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For a better future!

Nu finns det inte mer jag kan göra åt min sjukdom, nu får jag förlita mig på läkarvetenskapen.
Bengt Berkius 2011.

If it were not for the great variability among individuals, medicine might as well be a science and not an art.
Sir William Osler.
Abstract

Background
Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. When we began this project our knowledge about the outcome of COPD patients admitted to the ICU in Sweden was scarce.

Aims
To investigate the characteristics, survival and health-related quality of life (HRQL) of COPD patients admitted to Swedish ICUs. To investigate how ICU personnel decide whether to use invasive or non-invasive ventilatory treatment (NIV) of the newly admitted COPD patient in need of ventilatory support. To investigate outcome according to mode of ventilation.

Material and methods
Detailed data, including HRQL during recovery, from COPD patients admitted to ICUs that participated in the Swedish intensive care registry were analysed. A questionnaire was distributed to personnel in 6 of the participating ICUs in order to define factors deemed important in making the choice between invasive and non-invasive ventilation immediately after admission. The answers were analysed.

Results
The proportion of COPD patients admitted to Swedish ICUs in need of ventilatory support is 1.3-1.6 % of all admissions. The patients are around 70 years-old and are severely ill on admission, with high respiratory rates and most have life-threatening disturbances in their acid-base balance and blood gases. There are more women than men. The short- and long-term mortality is high despite intensive care treatment. The majority of patients are treated with NIV. The length of stay on the ICU is shorter when NIV is used. The choice between NIV and invasive ventilation in these patients may be irrational. It is guided by current guidelines, but other non-patient-related factors seem to influence this decision.

NIV seems to be preferable to invasive ventilation at admission, not only according to short-term benefits but also to long-term survival. Failure of NIV followed by invasive ventilation does not have a poorer prognosis than directly employing invasive ventilation.

The health-related quality of life of COPD patients after treatment on Swedish ICUs is lower than in the general population. However it does not decline between 6 and 24 months after ICU discharge. After 24 months the HRQL is quite similar to that of COPD patients not treated on the ICU.

Conclusions
COPD patients in need of ventilatory support admitted to Swedish ICUs are severely ill on admission, and their short- and long-term mortality is high despite ICU care and ventilatory treatment. Non-invasive ventilation should be the first line treatment on admission. NIV has short- and long-term benefits compared to invasive ventilation, without increasing mortality risk in case of failure. After discharge from the ICU and recovery, the HRQL of COPD patients is lower than in the general population, but comparable to COPD patients not treated on the ICU.
List of papers


Johan Berkius, Josefin Sundh, Lennart Nilholm, Mats Fredrikson, Sten M Walther.
Long-term survival according to ventilation mode in acute respiratory failure secondary to chronic obstructive pulmonary disease: A multicenter, inception cohort study.

What determines immediate use of invasive ventilation in patients with COPD?

A prospective longitudinal multicentre study of health related quality of life in ICU survivors with COPD.
Crit Care. 2013 Sep 24;17(5):R211. [Epub ahead of print]
Abbreviations

ADO index                       Age, Dyspnoea, Obstruction index.
AECOPD  Acute Exacerbation of Chronic Obstructive Pulmonary Disease.
APACHE II  Acute Physiologic and Chronic Health Evaluation II.
ATS  American Thoracic Society.
BODE index  BMI, Degree of airflow Obstruction, Dyspnoea and Exercise capacity index.
BMI  Body Mass Index.
BP  Bodily Pain.
BTS  British Thoracic Society.
COPD  Chronic Obstructive Pulmonary Disease.
CRP  C-Reactive Protein.
CPE  Cardiogenic Pulmonary oedema.
DOSE index  Dyspnoea, Obstruction, Smoking status and Exacerbation frequency index.
EFL  Expiratory Flow Limitation.
EMR  Estimated Mortality Risk.
EQ-VAS  EuroQoL Visual Analogue Scale.
EQ-5D  EuroQoL 5 Dimensions.
FEV1  Forced Expiratory Volume in one second.
FiO₂  Fraction of inspired oxygen.
FRC  Functional Residual Capacity.
FVC  Forced Vital Capacity.
GH  General Health.
GOLD  The Global Initiative for Chronic Obstructive Lung Disease.
HRQL  Health-related quality of life.
HCO₃⁻  Bicarbonate.
IC  Inspiratory Capacity.
ICD-10  International Classification of Diseases Tenth revision.
ICU  Intensive Care Unit.
MCS  Mental Component Summary Measure.
MH  Mental Health.
NCR 11  The Nursing Care Recording System for assessment of workload in the ICU.
NEMS  The Nine Equivalents of nursing Manpower use Score.
NIV  Non-invasive ventilation.
PaO₂  Partial pressure of the arterial oxygen tension.
PaCO₂  Partial pressure of the arterial carbon dioxide tension.
PCS  Physical Component Summary Measure.
PEEP  Positive End Expiratory Pressure.
PEEPi  Intrinsic Positive End Expiratory Pressure.
PF  Physical Functioning.
pH  Power of Hydrogen.
PH  Physical Health.
PIM 2  The Paediatric Index of Mortality 2.
RE  Role Emotional.
RP  Role Physical.
SAPS 3  Simplified Acute Physiology Score 3.
SAR  Small Airway Remodelling.
<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>SD</td>
<td>Standard Deviation.</td>
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<td>SF</td>
<td>Social Functioning.</td>
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<td>SF-36</td>
<td>Short Form 36 Health Survey.</td>
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<td>SIR</td>
<td>The Swedish Intensive Care Registry.</td>
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<td>TLC</td>
<td>Total Lung Capacity.</td>
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<td>UK</td>
<td>United Kingdom.</td>
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<td>US</td>
<td>United States of America.</td>
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<tr>
<td>VC</td>
<td>Vital Capacity.</td>
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<td>VT</td>
<td>Vitality.</td>
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Background

The history of COPD

Chronic obstructive pulmonary disease is a relatively new entity in the field of medicine. It is believed to have been introduced at the Aspen Emphysema Conference in 1965. Regarding the fact that one of the major causes of COPD is thought to be smoke from household stoves, it is logical to assume that the disease has been present for a much longer time. Indeed it has, but described in terms of two of the basic components; emphysema and chronic bronchitis.

