supplemental oxygen during air travel have been requested. In Paper II, a simple pre-flight evaluation algorithm based on the easily available sea-level (SL) values of pulse oximetry at rest (SpO$_2$SL) and during a six-minute walk test (SpO$_2$ 6MWT) was constructed and validated. Categories for SpO$_2$SL were >95%, 92-95%, and <92%, the cut-off value for SpO$_2$ 6MWT was calculated to 84%. Arterial oxygen pressure (PaO$_2$ HAST) <6.6 kPa was the criterion for recommending supplemental oxygen. The new algorithm had a sensitivity of 100% and a specificity of 80% when tested prospectively on an independent sample of COPD patients. Patients with SpO$_2$SL >95% combined with SpO$_2$ 6MWT ≥84% may travel by air without further assessment. In-flight supplemental oxygen is recommended if SpO$_2$SL
92-95% combined with SpO$_2$ \textsubscript{6MWT} <84%, or if SpO$_2$ \textsubscript{SL} <92%. Otherwise, HAST should be performed.

In the third study including patients with COPD referred for HAST, we found a high prevalence of in-flight respiratory symptoms (46%) and three quarter of the patients desaturated during a HAST to values below the limit for recommending in-flight supplemental oxygen (6.6 kPa). We found no difference pre-flight hypoxia-simulated in-flight PaO$_2$ between patients with and without respiratory symptoms during air travel (6.3 (0.7) kPa vs. 6.3 (0.6 kPa), respectively, p=0.926). Patients equipped with supplemental oxygen reported less respiratory symptoms when flying with, than without, such treatment (17% and 48%, p=0.039). This part of the study was not, however, placebo controlled.

In the last paper we verified that HAST can be used to identify patients needing supplemental oxygen during air travel, but some precautions must be taken when titrating supplemental oxygen. Due to a reservoir effect within the facemask, the given oxygen dose may be underestimated. When comparing various equipment for oxygen delivery in a hypobaric chamber simulating aircraft cabin altitude (8000 ft), compressed gaseous oxygen with continuous flow or with an oxygen conserving device gave the same PaO$_2$, while a portable oxygen concentrator gave significantly lower PaO$_2$ values.

To summarize, we found that a considerable number of patients with COPD travel by air and COPD patients have a high frequency of in-flight respiratory symptoms. Despite severe in-flight hypoxaemia, there was no association between hypoxaemia and respiratory symptoms. Severe hypoxaemia may, however, worsening cardiovascular co-morbidity, and prescription of in-flight supplemental oxygen to patients with severe hypoxaemia may prevent exacerbations of co-existing medical conditions and post-flight medical problems. A practical and reliable method for pre-flight evaluation of the need for supplemental oxygen has been lacking. We constructed and validated a pre-flight algorithm based on sea-level non-invasive arterial oxygen saturation at rest and during exercise. In addition, when titrating supplemental oxygen during hypoxia-altitude simulation test (HAST), we showed that precautions must be taken regarding the reservoir effect of the mask and differences between the oxygen equipment. The results from this thesis will hopefully be of interest for health care professionals managing COPD patients who plan to travel by air.
Key words: Chronic obstructive pulmonary disease, COPD, hypobaric hypoxia, normobaric hypoxia, hypoxaemia, air travel, dyspnoea, respiratory symptoms, prevalence, supplemental oxygen, oxygen equipment, pulse oximetry.
Abbreviations

6MWT: Six-minute walk test
AsMA: Aerospace Medical Association
AMS: Acute Mountain Sickness
ATS: American Thoracic Society
BCCS: Bergen COPD Cohort Study
BMI: Body mass index
BTS: British Thoracic Society
CI: Confidence interval
CO: Carbon dioxide
COPD: Chronic obstructive pulmonary disease
CPET: Cardiopulmonary exercise test
CRDQ: Chronic Respiratory Disease Questionnaire
CV: Coefficient of variation
DH: Dynamic hyperinflation
DL,CO: Diffusing capacity of the lung for carbon monoxide
ECG: Electrocardiogram
EELV: End-expiratory lung volume
ELF: European Lung Foundation
ERS: European Respiratory Society
ECSC: European Coal and Steel Community
F: Fraction
FiO₂: Fraction inspired oxygen
FEV₁: Forced expiratory volume in one second
FVC: Forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
HAST: Hypoxia-altitude simulation test
HV: Hyperventilation
HVR: Hypoxic Ventilatory Response
IATA: The International Air Transport Association
LHL: Landsforeningen for hjerte- og lungsenyke (the Norwegian Association of Heart and Lung Patients)
L: Litre
LPM: Litre per minute
LTOT: Long-term oxygen treatment
MCID: Minimal clinical important difference
MRC: Medical Research Council
NC: Nasal cannula
OCD: Oxygen conserving device
ODC: Oxyhaemoglobin dissociation curve
P: Pressure
PaCO₂: Partial pressure of arterial carbon dioxide
PaO₂: Partial pressure of arterial oxygen
PAO₂: Partial pressure of alveolar oxygen
PFT: Pulmonary function test
POC: Portable oxygen concentrator
PVR: Pulmonary vascular resistance
RCT: Randomised controlled trial
ROC: Receiver operating characteristics
RV: Residual volume
SaO₂: Arterial oxygen saturation
SD: Standard deviation
SL: Sea-level
SpO₂: Arterial oxygen saturation by pulse oximetry
TLC: Total lung capacity
TV: Tidal volume
V: Volume
VA: Alveolar volume
VC: Vital Capacity
VE: Minute ventilation
Publications included


**Paper III** Edvardsen A, Akerø A, Christensen CC, Ryg M, Skjønsberg OH. COPD and air travel: does hypoxia-altitude simulation testing predict in-flight respiratory symptoms? Accepted for publication in European Respiratory Journal, 9 December 2012.

1 General introduction

1.1 Introduction

Air travel is a common form of transportation, and the number of airline passengers has been increasing over the last decades. In 2011 nearly 2.7 billion passengers travelled by air (1-3). Also, the average age of the passenger is rising, making it more likely that persons with chronic medical disorders, like chronic obstructive pulmonary disease (COPD), will be among the passengers (4, 5). For most passengers, commercial air travel poses no significant health risk. However, the low atmospheric pressure in the aircraft cabin may cause significant in-flight hypoxaemia in patients with lung disease (6-8). The hypoxaemia may exacerbate medical conditions and some patients develop respiratory distress (1, 4, 6, 7, 9, 10). The many physiological problems of COPD, including gas-exchange inefficiency, increased ventilatory requirements and mild to moderate pulmonary arterial hypertension, may all be affected by the hypoxic environment in the aircraft cabin (11). To ensure a safe travel for patients with lung disease, pre-flight evaluation has focused on predicting in-flight hypoxaemia, and, if necessary, supplying the patient with oxygen. In-flight hypoxaemia is, however, difficult to predict (6, 7).

Further research addressing air travel in patients with chronic lung disease has been asked for (6). The aim of the thesis was to assess air travel habits and prevalence of in-flight symptoms in patients with COPD and to elucidate whether these symptoms are related to the development of in-flight hypoxaemia. Also, we wanted to construct and validate a practical and simple tool for pre-flight evaluation. Finally, we wanted to study different methods for pre-flight titration of oxygen from oxygen and the ability of various oxygen equipment to correct altitude induced hypoxaemia.

1.2 Chronic obstructive pulmonary disease (COPD)

Definition

COPD is a preventable and treatable respiratory disease characterised by complex and diverse pathophysiological and clinical manifestations. Expiratory flow limitation is the pathophysiological hallmark, and the airflow limitation is progressive, not fully reversible, and associated with an abnormal inflammatory response by the lung to noxious particles or
gasses. Of the many exposures that may be encountered over a lifetime, only tobacco smoke and occupational dusts and chemicals are known to cause COPD on their own (12-14).

COPD has some significant extrapulmonary effects that may contribute to the severity of the disease (12, 15). The most frequent symptoms from the respiratory system are dyspnoea, cough, and sputum production. The extrapulmonary effects include exercise limitation, weight loss and skeletal muscle dysfunction. COPD patients have a high prevalence of co-morbidities; the most common being arterial hypertension, coronary heart disease, osteoporosis, respiratory infection, depression, diabetes, sleep disorders, anaemia, and lung cancer (12). To what extent the extrapulmonary effects are caused by confounding factors related to lifestyle or co-morbidity, or directly by the COPD itself, is still a matter for discussion (16).

The airflow limitation is caused by a combination of small airway disease, parenchymal destruction (emphysema), and, in many cases, increased airway responsiveness. These findings tend to worsen with age, but are also affected by exacerbations and other events marked by an acute worsening (12, 15).

Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and to slow its progression (12, 13). Treatment of stable COPD includes bronchodilators, glucocorticoids, nutrition, pulmonary rehabilitation, ventilator support, long-term oxygen therapy (LTOT), and for some patients ambulatory supplemental oxygen (AMBOX) during activity and air travel (12, 13).

**Epidemiology**

COPD is a major public health problem and is today the fourth leading cause of death in the western world (12, 13, 17). Both morbidity and mortality due to this disease are increasing (12, 18, 19). The prevalence of COPD worldwide varies, but is estimated to be approximately 10% in the adult population (20, 21). Many COPD patients, however, seem to be undiagnosed (12, 15). In Norway, it is estimated that about 8% of the adult population suffers from moderate to very severe COPD (20).
1.3 COPD: diagnosis and assessment

Lung function

The essential function of the respiration is the exchange of oxygen and carbon dioxide between atmosphere and blood (22). The most commonly used method to assess lung volumes and function is spirometry. Spirometry is crucial in the diagnosis and assessment of COPD. Forced expiratory volume in one second (FEV$_1$) is the volume an individual is able to expire during the first second of a forced expiration after a maximal inspiration to the total lung capacity (TLC) (23). Forced expiratory volume (FVC) is the total amount of expired air during this forced manoeuvre. The presence of a post bronchodilator FEV$_1$/FVC $< 0.70$ and FEV$_1 < 80\%$ of predicted is used as criterion for diagnosing COPD, and spirometry provides a useful tool for describing the severity of the disease. Spirometric values are used for classification of COPD into four stages of severity according to the Global Initiative for obstructive Lung Disease (GOLD) (12) (Table 1).

Table 1. The GOLD classification of COPD severity. FEV$_1$: forced expiratory volume in one second; based on post-bronchodilator FEV$_1$; respiratory failure: arterial partial pressure of oxygen (PaO$_2$) less than 8.0 kPa with or without arterial partial pressure of carbon dioxide (PaCO$_2$) greater than 6.7 kPa breathing air at sea-level. Adapted from (12).

<table>
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<tr>
<th>Spirometric classification of COPD$^1$</th>
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<td>Stage I: Mild</td>
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<tr>
<td>FEV$_1$/FVC $&lt; 0.70$</td>
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<td>FEV$_1 \geq$ 80$%$ predicted</td>
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<td>Stage II: Moderate</td>
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<td>FEV$_1$/FVC $&lt; 0.70$</td>
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<tr>
<td>50$% \leq$ FEV$_1 &lt; 80$ predicted</td>
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<td>Stage III: Severe</td>
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<tr>
<td>FEV$_1$/FVC $&lt; 0.70$</td>
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<tr>
<td>30$% \leq$ FEV$_1 &lt; 50$ predicted</td>
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<tr>
<td>Stage IV: Very Severe</td>
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<tr>
<td>FEV$_1$/FVC $&lt; 0.70$</td>
</tr>
<tr>
<td>FEV$_1 &lt; 30$ predicted or FEV$_1 &lt; 50$ predicted and chronic respiratory failure$^2$</td>
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Following maximal expiration, a certain volume of air will remain in the lungs. This is called the residual volume (RV) and is estimated by body plethysmography (24). Patients with COPD tend to have an increased RV due to gas trapping distal to the small airways (25). Measurement of the diffusing capacity of the lung for carbon dioxide (CO; DL$_{CO}$)
provides information on the capacity of the lung to exchange gas across the alveolar-capillary interface (26). All patients with suspected COPD should perform spirometry (including bronchodilator reversibility). In addition, measurement of TLC, RV and DL,CO is recommended in selected patients (14). To fully assess the diagnosis of COPD, medical history and physical examination should be performed. Pulmonary function tests (PFTs) are often presented as per cent of predicted reference values. These values are dependent on age, sex, height and ethnicity. In the usual course of COPD, FEV\textsubscript{1} declines below reference values while TLC and RV increase above reference values (27, 28).

**Control of ventilation**

Knowledge of what controls ventilation is essential for understanding respiratory problems in patients with COPD. There are three basic elements of the respiratory control system; sensors, central controllers and effectors (Figure 1).

![Figure 1. Basic elements of the respiratory control system. Adapted from (29).](image)

The sensors (chemoreceptors, lung- and other receptors) gather information and feed it to the central controller in the brain (pons, medulla or other parts of the brain) which coordinates the information and sends the impulses to the effectors (respiratory muscles) used in ventilation. In addition, higher centres in the central nervous system modulate the respiratory activity, for example when coordinating behaviours like speaking, singing, swallowing, and in affective states like anxiety and fear (22).
The respiratory system has an integrated response to changes in the partial pressure of arterial oxygen (PaO$_2$), in the partial pressure of arterial carbon dioxide (PaCO$_2$) and in pH. Arterial PaCO$_2$ is the most important stimulus to breathe in healthy humans, and the ventilatory response to PaCO$_2$ is mediated by central and peripheral chemoreceptors (4, 25, 29-32). Arterial chemoreceptors also mediate the ventilatory response to changes in arterial PaO$_2$ and pH. The ventilatory response to a decrease in PaO$_2$ is called the hypoxic ventilatory response (HVR). This response is nonlinear (31, 33) (Figure 2). The HVR is also depending on PaCO$_2$ and varies between individuals (22, 34) (Figure 2).

An increase in ventilation does not occur before PaO$_2$ drops below approximately 6.6 to 8 kPa (50-60 mmHg). At this point, a further decrease in PaO$_2$ may cause a marked increase in VE (25, 34, 35) (Figure 2). An increase in minute ventilation (VE) is primarily caused by an increase in tidal volume rather than an increase in respiratory rate (2, 9, 31).

**Dyspnoea**

Dyspnoea is defined as “a term used to characterise a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” (36-38). Dyspnoea often causes great distress in patients with COPD (36). It is caused by multiple physiological, psychological, social, and environmental interactions, and may induce...
secondary physiological and behavioural responses (38, 39). Several pathophysiological factors contribute to dyspnoea in patients with COPD. Increased mechanical loading of inspiratory muscles, increased mechanical restriction of the thorax, increased ventilatory demand relative to the capacity, gas exchange abnormalities, dynamic airway compression and cardiovascular factors may contribute alone, or in combination, to the sensation of dyspnoea (37, 39-41).

Blood gas abnormalities correlate poorly with dyspnoea in the individual patient (38, 40), and the effect of arterial hypoxaemia on dyspnoea is complex and poorly understood (40). It has been speculated that hypoxaemia may have a direct effect on dyspnoea since administration of supplemental oxygen attenuates the sensation of dyspnoea, even in the absence of changes in ventilation (33, 38, 42-44).

Dynamic hyperinflation (DH) in flow-limited COPD patients is an important contributor to dyspnoea (28, 36, 39, 45-48). DH is frequently present at rest in patients with moderate-to-severe airway obstruction, and DH increases further during exercise (48). DH increases the mechanical load on the inspiratory muscles.

There seems to be a relationship between the sensation of dyspnoea and the underlying mechanisms that cause the discomfort (38, 39, 49). Patients with COPD use “increased work” or “effort to breathe” and “air hunger” as verbal descriptors of breathlessness (37, 38, 50, 51).

How to measure dyspnoea

Both psychophysical methods and clinical scales are used to assess dyspnoea. The Borg CR10 scale is the most widely used scale to rate dyspnoea during exercise testing in patients with lung disease, but it is also used to measure breathlessness under other kinds of stress (37, 52-54) (Appendix A). Borg CR10 is a category-ratio scale, and consists of numbers from 0 (no dyspnoea at all) to the anchor point of 10 (extremely strong dyspnoea), which is the highest intensity of dyspnoea the subject has ever experienced. Each number is connected to verbal descriptors. A number higher than 10 may be employed if the dyspnoea is more intense than the subject has previously experienced. The Borg scale is not useful for obtaining longitudinal records on dyspnoea (55).

The Medical Research Council (MRC) scale is a one-dimensional clinical dyspnoea scale based on the magnitude of tasks that provokes dyspnoea (56). The scale has five statements about perceived breathlessness, originally ranging from 1 to 5, but in the modified version, mMRC, ranges from 0 to 4 (57) (Appendix B). The mMRC is included in
the BODE index (58); an index designed to predict the risk of death among patients with COPD.

Several multidimensional quality of life questionnaires, such as the Chronic Respiratory Disease Questionnaire (CRDQ) have dyspnoea as one of the components. The CRDQ cannot be used for comparison between individuals, because the parameters are individual-specific (59). There are no specific questionnaires developed for air travel outcomes in patients with respiratory disease.

**Exercise limitation and exercise tests**

Reduced functional capacity and the associated disability is a significant symptom in patients with COPD. There is a general agreement that the level of disability is reflected by measures of exercise tolerance. Exercise tests may be grouped in field tests, mostly used for descriptive and epidemiologic purposes, and diagnostic tests, like the cardiopulmonary exercise test (CPET). Laboratory based CPET is the gold standard by which cardio-respiratory fitness should be assessed (60, 61). As an alternative to laboratory testing field-based exercise tests were developed. These are mostly walk tests, such as the six-minute walk test (6MWT) and the incremental shuttle walk test (ISWT) (62). In some studies step tests or cycle ergometer tests have been employed (63, 64). Walking is a common and acceptable form of activity to most patients with chronic lung disease.

The 6MWT is the most commonly used field test, and it is an essential tool in the assessment profile of COPD patients (14, 65, 66). The walking distance is the primary measure (60, 65-67), and in addition, oxygen saturation measured with pulse oximetry and perception of dyspnoea may be recorded (68, 69). The number of stops, use of supplemental oxygen and use of walking aids are also recorded. The test should be performed with standardised instructions and should include a practice session (67, 70). There are several reference equations established for the 6MWT and patients with COPD (71). The minimal clinical important difference (MCID) for 6MWT in patients with COPD is considered to be an increase in walking distance of 25-26 meters (72, 73).

**Hypoxia and hypoxaemia**

Hypoxia is defined as the failure of oxygenation at tissue level (lack of oxygen for proper cell function) (22), whereas hypoxaemia is characterised by abnormally low partial pressure of oxygen (PO₂) in arterial blood (22). Normally, the PaO₂ is approximately 11-13 kPa, with
some reduction with increasing age (74, 75). Hypoxaemia is defined as a PaO$_2$ <8 kPa (60 mmHg), or SaO$_2$ <90% (76). Hypoxaemia may also be classified at three levels; mild (PaO$_2$ 8.1-10.0 kPa), moderate (PaO$_2$ 7.3-8.0 kPa), and severe (PaO$_2$ <7.3 kPa) (77). Patients with advanced COPD often experience an exercise induced decrease in PaO$_2$ (40, 60, 78).

In the blood, oxygen is transported physically dissolved (PaO$_2$) or chemically combined with haemoglobin (HbO$_2$). The fraction of haemoglobin saturated with oxygen is the SaO$_2$. Arterial blood gas measurement is the “gold standard test” to detect hypoxaemia (76). However, in some settings, a non-invasive and continuous estimate of the oxyhaemoglobin saturation of arterial blood is obtained from a pulse oximeter (SpO$_2$). The oxygen dissociation curve (ODC) relates SaO$_2$ and PaO$_2$, and is an important tool for understanding how the blood carries and releases oxygen. The ODC describes the haemoglobin’s affinity for oxygen (29, 79), and the curve shifts to the right or to the left according to changes in temperature, pH, CO$_2$, and 2,3 DPG concentration in the blood, thereby facilitating or inhibiting the release of oxygen to the tissues (Figure 3). PaO$_2$ may be considerably reduced before there is a notable reduction on SaO$_2$ (Figure 3).

![Figure 3. The Oxygen Dissociation Curve (ODC).](image-url)
Tissue hypoxia can be classified according to its causes into four main categories (76, 80, 81):

- **Hypoxaemic hypoxia**: a reduced PaO$_2$ (reasons for hypoxaemic hypoxia follows below). Hypoxaemic hypoxia is by far the most common cause of tissue hypoxia (80).
- **Stagnant or circulatory hypoxia**: inadequate blood flow due to, for example, reduced cardiac output (PaO$_2$ is normal).
- **Anemic hypoxia**: a reduced level of haemoglobin available for oxygen transport (PaO$_2$ is normal).
- **Histotoxic hypoxia**: inability of the tissue to use oxygen due to a toxic agent interference with the cell’s metabolism. This is commonly known as oxygen affinity hypoxia and is found in, for example, CO poisoning.

Hypoxaemic hypoxia may be caused by (22):

- **Diffusion limitation**: as a result of a decrease in alveolar surface area (emphysema) or a thickening of the alveolar membrane.
- **Ventilation-perfusion mismatch**.
- **Hypoventilation**: caused by defect respiratory control or major obstructions of the upper airways.
- **Shunt**: abnormality of the lungs or cardiovascular system causing blood to bypass ventilated alveoli.
- **High altitude**: due to decrease in barometric pressure (hypobaric hypoxia).
- **Breathing a hypoxic gas mixture** (normobaric hypoxia) (31).

The studies in this thesis all deal with hypoxaemic hypoxia. In patients with COPD, diffusion limitation, ventilation-perfusion mismatch, hypoventilation and shunting alone or in combination may lead to a decrease in PaO$_2$ (22). When the patient is exposed to low atmospheric pressure at altitude or during an actual or simulated flight, a decrease in PaO$_2$ is seen (6, 7, 9, 10, 82, 83). In Paper II, III and IV, the patients were exposed to normobaric hypoxia, and in Paper IV also to hypobaric hypoxia.
1.4 Air travel – general aspects

Commercial air travel

Commercial air travel is increasingly accessible. Each year approximately 2 to 2.7 billion people travel aboard commercial airlines, and the number is increasing (1-3, 6, 84). Thirty years ago, it was estimated that 5% of commercial airline passengers had a pre-existing medical condition (85). It is claimed that the average passenger is older today than 30 years ago, making morbidities more frequent (6, 7).

Cabin environment

The usual cruising altitude of a commercial aircraft is approximately 11 582 m (38 000 ft) (6, 7, 86), but due to conditions like flight distance, traffic, weather conditions and type of aircraft (9, 87), the cruising altitude may vary from 6500 to 13 500 m (22 000 to 44 000 ft) (2) (Figure 4) (Appendix C. Conversion chart from feet to meters). The reason for flying that high is both technical and economical; low resistance, lower air density, and less friction help the aircraft fly more efficiently, and clouds, birds and insects are avoided. The hypobaric effects of these altitudes are, however, intolerable to humans, and the aircraft cabin is therefore pressurised to a level which corresponds to a moderate altitude above sea-level. The cabin altitude\(^1\) of an aircraft planning to cruise at 12 000 m (40 000 ft) is programmed to rise gradually from the altitude of the airport of origin to around a maximum of 2438 m (8000 ft) and thereafter to be reduced gently during descent until it matches the ambient air pressure of the destination. To avoid adverse effects of hypobaric hypoxia, both for crew and passengers, international regulations do not allow the cabin altitude to exceed 2438 m except in emergencies (1, 5, 7, 87). The partial pressure of oxygen in the cabin is at this altitude reduced from sea-level 21.3 kPa to 15.8 kPa, this equates to breathing 15.1% oxygen at sea-level (81).

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\(^1\) It is customary in aerospace medical literature to describe cabin pressures in terms of equivalent altitude.

\(^2\) The bar-headed goose, and some cranes and swans have been seen flying up to 33 000 ft.
The cabin altitude during a specific flight depends on the type of aircraft and the cruising altitude (87-89). One study of in-flight cabin altitudes on commercial aircraft reported a variation in cruising cabin altitude ranging from 1529-2438 m (5000 to 8000 ft), with a median exposure of 1894 m (6214 ft) (88). During flights of shorter duration (1 h), the maximal cabin altitude of 2438 m is not reached (81). The trend in new aircrafts is to lower the cabin altitude even further.

The other main effect of the aircraft cabin environment is the pressure-volume relationship, which implies that the volume of gas varies inversely with the surrounding pressure at a constant temperature (Boyle’s law\(^3\)). At a cruising altitude of 2438 m, one litre of gas at sea-level will expand to 1.4 L, and this may be of medical relevance if the gas is trapped in a restricted space such as the pleural cavity (emphysematous bullae), the middle ear, sinuses, or in a body cavity after surgery (1, 8).

In a modern aircraft, the air in the cabin is a combination of approximately 50% "outside air" and 50% "filtered air". The outside air at the cruising altitude is very cold and dry (about –55°C and 10% relative humidity), resulting in a cabin humidity of 14-19% (90). This may cause discomfort such as drying of the mucous membranes and the skin. To avoid airborne infection, modern airliners use "high efficiency particulate arresting" (HEPA) filters, which trap >99% of all bacteria and clustered viruses. It is suggested that the

\(^2\) The bar-headed goose, and some cranes and swans have been seen flying up to 33 000 ft.

\(^3\) Boyle’s law: At constant temperature, the pressure (P) of a given gas is inversely proportional to its volume (V): \(P \cdot V = \text{constant}\) (31).
recirculated air does not increase transmission of, for example, upper respiratory tract infections (7).

During long-haul flights, dehydration and seated immobility probably increase the risk for venous thrombosis (7). The risk seems not to be associated with hypobaric hypoxia (91). Air travel induced venous thrombosis is rare but serious, and may potentially be fatal (6, 7, 91, 92).

Altitude and the normal physiological response to altitude exposure

To fully understand the effect of air travel and the in-flight environment on clinical pathophysiology, and especially the implications for patients with COPD, it is necessary to appreciate the nature of the atmosphere and the physical consequences of ascent to high altitude. The proportion of oxygen in the air remains about 20.9% with increasing altitude up to 90 000 to 100 000 m (2, 8, 31). With increasing altitude there is a subsequent fall in barometric pressure and the air density. The barometric pressure is what determines the human body's response to altitude. Air density determines the aerodynamic properties of the air (81). The barometric pressure at sea-level is about 101.3 kPa (760 mmHg), and at the summit of Mt. Everest (8848 m) the barometric pressure is reduced to one third (33.3 kPa) (25, 81, 93). The pressure in the aircraft cabin at cruising altitude is reduced to about ¾ of sea-level (75 kPa) (Figure 5).

Figure 5. Relationship between altitude, barometric pressure and inspired PO₂. Adapted from (93).
Oxygen transport from ambient air to peripheral tissue depends on alveolar ventilation, matching of pulmonary ventilation and blood perfusion, diffusion of oxygen through the alveolar-capillary membrane, oxygen binding to haemoglobin, blood circulation, and diffusion into peripheral tissue. The fall in barometric pressure (P_B) with increasing altitude affects the PO_2 in inspired gas, as the partial pressure of oxygen falls (2, 8). The partial pressure of oxygen in the alveoli (P_AO_2) depends on the inspired partial pressure of oxygen. When air is inhaled into the upper airways, it is warmed and moistened, and the water vapour pressure is then 6.3 kPa (P_H2O) (47 mmHg). The partial pressure of oxygen available in the alveoli, P_AO_2 (kPa), can be calculated from the alveolar gas equation (simplified version)^4 (22, 94):

\[ P_{A\text{O}_2} = (P_B - P_{H2O}) \times F_iO_2 - P_{A\text{CO}_2} \times 1.2 \]

For example, when a P_ACO_2 of 5 kPa is used in the equation, the alveolar oxygen pressure (P_AO_2) will at sea level be 14 kPa, dropping to 8.5 kPa at 2438 m.

A number of physiological responses by different systems take place when the body is exposed to altitude and thereby hypoxia (2, 31). The response of the body to hypoxia depends crucially on the altitude, the duration of the altitude exposure, the rate of ascent, and the individual response to the altitude hypoxia (22, 31). Of all the changes taking place, those that increase ventilation are probably the most important (31). The adaptation to hypoxia includes acute responses (minutes to hours), acclimatization (hours to days/weeks) and adaptations (life long/generations) (Figure 6). This thesis will only deal with the acute responses.

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^4 P_ACO_2: alveolar PCO_2; FiO_2: Fraction inspired O_2; R: respiratory exchange ratio.
\[ P_{A\text{O}_2} = (P_B - P_{H2O}) \times F_iO_2 - P_{A\text{CO}_2} \times (F_iO_2 + (1-F_iO_2)/R). \] When R is 0.8: \( (F_iO_2 + (1-F_iO_2)/R) = 1.2 \)
Hyperventilation (HV) is the first compensatory response to acute hypoxia (2, 11, 31). The minute ventilation (VE) increases, primarily as a result of increased tidal volumes, rather than increased breathing frequency (2, 4, 9, 31, 32). As a result of the HV, both alveolar and arterial PO$_2$ increase. As a consequence, PaCO$_2$ decreases, limiting some of the ventilatory response (2, 31). Also, diffusion of oxygen through the alveolar-capillary membrane is less effective at altitude, because of a reduction in the pressure gradient between alveoli and capillaries and a reduction in transit time. The diffusion limitation is exacerbated by exercise (2, 31). Cardiac output increases with hypoxia, mainly due to increased heart rate, with a minimal change in stroke volume (2, 32, 95). Acute hypoxia also induces increased pulmonary vascular resistance (PVR) with a subsequent rise in pulmonary arterial pressure (2, 31). This reversible response varies between individuals (11, 31).

**Physiological responses to air travel hypoxia**

The moderate altitude exposure of air travel is usually well tolerated in healthy individuals (1, 9, 10, 96). The in-flight PaO$_2$ depends on the cabin pressure, the pre-flight PaO$_2$, age, and the individual HVR (4, 6, 9). At a cabin altitude of 2438 m (8000 ft), the PaO$_2$ in healthy individuals decreases from approximately 12.7 kPa (95 mmHg) at sea-level to 8.7
kPa (65 mmHg) (1, 4, 5, 9). The reduction in PaO₂ is on the flat part of the ODC (Figure 3), resulting in a decrease in arterial oxygen saturation (SO₂) of only 3-4% (1, 97) (Figure 7).

Figure 7. Response on arterial oxygen saturation (SpO₂) on a 3 hour commercial flight for a healthy man. NHIT: Normobaric hypoxic inhalation test. Adapted from (35).

Complaints (fatigue, headache, light-headedness and nausea) associated with acute mountain sickness (AMS) occurred in approximately 7% of adult volunteers in a hypobaric chamber study simulating up to 2438 m (8000 ft) exposure (97), and the frequency of reported symptoms was higher with increasing altitude. Differences in symptoms reported became more apparent after 3-9 h altitude exposure. Persons older than 60 years of age reported fewer symptoms than younger persons, and men were less likely than women, to report discomfort.

**Physiological responses to air travel hypoxia in patients with COPD**

Patients with respiratory disease may experience severe hypoxaemia during air travel (6, 7, 9, 98). The pressure drop during air travel will cause a decline in PaO₂, and consequently a reduced SaO₂. For healthy subjects this reduction will be minor. For subjects with hypoxaemia at sea level, however, the PaO₂ may move on to the steep part of the oxygen dissociation curve, thereby causing a more severe SaO₂ decline (Figure 8). At maximum cabin altitude, 2438 m, an average reduction in PaO₂ by approximately 3 kPa, will result in a larger percentage desaturation than in healthy individuals (1, 9, 10, 82) (Figure 8). Even
light physical exertion during the flight may increase the risk of an exacerbation of symptoms and more pronounced hypoxaemia (14, 82, 83).

Patients with COPD have a reduced ability to increase their ventilation in response to hypobaric hypoxia (2, 4). This is seen by their minimal changes in PaCO\(_2\) during air travel (96, 99, 100). Patients with severe COPD may also have poorly ventilated areas of the lung, or pre-existing pulmonary arterial hypertension, both of which could contribute to a decline in PaO\(_2\) (4, 11, 101). An additional, hypoxia-induced increase in PVR may cause an in-flight decrease in cardiac output and right heart failure (4, 11, 32). COPD patients may also develop respiratory symptoms (14, 99).

The link between hypoxia and clinical risk remains poorly understood (102). Data on in-flight symptoms, especially respiratory symptoms in patients with COPD, are limited. Two studies report symptoms in 18% of patients with respiratory disease, but both studies lack comparison with healthy subjects (99, 103). Studies on the relationship between in-flight hypoxaemia and respiratory symptoms during air travel have been lacking.

**Air travel habits in patients with COPD**

To what extent do lung patients travel by air? The frequency and outcome of commercial air travel in patients with COPD have not been extensively studied. The UK Flight Outcome study evaluated 616 patients with lung disease planning to travel by air, 243 of them with
COPD (103). Eleven per cent of the patients did not fly, either due to a worsening of the disease, difficulties arranging supplemental oxygen or due to advice from the physician. Another study of 100 patients with COPD showed that 44% had travelled by air within the last 28 months, with median flight duration of 3 h (99). However, these studies lack control groups. Paper I in the current thesis elucidates air travel habits in patients with COPD compared to a population without COPD.

**In-flight medical events**

Overall, air travel is safe, even for passengers with medical conditions. According to a recent estimate, medical incidents occur at a rate of 12 per million passengers, with only a small number of the incidents being serious (104), and death during air travel is rare (105). A survey of European airlines identified 10 000 in-flight medical emergencies during a 5-year period (106, 107). Due to the increasing age of passengers (7), however, the rate of events is probably increasing (108). Thirty years ago, 5% of commercial airline passengers were thought to have a pre-existing medical condition (85). The number is probably increasing. In-flight fatalities are fortunately rare (5, 9, 108).

Within the international airline community, there is no common agreement of reporting medical events, and no central registry for documenting in-flight medical emergencies has been established (6, 7, 106, 109, 110). Information on the outcome of medical emergencies that occur during or after air travel is lacking (107, 111). Calculation of the exact incidence of in-flight medical events has therefore been difficult to perform. Cardiac, neurologic, and respiratory problems make up the most serious events and account for the majority of unscheduled landings (5, 112). Respiratory related incidents are the third most common in-flight medical problem, representing 16-18% of the events (109). Most commercial airlines use ground-to-air medical support to provide medical advice and support during in-flight medical events (113). Paper I and III elucidate in-flight medical symptoms.

**In-flight emergency oxygen and medical equipment**

The aircraft emergency oxygen system, with drop-down masks, is intended for use when the cabin pressurisation system fails and the partial pressure of oxygen in the cabin atmosphere drops below a safe level. This will protect the passengers from dangerous hypoxia until the pilots have descended to a lower altitude (9). The emergency system consists of oxygen
masks stored in compartments above each passenger seat, and a central oxygen generator. All commercial aircrafts are also obliged to hold a minimum of oxygen equipment for medical emergency use only (9, 114). The oxygen bottles provide a limited supply, since they are low pressurised (125 bar) and have continuous flow (2 or 4 litre per minute (LPM)) (9).

All commercial aircrafts are obliged to carry emergency medical kits. These kits vary from one airline company to another (1, 5, 107), and emergency medical equipment may be sparse (110). Most commercial aircrafts carry an automated external defibrillator (1). A pulse oximeter is not included in the equipment.

1.5 Pre-flight assessment for patients with COPD

If there is doubt about the patients’ fitness to fly and if there are co-morbidities affecting fitness, pre-flight assessment is advised. The aim of the pre-flight assessment is to identify passengers likely to develop significant hypoxaemia and respiratory symptoms during air travel, thus preventing in-flight medical events (6-8).

The following patients should be assessed:

- Previous air travel intolerance with significant respiratory symptoms (dyspnoea, chest pain, confusion or syncope) (6, 7, 9, 10, 14).
- Severe COPD (FEV₁ <30% predicted) (6, 7, 9, 10, 18).
- Known or suspected hypoxaemia (10).
- Known or suspected hypercapnia (10, 14, 18).
- Bullous lung disease (6, 7).
- Co-morbidity worsened by hypoxaemia (cerebrovascular disease, cardiac disease or pulmonary hypertension) (6, 7, 9, 10, 14).
- Less than 6 weeks since hospital discharge for acute respiratory illness (6, 7, 9, 10, 14).
- Recent pneumothorax (6, 7).
- Pre-existing requirement for oxygen, CPAP or ventilator support (6, 7).

It is recommended that patients with the conditions listed above should be assessed with medical history and examination with particular emphasis on cardiorespiratory disease,
dyspnoea, and previous flight experience (6). Spirometric test and measurement of SpO2 should be performed (6). Blood gas measurement is preferred if hypercapnia is known or suspected (6, 10).

Acceptable PaO2 during air travel

The American Thoracic Society (ATS), the European Respiratory Society (ERS), the British Thoracic Society (BTS), GOLD, the Aerospace Medical Association (AsMA), and the Canadian Thoracic Society have published guidelines or statements where supplemental oxygen during air travel is recommended for patients where an in-flight decrease in PaO2 below 6.6 (6.7) kPa (50 mmHg) is anticipated (6-10, 12, 13, 115). The reason why the limit is set to either 6.6 or 6.7 kPa is because of different round-off rules when converting mmHg to kPa (1 kPa = 7.5 mmHg). The AsMA has chosen a somewhat higher cut-off, with oxygen recommendation when PaO2 <7.3 kPa (9). Both levels are arbitrarily chosen at a level most authors consider reasonable for in-flight hypoxaemia (6, 8, 96). A pre-flight evaluation should assess whether in-flight supplemental oxygen is needed, and establish the necessary oxygen dose. Several studies, including studies from our group, have shown that single resting sea-level characteristics, such as FEV1, PaO2, DL,CO and SpO2 do not reliably predict in-flight hypoxaemia and complications of air travel in passengers with COPD (6, 7, 82, 116, 117). For patients with anaemia (haemoglobin < 8.5 g/dL) special considerations should be made due to their decreased oxygen transport capacity (9).

When is it necessary to prescribe in-flight supplemental oxygen? It should certainly be prescribed to patients with COPD who already receive continuous or intermittent oxygen at home (6, 7, 118). For other patients with COPD, further pre-flight assessment may be necessary. The following methods for pre-flight fitness-to-fly evaluation and assessment of need for in-flight PaO2 have, in addition to sea-level FEV1, PaO2, DL,CO and SpO2, been suggested: walk tests, prediction equations and algorithms, and hypoxic challenge tests (1, 6, 8-10). It should be noted, however, that none of the pre-flight assessment methods simulate a real air travel experience accurately, including for example airport stress, carrying luggage etc. (6, 10)
Pre-flight methods to assess in-flight PaO$_2$

Walk and exercise tests

The ability to increase minute ventilation and cardiac output in response to an external load is a good test of cardiorespiratory reserve (6). Thus, walking on the ground is an approach to simulate the stress hypoxaemic patients will experience at rest during air travel. The ability to walk 50 m without severe distress has been stated to be a practical and simple fit-to-fly test (6, 9, 114). This test is, however, often the only subject of enquiry and not verified with a real walk. If performed, the test does not take into account possible hypoxaemia at rest or during exercise. The test has not been standardised or validated (4, 6).

Standardised walk tests like the 6MWT, or the endurance shuttle walk test (ESWT) (67, 119) are also proposed for pre-flight assessment (6). Failure to complete the task (whether distance or time), or moderate to severe respiratory distress, point towards a possible need for in-flight supplemental oxygen (6).

Pre-flight aerobic capacity and exercise desaturation has been shown to be well correlated with in-flight hypoxaemia (82, 83, 118, 120). Also, desaturation during a 6MWT is associated with in-flight PaO$_2$ (121, 122). Simple non-invasive exercise testing has been proposed to suffice for the prediction of good tolerance to in-flight hypoxaemia in COPD patients (118).

Predictive equations and algorithms

Several predictive regression equations for estimating in-flight PaO$_2$ have been published (6, 7, 9, 10, 96, 98, 123-125). The equations are based on sea-level measurements of PaO$_2$ and FEV$_1$, with HC exposure or HAST as the reference method. It has been shown that predictive equations overestimate the need for in-flight oxygen considerably (126) and are inappropriate in the individual evaluation (82, 102). Use of predictive equations is, however, still recommended in some guidelines (6, 7, 13).

In the BTS guidelines from 2002 (6), an algorithm based on sea-level SpO$_2$ is presented. According to this algorithm, patients with sea-level SpO$_2$ >95% or SpO$_2$ 92-95% without additional risk factors$^5$ can fly without further assessment. Patients with sea-level SpO$_2$ <92% should use in-flight supplemental oxygen, and patients with a SpO$_2$ 92-95% with additional risk factors should perform HAST. This algorithm was tested on an

$^5$ Hypercapnia, FEV$_1$ <50% predicted, lung cancer, restrictive lung disease, kyphoscoliosis, ventilatory support, cerebrovascular or cardiac disease, within 6 weeks after exacerbation.
independent COPD sample by Akerø et al, and was found to be inadequate with regard to discriminating between patients who fulfil the indications for in-flight supplemental oxygen, and patients who can travel without such treatment (117).

**Hypobaric hypoxic exposure; hypobaric chamber**

The “gold standard” for measuring PaO$_2$ during a simulated flight is to expose the patient for hypobaric hypoxia in a hypobaric chamber (HC) at 2438 m (8000 ft) (2, 6, 7, 127) (Figure 9). The HC is depressurised to an environment similar to a certain altitude above sea-level, and the persons breathe the ambient chamber air. The HC is operated by a chamber technician and it is compulsory to have at least one additional person inside the HC who is responsible for security. This method is expensive, and HCs are not widely available. In Norway, HCs are located at the Institute of Aviation Medicine at the University of Oslo, and at the Norwegian School of Sport Science (NIH), Oslo. A HC designed as an apartment is located in Trysil. HC exposure is used in Paper IV.

Other possibilities for hypobaric hypoxic exposure are the aircraft cabin itself, or altitude exposure in the mountains (Figure 9).

![Figure 9. Hypobaric hypoxia exposure: aircraft cabin, hypobaric chamber and altitude (Galdhøpiggen, 2469 m above sea-level). Private photos with permission.](image)

**Hypoxia-altitude simulation test (HAST)**

HAST is a normobaric hypoxic challenge test used to assess whether a patient requires in-flight oxygen (7, 96, 127, 128). HAST is considered as the best test in a clinical setting for assessment of need for in-flight supplemental oxygen, and the test is increasingly being
performed for pre-flight evaluation (111, 129). It should be noted that HAST is not a general “fitness-to-fly” test; other medical conditions like bullae, require HC testing.

During HAST the patient breathes a hypoxic gas mixture (15.1% O₂, rest N₂, in vivo quality) to simulate the maximum cruising cabin altitude of 2438 m (8000 ft) (Figure 10). The HAST has been shown to provoke similar degree of hypoxaemia as in HC (123, 130) and during real flight (111). The method was first described by Gong H Jr. et al in 1984 (96). The test was originally performed by having the patient breathe the hypoxic gas from a reservoir bag via a non-rebreathing valve and a mouthpiece. It may also be performed using a tight fitting face mask (6, 7, 127, 129), a Venturi mask with nitrogen as the driving gas to lower the oxygen content (7, 131, 132), or by using a body plethysmograph and lowering the ambient oxygen content to 15.1% (6, 115). The HAST only simulates the hypoxic exposure at 8000 ft; other cabin altitudes, flight duration and hypobaric conditions are not reproduced.

Figure 10. Hypoxia-altitude simulation test (HAST). Private photo with permission.
BTS has suggested the following limits for recommendation of in-flight supplemental oxygen after HAST (Table 2) (6). HAST is used in Paper II, III and IV.

Table 2. Results from hypoxic challenge test. Adapted from (6).

<table>
<thead>
<tr>
<th>Hypoxic challenge results</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{PaO}_2 &gt; 7.4 \text{ kPa (}&gt; 55 \text{ mmHg}) )</td>
<td>In-flight oxygen not required</td>
</tr>
<tr>
<td>( \text{PaO}_2: 6.6 - 7.4 \text{ kPa (50-55 mmHg)} )</td>
<td>Borderline; a walk test may be helpful</td>
</tr>
<tr>
<td>( \text{PaO}_2: &lt; 6.6 \text{ kPa (&lt; 50 mmHg)} )</td>
<td>In-flight oxygen (2LPM)</td>
</tr>
</tbody>
</table>

**Planned use of supplemental oxygen during air travel**

*Recommended dose of in-flight supplemental oxygen*

When the pre-flight evaluation with any of the possible methods has estimated a \( \text{PaO}_2 \) during air travel less than 6.6 (6.7) kPa, supplemental oxygen is recommended to preserve adequate oxygenation to the tissues and prevent hypoxic complications (6, 7, 9, 10, 13, 32, 114). Supplemental oxygen may reverse the hyperventilatory response to hypoxia (33, 133), and supplemental oxygen may to some extent reverse symptoms during simulated air travel (96). The given oxygen dose should be large enough to bring the arterial oxygen saturation back to adequate sea-level values, or at least to a \( \text{SpO}_2 > 90\% \) (13, 27). The in-flight oxygen should be used both at rest and when walking along the aisle (6), and the oxygen should preferably be given through a nasal cannula (7, 134). Studies on optimal in-flight oxygen doses are lacking. It is, however, suggested that patients already on LTOT should increase their personal resting sea-level oxygen dose by 1-2 LPM (6, 9, 27, 96, 114, 134). Usually this means that a sea-level dose exceeding 4 LPM is a contraindication to air travel (due to limitations of the oxygen equipment) (7). Patients not on LTOT are recommended to use in-flight oxygen at a dose of 2-3 LPM (4, 6, 7, 14, 135). The personal optimal dose of oxygen may be titrated during HAST (96, 102, 115, 133, 135). In Paper IV we show that such titration is encumbered with pitfalls since there may be an accumulation of oxygen under the mask, underestimating the true dose of oxygen needed (136). Evaluation of methods for oxygen titration with allowed in-flight oxygen equipment is presented in Paper IV. For patients with hypercapnia, to avoid a further increase in \( \text{PaCO}_2 \), the same reservations should be taken as to titrating oxygen at sea-level (76).
Planning the use of supplemental oxygen during air travel

Travelling with supplemental oxygen requires good planning in advance (4, 6, 7, 10), and the patient is responsible for most of this planning. The policies regarding planned use of in-flight oxygen vary widely among commercial airlines (32, 137-140), but common for all of them is that liquid oxygen aboard is prohibited (6, 7, 114). Oxygen for scheduled use must be clarified with the airline before travelling (6, 7, 9, 114, 140), and the clarification should preferably be made 4 to 6 weeks in advance. Most airlines have a minimum limit of 48 hours to arrange for oxygen use.

The patient should:

- get a statement from the physician confirming the need of oxygen and the dose required (1, 6, 7), since the airline and/or the security control often require such documentation. Some airlines also require a standardised Medical Information Form (MEDIF) ([www.iata.org](http://www.iata.org)) (7, 137).
- get information on the actual airline's policy regarding in-flight oxygen. Information is available on the airlines' websites. The European Lung Foundation (ELF) website has an informative “Air Travel Database” ([www.european-lung-foundation.org](http://www.european-lung-foundation.org)) (140). The Air Travel Database is not translated to Norwegian.

The options for planned use in-flight supplemental oxygen are:

1) The patient can bring his or her own oxygen equipment or rent the oxygen equipment from a distributor, or
2) The patient must rent oxygen equipment from the airline. Oxygen is usually delivered at 2 and 4 LPM, and patients requiring other flow rates must make arrangements in advance which is in agreement with their individual needs. Some airlines only provide facemasks for the oxygen delivery, and patients should therefore bring their own nasal cannula.
3) The airline does not allow the patient to bring his or her own oxygen equipment, neither does the airline rent out such equipment.