Emphysema was described by Bonnet in 1679, Morgagni in 1769, and not least by the inventor of the stethoscope Laënnec in 1821. Bronchitis was described by Badham in 1814. Two scientific meetings, the CIBA guest symposium 1959 and the American Thoracic Society’s Committee on Diagnostic Standards in 1962, defined the components of COPD. Several hypotheses on the pathology of COPD have been proposed since the 1950’s. A British hypothesis stated that infection and air pollution were the main causes of bronchitis, whereas a Dutch hypothesis stated that COPD was due to genetically determined hyper-reactivity of the airways. A Swedish hypothesis also involved the importance of genetic factors, and an American group stressed the importance of an impaired repair process.

The use of invasive ventilation in patients with COPD began in the early 1960’s. This was followed by the use of oxygen, which had a dramatic effect in patients with advanced COPD and chronic hypoxaemia at rest.

The development of national healthcare programmes started in the 1990’s, and GOLD (the Global Initiative of Obstructive Lung Disease) was launched by WHO in 2001.

The Swedish COPD healthcare programme was published in 2003.

COPD healthcare programmes

There are several COPD healthcare programmes at present. Their goal is to optimise diagnosis, treatment and care of patients with COPD.

GOLD (Global Initiative for Chronic Obstructive Pulmonary Disease) co-operates with healthcare professionals and public health officials to increase the awareness of Chronic Obstructive Pulmonary Disease (COPD) and to improve prevention and treatment of this lung disease throughout the world (www.goldcopd.com).

There are also several national guidelines. A Swedish healthcare programme for all stages of COPD may be found at www.SLMF.se/kol/.
COPD diagnosis

The diagnosis of COPD is dependent on current definitions. Previous COPD healthcare programmes were based on different definitions 5-6, but now global actors in this field are much more congruent in their definitions. The American Thoracic Society and the European Respiratory Society have together published COPD guidelines 7. But now most national COPD healthcare programmes follow the Global Initiative for Chronic Obstructive Pulmonary Disease guidelines as regards diagnosis 4.

The GOLD definition of COPD is: “chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases”.

The way in which the diagnosis is set is also defined by GOLD as follows: “for educational reasons, a simple spirometric classification of disease severity into four stages is recommended. Spirometry is essential for diagnosis and provides a useful description of the severity of pathologic changes in COPD. Specific spirometric cut points (e.g., post-bronchodilator FEV1/FVC ratio, 0.70 or FEV1, 80, 50, or 30 % predicted) are used for purposes of simplicity; these cut points have not been clinically validated. A study in a random population sample found that the post-bronchodilator FEV1/FVC exceeded 0.70 in all age groups, supporting the use of this fixed ratio. However, because the process of aging does affect lung volumes, the use of this fixed ratio may result in over-diagnosis of COPD in the elderly, especially in those with mild disease”.

The main goal for GOLD is to improve diagnosis, prevention and management of COPD 4. It is naturally of great importance that the GOLD definition of COPD is easy to understand and to apply.

There is however some concern regarding the current definition. The FEV/FVC ratio is not just dependent on age but also height. The limit FEV1/FVC should be defined as the lower fifth percentile of the normal value for the population in the country 8. However the limit seems to have been created by an expert panel and not based on studies. Because of this methodological deficiency there is a risk of over-diagnosis when we use the GOLD definition for COPD.

Symptoms are not obligate for a COPD diagnosis according to the GOLD guidelines that describe four stages of COPD. Symptoms such as shortness of breath, chronic cough and sputum production are present in Stages 2-4 4.

This has led to criticism of the GOLD COPD definition because: the classification is not evidence-based, does not advance our understanding of the pathophysiological mechanisms of COPD, bears no relationship to what is important for the patient and is based on FEV1 9. FEV1 correlates poorly to all the things that matter to the patient: symptoms, quality of life, exacerbation frequency, and exercise intolerance 9-10.

This criticism is of course important to keep in mind, but the main goal of the GOLD initiative is to improve diagnosis, management and prevention of COPD using a definition that is easy to understand. Previous when our studies began, the GOLD guidelines stated that the diagnosis COPD also could be made on the basis of clinical signs such as chronic cough, sputum production and shortness of breath 11.
COPD spirometry

Spirometry is the timed measurement of dynamic lung volumes and capacities during forced expiration and inspiration to quantify how effectively and quickly the lungs can be emptied and filled. Several measurements can be performed, the most common measurement used in COPD patients is the vital capacity either forced (FVC) or not forced (VC), or forced in one second (FEV1). A further spirometry measurement undergoing a renaissance is the inspiratory capacity (IC) i.e. the maximum volume of air that can be inspired from the end of quiet expiration [functional residual capacity (FRC) to total lung capacity (TLC)]. Spirometry is important to confirm the diagnosis in COPD patients. Apart from that, lung volumes, in the majority of patients, do not provide much additional information as regards clinical decision-making.

Acute exacerbation of COPD (AECOPD)

COPD is not a stable disease. Patients can experience a sudden deterioration in their breathing, so-called “Acute Exacerbation of COPD” (AECOPD). The definition of an exacerbation of COPD according to the current GOLD COPD guidelines is: “an event in the natural course of the disease characterised by a change in the patient’s baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD”. This definition is very broad and leads to great inclusion heterogeneity in studies on AECOPD. The definition has not been validated in clinical trials. Other definitions are also used, and this influences the effect of treatment reported in available studies. Respiratory infections, bacterial or viral, are the most common causes of AECOPD (80% of all cases). But environmental triggers such as air pollutants or change in air temperature can also initiate an exacerbation.

The type of infection responsible for the exacerbation is often unclear. Of respiratory infections, 40-50% are believed to be caused by bacteria and about 30% by virus. In some studies it has been difficult to isolate the bacterial or viral agent in patients admitted to hospital (36% positive). It is possible, therefore, that the rate of viral infections in AECOPD is even higher than expected; 53% according to a study from Greece. There is no clear definition of the grades of severity of AECOPD. Burge et al. proposed a definition comprising five grades from mild to life-threatening where patients with respiratory failure, acidosis and carbon dioxide retention are classified as having a life-threatening exacerbation. PaCO2 and breathing rate vary with the severity of the exacerbation.

There are clear guidelines for the treatment of AECOPD including oxygen, bronchodilating agents, steroids, antibiotics, mucolytic agents, non-invasive ventilation and invasive ventilation, and intensive care.