The costs associated with oxygen supplementation may be a challenge for the patient. The costs vary between airlines and distributors, and so do national policies (9, 84, 137, 138).

The patient must always plan on having sufficient oxygen or battery power for the duration of the flight. In addition, patients on LTOT must plan for the need of supplemental
oxygen at the airport, including a conservative estimate for extra oxygen in the event of unanticipated delay (7). There are no oxygen delivery services at airports. Due to the airlines' different policies on in-flight oxygen use, direct flights are preferable (10, 114, 141).

If the airline accepts that the passenger brings his or her own supplemental oxygen, the following equipment is allowed:

**Portable oxygen concentrator (POC)**

POC (a small version of stationary oxygen concentrator) produces oxygen-enriched gas from the ambient air by sieving the nitrogen out and concentrating the oxygen up to approximately 94% (142). The POCs operates with an oxygen conserving device (OCD) which delivers a pulsed dose of oxygen at the beginning of each inspiration as a response to the inspiration-induced negative pressure. Because oxygen delivered at the beginning of inhalation reaches the ventilated alveoli, small oxygen pulses are very effective (14). The amount of oxygen delivered (in mL/breath) depends on the pre-set dose. The pre-set doses on the different POCs range from pulse setting 1-6 (corresponding to approximately 6 LPM continuous oxygen). The POCs are relatively lightweight (about 3-4 kg) and operate with a chargeable battery. In addition, some aircrafts have electrical power on board which can be used to power the POC. However, availability varies with the airline, type of aircraft, and class of service. How long the oxygen delivery from a POC will last depends on battery capacity and varies between different models. An estimate of the battery capacity of POCs is that a POC with OCD and pulse setting 2 lasts for 4 hours. The patient should, if necessary, bring additional batteries.

**Compressed gaseous oxygen with oxygen conserving device (ODC)**

Portable composite cylinders with compressed gas are about 1 L in size and pressurised to 200 bar, corresponding to 200 L gaseous oxygen. The cylinders have an OCD (see POC) as an integral part of the regulator. Most OCDs are pneumatic and require no battery. With the OCD, the oxygen will last longer than with continuous flow. For example, cylinder with pulse setting 2 lasts approximately 8 hours.
Compressed gaseous oxygen with continuous flow

Compressed gaseous oxygen with continuous flow is not an ideal alternative during planned use of supplemental oxygen during air travel since a 1 L cylinder with 200 bar pressure will last only 1.5 hours at a flow of 2 LPM.

How do we arrange for in-flight oxygen in Norway?

At present there is no national guideline or recommendation for managing passengers with respiratory disease planning to travel by air. Extended pre-flight evaluation with HAST is available in five to six hospitals or out-patient clinics in Norway.

- For domestic air travel: when the patient needs to rent oxygen equipment, it is the local “Behandlingshjelpemiddelsentral” and “Helseforetak” (Health Trust's) responsibility to assist the patient. The patient may use his or her personal POC or cylinder with compressed oxygen or rent oxygen from the airline.

- When travelling abroad: patients who need in-flight supplemental oxygen, may have their expenses covered by the Norwegian Health Economics Administration (Folktetrygdloven §5-24, HELFO, www.helfo.no). The patient should make the agreement with HELFO before the trip.

General advice for lung patients travelling by air

The patients should receive optimal medical treatment before air travel, and their medication should be placed in the carry-on luggage, together with a list of necessary medications and documentation of the oxygen equipment (7). It is important that the patients have a travel insurance policy that covers not only acute medical care, but also exacerbations of their chronic disease. To avoid exhaustion, it is recommended that the patients order ground transport assistance at the airport in advance (7, 9).

It is advised to book an aisle seat, and if possible, near the toilets. Walking along the aisle should be minimised, and when walking, the oxygen equipment should be used (10, 114, 143). The patients should be advised to exercise their legs while seated, to use flight compression hosiery, and to keep well hydrated (6, 7, 9). It is recommended to avoid or minimise use of alcohol and sedatives (7, 10).
2. Study aims

The purpose of the thesis was to assess air travel habits and prevalence of in-flight symptoms in patients with COPD, to evaluate the relationship between sea-level characteristics and simulated in-flight PaO₂, to construct and evaluate methods for pre-flight assessment of patients with COPD, and to evaluate methods for titration of in-flight supplemental oxygen.

Specifically, the research questions were:

Paper I
- What are the air travel habits of patients with COPD and a general non-COPD group?
- What is the prevalence of symptoms during air travel in patients with COPD and a group of subjects without COPD?
- Are in-flight symptoms in COPD patients related to sea-level spirometric values, arterial blood gas levels, exercise dyspnoea, walking distance or exercise desaturation?

Paper II
- Can resting and exercise SpO₂ be used to construct a pre-flight evaluation algorithm for patients with COPD?
- Is the new pre-flight evaluation algorithm valid in a prospectively recruited, independent sample of COPD patients?
- May arterial oxygen saturation measured by pulse oximetry be used as a substitute for arterial blood gas measurement during HAST?

Paper III
- Are in-flight respiratory symptoms related to the degree of hypoxaemia obtained during hypoxia-altitude simulation testing?
Paper IV

- Can HAST, performed with a tight fitting mask, be used to establish the optimal dose of oxygen needed during air travel in patients with COPD?
- What is the effect of oxygen supplementation on PaO₂ during a simulated flight, when oxygen is given from three different oxygen delivery systems?
3. Material and methods

The four studies include COPD patients in a stable phase of their disease recruited from three different sites; Haukeland University Hospital, Glittreklinikken and Oslo University Hospital, Ullevål, Norway. Paper I also includes a non-COPD reference group.

3.1 Subjects

Table 3. Patient characteristics

<table>
<thead>
<tr>
<th>Paper</th>
<th>Diagnosis</th>
<th>Gender, M/F</th>
<th>Age, years</th>
<th>FEV\textsubscript{1}, %pred</th>
<th>PaO\textsubscript{2}, kPa</th>
<th>PaCO\textsubscript{2}, kPa</th>
<th>SpO\textsubscript{2}, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>COPD</td>
<td>237/154</td>
<td>63 (7)</td>
<td>49 (14)</td>
<td>9.3 (1.1)</td>
<td>5.3 (0.6)</td>
<td>95 (1)</td>
</tr>
<tr>
<td>I</td>
<td>Reference group</td>
<td>94/90</td>
<td>54 (8)</td>
<td>103 (9)</td>
<td>10.8 (1.1)</td>
<td>5.2 (0.4)</td>
<td>98 (3)</td>
</tr>
<tr>
<td>II</td>
<td>COPD</td>
<td>42/58</td>
<td>65 (8)</td>
<td>41 (13)</td>
<td>9.0 (1.1)</td>
<td>5.0 (0.6)</td>
<td>93 (3)</td>
</tr>
<tr>
<td>II</td>
<td>COPD</td>
<td>25/25</td>
<td>64 (8)</td>
<td>40 (15)</td>
<td>9.0 (1.1)</td>
<td>5.1 (0.6)</td>
<td>93 (3)</td>
</tr>
<tr>
<td>III</td>
<td>COPD</td>
<td>34/48</td>
<td>65 (7)</td>
<td>41 (13)</td>
<td>9.0 (1.1)</td>
<td>5.1 (0.6)</td>
<td>93 (3)</td>
</tr>
<tr>
<td>IV</td>
<td>COPD</td>
<td>11/5</td>
<td>62 (7)</td>
<td>37 (11)</td>
<td>9.3 (1.1)</td>
<td>4.6 (0.5)</td>
<td>94 (2)</td>
</tr>
</tbody>
</table>

Data are presented as n or mean (SD). M: male; F: female; FEV\textsubscript{1}, %pred: forced expiratory volume in one second in per cent of predicted; PaO\textsubscript{2} and PaCO\textsubscript{2}: arterial partial pressure of oxygen and carbon dioxide, respectively; SpO\textsubscript{2}: arterial oxygen saturation by pulse oximetry.

Paper I

The patients were participants in the Bergen COPD Cohort Study (BCCS). The BCCS recruited patients from outpatient clinics at several hospitals in Western Norway, and from private specialist practices in Bergen, Norway (144). The COPD sample included patients in GOLD stage II-IV (12). The reference group was recruited among participants in a previous population survey from the same area, the Hordaland County Cohort Study, and the subjects all had a smoking history without having developed of COPD (145). Data were collected from 2006 to 2008.
Paper II and III
From October 2009 to December 2010, 139 patients with moderate to severe COPD continuously referred to HAST at Glittreklinikken, Norway, were consecutively evaluated for inclusion in the study. Of these, 39 patients either did not meet the inclusion criteria or were excluded, resulting in a study sample of 100 patients with COPD (Paper II). In addition, 50 COPD patients were prospectively included for validation of the new algorithm. The inclusion and exclusion criteria were the same as in the initial sample.

In Paper III, 82 of the 100 patients from Paper II who had performed a HAST and had travelled by air without supplemental oxygen within the last two years before referral to HAST were included.

Paper IV
In paper IV, patients were recruited from two outpatient clinics (Glittreklinikken and Oslo University Hospital, Ullevål). Sixteen patients with moderate to very severe COPD (GOLD stage II-IV) (12) who planned to travel by air, and who had previously been evaluated by HAST with a PaO$_2$$_{HAST}$ < 6.7 kPa, indicating a need for in-flight supplemental oxygen, were included. The study was performed in 2008.

3.2 Design

Table 4. Design and methods of the four included papers.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Method</th>
<th>N</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cross-sectional</td>
<td>Questionnaire</td>
<td>391/184</td>
<td>Reference group</td>
</tr>
<tr>
<td>II</td>
<td>Cross-sectional</td>
<td>HAST</td>
<td>100/50</td>
<td>Validation group</td>
</tr>
<tr>
<td>III</td>
<td>Observational</td>
<td>HAST/Questionnaire</td>
<td>82</td>
<td>No</td>
</tr>
<tr>
<td>IV</td>
<td>Randomised cross-over</td>
<td>HC/HAST</td>
<td>16</td>
<td>Cross-over</td>
</tr>
</tbody>
</table>

HAST: Hypoxia-altitude simulation test; HC: Hypobaric chamber

In Paper I, we performed a cross-sectional study of patients with COPD and a non-COPD reference group. Baseline data on lung function, arterial blood gases, pulse oximetry, 6MWT, and mMRC dyspnoea score were collected at the BCCS Visit 1 and 4. At the one-
year follow-up from Visit 1, all participants answered an air travel questionnaire (Appendix D) elucidating air travel habits and symptoms experienced during air travel within the previous two years.

In Paper II, a cross-sectional study based on sea-level pulse oximetry values at rest and during exercise was performed for the construction of a new pre-flight evaluation algorithm for patients with COPD. Patients underwent HAST and 6MWT. The constructed algorithm was validated on a new, prospectively recruited group of patients with COPD.

Paper III is an observational study including patients with COPD also included in Paper II, who, in addition, had travelled by air without supplemental oxygen within the last two years. The patients performed a HAST and answered an air travel questionnaire twice, elucidating in-flight respiratory symptoms, use of unscheduled supplemental oxygen and the need of unexpected post-flight medical care. The questionnaire was answered before the HAST (first questionnaire) and 6-12 months after the HAST (second questionnaire).

In Paper IV, we performed a randomised cross-over study to 1) to compare titration of supplemental oxygen during HC exposure at 2438 m altitude and during HAST, and 2) to study the effect on PaO$_2$ of various oxygen equipment at 2438 m altitude. The three different principles of oxygen equipment were: a) compressed gaseous oxygen with continuous flow, b) compressed gaseous oxygen with an OCD, and c) a POC. Patients were tested in random order with the three oxygen devices both during HC and HAST exposure. Lung function, medical history and clinical examination were assessed 1-2 weeks before the actual test day, and at the day of the study. Pre-test arterial blood gas analysis, pulse oximetry and electrocardiography (ECG) were assessed at the day of the study.

### 3.3 Measurements and outcome assessment

**Air travel questionnaire**

In Paper I and III, the COPD patients (in Paper I also the non-COPD reference group) answered an air travel questionnaire. Since there were no questionnaires developed for this purpose, we had to construct a suitable instrument. The air travel questionnaire was constructed to evaluate symptoms during air travel. In addition, air travel habits, reasons for not flying, pre-flight physician consultation, unscheduled use of in-flight oxygen and use of medical care within 48 h post-flight were recorded. The choice of wording for the questionnaire was, in addition to being discussed in the research group, also discussed with
a selection of patients with COPD. Thereafter, the questionnaire was controlled for comprehension in a new group of patients. In-flight symptoms were classified as respiratory symptoms (dyspnoea and air hunger), hypoxia related (dyspnoea, air hunger, dizziness, headache, chest pain, cough, fainting, palpitations), or not related to hypoxia (ear pressure, sinus pressure, swollen legs). The wording of the air travel questionnaire and answering alternatives are given in Appendix D.

The air travel questionnaire was tested for test-retest reliability of respiratory symptoms by repeated administration on two consecutive days to 10 patients with COPD who had all travelled by air within the last two years. The test-retest reliability was very good with kappa=0.78.

The response rate of the questionnaire was 86% in Paper I, and in Paper III the response rate was 100% for the first questionnaire and 95% for the second questionnaire.

HAST

In Paper II, III and IV, normobaric hypoxic hypoxia simulation with HAST (96) was performed at Glittreklíniken, Oslo University Hospital, Ullevål and at the Institute of Aviation Medicine. The patients used a tight and personally fitted facemask (Size Small or Medium) (Mirage Full Face Mask, ResMed Corp, Poway, USA) equipped with a non-rebreathing valve (Y-valve, Hans Rudolph Inc., Kansas City, USA). The mask was thoroughly checked for leakages before and during the test. The patients were sitting in a chair breathing 15.1% oxygen (15.1 ± 0.1% O₂, 84.9% N₂, AGA, Oslo, Norway) from a 170 L non-diffusing gas collection bag (Douglas bag, Hans Rudolph Inc., Kansas City, USA), simulating 2438 m (8000 ft) altitude.

Pulse oximetry values and ECG were continuously monitored and symptoms were recorded using both the Borg CR10 scale (53) for dyspnoea and verbal descriptors for any possible other symptoms. Arterial blood gases were drawn from an arterial line in the sitting position before the HAST and at the end of the HAST. In addition, an arterial blood gas sample was drawn if the SpO₂ dropped below 85% before the end of the test. In Paper II and III the patients were exposed to the hypoxic gas for 15 minutes. If the SpO₂ was not stable after 15 minutes, the test was prolonged to 20 minutes. The exposure duration in Paper IV was 20 minutes. Both 15 and 20 minutes are regarded as sufficient time for the hypoxic exposure (96, 123, 130). In study IV, oxygen from three different oxygen devices was given through a nasal cannula underneath the face mask during the HAST.
Patients desaturating below 6.6 kPa during the HAST were advised to use in-flight supplemental oxygen (6). The patients were thoroughly informed about the practical aspects on air travel with supplemental oxygen, and all patients received a physician's statement describing the need of in-flight oxygen and the recommended oxygen dose.

**Hypobaric chamber**

In paper IV air travel was simulated by exposing the patients to hypobaric hypoxia in the HC at the Institute of Aviation Medicine in Oslo (Figure 11). A certified operator controlled the chamber, and two physicians were inside the chamber together with the patient. The patients were exposed to 2438 m (8000 ft). The simulated altitude in the HC was accurate within 15 m (50 ft) and ascended/descended at a rate of 150-333 m/min (500-1000 ft/min), simulating a commercial flight. If the patient had problems equalising the pressure in the ears or sinuses, descent was halted and continued at a slower pace. Oxygen and carbon dioxide levels in the chamber were continuously monitored and adjusted to maintain normal levels. The patients stayed in the HC for about 2.5 hours. Two patients were tested each day.

![Figure 11. The hypobaric chamber at the Institute of Aviation Medicine, Oslo. Private photo with permission.](image)

The patients (one at the time) were exposed to 2438 m (8000 ft) for 20 minutes without supplemental oxygen, followed by oxygen supplementation in random order from three different devices. Each titration was followed by a 10-min washout period without supplemental oxygen before testing with the next oxygen equipment. The SpO₂ and ECG were continuously monitored, and dyspnoea (Borg CR10) and other possible symptoms were recorded. During the HC exposure, arterial blood gas samples were drawn at the end of
each exposure. The specimens were immediately placed on ice and passed through the airlock of the chamber for analyses outside the chamber at sea-level.

**Arterial blood gases**

Gas exchange and acid base status are measured via arterial blood gases. Arterial blood gas samples were obtained in a sitting position in all four papers. In Paper I, arterial blood gas samples were assessed from a single puncture of the radial artery, and in Paper II, III, and IV the samples were drawn from a radial artery catheter inserted under local anaesthesia (1-1.5 mL Lidocaine 10 mg/mL). Samples were drawn after at least 5 minutes rest. At least three times the dead space from the arterial line was removed before the sample was drawn. Pre-heparinised syringes were used (PICO 50, Radiometer, Denmark), air bubbles were immediately removed, and the samples analysed within 10 minutes. The radial artery catheter was removed immediately after the test, and the puncture site was compressed for about 5 minutes and a compression bandage was put on for 3 hours. There were no complications observed during or after this procedure.

The blood gas analysers used were calibrated and quality controlled several times daily according to recommendations from the manufacturer (ABL 825 Flex, ABL 725, Radiometer, Denmark). In addition the analysers' precision and accuracy were controlled by an external laboratory quality system (Labquality Oy, Helsinki, Finland). The blood gas analyses were performed by experienced personnel.

**Arterial oxygen saturation by pulse oximetry**

Pulse oximetry provides, unlike arterial blood gas analysis, a non-invasive, a continuous estimation of the oxyhaemoglobin saturation of arterial blood. Pulse oximetry is commonly used in clinical and research settings (146-150). SpO₂ in arterial blood is measured by comparing the transmission of two wavelengths of red and infrared light through, in our case, a finger. The pulse oximeter detects oxygenated blood (HbO₂) and unoxygenated blood (HHb), and computes the saturation (SpO₂, %). The pulse oximeter is dependent on a pulsatile flow. New-generation pulse oximeters are manufactured with improved algorithms that minimize motion-related data errors by filtering out body motions (146).

In all four papers, handheld or wrist oximeters were used (NONIN 8500 (Paper I); NONIN 2500 Palm Sat Paper and NONIN 3100 Wristox, NONIN Medical Inc, USA (Paper II, III and IV). Nail polish was removed. The pulse oximetry probe was placed on a warm
finger tip (not the thumb or little finger), and at rest, the \( \text{SpO}_2 \) was measured after 5 minutes in the sitting position. During the 6MWTs (Paper I, II), the \( \text{SpO}_2 \) was measured before, during (every minute), and after the test. The pulse oximeters were controlled for possible sources of error such as motion artefacts or poor perfusion by ensuring a trustworthy heart rate and absence of short drops in \( \text{SpO}_2 \). Pulse oximeters have an accuracy of 1-2\% compared to directly measured arterial oxygen saturation (146, 148, 151). It is not possible to calibrate a pulse oximeter. However, the pulse oximeters were validated with arterial oxygen saturation measurements (\( \text{SaO}_2 \)) on a blood gas analyser.

**Exercise performance and exercise desaturation; the 6MWT**

The 6MWT is the most frequently used field test for evaluation of exercise performance in patients with COPD (60, 65, 66). In Paper I, II and III all patients were assessed with a 6MWT. The non-COPD group in Paper I did not perform 6MWT. The 6MWT was performed according to standardised criteria (67, 152) in a 30 m long corridor. The test leader gave standardised encouragement every minute, and the patients were asked not to talk during the test, unless they had a problem or a question. According to security criteria, the test should be stopped if the patients had chest pain, intolerable dyspnoea, evolving mental confusion, evolving light-headedness or for any other clinically relevant reason. None of the patients in the studies were stopped due to adverse events. \( \text{SpO}_2 \) (NONIN 8500 and 3100 Wristox, NONIN Medical Inc. USA) was continuously monitored (68, 69) by pulse oximetry. Distance walked is usually the primary outcome of the 6MWT. In this thesis, \( \text{SpO}_2 \) was the primary measure, and the lowest measured \( \text{SpO}_2 \) during the test (nadir \( \text{SpO}_2 \)), the \( \text{SpO}_2 \) at stop and delta \( \text{SpO}_2 \) (difference from start to stop) were used in the analysis. Dyspnoea score (Borg CR10) was recorded before and at the end of the test. Patients dependent on walking aid used a walker during the test. None of the patients used supplemental oxygen during the test.

**Lung function testing**

All lung function measurements were performed by experienced personnel according to standardised criteria (23, 24, 26, 153, 154). Reference values were based on equations from the European Coal and Steel Community (ECSC) and post-bronchodilator FEV\(_1\) values from Johannessen et al. (155, 156).
Post bronchodilator spirometry testing, diffusing capacity of the lung (DL,CO) and total lung volumes were performed at three hospitals and with different analysers (Viasys Masterscope, Viasys, Germany and SensorMedics Vmax Encore, VIASYS Healthcare Respiratory Technologies, USA (Paper I); MasterScreen Pneumo, Jaeger-Toennis, Germany (Paper II, III); MasterLab, Jaeger-Toennies, Germany, and Vmax 22 Encore, SensorMedics, The Netherlands (Paper IV). Volume calibration was performed daily with a 3 L syringe, and in addition, biological quality controls were performed weekly.

**Measurements of dyspnoea**

Two different scales were used to measure dyspnoea. The Norwegian version of the Borg CR 10 scale (52, 53, 157) was used to estimate perceived breathlessness during 6MWT (Paper I and II) and the difference in dyspnoea from sea-level to simulated flight, both during HAST and HC exposure (Paper II, III, and IV) (Appendix A). The scale-instruction was in advance explained to the patients in advance. The patient either gave a verbal response or pointed at the scale to express the dyspnoea sensation, and the corresponding number was recorded.

The 5-point mMRC dyspnoea scale is a simple and standardised self-administered grading system to assess a patient’s level of dyspnoea on daily life activities such as walking and dressing. The Norwegian version of the mMRC scale was used in Paper I and III (56, 57) (Appendix B).

**Supplemental oxygen**

In Paper IV, supplemental oxygen was given during HAST and HC exposure. The oxygen was administered via a nasal cannula (Salter Labs E1600) and from either a steel cylinder with compressed gas (99.6% O₂, 200 bar, AGA Linde Gas Therapeutics, Norway) with continuous flow, a composite cylinder with compressed gas (99.6% O₂, 1 L, 200 bar, AGA Linde Gas Therapeutics, Norway) with OCD (EasyPulse5, Precision Medical Inc, USA), or a POC (FreeStyle, AirSep Corp, USA) (Figure 12). The oxygen concentration in the POC is estimated to be 90 ± 3% both at sea-level and 10 000 ft (3048 m) when producing 1-2 litre O₂ per minute. The POC was fully charged during the tests and operated with battery power. According to the manufactures’ specifications, all used devices can be used up to an altitude of 10 000 ft. The oxygen was given at a flow rate of 1 and 2 LPM or at pulse setting 1 or 2 from the OCD and the POC, followed by a 10 min wash-out period without supplemental
oxygen before, in random order, testing with new equipment. According to results from previous studies (115, 123, 127), 10 minutes is regarded as sufficient time to reach steady state during oxygen supplementation.

Figure 12. Three different oxygen delivery systems used in Paper IV. Compressed gaseous oxygen without OCD, cylinder with compressed gaseous oxygen and OCD, and a POC. OCD: oxygen conserving device, POC: portable oxygen concentrator.

Statistics

Sample size calculations were performed for Paper II, III and IV. To calculate sample size in Paper II, we assumed that sensitivity and specificity would be approximately 80% in the planned study. It was then shown that 100 patients were needed to construct a new algorithm in which sensitivity and specificity should have CI length <16%. In Paper III, to get an impression of the statistical power, the sample size was retrospectively evaluated, and it would allow detection of mean PaO$_2$$_{HAST}$ difference of 0.45 kPa with a power of 80%. In Paper IV the sample size was calculated from the SD of the difference in PaO$_2$ found in a previous study from our group (83). A change in PaO$_2$ of 0.5 kPa was considered clinically significant and power was set to 80%.

Normally distributed data are presented as mean ± standard deviation (SD), unless otherwise specified. Normal distribution was assessed by visual inspection of histogram and QQ-plots or by Shapiro Wilks test statistics. A p-value <0.05 was considered to be statistically significant.

In Paper I associations between categorical variables were analysed by Chi-square test. Differences in continuous variables between the COPD group and the non-COPD group were tested by two sample t-test, or the Mann Whitney test, as appropriate. For identifying factors associated with prevalence of in-flight symptoms, a logistic regression model was used. Adjustment was made for smoking, age, and gender. In Paper II, Pearson’s
correlation coefficient and one-way repeated measures ANOVA were used to evaluate relations between PaO$_2$$_{HAST}$ and baseline patient characteristics. Receiver operating characteristics (ROC) analyses were performed with sea-level SpO$_2$, SpO$_2$$_{6MWT}$ and walking distance against PaO$_2$$_{HAST}$ < 6.6 kPa as the discriminating variable. In Paper III, univariate analysis (independent samples t-test and $\chi^2$ test, as appropriate) was used for assessment of relationship between PaO$_2$$_{HAST}$ and respiratory symptoms. Univariate exploratory analyses were performed using McNemar, Pearson $\chi^2$ test or Fisher Exact Test for categorical variables. Kappa statistic was used to measure test-retest reliability of the air travel questionnaire. In Paper IV, the relationship between HAST and HC exposure was assessed by linear regression analysis and Bland-Altman plot.

Calculations were performed using SPSS 16.0 to 18.0 for Windows and Sample power 2.0 (SPSS Inc., Chicago, USA), and Excel 2003 for Windows.
4. Main results

**Paper I**

In this cross-sectional study, the study aims were to evaluate air travel habits and in-flight symptoms. Data on 391 COPD patients and 184 non-COPD subjects who completed a flight outcome questionnaire is presented. According to the GOLD classification, 48%, 36%, and 16% of the COPD patients were in stages II, III, and IV, respectively. Fifty-four per cent of the COPD patients and 86% of the non-COPD subjects had travelled by air within the previous two years. Eighty-two per cent of the COPD patients had two or more flights, usually lasting 3-6 h. The COPD patients who did not fly were older, had more reduced lung function, lower PaO₂, a more pronounced exercise desaturation and shorter 6MWT walking distance. The reported reasons for not flying were: no travelling plans (79%), fear of flying due to their lung disease (9%), 3% had been advised by a health care professional not to travel by air, and 9% stated other reasons.

Symptoms during air travel were more frequent in the COPD group, and 25% of the COPD patients versus 9% in the non-COPD group reported symptoms classified as hypoxia-related. The most frequent hypoxia-related symptom in the COPD group was dyspnoea and air hunger (21%, hereafter named respiratory symptoms); compared to 4% in the non-COPD group. There was no difference between the groups with regard to symptoms which were not hypoxia-related (ear pressure, sinus pressure and swollen legs). After adjustment for confounders (smoking status, age and gender), patients with COPD had a more than 3-fold increased risk of experiencing hypoxia-related symptoms compared to those without COPD. For the respiratory symptoms, the risk was nearly 7-fold.

In COPD patients, only the modified MRC dyspnoea score and exercise SpO₂ showed a significant relation to in-flight respiratory symptoms. A logistic regression model showed a nearly 5-fold increase in risk of experiencing in-flight respiratory symptoms for patients with modified MRC score 2 or higher compared to score 0.

Before planning to travel by air, 6% (23) of the patients consulted a physician and 14 (4%) of them were advised not to travel. Nine of those patients travelled despite the physician's advice, and five of them experienced hypoxia-related symptoms. Two of the patients who travelled by air used LTOT. They both travelled with supplemental oxygen, and none of them reported in-flight symptoms. Two (1%) of the COPD patients not using LTOT needed acute in-flight supplemental oxygen.
This prospective cross-sectional study included 100 patients with COPD and aimed to construct a pre-flight evaluation algorithm based on resting and exercise SpO2. The second aim was to study if arterial oxygen saturation by pulse oximetry may be used as a substitute for arterial blood gas measurement during HAST. According to the GOLD classification (12), 22%, 46% and 32% were in the categories II, III and IV, respectively.

All patients were tested with HAST and 6MWT. Mean HAST values for PaO2 and SpO2 were 6.3 (0.6) kPa and 83 (4) %, respectively. Seventy-three per cent of the patients had a PaO2 HAST below 6.6 kPa, indicating that they, in accordance with current guidelines, should use in-flight supplemental oxygen. During the 6MWT, the patients covered a distance varying from 150 to 604 m. The mean decrease in SpO2 during the 6MWT was 10 (5)% (p<0.001), and the mean SpO2 6MWT was 83 (6)%.

With regard to associations between in-flight PaO2 and sea-level characteristics, PaO2 SL, SpO2 6MWT, and SpO2 SL had the strongest correlation with PaO2 HAST. PaO2 SL was not included in the further analyses since the aim was to develop a non-invasive evaluation method. ROC analyses were then used as the basis for developing the pre-flight evaluation algorithm. Both SpO2 SL and SpO2 6MWT showed good diagnostic properties for detection of in-flight PaO2 below 6.6 kPa with an area under the curve 0.78 and 0.79, respectively. The patients were grouped, and data analysed, according to the BTS pulse oximetry categories, SpO2 SL >95%, 92-95%, and <92%. In the group with sea-level SpO2 SL <92%, 30 of 33 (91%) patients dropped below the recommended level for minimum in-flight PaO2 (6.6 kPa), and were thereby in need of supplemental oxygen during air travel. Regarding the 55 patients in the group with SpO2 SL from 92-95%, a ROC analysis with SpO2 6MWT suggested a cut-off value of SpO2 6MWT <84% for detection of in-flight PaO2 <6.6 kPa. With regard to patients with SpO2 SL >95%, five of twelve (42%) had an in-flight PaO2 below 6.6 kPa. In this group, as well, ROC analysis showed exercise desaturation as a good prognostic variable, with an optimal cut-off value for SpO2 6MWT <84%.

Based on these results, a pre-flight evaluation algorithm was constructed. The algorithm was based on sea-level resting pulse oximetry and exercise desaturation during 6MWT as the primary and secondary discriminator for evaluating whether the patient was a) fit to fly without further assessment, b) in need of further evaluation with HAST or c) should receive in-flight supplemental oxygen without further evaluation (Appendix E). The pre-flight evaluation algorithm had a sensitivity of 99% (95% CI 96-100) and a specificity
of 82% (95% CI 67-96). According to the algorithm, one third of the patients would be advised to perform extended pre-flight testing with HAST. Six per cent of the patients were not correctly classified by the algorithm; of these, one patient was misclassified as fit to fly despite a PaO₂_HAST below 6.6 kPa, and five patients would have been advised to use in-flight oxygen without, in fact, having a PaO₂_HAST < 6.6 kPa. The patients whom the algorithm selected for further pre-flight evaluation with HAST, had a mean PaO₂_HAST of 6.6 (0.6) kPa.

After the algorithm was established, it was prospectively validated on an independent sample of 50 COPD patients who were referred to HAST. Sixteen per cent of the patients had SpO₂ SL > 95%, 54% had SpO₂ SL 92-95% and 30% patients had SpO₂ SL < 92%. For all but four patients a correct choice was obtained with regard to use of in-flight supplemental oxygen. These four patients were recommended supplemental oxygen, without having a PaO₂_HAST < 6.6 kPa. It should be noted, however, that they all had PaO₂ HAST values close to the recommended limit (mean PaO₂_HAST 6.6 (0.1) kPa). The sensitivity and specificity for the algorithm in this independent sample of patients were 100% (95% CI 90-100) and 80% (95% CI 60-95), respectively. The 20 patients which the algorithm selected for further pre-flight evaluation with HAST had a mean PaO₂_HAST 6.9 (0.5) kPa.

The secondary aim was to evaluate if HAST can be performed with SpO₂ as a substitute for PaO₂. There was a strong correlation between PaO₂ and SpO₂ (r=0.81, p<0.001) during HAST. A ROC analysis suggested a cut-off value for SpO₂_HAST ≤ 85% when SpO₂_HAST was used as a substitute for PaO₂_HAST < 6.6 kPa. When using SpO₂_HAST instead of PaO₂_HAST on an independent sample of 50 COPD patients, we obtained a sensitivity of 90% (95% CI 77-100) and a specificity of 85% (95% CI 70-100).

Paper III

This prospective observational study aimed to evaluate associations between pre-flight hypoxia-induced PaO₂ and in-flight respiratory symptoms. For this purpose, 82 patients with moderate to very severe COPD, who had travelled by air within the last two years, were tested with HAST, and, were invited to answer an air travel questionnaire about in-flight symptoms and need of medical care in the days following air travel. The patients also answered the questionnaire within one year after the HAST. According to the GOLD classification (27), 23%, 60% and 17% were in the categories 2, 3 and 4, respectively.
The mean PaO$_2$ HAST was 6.3 (0.6) kPa. Seventy-six per cent of the patients had PaO$_2$ HAST <6.6 kPa and were recommended to use in-flight supplemental oxygen. Respiratory symptoms were experienced by 38 (46%) patients. There was no difference in mean PaO$_2$ HAST in those with and those without in-flight respiratory symptoms (6.3 (0.7) kPa vs. 6.3 (0.6), respectively, p=0.926). There was a tendency towards more respiratory symptoms for patients with PaO$_2$ HAST below the median value 6.3 kPa (54%) vs. PaO$_2$ HAST above 6.3 kPa (39%), p=0.184. Twenty-three of the 54 (43%) patients who travelled by air after HAST used supplemental oxygen during their latest flight. There was a significant decrease in the prevalence of respiratory symptoms when travelling with supplemental oxygen (17%) compared to travelling without oxygen treatment (48%) (p=0.039). When flying again after HAST, 4% of the patients reported need for medical care within 48 hours after the flight as compared to 17% before HAST (p=0.039). The mean PaO$_2$ HAST for patients needing post-flight health care before HAST was 6.0 (0.6), and all of those patients had PaO$_2$ HAST <6.6 kPa.

**Paper IV**

In this randomised cross-over study, we compared oxygen supplementation during HAST and HC exposure, aiming to evaluate if HAST can be used to establish the sufficient dose of oxygen needed for air travel. In addition, we evaluated if oxygen supplementation given with the three types of oxygen equipment permitted for commercial air travel gave similar in-flight PaO$_2$.

When comparing the three oxygen delivery systems in the HC, a similar PaO$_2$ was obtained when the oxygen was given with either continuous flow or with OCD from a compressed oxygen cylinder. Oxygen delivery from the POC showed, however, a significantly lower PaO$_2$ compared to oxygen supplementation with compressed gaseous oxygen. Supplemental oxygen from the POC at pulse setting 2 gave similar PaO$_2$ as compressed gaseous oxygen at pulse setting 1 with the OCD and 1 LPM with continuous flow.

The three types of oxygen equipment were tested during HAST and HC. During oxygen titration with 1 LPM (pulse setting 1), the PaO$_2$ obtained with oxygen at continuous flow and with the OCD showed significantly higher values during HAST compared to HC exposure. No such difference in PaO$_2$ was observed during oxygen titration with POC at pulse setting 1. During oxygen titration with 2 LPM (pulse setting 2), the difference in PaO$_2$
between HAST and HC was more pronounced, being statistically significant also for the POC. We observed higher PaO₂ values when titrating supplemental oxygen during HAST than during HC exposure, indicating an accumulation of oxygen within the face mask.
5. General discussion

Air travel habits

Is the COPD patient a travelling patient? There have been few studies on air travel habits among patients with COPD. Twenty years ago, 44% of the subjects in a North American COPD study and 35% of the patients in a study from Great Britain (8, 99), had travelled by air during a period of approximately two years. Fifty-four per cent of the COPD patients studied in Paper I had travelled by air during the last two years. There has been a general increase in commercial travel during the last decades which may explain the increase in travel frequency among COPD patients. In addition, the prevalence of COPD is high and increasing, and therefore, it is likely that the number of air travel passengers with COPD will continue to increase. In the two studies which have reported flight duration for COPD patients, a median duration of 3 h and 6 h, has been reported (99, 103). This corresponds well with the results from Paper I where a median flight duration of 3-6 h was found. Forty-six per cent of the patients did not travel by air. In accordance with other studies, these patients had poorer lung function (99, 103), they were older, and had more pronounced exercise desaturation and a shorter 6MWT distance than those who flew.

Pre-flight medical care

A minority of the COPD patients (6%) in Paper I had consulted a physician before travelling. In a study from Dillard et al (99), approximately one-fourth of the patients had consulted a physician. The difference may be explained by less severe disease in our unselected COPD cohort. Another explanation is that patients in our study might not have been aware of the potential risk of hypoxaemia during air travel. Sixty-one per cent of the COPD patients who consulted a physician were advised not to travel by air. Nine of those patients travelled despite the physician's advice, and five of them experienced hypoxia-related symptoms. In spite of recommendation to use in-flight supplemental oxygen, nearly half of the patients in Paper III travelled without such equipment. Unfortunately, we do not have any information on the reason for not following the advice to use supplemental oxygen. However, logistic, stigma, and cost factors may play a role, and Coker et al. (103) reported that 11 of 69 patients dropped their travel plans due to logistic problems with the oxygen equipment.
Prevalence of symptoms during air travel

Paper I is the first flight outcome study comparing COPD patients with non-COPD subjects. One fourth of the COPD patients experienced hypoxia-related symptoms during air travel, compared to nine per cent of individuals without COPD. Our data show that patients with COPD have a 3-fold increase in hypoxia-related symptoms and a near 7-fold increase in respiratory symptoms, compared to the non-COPD subjects. Symptoms classified as hypoxia-related may have other causes than hypobaric hypoxia. However, the study was not designed to answer causality relationships. The occurrence of other air travel related symptoms such as ear pressure, sinus pressure and swollen legs were scarcely reported in Paper I and III. These symptoms did not differ between the groups in Paper I, indicating that the COPD patients were not more prone to report symptoms in general. In Paper III, nearly fifty per cent of the patients reported respiratory symptoms. This is a considerably higher percentage than in previous studies, which reported 18-21% (99, 103). This discrepancy may be explained by more severe COPD in the patients included in Paper III. Further, in contrast to the other studies (99, 103) all our patients were referred to HAST, and one of the referral criteria was symptoms during previous flights (6, 9).

Since thirty-one of the patients in Paper III did not use supplemental oxygen during any of the flights, it was possible to study the test-retest reliability for respiratory symptoms. The prevalence of respiratory symptoms reported in the two questionnaires for these patients showed no significant difference (36% and 45%, respectively, p=0.453). Twenty-four of the 31 (77%) patients gave identical answers in the first and second questionnaire, and the kappa was 0.54. This confirms our clinical observation that occurrence of respiratory symptoms during air travel is reproducible. This issue has, to my knowledge, not previously been studied.

The studies in Paper I and III have some limitations. The time span between the measurements and air travel could have been one to two years, and possible worsening or exacerbation of the lung disease may have influenced the results. In addition, the severity of the symptoms was not recorded. The design of the studies may imply recall bias, which might result in under-reporting or over-reporting of symptoms. However, a design where the participants are asked to record respiratory distress during actual flights might lead to increased symptom awareness, and thereby over-reporting of symptoms. We have no information of the actual cabin pressure during the flights, which may vary between 1529 and 2438 m (5000 and 8000 ft), thereby influencing the severity of hypoxaemia (7, 88). It is
possible that different aircraft cabin altitudes may explain some of the variations in symptoms reported.

**Predicting in-flight symptoms**

Associations between in-flight respiratory symptoms and sea-level characteristics have not previously been studied. The results in Paper I showed that sea-level mMRC dyspnoea scores were strongly associated with in-flight respiratory symptoms. This is an interesting observation, which may be clinically useful and the study is cited in the 2011 updated BTS air travel recommendations (7). Desaturation during 6MWT also showed a significant relationship with in-flight respiratory symptoms and corroborates earlier observations of associations between exercise desaturation and in-flight hypoxemia (121). We concluded that inclusion of both mMRC dyspnoea score and exercise desaturation may possibly be valuable in pre-flight evaluation algorithms. We found, however, in the population in Paper III, no significant associations between mMRC dyspnoea score and in-flight respiratory symptoms. This may be explained by a more severe COPD in Paper III with higher mMRC score. In Paper I, HAST was not performed. In previous studies, COPD patients reporting respiratory symptoms during HAST, also had severe hypoxaemia during HAST (96, 117). Thus, it seems reasonable to assume that the symptomatic patients in Paper I suffered from hypoxaemia and that pre-flight testing would have resulted in the use of supplementary oxygen. It should be noted, however, that patients may become severely hypoxaemic during hypobaric and normobaric hypoxia without experiencing symptoms (82, 83, 96, 100, 116). Therefore, in Paper III, we designed a study aiming to assess the relationship between pre-flight hypoxia-induced PaO$_2$ and in-flight respiratory symptoms. In this study of patients with moderate to very severe COPD, we found no significant association between respiratory symptoms during air travel and PaO$_2$ HAST. In general, however, dyspnoea correlates poorly with blood gas abnormalities, both at rest and during exercise (38, 40), and there is a wide range of the individual responses to hypoxaemia (33). The physiological compensation for acute hypoxaemia is a nonlinear increase in ventilation (2, 7, 31) with a decrease in PaCO$_2$, and a moderate tachycardia (25, 31). The PaO$_2$ can be reduced to about 6.7-8 kPa before there is an appreciable increase in ventilation (2, 35, 43). Hypoxaemia may act indirectly on the sensation of dyspnoea, by increase in ventilation, or directly, independent of change in ventilation (11, 38, 108, 133). Other pathophysiological factors known to contribute to dyspnoea in patients with COPD are increased mechanical loading of
inspiratory muscles in hyperinflated lungs (40), and hypoxic effects on the cardiac pump and the pulmonary vasculature (25). Also, psychological factors like anxiety may contribute to or worsen the symptoms (38). Ventilation was not measured during HAST. To elucidate if the dyspnoea sensation during air travel is related to a hypoxia-induced increase in ventilation, future studies with measurement of ventilation in hypobaric hypoxia is warranted.

**Prevalence of in-flight hypoxaemia**

Studies of the prevalence of in-flight hypoxaemia in a general COPD population are lacking. Approximately three-quarter of the patients in Paper II and III had a PaO$_2$ $<$ 6.6 kPa, indicating that they, in accordance with current guidelines, should use in-flight supplemental oxygen. In Paper IV the inclusion criteria was a positive HAST, and hence all patients had in-flight PaO$_2$ below 6.6 kPa. It would be of interest to get an estimate of the prevalence of in-flight hypoxaemia in a general COPD population. This issue remains to be studied.

**Predicting in-flight hypoxaemia**

Various equations and single sea-level variables like FEV$_1$, PaO$_2$, DL, CO or SpO$_2$ have proven not to predict in-flight hypoxemia with satisfactory precision (6, 7, 82, 100, 103, 117, 131). In Paper II, the highest significant correlations between in-flight PaO$_2$ were found for baseline PaO$_2$, exercise SpO$_2$, and baseline SpO$_2$. Different exercise outcomes have been discussed as appropriate for pre-flight evaluation. The 50 m walk test has been proposed as a simple and clinical test for the fitness to fly (6, 7, 9, 114), but the test does not discriminate properly between those patients who desaturate below the recommended limit for in-flight PaO$_2$ and those who do not (83, 117). Neither was there any relationship between in-flight PaO$_2$ and walking distance during a 6MWT in a study from Kelly et al (111). We found, however, a modest correlation between in-flight PaO$_2$ and walking distance. Differences in patient samples and small study groups may explain the discrepancy. Gas exchange variables from more standardised pre-flight exercise testing with CPET (aerobic capacity) and 6MWT (exercise SpO$_2$) have shown strong correlations with in-flight PaO$_2$ (82, 83, 120, 121). The 6MWT is a widely used and reproducible test to assess exercise performance and exercise desaturation in patients with COPD (70, 158), and
the test is much more available than HAST. The model for the construction of the pre-flight algorithm in Paper II was based on the above observations.

**Pre-flight evaluation algorithm**

Our group has previously shown that the BTS algorithm based solely on sea-level SpO\textsubscript{2} can not discriminate between patients who need supplemental oxygen and those who do not (117). As a consequence of this findings, the BTS pre-flight algorithm is removed in the 2011 updated BTS recommendations for air travel (7). However, simple and consistent pre-flight assessment guidance regarding the need of in-flight supplemental oxygen is requested (1, 6, 7, 77). Since oxygen saturation measured with pulse oximetry, both at rest and during a 6MWT, is frequently used in the medical care of patients with COPD (60, 70, 159), an algorithm employing a combination of these two variables would be simple to implement in a busy clinical practice. In Paper II, we constructed and validated a simple and clinically feasible algorithm for pre-flight assessment of patients with COPD, based on sea-level resting SpO\textsubscript{2} and SpO\textsubscript{2} values during a 6MWT.

Our results showed that patients with COPD, with sea-level SpO\textsubscript{2} higher than 95% and without severe exertional desaturation (SpO\textsubscript{2} ≥84%) can travel safely by air without further pre-flight assessment. Neither is further pre-flight assessment necessary in patients with SpO\textsubscript{2SL} below 92% (6, 117), nor in patients with SpO\textsubscript{2SL} 92-95% and SpO\textsubscript{26MWT} <84%. These patients should, according to our results, be equipped with supplemental oxygen during the flight. Thus, extended pre-flight assessment with HAST may be limited to patients with either the combination of resting SpO\textsubscript{2SL} >95% and severe exercise desaturation (SpO\textsubscript{2} <84%) or, the patients with SpO\textsubscript{2SL} between 92-95% without severe exercise desaturation (≥84%). In these two categories of patient, the level of in-flight hypoxemia was difficult to predict, underlining the need for pre-flight testing with HAST.

The new algorithm has a high sensitivity, which was reproduced when applied prospectively to a separate group of patients with COPD. None of the study subjects were misclassified as fit to fly without supplemental oxygen. Due to somewhat lower specificity, the algorithm overestimated the risk of in-flight hypoxemia, resulting in unnecessary use of supplemental oxygen in 8% of the patients.
Non-invasive HAST

HAST is increasingly used in pre-flight assessment (117, 129). However, the test is not widely available (8, 77). HAST has been shown to be a good predictor of in-flight PaO\(_2\) (111, 123, 130) and the results obtained are reproducible. One might find it cumbersome, however, to take repeated arterial blood samples or insert a radial artery catheter, and substitution of arterial blood gas measurement with pulse oximetry would simplify the HAST procedure considerably. To our knowledge, comparison of arterial blood gases and pulse oximetry during HAST has not previously been published. As expected, a strong correlation between PaO\(_2\)\(_{\text{HAST}}\) and SpO\(_2\)\(_{\text{HAST}}\) was observed, and when using a cut-off value for SpO\(_2\)\(_{\text{HAST}}\) ≤85% as a substitute for a PaO\(_2\)\(_{\text{HAST}}\) < 6.6 kPa, acceptable values for sensitivity and specificity were obtained. Our results show, however, that the use of pulse oximetry during HAST may underestimate the need for in-flight oxygen. Thus, our conclusion is that arterial blood gas measurements during HAST is the method of choice.

Use of unscheduled in-flight oxygen

Because airlines are not required to report requests for medical oxygen, the number of passengers needing unscheduled in-flight supplemental oxygen is not known (6-8, 114). In the group of COPD patients studied in Paper I, only two (<1%) patients reported use of acute in-flight oxygen. This is in accordance with the results from the UK Flight Outcome study (103). Patients in the UK Flight Outcome study had, however, in contrast to patients in Paper I, undergone pre-flight assessment, and patients expected to obtain an in-flight PaO\(_2\) below 6.6 kPa were equipped with supplemental oxygen. Ten per cent of the patients in Paper III reported need of acute in-flight oxygen. However, some of the patients in this study were referred to HAST due to previous air travel intolerance, and the number was therefore expected to be high.