There is no indication for acute spirometry in patients with AECOPD. Several studies conclude that an exacerbation leads to a decrease in FEV1, and that frequent exacerbations increases the rate of FEV1 decline, but this statement is also questioned. AECOPD does not necessarily occur in all patients, and 40% of patients do not develop AECOPD at all.
Differential diagnosis of COPD and AECOPD

The differential diagnoses of COPD according to GOLD are: asthma; congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis; and diffuse panbronchiolitis. The main differential diagnoses of AECOPD are respiratory symptoms caused by comorbidity, for example: cardiac events such as acute heart failure and cardiac arrhythmias; pulmonary events such as pneumothorax, lung cancer and pulmonary embolism.

COPD epidemiology

The prevalence of COPD in the world is said to be between 4 and 10%. In Sweden it is 8.1% according to the BTS guidelines and 14.3% according to the GOLD guidelines in the population aged 45 years and older in the OLIN study, a prevalence comparable to 13.4% in subjects aged 40 years and older in Korea. COPD is underdiagnosed. The prevalence is influenced by age, exposure to smoke from tobacco and from environmental sources, and is also dependent on the definition of COPD used in studies. Smoking is very common in the world today. In Sweden about 20% of adults smoke, and about 50% have smoked in their lifetime.

Data from the OLIN study provides reliable data about the COPD prevalence in Sweden. The distribution of stages in the population is as follows:

- according to the BTS guidelines: moderate COPD 5.3%, severe COPD 2.2% and very severe 0.6%.
- according to the GOLD guidelines: mild 8.2%, moderate 5.3%, severe 0.7%, and very severe 0.1%.

COPD phenotypes

COPD may be graded according to degree of airflow limitation. On the other hand, airflow limitation explains less than 10-25% of the impact on the patient’s quality of life. COPD is a complex disease with numerous pulmonary and extra-pulmonary components. Patients present in many different ways regarding clinical signs, physiology, imaging, response to therapy, decline in lung function, and survival.

A new way of describing patients with COPD is to relate to their COPD phenotype. COPD phenotypes have not yet been strictly defined, but one can divide COPD into various subgroups according to: physiological manifestations such as hypercapnia and resting hypoxia, radiologic features according to CT scanning, exacerbation rate, the magnitude of systemic inflammation assessed by biomarkers, the presence of co-morbidity and the results of various multidimensional indexes such as the BODE index.
COPD and gender

It has long been stated that female smokers are more susceptible to tobacco smoke than men \cite{32,33}. It is now questioned if women are more susceptible to COPD \cite{34}. However, women with COPD show an accelerated decline in FEV1 compared to men \cite{35}. Women also suffer from more severe dyspnoea and poorer health status, and suffer more frequent exacerbations, more anxiety and depression, and more airway hyper-responsiveness compared to men with a similar level of tobacco exposure \cite{36}. Death rates and causes of death in male and female COPD patients do not show any statistically significant difference when covariates such as airflow obstruction, BMI and others are taken into account \cite{37}.

COPD nutritional status and BMI

The nutritional status of patients admitted to hospital with an acute exacerbation of COPD is important for the long-term prognosis. Studies from Copenhagen have shown that low body mass index (BMI) is a marker of poor prognosis in chronic obstructive pulmonary disease \cite{38}. A Scandinavian study has also shown that a low BMI has an impact on long-term survival after hospital admission for AECOPD \cite{39}. COPD patients with a low BMI are more difficult to wean from ventilator support compared to patients with a normal weight \cite{40}. The fat-free mass of the body is believed to reflect the systemic effects of COPD. Even in patients with a normal BMI, a low fat-free mass index is associated with an unfavourable prognosis \cite{41}. The mechanisms behind the fall in fat-free mass are complicated and also have effects on the respiratory chain in the mitochondria of muscle cells \cite{42}. On the other hand, weight gain is a predictor of longer survival \cite{43}.

COPD and genetics

Not all smokers develop COPD. It is believed that COPD results from a gene-environment interaction \cite{4}. It is also well-known that a severe hereditary deficiency of alfa1-antitrypsin can lead to COPD \cite{4}. Intense research in this area is under way, and at present 192 genes correlated to COPD have been identified. However, the specific genes responsible for enhanced risk or host differences in susceptibility to smoke exposure remain poorly understood \cite{44}.

COPD and animal research

There are several animal models for COPD research, but they have limitations. The models represent only mild forms of the disease (Gold Stages 1 and 2), the animals never develop spontaneous exacerbations, they are often treated as though they have mild forms of the disease and very early after exposure to smoke \cite{45}.
Results from animal research have been encouraging as several substances have been able to prevent emphysema in mice, but unfortunately their effect in humans have been very mild or absent. However, animal research provides important data on the heterogeneity of the pathophysiology of COPD, including four different anatomic lesions: emphysema; small airway remodelling (SAR); vascular remodelling associated with pulmonary hypertension; and excessive large airway mucus secretion (chronic bronchitis). These may be independent processes all driven by direct effects of cigarette smoke on specific compartments of the lung, but not necessarily occurring by the same mechanisms.

**Co-morbidity in COPD**

Unfortunately there is no universally accepted definition of co-morbidity. Rodriguez-Roisin et al. proposed the following definition: “The presence of one or more distinct disorders (or diseases) in addition to COPD, regardless of whether the co-morbid conditions are or are not directly related to, or caused by COPD, and regardless of whether they are or are not part of the spectrum of the natural history of COPD.”

It is believed that COPD is associated with a persistent low-grade systemic inflammation independent of smoking status. The “spill-over” of inflammatory mediators into the circulation may result in important systemic manifestations of the disease such as skeletal muscle wasting and cachexia. Systemic inflammation may also initiate or worsen co-morbid diseases, such as cardiovascular disease, osteoporosis, normocytic anaemia, lung cancer, depression, diabetes, muscle wasting and asthma.

There is increasing awareness that data on co-morbidity is of great importance in studies using mortality as an endpoint. The Charlson co-morbidity index was developed in 1987. It investigated the 10 year mortality in patients with breast cancer. The mortality risk was related to the presence of 19 medical conditions with a weighted score of 1-6 points according to the relative risk for death from a certain condition within 12 months. The system can generate scores from 0-37 points. In some calculations age is also included as one point per decade. The maximum value when age is included is 43.