Titration of supplemental oxygen dose required during air travel

The individual increase in PaO\(_2\) with administration of supplemental oxygen is variable (13, 115, 132, 133, 135). For titration of the individual oxygen dose during HAST, administration of supplemental oxygen via a NC underneath the facemask has been recommended (10, 127, 129). A reservoir effect has, however, in our clinical practice, been observed using this method. The results in Paper IV confirmed this observation.
Significantly higher PaO$_2$ values were achieved when oxygen was given during HAST compared with titration in the HC. The reservoir effect was depended on both oxygen flow and the different oxygen equipment used.

When comparing differences between oxygen equipment permitted for air travel, the HC was used to avoid the reservoir effect. Oxygen given with continuous flow gave the same PaO$_2$ as oxygen given from a cylinder with compressed gas and an OCD. When using a POC, a higher oxygen dose was required to obtain a similar PaO$_2$ as when using compressed oxygen. Other POCs and OCDs may deliver other doses or concentrations of oxygen and thereby influencing the PaO$_2$ (142, 160). It is important that health care professionals are aware of these discrepancies between the oxygen supply systems.

**Use of post-flight health care**

As shown in Paper III a relatively high proportion (17%) of patients needed medical care or assistance after arrival. All but one of them had PaO$_2$ _HAST_ below the recommended limit for supplemental oxygen, and only one had used in-flight supplemental oxygen during the flight. In contrast, Coker et al found no appreciable increase in the need for unscheduled health care after air travel in a population comprising patients with various lung diseases (103). Two per cent of the COPD patients included in Paper I needed health care after arrival, and almost half of these patients reported symptoms during the flight. The differences in Paper I and III may be explained by the fact that the subjects in the last Paper had more severe COPD.

**Possible physiological effects of in-flight hypoxaemia and effects of supplemental oxygen during air travel**

What then are the potential hazards of in-flight hypoxaemia? The effect of acute hypoxaemia on patients with stable COPD is not fully elucidated (2, 8, 10). The hypoxic ventilatory response is probably the most important compensatory response to the hypobaric hypoxia in the aircraft cabin (2, 4, 7). This response is not harmful per se, but may be linked to in-flight respiratory symptoms. The increased minute ventilation is considered to be caused by an increase in tidal volume (2, 4, 9, 31). Patients in Paper I and especially in Paper III, were hyperinflated. It is well known that dynamic hyperinflation, as seen during exercise in some patients with COPD, results in dyspnoea (40, 46, 161, 162). It is possible
that the hypoxaemia induced increase in TV and minute ventilation, further increases the RV and thereby elevates the end-expiratory lung volume (EELV) with dyspnoea as a result.

The acute hypoxaemia may also induce a pulmonary vasoconstriction (2, 4, 10). There is, however, considerable individual variability as to the magnitude of the pulmonary vasoconstriction (4, 11). Acute hypoxia may also induce a significant increase in pulmonary artery pressure (10, 163). In the last decade, the theory that hypoxia can induce inflammation, has gained general acceptance (164, 165). Hypoxia may result in an imbalance between oxygen demand and delivery, causing an increase in cardiac troponin T as a marker for myocardial injury (166, 167). Whether the hypoxic exposure during air travel induces inflammation, an increase in cardiac troponin T or an increase in pulmonary artery pressure in patients with COPD has not been studied.

A significant reduction of in-flight respiratory symptoms was observed in patients flying with supplemental oxygen (Paper III). This may be due to a reduction in ventilatory drive due to reduced chemoreceptor activity (168, 169). Another mechanism may be a reduction in dynamic hyperinflation caused by a decrease in minute ventilation, as shown during exercise with supplemental oxygen (170). It must be emphasised, however, that this part of the study was not placebo controlled, and that oxygen treatment is encumbered with a significant placebo effect (171). A double-blinded “real-flight” or hypobaric chamber RCT should be performed to evaluate this issue.

Guidelines and recommendations have rather arbitrarily selected the estimated hypoxaemia level where supplemental oxygen is advised (PaO2 <6.6 kPa) (7, 8, 172). It may be questioned whether this level could be lowered without medical consequences.

**Practical consequences of the results in the thesis**

A considerable number of patients with COPD travel by air (Paper I), and in-flight respiratory symptoms are frequently reported. Simple and practical pre-flight methods to predict the need for in-flight supplemental oxygen has been asked for. Our new pre-flight algorithm based on sea-level SpO2 at rest and during a 6MWT is simple and reliable, and might be useful for physicians treating patients with COPD (Paper II). However, some patients with COPD will still need HAST to determine in-flight PaO2. When titrating supplemental oxygen during HAST, precautions must be taken regarding the reservoir effect of the mask. Oxygen equipment permitted for air travel corrects PaO2 to an adequate level.
when tested during in-flight simulation in a hypobaric chamber. There are, however, differences between the oxygen delivery systems (Paper IV).

The results in Paper III indicate that there is no association between in-flight respiratory symptoms and PaO$_2$ obtained during hypoxia-altitude simulation test. HAST might therefore be of no or limited value for predicting in-flight respiratory symptoms. Relief of respiratory symptoms is not, however, the main reason for giving supplemental oxygen during air travel. Worsening of co-morbidities like cardiovascular diseases, very common in the COPD population, is the most threatening consequence of severe hypoxaemia. Therefore, it seems reasonable to recommend in-flight supplemental oxygen to patients with COPD expected to fall in PaO$_2$ below the recommended limit of 6.6 kPa during air travel, in order to avoid in- or post-flight exacerbation of chronic medical conditions.
6. Conclusions

Paper I
In this cross-sectional study including 391 COPD patients and 184 non-COPD subjects we found that:

- More than half of the COPD patients travelled by air during a two-year period, compared with 85% of the non-COPD subjects.
- In-flight hypoxia-related symptoms were experienced by 25% of the COPD patients and 9% of the non-COPD subjects.
- Patients with COPD have a 3-fold increased risk of hypoxia-related symptoms compared to the non-COPD group. The risk of experiencing respiratory symptoms during air travel was nearly 7-fold higher in the COPD group.
- In-flight respiratory symptoms were associated with sea-level mMRC dyspnoea score and exercise desaturation.

Paper II
In this cross-sectional study consisting of 100 patients with moderate to very severe COPD, and 50 COPD patients in a validation cohort, we found that:

- A combination of arterial oxygen saturation measured by pulse oximetry at rest and during 6MWT may by used to construct an algorithm elucidating whether the patient a) is fit to fly without further assessment, b) needs further evaluation with HAST or c) should receive in-flight supplemental oxygen without further evaluation.
- The algorithm was validated on a separate, prospective group of COPD patients and a high sensitivity and specificity was documented.
- Pulse oximetry may be used as a substitute for arterial blood gas during HAST for assessing in-flight hypoxaemia, but due to somewhat lower sensitivity, arterial blood gas measurement is preferred.
**Paper III**

In this observational study including 82 patients with moderate to very severe COPD, we found that:

- No difference in PaO\textsubscript{2} obtained during hypoxia-altitude simulation testing was found between COPD patients with and without respiratory symptoms during air travel.
- There was a lower prevalence of in-flight respiratory symptoms in patients using supplemental oxygen during air travel (not placebo controlled).

**Paper IV**

In this randomised cross-over trial consisting 16 patients with COPD, we found that:

- HAST is equivalent to the gold standard HC exposure for simulating air travel hypoxia, and may be used to identify patients with COPD needing supplemental oxygen during air travel.
- Titration of oxygen with continuous flow during HAST using a NC underneath a tight fitting face mask causes accumulation of oxygen and thus, underestimation of the required oxygen dose.
- Compressed oxygen equipped with OCD administered with NC gives similar PaO\textsubscript{2} as oxygen with continuous flow during HC exposure. To minimise oxygen cylinders during flight, OCD should be used.
- A POC gave acceptable in-flight PaO\textsubscript{2} values, but a higher pulse setting than when using compressed oxygen flow was needed.
7. Perspectives

This thesis has highlighted some important questions regarding pre-flight evaluation and use of in-flight supplemental oxygen. Our new pre-flight evaluation algorithm is simple, reliable and easy to adapt into a busy clinical practice. There are, however, still questions to be answered.

Suggestions for further research:

- To evaluate if the arbitrarily chosen cut-off value for recommendation of in-flight supplemental oxygen (6.6 kPa) could be lowered.
- To study the prevalence of post-flight medical complications and if such complications are related to flight duration, estimated in-flight PaO$_2$ or use of in-flight supplemental oxygen.
- To study the effect of long-haul flights on the development of in-flight hypoxaemia and hypercapnia.
- To perform a double-blind RCT during real or simulated air travel, elucidating the effect of in-flight supplemental oxygen on respiratory symptoms.
- To perform an experimental study of the in-flight HVR on air travel hypoxaemia and in-flight respiratory symptoms in patients with COPD.
- To study the prevalence of in-flight hypoxaemia measured by HAST in a general COPD cohort.
- To perform a descriptive study on respiratory related in-flight medical incidents.
- To study if the pre-flight algorithm presented in Paper II can be applied in other lung diseases than COPD.
- To study if the acute hypoxaemia obtained during air travel may have cardiovascular consequences in patients with COPD; are there any effects on markers such as Pro-BNP and cardiac troponin T? Does acute air travel hypoxaemia induce an increase in pulmonary artery pressure in patients with COPD?
8. References


129. Mohr LC. The hypoxia altitude simulation test: an increasingly performed test for the evaluation of patients prior to air travel. *Chest* 2008;133(4):839-42.


9. Appendix

Appendix A

The Borg CR 10 scale, adapted from (52, 53, 157)

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Appendix B

The modified Medical Research Council (MRC) Dyspnoea Scale (mMRC). Adapted from (57).

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

Conversion chart from feet to meters. Adapted from (7).

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Appendix D
Air travel questionnaire

Questionnaire on medical problems in relation to air travel

Air travel is a safe and convenient mode of travel. However, the air pressure is lower in the aircraft cabin than on the ground ("thinner air"), and this may cause symptoms in some persons with lung disease.

The aim of this questionnaire is to evaluate medical problems in connection with air travel in healthy persons and in persons with lung disease.

Name: ____________________________ Birth date: ______________
Date: ____________________________

First, we ask you if you have travelled by air within the last two years.

1. I have travelled by air within the last two years. YES □ NO □
   a) If the answer is NO; why didn't you travel by air:
      I had no reason to travel by air. □
      For COPD patients; I don't dare to travel by air because of my lung disease. □
      Other: □ ____________________________
      Move forward to question 2.
   b) If the answer is YES;
      How often have you travelled by air within the last two years?
      1 time □  2-4 times □  more than 4 times □

      How long was the longest non-stop flight?
      0-1 hour □  1-3 hours □  3-6 hours □  more than 6 hours □  more than 10 hours □

We would like to learn about your experiences with health care providers in connection with planning air travel.

2. Has your physician or any other health care provider advised you against travelling by air? YES □ NO □

3. Have you had a medical evaluation with regards to air travel? YES □ NO □
Air travel may be strenuous both for healthy persons and for persons with lung disease. Recall any air travel you have taken within the last two years when answering the questions below (please do not answer question 4 - 7 if you haven’t travelled by air):

4. Have you ever felt in-flight discomfort? You can mark more than one symptom.
   - No discomfort
   - Dyspnea
   - Dizziness
   - Headache
   - Chest pain
   - Feeling of not enough air (Air hunger)
   - Cough
   - Fainting
   - Palpitations
   Other: ______________________

5. If you experienced in-flight discomfort; in which situation did it occur? (You may mark one or both alternatives)
   - When seated
   - When walking along the aisle/visiting the toilet

6. If you experienced discomfort, did the cabin crew give you oxygen? YES ☐ NO ☐

7. Have you ever felt discomfort within 24 hours after air travel? If you have, which kind of symptom or symptoms?
   - No discomfort
   - Dyspnea
   - Dizziness
   - Headache
   - Chest pain
   - Feeling of not enough air (Air hunger)
   - Cough
   - Fainting
   - Palpitations
   Other: ______________________

8. Have you ever had the need to visit a physician or been hospitalised within two days after air travel? (mark only one alternative)
   - No ☐ Visiting a physician ☐ Hospitalised ☐

We wish to ease planning of air travel for persons with lung disease, and want to know how we best can reach you with information (Healthy persons don’t need to answer the following questions).

9. Do you need more information about air travel and lung disease? YES ☐ NO ☐

10. If your answer is YES; how would you like to receive the information? You may mark multiple alternatives
    - Verbal information from your physician ☐
    - Verbal information from other healthcare provider ☐
    - Leaflet/brochure ☐ Information on internet ☐
    Other: ______________________

Thank you for taking the time to answer the questionnaire!
Appendix E

Pre-flight evaluation algorithm for patients with COPD
Paper I
High prevalence of respiratory symptoms during air travel in patients with COPD

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Received 26 May 2010; accepted 6 October 2010
Available online 25 October 2010

Summary

Objective: The reduced pressure in aircraft cabins may cause severe hypoxemia and respiratory distress in patients with chronic obstructive pulmonary disease (COPD). The primary objective of this study was to determine the prevalence of in-flight symptoms in COPD patients and non-COPD subjects, and evaluate associations between these symptoms and pre-flight variables.

Methods: In a cross-sectional study of 391 COPD patients and 184 non-COPD subjects, we recorded lung function, blood gas values, exercise capacity, air travel habits and in-flight symptoms.

Results: Fifty-four percent of the COPD patients had travelled by air the last two years. Hypoxia-related symptoms during air travel were experienced in 25% of the COPD patients and 9% of the non-COPD subjects ($p < 0.001$). After adjusting for smoking status, age and gender, the odds ratio for COPD patients to experience dyspnea or air hunger was 6.6 (95% CI 2.5–17.3, $p < 0.001$) compared to non-COPD subjects. In the COPD patients, in-flight dyspnea or air hunger was strongly associated with pre-flight score on the Medical Research Council (MRC) Dyspnea scale ($p < 0.001$).

Conclusion: COPD patients had significantly increased risk of in-flight dyspnea or air hunger compared to non-COPD subjects. In COPD patients these symptoms were strongly associated with pre-flight MRC Dyspnea score.

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0954-6111/S - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2010.10.006
Introduction

Commercial airlines transport nearly two billion passengers every year.\(^1\) At maximal cruising altitude, the cabin pressure is allowed to decrease to the equivalent of 2438 m altitude. This may cause a significant decrease in arterial oxygen tension (PaO\(_2\)) in patients with respiratory disease, such as chronic obstructive pulmonary disease (COPD).\(^{1-6}\)

Previous literature has focused on hypoxemia during air travel,\(^4,7-11\) whereas data on in-flight symptoms are limited. Two studies report symptoms in 18% of patients with respiratory disease during air travel.\(^{12,13}\) These studies lack comparison with healthy subjects. Moreover, it is not known whether the occurrence of in-flight symptoms can be predicted on the basis of pre-flight examination of the patient.

Here we report a study on unselected, well characterized COPD patients and a group of subjects without COPD. The primary objectives were to determine the prevalence and kind of symptoms during air travel in COPD patients and in a community sample, and to assess whether sea-level values of lung function, arterial blood gases, exercise dyspnea, walking distance or desaturation during exercise were related to in-flight symptoms. Secondary aim was to determine air travel habits.

Methods

Study design

The present cross-sectional survey included 433 COPD patients and 233 subjects without COPD from the Bergen COPD Cohort Study (BCCS). The patients were recruited through outpatient clinics from several hospitals in Western Norway, and from three private specialist practices in Bergen (Norway).\(^4\) The control subjects were among earlier participants of a large general population survey from the same area.\(^15\)

All COPD patients had a smoking history of at least 10 pack-years, post-bronchodilator FEV\(_1/FVC<0.7\), and FEV\(_1<80\%\) predicted. The BCCS baseline visit in 2006 included clinical examination, Medical Research Council (MRC) Dyspnea scale\(^16\) scoring, arterial blood gas sampling, pulse oximetry, and lung function testing. The COPD patients also performed a 6-min walk test (6MWT).\(^17\) At the one-year follow-up visit, we collected questionnaire data on air travel habits and symptoms experienced during air travel within the previous two years. Of the eligible subjects, 575 (86%) completed the questionnaire and were included in the further analyses.

Written informed consent was obtained from all participants. The study was approved by The Regional Committee for Medical Research Ethics.

Questionnaire

The questionnaire included questions on air travel habits, reasons for not flying (if applicable), number and duration of flights within the last two years, pre-flight physician consultation, and in-flight symptoms. Unscheduled use of in-flight oxygen and healthcare within 48 h post-flight were registered. Symptoms were classified as hypoxia related (dyspnea, dizziness, headache, chest pain, air hunger, cough, fainting, palpitations) or hypoxia unrelated (ear pressure, sinus pressure, swollen legs). Wording of the questionnaire and alternatives for answering are given in the Online supplement.

Pulmonary function testing, blood gas measurement and functional walking test

Methods for spirometry and arterial blood gas measurements were performed as previously described.\(^14\) Diffusing capacity of the lung (DL,CO) and total lung volumes were measured according to standardised criteria (SensorMedics V\(_{max}\) Encore, VIASYS Healthcare Respiratory Technologies, Yorba Linda, USA).\(^18,19\) Reference values were based on equations from the European Community for Coal and Steel, or post-bronchodilator values from Johannessen et al.\(^20,21\) Dyspnea during the 6MWT was measured with the Borg CR10 scale.\(^17,22\) Data for DL,CO, blood gases, MRC Dyspnea scale, and 6MWT were missing in 123 (21%), 40 (7%), 33 (6%), 37 (9%) subjects, respectively.

Statistical analysis

Chi-squared tests, two sample t-tests and Mann Whitney tests were applied as appropriate. For identifying factors associated with prevalence of symptoms, a logistic regression model was used. Adjustment was made for smoking, age, and gender. A significance level of 5% was considered as statistically significant. The analysis was performed with SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results

Population characteristics, entire study group

Of the 575 subjects who completed the flight outcome questionnaire, there were 391 COPD patients and 184 non-COPD subjects (Fig. 1). The COPD group included significantly more men, and had a higher mean age (Table 1). According to the GOLD classification, 189 (48%), 141 (36%), and 61 (16%) of the COPD patients were in GOLD stages II, III, and IV, respectively.\(^23\)

![Figure 1](Image 308x90 to 536x239)

*Figure 1 Flow chart of the subject selection. BCCS: Bergen COPD Cohort Study.*\(^14\)
COPD patients who did not fly the previous two years

Forty-six percent of the COPD patients did not travel by air, compared to 13.6% of those without COPD (p < 0.001). The COPD patients who did not fly were older, had more reduced lung function, lower PaO₂, a more pronounced exercise desaturation and a shorter 6-min walking distance than those who flew (Table 2).

Of the 180 COPD patients who did not fly, 143 (79.4%) had no reason to travel by air during the previous two years, 16 (8.9%) did not dare to fly due to their lung disease, 16 (8.9%) stated other reasons (general fear of flying, economy, and hypersensitivity to perfume), and 5 (2.8%) were advised by a physician or other health professionals not to fly. As for the subjects without COPD, one patient (4.0%) did not fly due to fear of flying, and 24 (96.0%) reported no reason to fly.

Characteristics of COPD and non-COPD subjects who flew

Two-hundred eleven (54.0%) of the COPD patients and 159 (86.4%) of those without COPD flew during the previous two years (p < 0.001) (Fig. 2). During this period, 82.5% of the COPD patients had two or more flights, with a most common duration of 3–6 h (Fig. 2). The COPD patients travelled less frequently than those without COPD (median number 2–4 flights vs. more than 4 flights, respectively, p < 0.001).

The COPD group had higher mean age and pre-flight MRC Dyspnea score, and significantly lower FEV₁% predicted, DL₆₆% predicted, PaO₂ and SpO₂ than the non-COPD subjects (Table 2).

Symptoms

Symptoms during air travel were more frequently experienced in the COPD group (28.4%) than the non-COPD group (16.4%) (OR = 2.0, 95% CI 1.2–3.4, p < 0.001) (Fig. 3). One or more hypoxia related symptoms were reported by 52 (24.6%) of the COPD patients and by 14 (8.8%) of the non-COPD subjects (OR = 3.4, 95% CI 1.8–6.4, p < 0.001) (Fig. 3). The most frequent hypoxia related symptoms in the COPD group were dyspnea and air hunger, which were significantly higher in the COPD than in the group without COPD (p < 0.001) (Table 3). There was no significant difference between the groups with regard to symptoms that were not hypoxia related; ear pressure, sinus pressure, and swollen legs (OR = 0.7, 95% CI 0.3–1.6) (Fig. 3).

After adjustment for confounders (smoking status, age, and gender), patients with COPD had a more than 3-fold higher risk of experiencing hypoxia related symptoms than those without COPD (OR = 3.3, 95% CI 1.6–6.7). For the respiratory symptoms, dyspnea or air hunger, the risk was nearly 7-fold higher (OR = 6.6, 95% CI 2.5–17.3).

Associations between pre-flight parameters and in-flight symptoms

Only the MRC Dyspnea score and exercise SpO₂ showed a significant relationship to in-flight dyspnea and air hunger.
in COPD patients (Table 4). As for DL,CO and walking distance, there was a non-significant tendency towards a relationship. A logistic regression model including age, gender, MRC Dyspnea score, exercise desaturation, walking distance, and DL,CO was used to study associations between pre-flight variables and symptoms during air travel in patients with COPD. The risk for experiencing dyspnea and air hunger during flight was significantly related to the MRC Dyspnea score. Level 2 or higher on the MRC Dyspnea scale gave an OR 4.8 (95% CI 1.2–19.3) for in-flight dyspnea and air hunger compared to MRC Dyspnea score 0. The OR for experiencing in-flight dyspnea and air hunger was 0.93 (95% CI 0.87–0.99) per year increase in age. No other statistically significant associations were found.

Use of in-flight oxygen and healthcare before and after the flight

Before planning to travel by air, twenty-three (5.9%) of the COPD patients had consulted a physician, while two (1.1%) of those without COPD had a pre-flight physician consultation (p < 0.001). Fourteen of the twenty-three COPD patients were advised not to travel. Nine of those patients travelled despite the physicians’ advice, and five of them experienced hypoxia related symptoms. Eleven of the 391 COPD patients were on long-term oxygen therapy (LTOT). Two of them flew, both with supplementary oxygen, and none of them reported symptoms during air travel. Two of the 209 patients without LTOT needed unscheduled use of

Table 2  Comparison of COPD patients who flew and did not fly and subjects without COPD who flew.

<table>
<thead>
<tr>
<th></th>
<th>COPD patients n = 391</th>
<th>Subjects without COPD n = 184</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flew n = 211</td>
<td>Did not fly n = 180</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>124/87</td>
<td>113/67</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>61.9 (6.7)</td>
<td>63.9 (6.7)</td>
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<tr>
<td>FEV1, % of predicted</td>
<td>51.6 (12.6)</td>
<td>45.7 (15.2)</td>
</tr>
<tr>
<td>DL,CO, % of predicted</td>
<td>61.4 (17.9)</td>
<td>54.7 (18.6)</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>43.1 (9.2)</td>
<td>47.8 (11.0)</td>
</tr>
<tr>
<td>Blood gases and pulse oximetry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2, kPa</td>
<td>9.5 (1.0)</td>
<td>9.1 (1.3)</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>95.5 (2.3)</td>
<td>94.3 (3.0)</td>
</tr>
<tr>
<td>Six-minute walk test</td>
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<td></td>
</tr>
<tr>
<td>Distance, m</td>
<td>459 (99)</td>
<td>401 (106)</td>
</tr>
<tr>
<td>End SpO2, %</td>
<td>92.0 (4.7)</td>
<td>89.9 (6.6)</td>
</tr>
<tr>
<td>MRC Dyspnea scale</td>
<td>n = 194</td>
<td>n = 167</td>
</tr>
<tr>
<td>Stage 0</td>
<td>35 (18)</td>
<td>24 (14)</td>
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<td>Stage 1</td>
<td>87 (45)</td>
<td>42 (25)</td>
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<tr>
<td>Stage 2</td>
<td>52 (27)</td>
<td>58 (35)</td>
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<td>22 (13)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>6 (3)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean (SD). FEV1,%predicted: forced expiratory volume in 1 s in percent of predicted; DL,CO: diffusing capacity of the lung for carbon monoxide; TLC: total lung capacity; RV: residual volume; PaO2: arterial partial pressure of oxygen; SpO2: arterial oxygen saturation by pulse oximetry; MRC: modified Medical Research Council. *: test not performed. p1) = between COPD patients who flew and did not fly; p2) = between COPD patients who flew and subjects without COPD who flew.

Figure 2  Frequency and duration of flights in COPD patients and subjects without COPD. □: COPD patients, ■: subjects without COPD. *:*p < 0.001.
supplementary oxygen during flight. The pre-flight PaO₂ in these patients were 9.6 kPa and 8.3 kPa, and their FEV₁% pred were 52% and 30%, respectively.

In the time span of 48 h after air travel, nine (4.3%) COPD patients needed unscheduled healthcare, of these, four (1.9%) were hospitalized. Four of the nine patients had hypoxia related symptoms during flight. One of the subjects without COPD was hospitalized after air travel, but the subject in question did not report any symptoms during flight.

Discussion

More than fifty percent of an unselected, western COPD population had travelled by air during the previous two years. One fourth of them experienced hypoxia related symptoms during air travel, compared to nine percent of individuals without COPD. The risk of experiencing dyspnea or air hunger was almost seven times higher in the COPD group than in those without COPD. In patients with COPD, there was a strong association between in-flight dyspnea or air hunger and sea-level MRC Dyspnea score. Desaturation during 6MWT was also related to in-flight symptoms.

In 1991 and 1993 two studies from USA and Britain reported that 44% and 35% of the COPD patients had travelled by air. In the present study, 54% of the COPD patients had travelled by air, most of them more than once during the previous two years. Taking into account the high and increasing prevalence of COPD, the number of flight passengers suffering from this disease is considerable and likely to increase further.

To our knowledge, this is the first flight outcome study that compares COPD patients with non-COPD subjects. Our data show a 3-fold increase in hypoxia related symptoms, and a near 7-fold increase in dyspnea and air hunger. Altogether, one fourth of the COPD patients experienced hypoxia related symptoms during flight. We acknowledge that symptoms classified as hypoxia related may have other causes than hypobaric hypoxia. However, the occurrence of other air travel related symptoms like ear pressure, sinus pressure, and swollen legs did not differ between the groups, indicating that the COPD patients were not more prone to report symptoms in general.

Although the COPD population in the present study had a milder disease than in the study by Coker et al, the prevalence of in-flight symptoms was higher. This discrepancy can probably be explained by difference in patient selection. The patients in Coker’s study either used supplementary oxygen during flight or, according to a respiratory specialist assessment, were not expected to develop in-flight hypoxemia. Thus, it seems reasonable to assume that the prevalence of symptoms presented in the current study is more representative for an unselected population of flight passengers with COPD.

The difference in symptom prevalence between the COPD and the non-COPD group might have been influenced by difference in age, gender and smoking habits. Correcting for these parameters, however, did not influence the outcome variables significantly.

In previous studies, the majority of COPD patients reporting in-flight symptoms had severe hypoxemia during subsequent testing with Hypoxia-altitude simulation test (HAST). Thus, it seems reasonable to assume that the symptomatic patients in the current study suffered from hypoxemia, and that pre-flight testing would have resulted in the use of supplementary oxygen. It should be noted, however, that patients may become severely hypoxic during hypobaric and normobaric hypoxia without experiencing symptoms.

Nine patients needed healthcare after arrival, and almost half of those patients had symptoms during flight. It is worth noting that a large proportion of those who travelled against the advice of their physician experienced in-flight symptoms.

There are various methods for predicting in-flight hypoxemia, but as far as we know, prediction of in-flight symptoms

### Table 3: Hypoxia related symptoms in COPD patients and subjects without COPD.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>COPD patients n = 211</th>
<th>Subjects without COPD n = 159</th>
<th>p</th>
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<tbody>
<tr>
<td>Dyspnea</td>
<td>31 (14.7)</td>
<td>2 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Air hunger</td>
<td>24 (11.4)</td>
<td>4 (2.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>10 (4.7)</td>
<td>3 (1.9)</td>
<td>0.140</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (4.7)</td>
<td>6 (3.8)</td>
<td>0.651</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (3.8)</td>
<td>1 (0.6)</td>
<td>0.084</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5 (2.4)</td>
<td>2 (1.3)</td>
<td>0.703</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (1.4)</td>
<td>0 (0.0)</td>
<td>0.263</td>
</tr>
<tr>
<td>Fainting</td>
<td>1 (0.5)</td>
<td>1 (0.6)</td>
<td>~1</td>
</tr>
</tbody>
</table>

Data are presented as n (%).
has not previously been studied.\textsuperscript{2,3,27} Whereas lung function is only weakly correlated with in-flight hypoxemia, exercise related variables may give useful information for pre-flight assessment.\textsuperscript{4,10,28} We evaluated the association between these variables and the occurrence of in-flight symptoms. The MRC Dyspnea score at sea-level was strongly associated with in-flight dyspnea and air hunger. This is an interesting and not previously described observation, which may be clinically useful. Desaturation during a 6MWT also showed a significant relationship with in-flight dyspnea and air hunger and corroborates earlier observations of associations between exercise desaturation and in-flight hypoxemia.\textsuperscript{28} Inclusion of both MRC Dyspnea score and exercise desaturation may possibly be valuable in pre-flight evaluation algorithms.

It would have been of interest to establish whether in-flight symptoms were associated with development of hypoxemia during HAST, but hypoxic challenge testing was not performed. In addition, the current study has some other limitations. The time between the measurements and air travel could have been up to one year, and possible worsening of the lung disease may have influenced the results. In addition, the severity of the symptoms was not recorded. Also, the design of the study may give recall bias, which might result in under-reporting of symptoms. On the other hand, a design where the participants are asked to record respiratory distress during actual flights might lead to increased symptom awareness, and thereby over-reporting of symptoms. Although age and gender differences between subjects with and without COPD were corrected for in the analyses, these differences could conceivably have influenced the results.

In conclusion, a large proportion of patients with moderate to severe COPD travel by air. One fourth of them reported hypoxia related symptoms during air travel. The COPD patients had a near 7-fold higher risk of experiencing dyspnea or air hunger than those without COPD. The symptoms were strongly associated with MRC Dyspnea score, and an association between exercise desaturation during a 6MWT was also observed. The high prevalence of symptoms seems to justify pre-flight evaluation of COPD patients. The optimal algorithm for this evaluation remains to be established, but our results indicate that a symptom-based approach in the pre-flight evaluation might be useful.

Acknowledgments

The authors would like to thank professor in Medical Statistics, L. Sandvik, University of Oslo, for statistical support.

Sources of support

The study was funded by grants from The Norwegian Heart and Lung Patient Organization, The Norwegian Foundation for Health and Rehabilitation, The Foundation for Respiratory Research, University of Bergen, Norway and by grants from Center for Clinical Research, Haukeland University Hospital, Norway.

Conflict of Interest Statement

None.

Supplementary data

The supplementary data associated with this article can be found in the on-line version at doi:10.1016/j.rmed.2010.10.006.
References

Paper II
Air travel and chronic obstructive pulmonary disease: a new algorithm for pre-flight evaluation

Anne Edvardsen, 1, 3 Aina Akerø, 2 Carl C Christensen, 1 Morten Ryg, 1 Ole H Skjønsberg 2, 3

ABSTRACT

Background The reduced pressure in the aircraft cabin may cause significant hypoxemia and respiratory distress in patients with chronic obstructive pulmonary disease (COPD). Simple and reliable methods for predicting the need for supplemental oxygen during air travel have been requested.

Objective To construct a pre-flight evaluation algorithm for patients with COPD.

Methods In this prospective, cross-sectional study of 100 patients with COPD referred to hypoxia-altitude simulation test (HAST), sea level pulse oximetry at rest (SpO2 SL) and exercise desaturation (SpO2 6MWT) were used to evaluate whether the patient is fit to fly without further assessment, needs further evaluation with HAST or should receive in-flight supplemental oxygen without further evaluation. HAST was used as the reference method.

Results An algorithm was constructed using a combination of SpO2 SL and SpO2 6MWT. Categories for SpO2 SL >95%, 92–95% and <92%, the cut-off value for SpO2 6MWT was calculated as 84%. Arterial oxygen pressure (PaO2 HAST) <8.6 kPa was the criterion for recommending supplemental oxygen. This algorithm had a sensitivity of 100% and a specificity of 80% when tested prospectively on an independent sample of patients with COPD (n=50). Patients with SpO2 SL >95% combined with SpO2 6MWT ≥84% may travel by air without further assessment. In-flight supplemental oxygen is recommended if SpO2 SL=92–95% combined with SpO2 6MWT <84% or if SpO2 SL <92%. Otherwise, HAST should be performed.

Conclusions The presented algorithm is simple and appears to be a reliable tool for pre-flight evaluation of patients with COPD.

INTRODUCTION

The reduced atmospheric pressure in the aircraft cabin may cause severe in-flight hypoxaemia and respiratory symptoms in patients with lung disease, for example, chronic obstructive pulmonary disease (COPD). 1–12 With the growing prevalence of COPD 10 and a large proportion of patients with COPD travelling by air, 11–15 simple and practical methods for pre-flight evaluation of the patients’ fitness to air travel have been requested. 1–11, 15

Current air travel statements 1–2, 11–12 recommend supplemental oxygen when the arterial oxygen pressure (PaO2) is expected to fall below 6.6 or 7.3 kPa (50 or 55 mm Hg). Various lung function variables, prediction equations and algorithms have been proposed to estimate in-flight PaO2, the need for in-flight supplemental oxygen, and to select patients needing more advanced pre-flight testing, such as the hypoxia-altitude simulation test (HAST). 1–6, 13–20 HAST is considered to be the clinical ‘gold standard’ 3–11 but is time consuming and not widely available. Thus, it is important to minimise the number of patients needing referral to HAST. Prediction equations, sea level PaO2 and spirometric values alone have proven not to be reliable tools for estimating the risk of severe in-flight hypoxaemia. 1–3, 5–16, 22 In an algorithm published by the British Thoracic Society (BTS), sea-level oxygen saturation by pulse oximetry (SpO2 SL) was used as a discriminating variable, 15 and it was recently confirmed that a SpO2 SL<92% seems to be an appropriate cut-off value for recommending in-flight supplemental oxygen without further pre-flight evaluation. 23 For SpO2 SL≥92%, however, the predictive properties for detecting in-flight hypoxaemia were lower. 23 It has been shown that both exercise desaturation 15, 24, 25 and aerobic capacity 5 correlate significantly with in-flight PaO2. Thus, it would be of interest to study if a combination of SpO2 SL and standardised exercise testing could be used to minimise the number of patients needing more cumbersome pre-flight testing.
To further pre-flight evaluation with HAST. To this hypothesis, SpO2 was measured in a group of patients with COPD at rest and during a 6MWT, and the results were compared with oxygen tension and saturation obtained during HAST. The primary aim of the study was to develop a simple and reliable algorithm for pre-flight evaluation of patients with COPD based on these variables. The secondary aim of the study was to evaluate if HAST can be performed with certain medical conditions, such as SpO2 levels, since use of a non-invasive HAST could make the test simpler to perform and thereby more available.

METHODS
This prospective cross-sectional study was performed at a pulmonary rehabilitation hospital in Norway. The Regional Committee for Medical Research Ethics approved the study (S-08640b), and written informed consent was obtained from the participants. The study was recorded in ClinicalTrials.gov (NCT00896584).

Construction of the algorithm
The construction of the algorithm was based on sea-level measurements of lung function, blood gases, pulse oximetry and 6MWT. For recommending in-flight oxygen, PaO2 HAST < 6.6 kPa was chosen. To make the algorithm practical and clinically useful, the non-invasive variables with highest correlation to PaO2 HAST were analysed with receiver operating characteristics (ROC) analysis, first including all participants and second with subjects grouped according to SpO2 > 95%, 92–95% and < 92%. Results from the ROC analyses served as a basis for the construction of the algorithm, and thereafter all subjects were individually tested for calculation of the sensitivity and specificity of the new algorithm. Finally, the algorithm was prospectively validated on an independent sample of patients with COPD.

Subjects
One hundred and thirty-nine consecutive patients with COPD who were referred from chest physicians in southern Norway to pre-flight evaluation were invited to participate in the study. The referral criteria were moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Previous air travel intolerance, or SpO2 SL ≤ 95%, Lack of laboratory capacity (n=22) Unwell/unmanageable (n=7) LTOT (n=6) Unable to perform 6MWT (n=5) Other reasons (n=2) Excluded (n=39)

Total number of patients with COPD (n=139)

Figure 1 Flow chart describing the patient selection. COPD, chronic obstructive pulmonary disease; 6MWT, 6 min walk test; HAST, hypoxia-altitude simulation test; LTOT, long-term oxygen treatment.

RESULTS
Patient characteristics
The study comprised patients with COPD (n = 100), with demographic characteristics as presented in table 1. According to the GOLD classification, 22% (22 of 100), and 22% (22 of 100), and 22% (22 of 100), respectively.

Sea-level measurements and HAST
Lung function tests were performed according to standard criteria. SpO2 SL was measured with pulse oximetry (Nonin 3100 Wristox or Nonin PalmSat 2500, Nonin Medical Inc, North Plymouth, Massachusetts, USA), and simultaneously an arterial blood sample was drawn from a radial artery catheter and immediately analysed (ABL800 Flex, Radiometer, Copenhagen, Denmark). Exercise-related dyspnoea was measured with the modified Medical Research Council Dyspnoea Scale (mMRC).

The 6MWT was performed in accordance with standard criteria, and SpO2 and dyspnoea (Borg CR10) were recorded every minute. None of the patients used supplemental oxygen during the 6MWT.

HAST was used to simulate a cabin pressure corresponding to an altitude of 2438 m above sea level (8000 ft). The subjects breathed 15.1% oxygen (15.1% O2, 84.9% N2, Yara Praxair, Norway) from a non-diffusing gas collection bag (170 litre Douglas-bag, Hans Rudolph Inc, Shawnee, USA) through a facemask (Mirage Full Face Mask, ResMed Corp, Poway, California, USA), and arterial blood samples were taken after 15 min hypoxic exposure. The SpO2 should be stable for 5 min before arterial blood sampling, otherwise the test was prolonged to 20 min. Electrocardiogram, SpO2 and dyspnoea were continuously monitored. The patients were recommended in-flight supplemental oxygen if PaO2 HAST was < 6.6 kPa.

Statistics
To calculate sample size, we assumed that sensitivity and specificity would be approximately 80% in the planned study. It was then shown that 100 patients were needed to construct a new algorithm in which sensitivity and specificity should have CI length < 16%. Patient characteristics are presented as mean and SD, unless otherwise specified. Relations between PaO2 HAST and patient characteristics were assessed from Pearson’s correlation coefficient and one-way repeated measures analysis of variance. ROC analyses were performed with a new algorithm.

HAST
All patients were tested with HAST. Mean HAST values for PaO2 and SpO2 were 6.3 kPa (SD 0.6 kPa) and 83% (SD 4%), respectively. Seventy-three per cent of patients had a PaO2 HAST < 6.6 kPa, indicating that they, in accordance with current...
showed no sign

Six min walk test

BMI, kg/m²

Age, years

Dyspnea, mMRC*

Grade 0–1

Grade 2

Grade 3

Grade 4

Lung function

FEV₁, litres

FEV₁/FVC

DL,CO, mmol/min/kPa

DL,CO/VA, mmol/min/kPa/litre

TLC, litre

RV, litre

Blood gases and pulse oximetry at sea level

PaO₂, kPa

PaCO₂, kPa

SpO₂, %

Six min walk test

Distance, m

Exercise SpO₂, %

Dyspnea, Borg CR10

HAST blood gases and pulse oximetry

PaO₂, kPa

PaCO₂, kPa

SaO₂, %

SpO₂, %

Table 1  Baseline patient characteristics, n=100

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<td>Dyspnea, mMRC*</td>
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<tr>
<td>Grade 0–1</td>
<td>16 (16%)</td>
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<tr>
<td>Grade 2</td>
<td>49 (50%)</td>
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<td>Grade 3</td>
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<td>Grade 4</td>
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<td>TLC, litre</td>
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<td>RV, litre</td>
<td>4.4 (1.4)</td>
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<td>PaO₂, kPa</td>
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<td>PaCO₂, kPa</td>
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<td>SpO₂, %</td>
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<td>Distance, m</td>
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<td>PaO₂, kPa</td>
<td>6.3 (0.7)</td>
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<td>PaCO₂, kPa</td>
<td>4.9 (0.6)</td>
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<tr>
<td>SaO₂, %</td>
<td>83 (5)</td>
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<tr>
<td>SpO₂, %</td>
<td>83 (4)</td>
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</table>

Data are presented as n (%) and mean (SD).

* n=98.

BMI, body mass index; DL,CO, diffusing capacity of the lung for carbon monoxide; FEV₁/FVC, forced expiratory volume in 1 s in per cent of predicted; FVC, forced vital capacity; HAST, hypoxia-altitude simulation test; mMRC, modified Medical Research Council Dyspnea Scale; PaCO₂, arterial carbon dioxide pressure; PaO₂, arterial oxygen pressure; RV, residual volume; SaO₂, arterial oxygen saturation; SpO₂, arterial oxygen saturation by pulse oximetry; TLC, total lung capacity; VA, alveolar volume.

guidelines, should use in-flight supplemental oxygen. There was an increase of 0.8 (SD 1.0) in dyspnoea score (Borg CR10) (p<0.001). Eighteen per cent of patients reported moderate to strong dyspnoea (Borg score 3–6), but there was no significant correlation between dyspnoea score and PaO₂_{HAST} (r=0.16, p=0.115). None of the patients experienced hypoxia-induced myocardial ischaemia or arrhythmias.

Walking test

The patients covered a distance varying from 150 to 604 m during the 6MWT (table 1). The mean decrease in SpO₂ during the 6MWT was 10% (SD 5%) (p<0.001), and the mean SpO₂_{6MWT} was 83% (SD 6%) (table 1).

Associations between in-flight PaO₂ and sea-level characteristics

Significant correlations between sea-level characteristics and in-flight PaO₂ are presented in table 2. PaO₂_{SL}, PaO₂_{6MWT} and PaO₂_{HAST} showed the strongest correlation with PaO₂_{HAST} PaO₂_{SL} was not included in the further analyses since one aim of the study was to develop a non-invasive evaluation method. Diffusing capacity of the lung for carbon monoxide (DL,CO), DL,CO/alveolar volume, total lung capacity (TLC), residual volume (RV), RV/TLC and dyspnoea measured with mMRC showed no significant relationship with in-flight PaO₂.

ROC analyses were used as the basis for developing the pre-flight evaluation algorithm. PaO₂_{SL} and PaO₂_{6MWT} showed good diagnostic properties (area under curve 0.78 and 0.79, respectively) for detection of in-flight PaO₂ <6.6 kPa (figure 2). The patients were grouped and data analysed according to the BTS pulse oximetry categories, PaO₂_{SL} >95%, 92–95% and <92% (figure 3). In the group with sea-level PaO₂ <92%, 30 of 33 (91%) patients dropped below the recommended level for minimum in-flight PaO₂ (6.6 kPa), and were thereby in need of supplemental oxygen during air travel. Regarding the 55 patients in the group with PaO₂_{SL} from 92% to 95%, a ROC analysis with PaO₂_{6MWT} showed good diagnostic properties (area under curve 0.80) for detection of in-flight PaO₂ <6.6 kPa. The suggested cut-off value was PaO₂_{6MWT} <84% (sensitivity 88%, 95% CI 80% to 96%; specificity 69%, 95% CI 52% to 85%). With regard to patients with PaO₂_{SL} >95%, 5 of 12 (42%) had an in-flight PaO₂ <6.6 kPa. In this group, ROC analysis showed exercise desaturation as a good prognostic variable, with an optimal cut-off value for PaO₂_{6MWT} <84% (area under curve 0.71; sensitivity 80%, 95% CI 40% to 100%; specificity 71%, 95% CI 29% to 100%).

Algorithm

Based on the above analyses a pre-flight evaluation algorithm was constructed (figure 4). The algorithm was based on a sea-level resting pulse oximetry (PaO₂_{SL}) and exercise desaturation during the 6MWT (PaO₂_{6MWT}) as the primary and secondary discriminator for evaluating whether the patient was fit to fly without further assessment, in need of further evaluation with HAST or should receive in-flight supplemental oxygen without further evaluation.

Before the pre-flight evaluation algorithm had a sensitivity of 99% (95% CI 96% to 100%) and a specificity of 82% (95% CI 67% to 96%) when all 100 subjects were individually tested. According to the algorithm, one-third (33%) of the patients would be advised to perform extended pre-flight testing with HAST. Six per cent of the patients were not correctly classified by the algorithm; of these, one patient was misclassified as fit to fly despite a PaO₂_{HAST} <6.6 kPa (PaO₂_{SL} 97% and PaO₂_{6MWT} 87%, measured PaO₂_{HAST} 6.3 kPa), and five patients would have been recommended to use in-flight oxygen without, in fact, having a PaO₂_{HAST} <6.6 kPa (mean PaO₂_{HAST} 7.2 kPa (SD 0.3 kPa)). The patients selected by the algorithm for further pre-flight evaluation with HAST had a mean PaO₂_{HAST} of 6.6 kPa (SD 0.6 kPa).

After the algorithm was established, it was prospectively validated on an independent sample of 60 patients with COPD who were referred to HAST (table 3). Eight patients had PaO₂_{SL} >95% (16%), 27 patients had PaO₂_{SL} 92–95% (54%) and 15 patients had PaO₂_{SL} <92% (30%). For all but four patients a correct choice was obtained with regard to use of in-flight supplemental oxygen. These four patients were recommended...
supplemental oxygen without having a PaO₂ < 6.6 kPa. However, it should be noted that they all had PaO₂ HAST values close to the recommended limit (mean PaO₂ HAST 6.6 kPa, SD 0.1 kPa). The sensitivity and specificity for the algorithm in this independent sample of patients were 100% (95% CI 90% to 100%) and 80% (95% CI 60% to 95%), respectively. The 20 patients which the algorithm selected for further pre-flight evaluation with HAST had a mean PaO₂ HAST of 6.9 kPa (SD 0.5 kPa).

**HAST: PaO₂ versus SpO₂**

The secondary aim was to evaluate if HAST can be performed with SpO₂ as a substitute for PaO₂. There was a strong correlation between PaO₂ HAST and SpO₂ HAST (r = 0.81, p < 0.001) during HAST. The area under the ROC curve when using pulse oximetry to detect in-flight PaO₂ < 6.6 kPa was 0.93, indicating strong prognostic properties for the method (figure 5). The analysis suggested a cut-off value for SpO₂ HAST ≥ 85% with a sensitivity of 99% (95% CI 81% to 96%) and a specificity of 81% (95% CI 67% to 96%) when SpO₂ HAST was used as a substitute for PaO₂ HAST < 6.6 kPa (figure 5). When using SpO₂ HAST, instead of PaO₂ HAST in an independent sample of 50 patients with COPD, we obtained a sensitivity of 90% (95% CI 77% to 100%) and a specificity of 85% (95% CI 70% to 100%). Three patients were misclassified as fit by despite having PaO₂ HAST < 6.6 kPa (mean PaO₂ HAST 6.3 kPa), and three patients would have been recommended to use in-flight oxygen without, in fact, having a PaO₂ HAST < 6.6 kPa (mean PaO₂ HAST 6.7 kPa).