This score has been shown to relate to long-term survival after intensive care.

**Disease severity in COPD**

Disease severity in COPD is not strictly defined. Forced expiratory volume in one second (FEV1) is used to define and stage COPD. FEV1 has been used as a global marker of COPD, but it does not fully reflect the burden of COPD on patients. Patients with COPD have systemic manifestations that are not reflected by the FEV1. The predictive value of FEV1 for mortality is weak when it is higher than 50 % of the predicted value. Other systems have been developed that assess the respiratory and systemic expressions of COPD in order to categorise and predict outcome in COPD patients.

For example:
- the BODE index (BMI, Degree of airflow Obstruction, Dyspnoea and Exercise capacity).
- the ADO index (Age, Dyspnoea, Obstruction).
- the DOSE index (Dyspnoea, Obstruction, Smoking status, and Exacerbation frequency).
These indexes can predict mortality, health status, hospital admissions, exacerbations and respiratory failure.\textsuperscript{55}.

**COPD and biomarkers**

There is a need for biomarkers in COPD, not least to identify exacerbations. In 2006 Franciosi et al. stated that there are no reliable biomarkers.\textsuperscript{20} Nevertheless research in this area is intense and there are some reports of progress. Simultaneously elevated CRP, fibrinogen and leukocyte count can predict exacerbation in stable COPD patients.\textsuperscript{61} Elevated fibrinogen levels can predict progression of COPD, hospitalisation and mortality.\textsuperscript{62} Serum myeloperoxidase is related to rapid decline in lung function in COPD patients.\textsuperscript{63} Research on exhaled volatile organic compounds in pulmonary disease, and the balance between inflammatory and repair serum biomarker patterns is promising.\textsuperscript{64-65}

**COPD pathophysiology**

The pathophysiology of COPD affects several structures in the lung. It involves the airways, the lung parenchyma and the pulmonary vasculature.\textsuperscript{66} Four anatomic lesions predominate; emphysema, small airway remodelling (SAR), vascular remodelling associated with pulmonary hypertension, and excessive large airway mucus secretion (chronic bronchitis).\textsuperscript{66} The main cause of COPD is exposure to smoke, mainly from tobacco but also household fires and other sources of smoke in the environment. Inhaled smoke leads to disruption of the epithelial layer in the airways and inflammation.\textsuperscript{67} The airways affected cannot repair damage caused by this inflammation. The ciliar function in the airways is reduced leading to impaired clearance of mucus. The epithelial layer in the airways is irritated by the chronic inflammation leading to a persistent cough. The blood vessels in the lungs are also affected by the chronic inflammation leading to a thicker intimal layer. In the later stages of the disease the lung tissue mass is reduced leading to reduced gas exchange and a larger dead space. This also affects the elastic properties of the lung resulting in decreased elastic recoil and a change in chest wall mechanics to provide sufficient lung ventilation.\textsuperscript{66-67} Air exchange occurs at higher lung volumes leading to an increase in chest size and FVC.\textsuperscript{1} A decline in FEV1 is closely related to the progress of emphysema, and dynamic collapse of the central airways is related to this reduction in FEV1. Emphysema is characterised by both hyperinflation and increased FVC. Mucus gland hyperplasia is not correlated to changes in airflow.\textsuperscript{1} These changes all contribute to the three main symptoms of COPD; breathlessness, cough, and sputum production.

COPD can also develop in non-smoking individuals, furthermore not every smoker develops COPD. It is believed that about 15-50 % of smokers develop the disease.\textsuperscript{1,68} We know that genetic factors contribute to some of these cases such as alfa-1 antitrypsin deficiency, but the precise mechanism behind this susceptibility is not known.\textsuperscript{66-67,69} The pathophysiology of COPD is also described in terms of a pathogenic triad consisting of oxidative stress, protease-antiprotease imbalance, and inflammation.\textsuperscript{70} This process is believed to be influenced by genes and environmental factors.\textsuperscript{70} Furthermore an imbalance in apoptosis and proliferation, between acetylases and deacetylases, and an accelerated aging
process, are present \(^{71}\). These changes lead to altered levels of several inflammatory biomarkers in the lung tissue such as cytokines, acute phase proteins and circulating cells \(^{49,67}\).

**COPD and respiratory physiology**

When the inspiratory muscles and the diaphragm contract in healthy humans, the alveolar pressure falls below the barometric pressure and the alveoli are filled with air. When the inspiratory muscles relax, the thoracic cavity and lung recoils and the alveolar pressure rises above the barometric pressure and the lung is emptied. At the end of expiration the alveolar pressure returns to zero. At this point the volume of air left in the lungs is equal to the functional residual capacity (FRC) \(^{72}\). In patients with COPD the recoil force of the lung elastic tissues is reduced resulting in a prolonged expiration and a new equilibrium point between inspiration and expiration \(^{72}\). This leads to a closing volume that exceeds the FRC \(^{73}\). COPD patients have an expiratory flow limitation (EFL), with dynamic hyperinflation in the lung, an intrinsic PEEP (PEEPi) and dynamic airway collapse \(^{74}\). This leads to a concomitant increase in the work of breathing, functional impairment of inspiratory muscle function, and adverse effects on haemodynamics \(^{73}\). In an acute exacerbation of COPD, the increased expiratory effort simply increases the alveolar pressure without improving expiratory airflow \(^{73-74}\). With the help of new physiological tools such as the negative pressure method, optoelectric plethysmography, and ultrasound, the dynamic and heterogeneity of expiratory flow limitation and dynamic hyperinflation can be further investigated \(^{73,59}\).

**COPD and the respiratory musculature**

Muscle dysfunction is prevalent in all stages of COPD. The diaphragm is the principal inspiratory muscle. The intercostal and scalene muscles are also important in inspiration. The sternocleidomastoid muscles can also be used in inspiration but only when respiratory demands are very high. The most important muscles in expiration are the abdominal muscles \(^{76}\).