**DISCUSSION**

A large number of patients with COPD travel by air, most of them without severe in-flight medical problems. However, some patients develop severe hypoxaemia. Thus, simple and consistent pre-flight assessment guidance regarding the need for in-flight supplemental oxygen has been requested. In the present study we have constructed and validated a simple and clinically feasible algorithm for pre-flight assessment of patients with COPD based on sea-level resting SpO₂ and SpO₂ values during a 6MWT.
**Table 3** Baseline characteristics for patients used in the separate validation of the algorithm, n=50

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<th>Sex, M/F</th>
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<tr>
<td>Age, years</td>
<td>64 (8)</td>
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<td>Lung function</td>
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<tr>
<td>FEV1, litres</td>
<td>1.1 (0.4)</td>
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<tr>
<td>FEV1/FVC</td>
<td>0.41 (0.09)</td>
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<tr>
<td>DLCO, mmol/min/kPa</td>
<td>3.0 (1.5)</td>
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<td>DLCO/VA, mmol/min/kPa/litre</td>
<td>0.6 (0.3)</td>
</tr>
<tr>
<td>TLC, litres</td>
<td>7.6 (1.6)</td>
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<tr>
<td>RV, litres</td>
<td>4.4 (1.3)</td>
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<tr>
<td>Blood gases and pulse oximetry at sea level</td>
<td></td>
</tr>
<tr>
<td>PaO2, kPa</td>
<td>9.0 (1.1)</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>5.1 (0.6)</td>
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<tr>
<td>SpO2, %</td>
<td>93 (3)</td>
</tr>
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<td>Six min walk test</td>
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<tr>
<td>Distance, m</td>
<td>425 (109)</td>
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<tr>
<td>Exercise SpO2, %</td>
<td>92 (4)</td>
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<td>Dyspnoea, Borg CR10</td>
<td>6.4 (2.2)</td>
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<td>HAST blood gases and pulse oximetry</td>
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<tr>
<td>PaO2, kPa</td>
<td>6.5 (0.5)</td>
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<td>PaCO2, kPa</td>
<td>4.9 (0.6)</td>
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<tr>
<td>SaO2, %</td>
<td>85 (4)</td>
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<tr>
<td>SpO2, %</td>
<td>85 (4)</td>
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</table>

Data are presented as n (%) and mean (SD).

| FEV1/FVC | 40.2 (15.1) |
| DLCO/VA | 36 (17) |
| TLC/VA  | 127 (21) |
| RV/VA   | 198 (50) |

Various proposed equations and single sea-level variables have proven not to predict in-flight hypoxaemia with a satisfactory precision. Several authors have suggested that exercise-related outcomes may be useful discriminators. Previous studies from our group show that aerobic capacity correlates with in-flight hypoxaemia. Chetta et al showed that desaturation during the 6MWT provides useful information in the pre-flight assessment. Since oxygen saturation measured with pulse oximetry, at rest and during a 6MWT, is frequently used in the medical care of patients with COPD, an algorithm employing a combination of these variables would be simple to implement in a busy clinical practice. An assessment algorithm that can discriminate between patients who will need supplemental oxygen during air travel and those who can travel without such equipment would be of considerable value in the evaluation of patients with COPD intending to travel by air, especially if the number of unequivocal findings needing more extensive pre-flight evaluation is reduced.

The results from our group have previously indicated that the BTS algorithm with only sea-level SpO2 cannot be used with confidence to predict in-flight hypoxaemia. A large number of patients at risk of developing severe hypoxaemia was not detected, and a considerable number of patients needed more advanced pre-flight evaluation. By adding a 6MWT, including measurement of SpO2, the current study shows that the number of patients needing referral to HAST was markedly reduced. The 6MWT is a widely used test to assess exercise performance in patients with COPD, and is much more available than HAST. However, it is important that the 6MWT is performed according to guidelines, and it must be stressed that shortcuts must be avoided. The suggested algorithm has a high sensitivity, which was reproduced when applying it prospectively on a separate group of patients with COPD. None of these study subjects were misclassified as fit to fly without supplemental oxygen. Due to somewhat lower specificity, the algorithm overestimated the risk of in-flight hypoxaemia, resulting in unnecessary use of supplemental oxygen in 8% of the patients.

According to our results, patients with COPD who have SpO2 SL >95% and without severe exertional desaturation (SpO2 <84%) can travel safely by air without further pre-flight assessment. In addition, further pre-flight assessment is not necessary in patients with SpO2 SL <92% or in patients with SpO2 SL 92–95% and SpO2 6MWT <84%. These patients should, according to our results, be equipped with supplemental oxygen during the flight. Thus, extended pre-flight assessment with HAST might be limited to patients with either the combination of resting SpO2 SL >95% and severe exercise desaturation (SpO2 <84%) and to patients with SpO2 SL between 92% and 95% without severe exercise desaturation (≥84%). In these two groups of patients, the level of in-flight hypoxaemia was difficult to predict, underlining the need for pre-flight testing with HAST.

Even though HAST is increasingly used in pre-flight assessment, it is not widely available. HAST has been shown to be a good predictor of in-flight PaO2 and the results obtained are reproducible. However, one might find it cumbersome to take repeated arterial blood samples or insert a radial artery catheter, and substitution of arterial blood gas measurement with pulse oximetry would simplify the HAST procedure considerably. To our knowledge, comparison of arterial blood gases and pulse oximetry during HAST has not previously been published. As expected, a strong correlation between PaO2 HAST and SpO2 HAST was observed, and when using a cut-off value for SpO2 HAST ≤85% as a substitute for a PaO2 HAST <6.6 kPa, acceptable values for sensitivity and specificity of the test were obtained. Our results show that use of pulse oximetry during HAST may underestimate the need for in-flight oxygen. Thus, the authors would recommend arterial blood gas measurement during HAST as the method of choice.

To our knowledge, this is the first prospective study to use a set of common baseline characteristics for the construction of a pre-flight evaluation algorithm. The good prognostic properties of the algorithm were confirmed by a prospective validation on a separate group of subjects with COPD. However, it should be noted that a selected group of patients was studied; they were all referred for pre-flight evaluation. These are the patients for which the algorithm was validated. This might limit the generalizability of our results.
whom the algorithm is intended. One must also keep in mind that the present study only comprised patients with moderate to very severe COPD \(^2\) and that the algorithm may not be applicable to patients with other lung diseases.

In conclusion, an algorithm for pre-flight evaluation of patients with COPD is presented, employing simple non-invasive oximetry at rest and during walking. By using the algorithm, the majority of a population consisting of patients with moderate to very severe COPD could be classified as fit to fly or in need of supplemental oxygen without more advanced pre-flight assessment.

Acknowledgements Leiv Sandvik, Professor in Biostatistics, Oslo University Hospital, is gratefully acknowledged.

Contributors AE and MR: conception and design of the study, collecting, analysing and interpreting the data, drafting and revising the manuscript. AA: conception and design of the study, interpreting the data, drafting and revising the manuscript. OHS: conception and design of the study, analysing and interpreting the data, drafting and revising the manuscript.

Funding The study was funded by grants from The Norwegian Heart and Lung Patient Organisation and The Norwegian Foundation for Health and Rehabilitation.

Competing interests None.

Ethics approval Ethics approval was provided by The Regional Norwegian Committee for Medical Research Ethics.

Provenance and peer review Not commissioned; externally peer reviewed.

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Paper III
COPD and air travel. New title exceeds the limit a little. Full title; see Main Body Text

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COPD and air travel: does hypoxia-altitude simulation testing predict in-flight respiratory symptoms?

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Key Words: chronic obstructive pulmonary disease, COPD, dyspnoea, hypoxaemia, air travel, oxygen.
Abstract

The reduced pressure in the aircraft cabin may cause significant hypoxaemia and respiratory symptoms in patients with chronic obstructive pulmonary disease (COPD). The current study evaluated whether there is a relationship between hypoxaemia obtained during hypoxia-altitude simulation testing (HAST), simulating 2438 m altitude, and the reporting of respiratory symptoms during air travel.

Eighty-two patients with moderate to very severe COPD answered an air travel questionnaire. Arterial oxygen pressures during HAST (PaO₂ HAST) in subjects with and without in-flight respiratory symptoms were compared. The same questionnaire was answered within one year after the HAST.

Mean PaO₂ HAST was 6.3 (0.6) kPa, and 62 (76%) of the patients had PaO₂ HAST <6.6 kPa. Thirty-eight patients (46%) had experienced respiratory symptoms during air travel. There was no difference in PaO₂ HAST in those with and those without in-flight respiratory symptoms (6.3 (0.7) kPa vs. 6.3 (0.6) kPa, respectively, (p=0.926)).

Fifty-four patients (66%) travelled by air after the HAST, and patients equipped with supplemental oxygen (n=23, 41%) reported less respiratory symptoms when flying with than without such treatment (4 (17%) vs. 11 (48%), p=0.039).

In conclusion, no difference in PaO₂ HAST was found between COPD patients with and without respiratory symptoms during air travel.

Word count abstract: 200
Introduction

The low atmospheric pressure in an aircraft cabin may cause significant in-flight hypoxaemia in patients with lung disease [1-3]. In guidelines, recommendations and reviews dealing with air travel and lung disease, both respiratory symptoms and complications related to the negative effect of hypoxia on other organs, such as the heart, are addressed [1-3]. To ensure safe travel for patients with lung disease, pre-flight evaluation has focused on predicting in-flight hypoxaemia, and, if necessary, to supply the patients with oxygen during the flight.

Planned use of in-flight supplemental oxygen is recommended if in-flight arterial oxygen pressure (PaO₂) is anticipated to fall below 6.6 kPa [1, 3]. In-flight hypoxaemia has proven difficult to predict; neither sea level arterial oxygen levels nor spirometric values alone seem to be reliable tools for this purpose [1]. In a recent study, we have shown that a combination of arterial oxygen saturation by pulse oximetry (SpO₂) at rest and SpO₂ during exercise at sea level predicts in-flight hypoxaemia with high sensitivity and specificity in patients with chronic obstructive pulmonary disease (COPD) [4]. Some patients, however, are in need of more advanced pre-flight testing with a hypoxia-altitude simulation test (HAST) breathing a gas mixture with 15.1 % oxygen, corresponding to an aircraft cabin altitude of 8000 ft (2438 m) [5-7].

In another study, we found that respiratory symptoms (dyspnoea or air hunger) during air travel were reported by 21% of patients with COPD, compared to 4% of healthy individuals [8]. Studies regarding the relationship between in-flight symptoms and hypoxaemia, however, are lacking. The effect of hypoxaemia on dyspnoea in patients with COPD is complex and poorly understood, and in general the sensation of dyspnoea seems to be more related to increase in ventilation than to decreased arterial oxygen tension per se [9-11]. The physiological and clinical basis for recommending pre-flight hypoxia testing has previously been questioned by Naeije [12].

The objective of the present observational study was to evaluate whether the patients reporting symptoms during air travel are those who develop severe hypoxaemia when tested with HAST. For this purpose, patients with moderate to very severe COPD were invited to answer a questionnaire regarding in-flight symptoms and
the need of health care in the days following air travel. Subsequently, all patients performed a HAST. Finally, the patients answered the same questionnaire within one year after the HAST, enabling us to study the consistency of symptoms in patients who did not use in-flight supplemental oxygen, and in addition, the subjective effect of supplemental oxygen during the flight in patients receiving such treatment.
Methods

The current observational study was performed at a pulmonary rehabilitation hospital in Norway. Patients with moderate to very severe COPD [13] who were referred to pre-flight evaluation with HAST and who had travelled by air without supplemental oxygen within the last two years were consecutively invited to participate (Figure 1). The most frequent reasons for referral to pre-flight evaluation were previous air travel intolerance or severe and very severe COPD according to the GOLD spirometric classification [13]. The Regional Committee for Medical Research Ethics, Health Region East (Oslo, Norway) approved the study, and written informed consent was obtained from the participants. The study was recorded in ClinicalTrials.gov (NCT00896584).

Subjects

The study population comprised 82 patients (previously included in [4]) (Figure 1). The inclusion criteria were moderate to very severe COPD [13] and air travel without supplemental oxygen performed within the last two years. Exclusion criteria were unstable angina, uncontrolled hypertension, uncontrolled arrhythmia or long-term oxygen treatment. Fifty-seven (70%) of the participants had known co-morbidities; the most frequent being systemic arterial hypertension, muscular-skeletal disorders, and ischemic heart disease. All patients were in a stable phase of their COPD and co-morbidities during both air travel and HAST, and they used their regular medication.

Pulmonary function tests and blood gases

Lung function tests included measurement of post bronchodilator spirometry, diffusing capacity for the lung (DL,CO), and total lung volumes (MasterScreen Pneumo, Jaeger-Toennis, Hoechberg, Germany). Reference values were based on equations from the European Community for Coal and Steel [14].

After 10 minutes of rest in a sitting position, an arterial blood sample (PICO50, Radiometer, Copenhagen, Denmark) was drawn from a radial artery cannula. The sample was immediately analysed (ABL825 Flex,
Radiometer, Copenhagen, Denmark). Arterial oxygen saturation by pulse oximetry (SpO₂) (NONIN 2500 Palm Sat, Nonin Medical Inc., North Plymouth, USA) was simultaneously measured.

**Hypoxia-altitude simulation test**

HAST was used to simulate a cabin pressure corresponding to an altitude of 8000 ft (2438 m) above sea level. During HAST the subjects breathed 15.1% oxygen (15.1% O₂, 84.9% N₂, Yara Praxair, Norway) from a non-diffusing gas collection bag (170 L Douglas-bag, Hans Rudolph Inc., Shawnee, USA) and through a tight fitting facemask (Mirage Full Face Mask, ResMed Corp, Poway, USA). After 15 minutes arterial blood samples were drawn from a radial arterial cannula and immediately analysed [5, 15]. The SpO₂ should be stable for 5 minutes before arterial blood sampling; otherwise the test was prolonged to 20 minutes. Electrocardiogram, SpO₂ and symptoms (Borg CR10 scale) [16] were continuously monitored. Patients with PaO₂ HAST <6.6 kPa were recommended to use in-flight supplemental oxygen [1].

**Questionnaire**

All patients completed an air travel questionnaire [8] elucidating in-flight symptoms; dyspnoea or air hunger (hereafter defined as respiratory symptoms), dizziness, headache, chest pain, cough, fainting, and palpitations experienced during flights performed within the last two years prior to the HAST. The patients also reported use of acute supplemental oxygen, and need of medical care after the air travel. In addition, all patients were asked to answer an identical air travel questionnaire within 6-12 months after the HAST.

**Statistics**

Descriptive data are presented as mean and standard deviation, unless otherwise specified. Univariate analyses (independent samples t-test and χ² test as appropriate) were used for assessment of relationship between respiratory symptoms and PaO₂ HAST. Univariate exploratory analyses were performed using McNemar, Pearson χ² test or Fisher Exact Test for categorical variables. A significance level of 5% was used. The kappa statistic was used to measure test-retest reliability of the air travel questionnaire. To get an impression of the statistical
power, the present sample size would allow detection of a mean $\text{PaO}_2 \text{ HAST}$ difference of 0.45 kPa with a power of 80%.
Results

Subject characteristics

Data from 82 patients with moderate to very severe COPD who had travelled by air within the last two years are presented in Table 1. According to the GOLD classification of severity of airflow limitation [13] there were 19, 49 and 14 (23%, 60%, and 17%) patients with COPD grade 2, 3 and 4, respectively.
Table 1. Subject characteristics, n=82

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>34/48</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>65 (7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.9 (4.8)</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.0 (0.4)</td>
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<tr>
<td>FVC, L</td>
<td>2.4 (0.8)</td>
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<tr>
<td>FEV₁/FVC</td>
<td>0.45 (0.10)</td>
</tr>
<tr>
<td>DL₃CO, mmol·min⁻¹·kPa⁻¹</td>
<td>3.2 (1.3)</td>
</tr>
<tr>
<td>RV, L</td>
<td>4.4 (1.5)</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>60.3 (9.6)</td>
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<tr>
<td>Blood gases and pulse oximetry at sea level</td>
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</tr>
<tr>
<td>PaO₂, kPa</td>
<td>9.0 (1.1)</td>
</tr>
<tr>
<td>PaCO₂, kPa</td>
<td>5.1 (0.6)</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>93 (3)</td>
</tr>
<tr>
<td>HAST blood gases and pulse oximetry</td>
<td></td>
</tr>
<tr>
<td>PaO₂, kPa</td>
<td>6.3 (0.6)</td>
</tr>
<tr>
<td>PaCO₂, kPa</td>
<td>4.9 (0.6)</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>83 (4)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) and mean (SD). BMI: body mass index; FEV₁ %predicted: forced expiratory volume in one second in per cent of predicted; FVC: forced vital capacity; DL₃CO: diffusing capacity of the lung for carbon monoxide; RV: residual volume; TLC: total lung capacity; PaO₂: arterial oxygen pressure; PaCO₂: arterial carbon dioxide pressure; SpO₂: arterial oxygen saturation by pulse oximetry; HAST: hypoxia-altitude simulation test.

**HAST results**

The mean PaO₂ HAST was 6.3 (0.6) kPa. Sixty-two patients (76%) had PaO₂ HAST <6.6 kPa and were recommended to use in-flight supplemental oxygen. Mean PaCO₂ HAST was 4.9 (0.6) kPa (Table 1). There was a significant increase in dyspnoea score during HAST (0.5 to 1.3, p<0.001). No difference in median dyspnoea score between those with (1, range 0-6) and those without (1, range 0-4.5) in-flight respiratory symptoms was observed (p=0.262). None of the patients had arrhythmias or signs of ischemia in the electrocardiogram during the HAST.
Air travel, symptoms and use of medical care

All patients had travelled by air without supplemental oxygen before referral to HAST. In the first questionnaire, respiratory symptoms were by far the most common and were experienced by 38 (46%) patients. Dizziness and headache were reported by 6 (7%) vs. 5 (6%) patients, respectively (Figure 2). Eight (10%) patients had needed unscheduled, acute oxygen treatment in the aircraft cabin; seven patients due to respiratory symptoms and one due to fainting. Fourteen patients (17%) needed medical care within 48 hours after arrival. Of these, mean PaO$_2$)$_{HAST}$ was 6.0 (0.6), and all had PaO$_2$)$_{HAST}$ <6.6 kPa. Seven (8%) of these patients were admitted to hospital and seven (8%) patients received out patient treatment. Those who did not require medical care had a mean PaO$_2$)$_{HAST}$ 6.3 (0.7) kPa (p=0.093).

Association between in-flight respiratory symptoms and PaO$_2$)$_{HAST}$

There was no difference in PaO$_2$)$_{HAST}$ between those with and those without in-flight respiratory symptoms (6.3 (0.7) kPa vs. 6.3 (0.6) kPa, p=0.926). (Figure 3). There was a tendency towards more respiratory symptoms for patients with PaO$_2$)$_{HAST}$ below the median value 6.3 kPa (54%) vs. PaO$_2$)$_{HAST}$ above 6.3 kPa (39%), p=0.184. There was no association between PaO$_2$ values obtained during HAST and other in-flight symptoms.

Second questionnaire

Seventy-eight of the 82 patients (95%) answered the second questionnaire within 12 months after the HAST (Figure 1). Fifty-four patients (66%) had travelled by air in the interval between the first and the second questionnaire. Thirty-one of these patients did not use supplemental oxygen during any of the flights, and the prevalence of respiratory symptoms reported in the two questionnaires by these patients showed no significant difference (36% and 45%, respectively, p=0.453) (Figure 4). For these patients there was good consistency in the reporting of respiratory symptoms; 24 of the 31 (77%) patients gave identical answers in the first and the second questionnaire (kappa=0.54). Three of the 31 patients (10%) who travelled without supplemental oxygen needed unscheduled, acute oxygen treatment due to respiratory symptoms when travelling after HAST, a
similar percentage as in the first questionnaire, and one patient (3%) reported need of health care within 48 hours after the flight compared to 17% (14 of 82) in the first questionnaire (p=0.039).

In-flight respiratory symptoms when using supplemental oxygen

Twenty-three of the 54 (43%) patients used planned, supplemental oxygen during their flight after HAST, and there was a significant decrease in the prevalence of respiratory symptoms when travelling with supplemental oxygen compared to travelling without oxygen treatment, 17% vs. 48%, respectively (p=0.039) (Figure 5). The 23 patients who used supplemental oxygen also had significantly lower prevalence of in-flight respiratory symptoms than the 31 patients who did not use such treatment (17% vs. 45%, respectively, p=0.032) (Figure 6).
Discussion

The aim of pre-flight assessment in patients with lung disease is to enhance air travel safety, with identification of patients likely to develop severe in-flight hypoxaemia. The decreased oxygen saturation may exacerbate co-existing medical conditions, such as coronary heart disease, and may also be related to the development of respiratory distress during or after the flight [1-3, 11]. Respiratory symptoms during air travel are reported by approximately one of five patients with COPD [8, 17, 18], and development of severe hypoxaemia is well documented, both during real and simulated flights [1, 3, 15, 19-21]. The association between in-flight respiratory symptoms and hypoxaemia has, however, not been studied. In the current study, comprising patients with moderate to very severe COPD, we found no difference in PaO₂ obtained during a simulated flight in those experiencing respiratory symptoms during air travel and those who did not. Somewhat contradictory to this finding, planned use of in-flight supplemental oxygen in patients with PaO₂ HAST <6.6 kPa resulted in a lower frequency of respiratory symptoms.

Almost 50% of the patients in the current study reported respiratory symptoms. This is considerably higher than in previous studies, which have reported 18-21% [8, 17, 18]. The discrepancy may be explained by COPD severity and the fact that some of our patients were referred to HAST because of symptoms during previous flights. The kappa value when comparing respiratory symptoms reported by the patients who flew both times without supplemental oxygen was high, indicating an acceptable test-retest reliability. In accordance with our previous study [8], other symptoms like dizziness, fainting and headache were scarcely reported. This strengthens the finding of respiratory symptoms as a dominating concern during air travel for patients with COPD. The lack of association between respiratory symptoms and PaO₂ during HAST is in agreement with observations at sea-level where dyspnoea in general is poorly correlated with blood gas abnormalities, both at rest and during exercise [9, 22]. Also, it has been shown that patients with COPD may become severely hypoxaemic during air travel without having any symptoms [23]. Dyspnoea represents a variety of qualitatively distinct sensations and is the result of stimulation of a number of mechanoreceptors throughout the airways,
lungs, and chest wall in addition to inadequate delivery of oxygen to peripheral muscles [9]. Other
pathophysiological factors claimed to contribute to dyspnoea in patients with COPD are increased mechanical
loading of inspiratory muscles in hyperinflated lungs [9], and also hypoxic effects on the cardiac pump and the
pulmonary vasculature [24]. In addition, there seems to be a considerable variability between individuals in
how these sensations are interpreted and to what extent they report dyspnoea or respiratory distress [9]. The
physiological compensation for acute altitude hypoxia is a nonlinear increase in ventilation which may
contribute to the feeling of dyspnoea [1, 10]. There is, however, a considerable individual variation with regard
to the level of hypoxaemia needed to increase ventilation, ranging from PaO₂ 6.7 to 8 kPa, before an
appreciable increase in ventilation is observed [25]. Taken together, there seems to be a poor relationship
between dyspnoea and the degree of hypoxaemia both at sea level and, as presented in the current study, during
air travel.

In contrast to the lack of association between respiratory symptoms and HAST-induced hypoxaemia, the COPD
patients experienced significantly less respiratory symptoms when flying with than without supplemental
oxygen. This is in concordance with studies on COPD patients using supplemental oxygen during exercise [26,
27]. It has been shown that supplemental oxygen may reverse the hyperventilatory response to hypobaric
hypoxia in patients with COPD, thereby having a positive influence on the feeling of dyspnoea [28].
Supplemental oxygen may also cause beneficial haemodynamic changes [29]. It should be noted, however, that
the effect of supplemental oxygen in the current study was not placebo controlled, and it has previously been
shown that oxygen treatment is encumbered with a considerable placebo effect [30]. Therefore, randomised and
placebo-controlled studies are needed to elucidate the effect of supplemental oxygen on in-flight dyspnoea.

Air travel is safe for most passengers with respiratory disease, but it is worth noting that respiratory related
medical problems are the third most reported cause of in-flight emergencies [1, 17], and may cause medical
flight diversions [1]. The current study indicates that pre-flight evaluation with HAST has no value for
predicting in-flight respiratory symptoms. Relief of respiratory symptoms is not, however, the main reason for
giving supplemental oxygen during air travel. Worsening of co-morbidities such as cardiovascular diseases,
which is very common in the COPD population, is the most threatening consequence of severe hypoxaemia [1-3]. In addition, we recorded a high proportion of patients needing health care assistance after arrival. Whether this is related to the hypoxic exposure is not known. It should be noted that all but one of these patients had \( \text{PaO}_2 \) below the recommended limit for supplemental oxygen, and only one had used in-flight supplemental oxygen. Little information exists regarding medical events occurring after air travel [31] and, as requested in the BTS recommendations, further studies designed to evaluate post-flight outcomes in patients with COPD are warranted [1].

The current study has some limitations. The authors have no data on the actual cabin pressure during the individual flights, which may vary between 6000 and 8000 ft [1]. This may possibly explain some of the variation in symptoms reported. In addition, worsening of the disease and recall bias in the time span between air travel and HAST may have influenced the results. On the other hand, a prospective design where participants are asked to record in-flight respiratory distress may lead to increased symptom awareness, and thereby over-reporting of symptoms [8]. As shown in the second questionnaire, almost half of the patients with a \( \text{PaO}_2 \) \(<6.6\) kPa chose to fly without supplemental oxygen despite our recommendations. This may imply a selection bias with regard to the subjective effect of oxygen treatment on respiratory symptoms. In addition, the oxygen treatment was not placebo controlled. Thus, the positive effect of supplemental oxygen is encumbered with uncertainty.

In conclusion; the current study comprising patients with moderate to very severe COPD showed no significant relationship between respiratory symptoms during air travel and the degree of hypoxaemia during a simulated flight.

Word count: 2677
Acknowledgement: Leiv Sandvik, Professor in Biostatistics, Oslo University Hospital, is gratefully acknowledged.
Figure legends

Figure 1. Flow chart describing the patient selection. Patients with COPD evaluated by HAST who had travelled by air without supplemental oxygen and answered an air travel questionnaire. Reasons for not travelling were: not topical (n=11), worsening of the disease (n=3), afraid of flying (n=5), other reasons (n=5). COPD: chronic obstructive pulmonary disease; HAST: hypoxia-altitude simulation test; LTOT: long-term oxygen treatment.

Figure 2. Symptoms during air travel before pre-flight evaluation with HAST (n=82). HAST: hypoxia-altitude simulation test.

Figure 3. Dyspnoea or air hunger and PaO₂ HAST. PaO₂: arterial oxygen pressure; HAST: hypoxia-altitude simulation test (n=82).

Figure 4. Symptoms during air travel for patients who flew both the first (dark grey bars) and the second time (light grey bars) without supplemental oxygen (n=31). NS: not significant.

Figure 5. Symptoms during air travel for patients who flew the first time without (dark grey bars) and the second time with (light grey bars) supplemental oxygen (n=23). NS: not significant.

Figure 6. Symptoms during air travel for patients who flew the second time without (dark grey bars, n=31) and with (light grey bars, n=23) supplemental oxygen. NS: not significant.
Reference list


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Symptoms during air travel before pre-flight evaluation with HAST (n=82). HAST: hypoxia-altitude simulation test.
87x61mm (300 x 300 DPI)
Figure 3

Dyspnoea or air hunger and PaO2 HAST. PaO2: arterial oxygen pressure; HAST: hypoxia-altitude simulation test (n=82).

87x75mm (300 x 300 DPI)
Figure 4

Symptoms during air travel for patients who flew both the first (dark grey bars) and the second time (light grey bars) without supplemental oxygen (n=31). NS: not significant.

87x68mm (300 x 300 DPI)
Figure 5

Symptoms during air travel for patients who flew the first time without (dark grey bars) and the second time with (light grey bars) supplemental oxygen (n=23). NS: not significant.

87x68mm (300 x 300 DPI)
Symptoms during air travel for patients who flew the second time without (dark grey bars, n=31) and with (light grey bars, n=23) supplemental oxygen. NS: not significant.

87x69mm (300 x 300 DPI)

p = 0.032
Paper IV
Passengers with respiratory disease may develop severe hypoxemia during air travel because of the lowered oxygen pressure in the cabin. Commercial aircraft are pressurized to a maximum cabin altitude of 2,438 m (8,000 ft), and the altitude exposure results in a drop in partial oxygen tension to the equivalent of breathing 15.1% oxygen at sea level. To minimize the risk of flight-related complications, the current guidelines recommend supplemental oxygen if a drop in PaO$_2$ below 6.6 to 7.3 kPa (50-55 mm Hg) is anticipated. If these guidelines are followed, a considerable number of patients need preflight evaluation to determine if in-flight supplemental oxygen is required.

**Background:** Patients with COPD may need supplemental oxygen during air travel to avoid development of severe hypoxemia. The current study evaluated whether the hypoxia-altitude simulation test (HAST), in which patients breathe 15.1% oxygen simulating aircraft conditions, can be used to establish the optimal dose of supplemental oxygen. Also, the various types of oxygen-delivery equipment allowed for air travel were compared.

**Methods:** In a randomized crossover trial, 16 patients with COPD were exposed to alveolar hypoxia: in a hypobaric chamber (HC) at 2,438 m (8,000 ft) and with a HAST. During both tests, supplemental oxygen was given by nasal cannula (NC) with (1) continuous flow, (2) an oxygen-conserving device, and (3) a portable oxygen concentrator (POC).

**Results:** PaO$_2$ kPa (mm Hg) while in the HC and during the HAST with supplemental oxygen at 2 L/min (pulse setting 2) on devices 1 to 3 was (1) 8.6 ± 1.0 (65 ± 8) vs 12.5 ± 2.4 (94 ± 18) (P < .001), (2) 8.6 ± 1.6 (64 ± 12) vs 9.7 ± 1.5 (73 ± 11) (P < .001), and (3) 7.7 ± 0.9 (58 ± 7) vs 8.2 ± 1.1 (62 ± 8) (P = .003), respectively.

**Conclusions:** The HAST may be used to identify patients needing supplemental oxygen during air travel. However, oxygen titration using an NC during a HAST causes accumulation of oxygen within the facemask and underestimates the oxygen dose required. When comparing the various types of oxygen-delivery equipment in an HC at 2,438 m (8,000 ft), compressed gaseous oxygen with continuous flow or with an oxygen-conserving device resulted in the same PaO$_2$, whereas a POC showed significantly lower PaO$_2$ values.

_Abbreviations:_ HAST = hypoxia-altitude simulation test; HC = hypobaric chamber; NC = nasal cannula; POC = portable oxygen concentrator; SpO$_2$ = arterial oxygen saturation by pulse oximetry.
is needed. Hypobaric chamber (HC) exposure is the ideal test but it is not widely available. The hypoxia-altitude simulation test (HAST), in which patients breathe 15.1% oxygen at sea level, replicates the hypoxia at 2,438 m (8,000 ft) and is considered to be the best available test in a clinical setting. The HAST is used with increasing frequency.

The dose of supplemental oxygen required during air travel seems to vary among individuals, and titrating the oxygen dose via a nasal cannula (NC) underneath the facemask during the HAST has been recommended. However, studies validating this practice are lacking. Moreover, no studies have evaluated the various types of oxygen equipment allowed for air travel. A variety of oxygen sources, delivery devices, and connection ports may be encountered.

The objective of the current study was to evaluate whether supplemental oxygen can be titrated reliably during the HAST. Also, we studied the effect of oxygen supplementation on PaO\textsubscript{2} in patients with COPD during simulated flight in an HC with the three principles of oxygen equipment allowed for air travel: compressed gaseous oxygen with continuous flow, an oxygen-conserving device, and a portable oxygen concentrator (POC). We hypothesized that (1) oxygen supplementation during a HAST gives the same PaO\textsubscript{2} as oxygen supplementation in the HC and (2) oxygen supplementation in the HC gives the same PaO\textsubscript{2} regardless of the oxygen equipment used.

**Materials and Methods**

A randomized crossover trial of oxygen titration during a HAST and in an HC was performed. The Regional Committee for Medical Research Ethics (Oslo, Norway) approved the study, and written informed consent was obtained from the participants. Primary outcome was the effect of oxygen titration on PaO\textsubscript{2} when supplemental oxygen was given during the HAST and compared with the gold standard of the HC. Secondary outcome was a comparison of the effect on PaO\textsubscript{2} of the various types of oxygen equipment in the HC.

**Subjects**

Patients were recruited from two outpatient pulmonary clinics. Patients with COPD who were planning to travel by air and had been evaluated previously with a HAST and showed a PaO\textsubscript{2} < 6.7 kPa (50 mm Hg) were included. Exclusion criteria were exacerbation or pneumothorax within the previous 6 weeks, hypoxia at 2,438 m (8,000 ft) and is considered to be the best available test in a clinical setting. The HAST is used with increasing frequency.

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without supplemental oxygen before testing with a new type of oxygen equipment. Each subject was tested with the three types of oxygen equipment in random order during exposure to both the HAST and the HC.

**Statistical Analysis**

Descriptive data in the text and tables are presented as mean ± SD, unless otherwise specified. Computations were performed using SPSS 16.0 for Windows (SPSS Inc: Chicago, Illinois). Paired Student t tests were used to evaluate differences among variables during HAST and HC exposure and the different oxygen equipment. Differences with two-tailed P values of < .05 were considered statistically significant. In a previous study, we found that the SD of the difference in PaO2 was 0.6. A power calculation showed that a sample size of 14 participants was needed to show a change in PaO2 of 0.5 kPa as significant with a power of 80%. Normal distribution was assessed by visual inspection of histograms. The relationship between PaO2_HAST and PaO2_8,000 ft was performed by Bland-Altman plot, in addition to a linear regression analysis.

**RESULTS**

**Preflight Tests**

Demographics, lung function, preflight arterial blood gases results, and pulse oximetry values are presented in Table 1.

**Simulated Flight and Oxygen Titration (HAST vs HC)**

Without supplemental oxygen, PaO2 was somewhat lower during the HAST than in the HC (Table 2). The Bland-Altman plot showed that there was no relationship between the difference in PaO2 during the HAST and in the HC and the average PaO2 recorded (Fig 2). The PaO2 values during the HAST and in the HC were highly correlated (r = 0.86, P < .001). Nine patients (56%) reported increased dyspnea during exposure to hypoxia, as evaluated by an increase in Borg score of more than one unit. Four patients experienced moderate to strong dyspnea (Borg 3–5). ECG monitoring showed no significant ischemia or arrhythmias.

During oxygen titration with 1 L/min (pulse setting 1), the PaO2 obtained with oxygen at continuous flow and with the oxygen-conserving device showed significantly higher values during the HAST compared with in the HC (Table 2). No such difference in PaO2 was observed during oxygen titration with POC at pulse setting 1. During oxygen titration with 2 L/min (pulse setting 2), the difference in PaO2 between the HAST and the HC was even more pronounced, being statistically significant also with regard to oxygen titration with the POC. No hypercapnia was observed.

**Comparison of Oxygen Equipment in the HC**

In the HC, a similar PaO2 was observed when compressed gaseous oxygen was given with either continuous flow or the oxygen-conserving device (Table 2). However, oxygen delivery with the POC showed a

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**Table 1—Baseline Characteristics of Study Population (n = 16)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>% Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62 ± 7</td>
<td>44-74</td>
<td>...</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175 ± 9</td>
<td>162-189</td>
<td>...</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79 ± 14</td>
<td>52-101</td>
<td>...</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 ± 4</td>
<td>19-38</td>
<td>...</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.1 ± 0.4</td>
<td>0.7-1.8</td>
<td>37 ± 11</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.0 ± 0.9</td>
<td>1.5-5.0</td>
<td>79 ± 20</td>
</tr>
<tr>
<td>FEV/FVC%</td>
<td>39 ± 9</td>
<td>19-52</td>
<td>...</td>
</tr>
<tr>
<td>DLCO, mmol/min/kPa</td>
<td>4.2 ± 1.8</td>
<td>1.8-8.4</td>
<td>45 ± 16</td>
</tr>
<tr>
<td>DLCO/VA, mmol/min/kPa/L</td>
<td>0.9 ± 0.3</td>
<td>0.5-1.6</td>
<td>62 ± 21</td>
</tr>
<tr>
<td>TLC, L</td>
<td>7.3 ± 1.2</td>
<td>5.0-9.7</td>
<td>111 ± 12</td>
</tr>
<tr>
<td>RV, L</td>
<td>4.0 ± 0.8</td>
<td>2.2-5.2</td>
<td>173 ± 25</td>
</tr>
<tr>
<td><strong>Blood gas and oximetry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2 kPa</td>
<td>9.3 ± 1.1</td>
<td>7.6-11.4</td>
<td>...</td>
</tr>
<tr>
<td>mm Hg</td>
<td>70 ± 8</td>
<td>57-86</td>
<td>...</td>
</tr>
<tr>
<td>PaCO2 kPa</td>
<td>4.6 ± 0.5</td>
<td>3.5-5.3</td>
<td>...</td>
</tr>
<tr>
<td>mm Hg</td>
<td>35 ± 4</td>
<td>26-40</td>
<td>...</td>
</tr>
<tr>
<td>Spo2, %</td>
<td>94 ± 2</td>
<td>90-96</td>
<td>...</td>
</tr>
</tbody>
</table>

All data are preflight values. DLCO = diffusion capacity of the lung for carbon monoxide; % pred = percent predicted; RV = residual volume; Spo2 = arterial oxygen saturation by pulse oximetry; TLC = total lung capacity; VA = alveolar volume.

*Study population consisted of 11 male and five female subjects.

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**Figure 1.** Flow diagram showing participants’ progress through the study. HAST = hypoxia-altitude simulation test; HC = hypobaric chamber at 2,438 m (8,000 ft).
Table 2—Oxygen Titration During HAST vs HC (n = 16)

<table>
<thead>
<tr>
<th>Oxygen Equipment</th>
<th>Dose</th>
<th>PaO₂</th>
<th>P Value</th>
<th>PaCO₂</th>
<th>P Value</th>
<th>SpO₂</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HAST</td>
<td>HC</td>
<td></td>
<td>HAST</td>
<td>HC</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>6.2 ± 0.7 (47 ± 5)</td>
<td>6.6 ± 0.7 (49 ± 5)</td>
<td>.005</td>
<td>4.6 ± 0.5 (35 ± 4)</td>
<td>4.4 ± 0.5 (33 ± 4)</td>
<td>.009</td>
</tr>
<tr>
<td>Continuous flow, L/min</td>
<td>1</td>
<td>9.4 ± 1.5 (70 ± 11)</td>
<td>7.8 ± 1.0 (58 ± 8)</td>
<td>&lt;.001</td>
<td>4.9 ± 0.4 (37 ± 3)</td>
<td>4.4 ± 0.6 (33 ± 5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12.5 ± 2.4 (94 ± 18)</td>
<td>8.6 ± 1.0 (65 ± 8)</td>
<td>&lt;.001</td>
<td>5.0 ± 0.6 (37 ± 5)</td>
<td>4.5 ± 0.6 (34 ± 4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oxygen-conserving device, pulse setting</td>
<td>1</td>
<td>8.5 ± 1.2 (46 ± 9)</td>
<td>7.9 ± 1.2 (50 ± 9)</td>
<td>&lt;.001</td>
<td>4.8 ± 0.6 (36 ± 4)</td>
<td>4.3 ± 0.6 (32 ± 5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>POC, pulse setting</td>
<td>2</td>
<td>9.7 ± 1.5 (73 ± 11)</td>
<td>8.6 ± 1.6 (64 ± 12)</td>
<td>&lt;.001</td>
<td>4.9 ± 0.5 (37 ± 4)</td>
<td>4.4 ± 0.6 (33 ± 5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>7.3 ± 1.0 (55 ± 7)</td>
<td>7.2 ± 0.8 (54 ± 6)</td>
<td>&lt;.001</td>
<td>4.7 ± 0.6 (35 ± 4)</td>
<td>4.3 ± 0.5 (32 ± 4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8.2 ± 1.1 (62 ± 8)</td>
<td>7.7 ± 0.9 (58 ± 7)</td>
<td>&lt;.001</td>
<td>4.7 ± 0.7 (36 ± 5)</td>
<td>4.3 ± 0.6 (32 ± 4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD in kPa. Numbers in parentheses are mean ± SD in mm Hg. HAST = hypoxia-altitude simulation test; HC = hypobaric chamber; POC = portable oxygen concentrator. See Table 1 for expansion of the other abbreviation.
achieved from oxygen supplementation during the HAST were considerably higher than in the HC. A tight-fitting facemask may alter the breathing pattern. However, there was no indication of hyper-ventilation during the HAST vs in the HC, and the mask was checked for possible leakages before oxygen titration. The higher PaO₂ values were, therefore, probably due to accumulation of oxygen within the mask. The observed reservoir effect was dependent on both oxygen flow and the type of oxygen equipment used. With continuous oxygen flow, supplemental oxygen given via an NC may leak from the nostrils into the HAST mask during both inspiration and expiration. With an oxygen-conserving device, oxygen is given at a relatively high flow rate at the beginning of each inspiration; however, according to our results, some of the oxygen may still leak from the nostrils into the HAST mask. The POC is also designed to deliver a pulsed dose of oxygen during inspiration. However, compared with compressed gaseous oxygen with the oxygen-conserving device, the tested POC delivers both a lower oxygen dose and concentration.

During simulated flight without supplemental oxygen, the PaO₂ during the HAST was somewhat lower than in the HC. The potential consequences of this minor difference would be that some patients might be advised to travel with supplemental oxygen without actually needing it. However, all patients needing supplemental oxygen during air travel were identified by the HAST, and in clinical practice the HAST may be regarded as a reliable test for assessing whether oxygen during air travel is required.³

We also observed that the PaCO₂ in the HC was lower than during the HAST. This difference may reflect a stimulation of ventilation in the HC, which may be noisy and confining, or a CO₂ accumulation within the HAST mask. These discrepancies cannot explain the difference in PaO₂ between the HAST and the HC during oxygen supplementation. On the contrary, the difference in PaO₂ during oxygen titration would probably have been even more pronounced if the baseline PaO₂,HAST values had not been lower than the PaO₂,8,000ft values.

The HAST technique described in the current study uses a tight-fitting facemask with 15.1% oxygen, which is the technique used in several laboratories.⁵⁻⁷,¹⁰,¹⁶ Others use a mouthpiece,¹⁰,¹⁰,¹²,¹⁵,¹⁶,¹³ and Gong et al¹⁶ found that the PaO₂ values exceeded the sea level values when supplemental oxygen of 1 L/min was added to the Hans Rudolph valve during concomitant inhalation of 15.1% oxygen. A mouthpiece in combination with an NC is also used for oxygen titration, but this method has not been evaluated. By adding supplemental oxygen of 2 L/min via an NC during altitude simulation in a modified body plethysmograph with FIO₂ 15%, another group found that the SpO₂ returned to sea level values.¹³ In other laboratories, a HAST technique employing a Venturi mask¹⁵,¹⁶ with continuous flow of nitrogen to establish the hypoxic environment is used. Oxygen titration with these hypoxic challenge techniques may give PaO₂ values different from those in the present study but, to our knowledge, it has not been compared with HC exposure.

To avoid the reservoir effect seen during the HAST, comparison of the different types of oxygen equipment allowed for air travel was performed in the HC. Oxygen delivery with compressed gaseous oxygen using continuous flow gives the same PaO₂,8,000ft value as with the tested oxygen-conserving device. Thus, use of an oxygen-conserving device seems preferable for reducing the number of oxygen cylinders needed for the journey. With regard to the tested POC, a higher oxygen dose is needed to obtain an in-flight PaO₂ similar to that obtained with compressed gaseous oxygen. It is important to recognize that the present study evaluates only the principles of the three oxygen systems allowed for air travel. Other POCs and oxygen-conserving devices may give other doses and concentrations.²⁷

The results of the current study may have clinical implications. Because titration of supplemental oxygen during a HAST using an NC underneath the facemask cannot be used with confidence, and the oxygen dose needed seems to vary among individuals,¹²⁻¹⁵ future research should focus on simple methods to determine the oxygen dose, and also on validating existing methods of oxygen titration during hypoxic challenge testing, such as the mouthpiece, the modified body plethysmograph, or the Venturi mask. By developing a HAST method suitable for oxygen titration, the actual oxygen equipment the patients will use during the flight can be tested. This is particularly important for the POC, which shows lower PaO₂ values than compressed gaseous oxygen. Also, patients needing more than 2 L/min may be identified, and possible hypercapnia may be detected. An alternative approach is to equip the patients with a pulse oximeter by which oxygen can be titrated in-flight by the patient, ensuring that the SpO₂ values do not exceed the sea level values, thereby also avoiding the potential risk of hypercapnia.⁴,¹⁵,¹⁶,²⁸ However, considering the limitations of pulse oximetry,²⁹ this approach may warrant further investigation. Until reliable methods are available, the oxygen dose to be prescribed may also be estimated arbitrarily from an individual evaluation based on the PaO₂,HAST value, previous flight experience,⁷ the patient’s overall clinical condition, and flight duration and altitude.⁸ If the oxygen equipment is rented from the airline, one should keep in mind that some aircraft oxygen systems are capable of providing only compressed oxygen with a fixed
continuous flow of 2 or 4 L/min. According to our results, continuous oxygen at 2 L/min or an oxygen-conserving device at pulse setting 2 is needed to reach an SpO₂ ≥ 90% in most patients. The POC at pulse setting 2 gave a Pao₂ ≥ 6.7 kPa (50 mm Hg) in all but one patient. However, our results indicate that to reach an SpO₂ ≥ 90% in most patients, the dose of the POC should be increased further. During in-flight physical activity, an even higher dose of supplemental oxygen is needed to prevent a drop in SpO₂. However, this depends on whether the equipment is capable of providing a sufficiently high oxygen dose. When prescribing supplemental oxygen, health-care workers have to be familiar with the equipment and ensure that the patients can trigger the pulsed-dose systems. The triggering may be tested at sea level, as can PaCO₂; if the PaCO₂ level does not increase while giving supplemental oxygen at sea level, hypercapnia is not likely to occur during air travel.

CONCLUSIONS

In summary, the HAST may be used to identify patients needing supplemental oxygen during air travel. However, oxygen titration using an NC during a HAST causes accumulation of oxygen within the facemask and underestimates the oxygen dose required. Use of an oxygen-conserving device gives similar PaO₂ values at 8,000 ft as oxygen with continuous flow and should, therefore, be used to minimize the number of oxygen cylinders needed. Acceptable in-flight PaO₂ values may also be obtained using a POC, but the flow has to be increased compared with compressed gaseous oxygen.

ACKNOWLEDGMENTS

Author contributions: Dr. Akerø: contributed to the conception and design of the study; collecting, analyzing, and interpreting the data; and drafting and revising the manuscript. Ms. Edvardsen: contributed to the design of the study, collecting and interpreting the data, and drafting and revising the manuscript. Dr. Christensen: contributed to the design of the study, collecting and interpreting the data, and drafting and revising the manuscript. Dr. Owe: contributed to the design of the study, collecting and interpreting the data, and drafting and revising the manuscript. Dr. Ryg: contributed to the design of the study, collecting and interpreting the data, and drafting and revising the manuscript. Dr. Skjønsberg: contributed to the conception, design, and supervision of the study; collecting and interpreting the data; and drafting and revising the manuscript.

Other contributions: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study; the collection and analysis of the data, or in the preparation of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

REFERENCES