In COPD patients the respiratory muscles adapt to the dynamic hyperinflation. The diaphragm is about 25% shorter due to the hyperinflation, which leads to a reduction in the capacity to contract \(^{76}\). Patients with COPD thus have a small reserve for diaphragmal shorting at end-inspiration, and the ability to increase the volume of the lower ribcage is reduced because of the hyperinflation \(^{76}\). The intercostal and scalene muscles are shortened and the mechanical advantage of these muscles decreases with hyperinflation and elevation of the sternum \(^{76-78}\). The abdominal muscles are often more active in COPD patients, particularly during late expiration \(^{76}\). Patients with COPD cannot increase their tidal volume by reducing the expiratory reserve capacity like healthy individuals. Instead they must increase the respiratory rate. Inadequate time to empty the airways can lead to an even more pronounced dynamic hyperinflation compromising the inspiratory muscles even more.

Dynamic hyperinflation is accompanied by intrinsic PEEP (PEEPi). This represents an inspiratory threshold load that must be overcome to initiate inspiration, this increases the work of breathing and the oxygen expenditure of breathing exponentially \(^{76-77}\). Apart from adaptation to the dynamic hyperinflation, muscle dysfunction is prevalent in all stages of COPD. The muscles most studied are the quadriceps muscle and the diaphragm, both showing changes in COPD. The patients quadriceps muscle is characterised by reduced
mass and loss of fatigue-resistant type 1 fibres and oxidative capacity. The diaphragm remodels to give a fatigue-resistant profile 79. COPD patients have an increased respiratory drive to the diaphragm, but this increase in frequency is not uniformly distributed to the major inspiratory muscles 76,80. Development of hypercapnia is not the result of impaired voluntary action of the diaphragm 80. Animal studies have shown that inspiratory loading causes respiratory failure and acidosis before output decreases or substrate is depleted in the diaphragm 80. In a study on failed ventilator weaning of COPD patients, Tobin et al, showed that most patients with COPD develop acute respiratory failure because of excessive mechanical load, insufficient respiratory muscle strength, or a combination of the two 80.

**COPD and pharmacologic treatment**

Pharmacologic therapy is used to prevent and control COPD symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease 4. Long term oxygen therapy for COPD patients with hypoxia at rest increases survival time 4. Previously it has been difficult defining what constitutes a response to pharmacological intervention in COPD, but recently important endpoints for COPD studies have been defined 56, though few pharmacological studies have used mortality as an endpoint 7.

The standard treatment of stable COPD, according to the current GOLD guidelines, aims at decreasing symptoms and/or complications 4. The pharmacological agents used include bronchodilators (long-acting β-2stimulators, anticholinergics and methylxanthines) and the inhalation of glucocorticosteroids in severe COPD with frequent exacerbations, though long-term treatment with systemic glucocorticosteroids should be avoided. Influenza vaccination can reduce serious illness 4.

The treatment of exacerbation includes short-acting β-2 stimulators, anticholinergics, glucocorticosteroids, oxygen, and antibiotics in severe exacerbations 4,81. This is a therapy tradition that has remained unchanged over at least the last ten years 81, despite the fact that the effect of inhaled drug therapy in very severe COPD has not yet been assessed 82.
The history of non-invasive ventilation

Non-invasive ventilation (NIV) first took the form of a body ventilator introduced by Daziel in 1838. The “iron lung” was invented by Drinkert in 1928, developed by Emerson and was regularly used for ventilator support for neuromuscular disorders until the polio outbreak in Copenhagen 1952. In Copenhagen many patients received invasive ventilation, and these had better survival rates than those who received non-invasive ventilation. The use of invasive ventilation for COPD patients on the ICU was introduced in the 1960’s. Non-invasive ventilation continued to be used for the ventilation of patients with neuromuscular disease.

The introduction of nasal masks for nocturnal ventilator support in patients with neuromuscular disease, and excellent results in correcting gas exchange disturbances in studies from France in the late 80’s initiated the increased use of NIV in COPD patients. In 1989 Meduri et al. were successful in treating respiratory failure with a facemask. In 1990 Brochard et al. showed the benefit of NIV compared to conventional treatment without ventilatory support for patients with an acute exacerbation of COPD. In 1993 Bott et al. using historical control patients for comparison showed beneficial results for COPD patients with nasal NIV compared to standard therapy. In 1995 in a randomised study Brochard et al. compared conventional therapy, invasive and non-invasive ventilation for the treatment of COPD patients. Non-invasive ventilation showed better hospital survival, fewer intubations, less complications and a shorter hospital stay. These findings have been confirmed in a comparison between NIV and standard therapy by Plant and others.

There has been considerable debate as to whether there are any factors that may be considered contraindications to NIV. The ATS conference in 2000 listed examples: need for secure airway; convulsive seizures; copious secretions; hemodynamic instability; agitation; and undue mask intolerance. These factors, however, were based on exclusion criteria in previous studies, and not because they were proven contraindications to NIV. Brochard and Elliot state that there are no absolute contraindications to NIV.

Indications for non-invasive and invasive ventilation in AECOPD

The indications for non-invasive ventilation in AECOPD are stated in the GOLD guidelines:

- moderate to severe dyspnoea with use of accessory muscles and paradoxical abdominal motion
- moderate to severe acidosis (pH < 7.35) and/or hypercapnia (PaCO2, >6.0 kPa, >45 mm Hg)
- respiratory rate > 25 breaths/min

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The indications for invasive ventilation according to the GOLD guidelines are:

- unable to tolerate NIV or NIV failure (or exclusion criteria)
- severe dyspnoea, with use of accessory muscles and paradoxical abdominal wall motion
- respiratory rate >35 breaths/min
- life-threatening hypoxaemia
- severe acidosis (pH <7.25) and/or hypercapnia (PaCO₂ >8.0 kPa, >60 mm Hg)
- respiratory arrest
- worsening of mental status despite optimal therapy
- cardiovascular complications (hypotension, shock)
- other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion).

The pH limit has been questioned, and NIV is also offered successfully to patients with a pH<7.25.

Non-invasive ventilation and respiratory physiology

In COPD patients with an acute exacerbation, non-invasive ventilation reduces respiratory muscle activity and improves the breathing pattern (respiratory rate and tidal volume). Gas exchange improves, with increasing pH, PaO₂ and decreasing PaCO₂. Diaphragmatic activity is reduced. NIV also reduces the work of breathing and promotes airflow as it overcomes intrinsic PEEP and enhances respiratory muscle performance as oxygenation improves. The improvement in PaO₂ is believed to be due to better alveolar ventilation rather than an improvement in the recruitment of non- or poorly ventilated alveolar units.

Non-invasive versus invasive ventilation in AECOPD

Some studies have investigated the difference in AECOPD patient outcomes between the ventilatory modes normally used. Vitacca et al. showed an improved one-year survival rate for COPD patients with NIV treatment compared to invasively ventilated patients in a retrospective study. Conti et al. noticed shorter hospital stays and fewer readmissions among patients treated with NIV compared to intubated patients, but no difference in one-year survival rate in a prospective randomised trial. Squadrone et al. found no difference in outcome between NIV treated COPD patients and matched controls with invasive ventilation, though there were fewer complications in the NIV group. Scala et al. showed fewer complications in the NIV group, but similar one-year survival rates when compared to intubated COPD patients, with a lower nosocomial infection rate and shorter duration of ventilation. Chandra et al. studied the use of NIV in the US. In the NIV failure group where patients were intubated after an NIV trial, mortality was high and increased with time. A finding contrary to the findings of Squadrone and Conti. Furthermore, in an audit of data from the UK the authors could not reproduce the benefits of NIV on survival found in these studies cited above. The reason for this discrepancy is unclear. Apart from different case mixes, the differences in hospital organisation and the setting where NIV is performed, could explain...
these conflicting results. Whatever, late failure after initial success is a bad prognostic sign associated with high mortality.

**NIV failure**

NIV failure does not have a standard definition. It is often considered as the need for endotracheal intubation or death without endotracheal intubation. The reasons for intubation can differ; it could be due to mask leakage or lack of improvement. Failure can be early (in hours) or late (>48 hours). Elliott states that a clear distinction needs to be made between failure of 'non-invasive' ventilation (i.e. a problem with the interface which may be solved by using another interface such as an endotracheal tube) and failure of ventilation i.e. no problem with the interface but despite this an inability to maintain effective ventilation, where invasive ventilation probably has little to offer. Late failure after initial success (despite therapy) is a bad prognostic sign associated with a high mortality.

The following table (Table 1) shows that the rate of failure differs between different ICU-studies. In other settings the failure rate is much lower (5%).

**Table 1: NIV failure in previous ICU studies.**

<table>
<thead>
<tr>
<th>Author, year.</th>
<th>NIV-patients Number</th>
<th>% NIV failure</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brochard 1995</td>
<td>43</td>
<td>26%</td>
<td>7.27-7.28</td>
</tr>
<tr>
<td>Vitacca 1996</td>
<td>30</td>
<td>26%</td>
<td>7.28</td>
</tr>
<tr>
<td>Conti 2002</td>
<td>23</td>
<td>52%</td>
<td>7.2 +/- 0.05</td>
</tr>
<tr>
<td>Carlucci 2003</td>
<td>208</td>
<td>17.2%</td>
<td>7.23</td>
</tr>
<tr>
<td>Girou 2003</td>
<td>294</td>
<td>11%</td>
<td>?</td>
</tr>
<tr>
<td>Squadrone 2004</td>
<td>64</td>
<td>62.5%</td>
<td>7.18</td>
</tr>
<tr>
<td>Confalonieri 2005</td>
<td>1033</td>
<td>30%</td>
<td>7.25-7.29</td>
</tr>
<tr>
<td>Demoule 2006</td>
<td>123</td>
<td>30%</td>
<td>7.30</td>
</tr>
<tr>
<td>Scala 2007</td>
<td>20</td>
<td>35%</td>
<td>7.22</td>
</tr>
</tbody>
</table>

Predictors of NIV success have been investigated in several studies. The NIV success rate is dependent on the severity of the exacerbation, the level of acidosis, the level of consciousness and the respiratory rate. The response to treatment is also important for the success rate, where improvement in pH and respiratory rate in the first 2 hours of treatment has a better prognosis. But the success rate is also dependent on good mask fit, the acceptance of NIV, and experience of the personnel providing NIV.

**Experience of NIV for AECOPD among personnel and patients**

Only a few studies have investigated this aspect of NIV. An AECOPD requiring ICU care is often a life-threatening condition. It is experienced as frightening and traumatic by the patient. NIV treatment with a mask is often experienced as demanding for the patient and personnel
alike. The patient feels anxiety over loss of control over the situation, they feel trapped and panic, and are completely dependent on the attending personnel. They often lack information about the treatment and how it is performed. The personnel often have problems in informing the patient because of the patient’s level of consciousness, their life-threatening situation, and dyspnoea. Personnel also feel that they must persuade or force the patient to accept NIV while the patient struggles and fights. This is a frustrating situation and creates an ethical dilemma for the attending personnel. Some experience feelings of helplessness, fear and concern about torturing the patient. Concern about the appropriateness of ICU admission and employment of a futile treatment method for the patient is also apparent amongst those interviewed.\textsuperscript{117-118}

Structural changes in the diaphragm during ventilation

The diaphragm is susceptible to the physiologic and biochemical changes that occur when a COPD patient is mechanically ventilated.

Animal studies have shown that prolonged mechanical ventilation alters both structure and function of the diaphragm.\textsuperscript{119} Mechanical ventilation can promote weakness of the diaphragm due to atrophy and contractile dysfunction, it is rapid in onset and is already seen after 12 hours of ventilation in animal studies.\textsuperscript{120} Controlled mechanical ventilation changes the ultrastructure of diaphragm muscle fibres, promotes diaphragmatic contractile dysfunction, leading to depression of diaphragmatic strength. The changes are most pronounced during controlled ventilation, but also appear with ventilatory support. Mechanical ventilation also leads to disturbance of diaphragmatic protein turnover, promotes oxidative injury, and changes diaphragmatic gene expression and cellular communication in animals.\textsuperscript{120}

Levine et al showed that 18 to 69 hours of controlled mechanical ventilation resulted in atrophy of the human diaphragm.\textsuperscript{121}

Juan et al. showed that a carbon dioxide tension of about 54 mmHg (7.2kPa) decreased the contractility of muscle fibres in the diaphragm and endurance time in humans.\textsuperscript{122} Jaber et al. showed that a short exposure to respiratory acidosis in pigs decreased diaphragmatic contractility proportional to the degree of hypercapnia.\textsuperscript{123} The diaphragm’s contractile function, structure and biochemistry are altered in COPD patients. These changes occur early in the course of the disease and show a strong negative correlation with respiratory muscle strength. The diaphragm in COPD patients is exposed to oxidative stress and sarcomeric injury leading to contractile protein wasting and consequently, loss of the force-generating capacity of diaphragm fibres. Even so the endurance of the diaphragm appears to be increased in COPD due to remodelling\textsuperscript{124}.

These changes are believed to make the diaphragm in COPD patients more susceptible to injury even in clinically stable COPD patients. Sarcomere disruption in the diaphragm is more evident in patients with COPD than in healthy subjects after inspiratory loading.\textsuperscript{125} In the study by Orozco-Levi et al. FEV1 was inversely correlated to sarcomere disruption intensity. Pulmonary hyperinflation explained up to 40% of the extent of diaphragm injury.\textsuperscript{125}

Advance directives

COPD is a chronic and progressive disease where some patients have reached the terminal stage. It is possible that terminal patients will not benefit from the treatment we offer on the ICU.
The prognosis of advanced COPD is very difficult to predict 126-128. Advance directives are important decisions to be made in severe COPD cases, in order to maintain their autonomy 126-127. Advance planning of ICU patient care is also important as it reduces stress, anxiety and depression in relatives 129. The fact is, however, that only 25% of patients with terminal COPD have such decisions available 130. Furthermore, compliance with these decisions in clinical practice is said to be low (< 15 %) 130. It may be that aids to decision-making and more information could improve the number of advance directives available in the future 128,130. Despite the poor prognosis, about 70 % of patients with severe COPD want cardiopulmonary resuscitation and mechanical ventilation 131 should such treatment be necessary. The in-hospital mortality rate in patients where intensive care treatment has been denied or withdrawn is very high, ranging from 80.3 to 95.4 % 132.

Predicting mortality in COPD

There is a great interest in exploring the possibility to predict mortality in COPD. This task is made very difficult because of the heterogeneity of COPD as a disease. Multiple factors reflecting degree of respiratory disease, the systemic influences of COPD, and co-morbidity, predict long- and short-term survival. Physiologic derangements such as airflow obstruction, hypoxaemia, lung hyperinflation, dyspnoea, exercise capacity, anaemia, cachexia, and reduction in lean body mass also relate to prognosis. Last but not least, health-related quality of life is also an important predictor of survival 133.

FEV1 has previously been considered to have a strong correlation with mortality following the studies by Fletcher and Peto 134. More recent research has shown that the relationship between FEV1 and mortality is weak 10.

Exercise capacity together with multidimensional risk assessments such as the BODE index are better predictors of mortality 10.

Prediction of mortality in AECOPD

It is difficult to predict survival for COPD patients in general, but it is particularly difficult to predict the survival of patients admitted to the ICU with an AECOPD requiring respiratory support. This has been shown in prospective studies on ICU patients 135-136, as well as in studies where doctors judged the likelihood of survival in a predefined case. Clinicians differ markedly in their decisions to admit and in their prediction of survival of identical patients 137-138.

When predicting survival in patients with AECOPD admitted to the ICU, premorbid variables, traditionally believed to have prognostic value, have not been shown to be predictive for intermediate survival. These include: age; functional capacity; quality-of-life; male sex; oral steroids; spirometry; previous hospital or ICU admissions; body mass index; smoking status; and long-term oxygen therapy 139.
Causes of death in COPD patients

In milder COPD, cancer and cardiovascular disease are more common causes of death than respiratory failure \(^{140}\). In more severe cases, the leading cause of death is respiratory disease \(^{10}\) or in more recent studies COPD itself \(^{141}\).

Long-term mortality after ICU-care in COPD patients

There are studies providing data on long-term mortality after ICU care. In a meta-analysis, Williams et al. found a 5-year mortality ranging from 40-58 %, for a mixed ICU population \(^{142}\). Wright et al. followed long-term mortality in one hospital and found a 5-year mortality rate of 47.1 % in the mixed population, and a mortality rate of 43.6 % in patients with respiratory disease. Mortality was 3.4 times higher than in a matched group from the general population. Mortality in the ICU group was higher than in the general population over a four-year study period \(^{143}\). The long-term mortality of COPD patients after ICU care is very high! Seneff et al. showed a one-year mortality rate of 59 % in COPD patients after ICU care \(^{144}\). Breen et al. studied the mortality in invasively ventilated patients and showed a one-year mortality rate of almost 48.6 % and a 3-year mortality of 64.5 % \(^{145}\). Ai Ping et al. studied the mortality in COPD patients with NIV and invasive ventilation. The mortality at 1, 3, and 5 years was 42.7 %, 61.2 %, and 75.9 % \(^{146}\). Chu et al. studied the long-term survival of COPD patients treated with NIV on the ICU and found a 1-year mortality of 49.1 %. A further study on COPD patients with a “Do not intubate” decision receiving NIV on the ICU showed a one-year mortality of 70.3 % \(^{147-148}\). Furthermore, Christensen et al. showed a one-year mortality rate of 40.4 % in COPD patients that had been invasively ventilated on the ICU \(^{149}\).

Table 2: Long-term mortality after ICU-care in COPD patients.

<table>
<thead>
<tr>
<th>Author</th>
<th>1-year mortality</th>
<th>3-year mortality</th>
<th>5-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seneff</td>
<td>59 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breen</td>
<td>48.6 %</td>
<td>64.5 %</td>
<td></td>
</tr>
<tr>
<td>Ai Ping</td>
<td>42.7 %</td>
<td>61.2 %</td>
<td>75.9 %</td>
</tr>
<tr>
<td>Chu</td>
<td>49.1 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chu</td>
<td>70.3 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christensen</td>
<td>40.4 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The EuroQol instrument

One of the most used instruments for the evaluation of health-related quality of life is the EuroQol (EQ-5D) \(^{150}\). The EQ-5D involves a health-state classification scheme comprising five items: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression, each having three alternatives \(^{150}\): no problems, some problems and extreme problems, thus defining 243 distinct health states. The answers in the first part range from 0 to 1. The second part of the EQ-5D is a Visual Analogue Scale (VAS), ranging from 0 (worst possible health-state) to 100 (best possible health-state) where respondents rate how they perceive their
health. Health-states can also be evaluated better than, equal to, or worse than death. For health-states evaluated as worse than death, the utility is negative.\textsuperscript{151}

**Short Form 36 Health Survey (SF-36)**

The SF-36\textsuperscript{152} was developed to investigate generic health concepts not specific to any age, disease or treatment group. It investigates physical, social and emotional functioning it has 36 questions and generates a health profile of eight sub-scale scores:

- physical functioning (PF).
- role limitations due to physical problems (RP).
- bodily pain (BP).
- general health (GH).
- vitality (VT).
- social functioning (SF).
- role limitations due to emotional problems (RE).
- mental health (MH).

The scores on all sub-scales are transformed to a scale from 0 (worst score) to 100 (best score)\textsuperscript{153}.

There are also two summary measures:

- Physical Component Summary Measure (PCS) consisting of values from:
  - PF (10 items); RP (4 items); BP (2 items); and GH (5 items).
- Mental Component Summary Measure (MCS) consisting of values from:
  - VT (4 items); SF (2 items); RE (3 items); and MH (5 items).

The patient also answers two questions:

- Compared to one year ago how would you rate your general health now?
- In general would you say your health is excellent, very good, good, fair or poor?\textsuperscript{154}

**APACHE II**

APACHE II (Acute Physiologic and Chronic Health Evaluation II) is a disease severity classification system developed by Knaus et al\textsuperscript{155} at the end of the 70’s. Their aim was to create a system able to systematically assess the severity of illness, to increase our knowledge about case mix adjustment, and to make it possible to assess critical care outcome using basic information that is more than just patient diagnosis\textsuperscript{156}.

The system generates two values; a disease severity score (APACHE II Score) and an Estimated Mortality Risk (EMR) predicting the patient's probability of hospital mortality. Apart from the diagnosis, these values are based on the patient’s age and physiological derangement in 12 domains assessed during the first 24 hours on the ICU (Acute Physiology Score=APS). And further, information on the patient’s chronic health: liver, cardiovascular, respiratory or renal insufficiency and immune deficiency (Chronic Health Evaluation=CHE).
The Estimated Mortality Risk is calculated according to the formula:
\[ \ln(R/1-R) = (-3.517 + (\text{APACHE II points} \times 0.146) + (0.603, \text{if the patient was taken to the op ambulant}) + (\text{the predefined value for the main diagnosis responsible for the ICU admission})]. 
The APACHE II score makes it easier to describe and understand the case mix of different populations of COPD patients treated on the ICU.

**NEMS and NCR 11**

The Nine Equivalents of Nursing Manpower Use Score (NEMS) and the Nursing Care Recording System for assessment of workload on the ICU (NCR 11) are two systems used in the measurement of workload among the personnel on the ICUs in Sweden. NEMS registers the workload in 9 and NCR 11 in 11 different dimensions connected to the care of ICU patients creating a daily score.

**The Swedish Intensive Care Registry (SIR)**

The Swedish Intensive Care Registry (SIR) is a co-operative endeavour initiated by Swedish Intensive Care Units (ICU) to audit and benchmark intensive care. It started to recruit general ICUs in Sweden during 2001, and currently covers 62 of 65 general ICUs. A comprehensive dataset has been jointly specified by participating units, with data collection guidelines available on the internet and annual training sessions. Registry data are recorded prospectively in local databases by physicians and nurses, then transmitted electronically to the registry using a common data transfer protocol that includes a validation script. Data with logical defects are returned for local validation and then returned centrally and entered into the master database. The dataset includes basic patient characteristics including a unique 12-digit personal number, reason for admission and severity of illness score. From the beginning the Acute Physiology and Chronic Health Evaluation II system (APACHE II) was employed, but now scores are according to the Simplified Acute Physiology Score 3 (SAPS 3) for adults, the Paediatric Index of Mortality 2 (PIM 2) for children, and Higgins’ ICU Score for patients on thoracic intensive care units that have undergone cardiac surgery. Resource consumption is assessed by recording length of stay, cumulative NEMS scores or cumulative NCR11 scores. A primary ICD-10 diagnostic code is given at discharge and used as principal diagnosis of the admission. Vital status is followed continuously for all admissions.

**Quality of ICU databases**

The quality of research using data from a medical registry is dependent on the quality of the data in the registry. Definitions of data quality given in the literature are frequently unclear. There will always be errors in databases such as insufficient data quality, incomplete data, non-adherence to data definitions and random errors. Furthermore there is a lack of clinical definitions for ICD-diagnoses. These weaknesses can be reduced and the quality of data improved with the aid of guidelines, training, quality control and education. Efforts to increase the quality of data in a national registry must be performed not only at the national level but also at the local level. Dutch studies on ICU registries have shown 4.8% inaccurate data and 3.3% incomplete data after manual data collection.
Aims of this thesis

The general aim of this thesis was to study characteristics, treatment and outcome in patients with an acute exacerbation of chronic obstructive pulmonary disease admitted to intensive care units in Sweden.

The specific aims as described in the following papers were:

I. To examine characteristics, resource use and long-term survival in patients with an acute exacerbation of chronic obstructive pulmonary disease that were admitted to Swedish intensive care units.

II. To investigate 5-year survival stratified by mechanical ventilation modality in chronic obstructive pulmonary disease patients treated on the intensive care unit.

III. To examine those patient characteristics and circumstances deemed important in the choice made between non-invasive ventilation and invasive ventilation on the intensive care unit.

IV. To examine health-related quality of life in patients with chronic obstructive pulmonary disease after discharge from the intensive care unit.
Material and methods

Study design

Study I
Study I is an observational study, with prospectively recorded data from the Swedish Intensive Care Registry.

Study II
Study II is an observational multicentre inception cohort study with prospectively collected data from 9 ICUs in the south-east region of Sweden.

Study III
Study III is divided in to two parts: the first part is an observational study with prospectively collected data from 9 ICUs in the south-east region of Sweden, the second part is a questionnaire answered by ICU personnel.

Study IV
Study IV is a longitudinal multicentre study with prospectively collected data from 3 ICUs in the south-east region of Sweden.

Participants and settings

Patients in Study I
1009 patients with 1199 admissions on 42 ICUs in Sweden with a primary diagnosis of COPD were analysed according to characteristics, resource use and long-term survival.

Patients in Study II
93 patients on 9 ICUs in Sweden were analysed according to their 5-year survival stratified by mode of mechanical ventilation.

Patients and participants in Study III
95 admissions of AECOPD patients on 9 ICUs in Sweden were analysed, variables associated with immediate intubation were identified. Doctors, nurses and assistant nurses on 6 ICUs in Sweden answered a questionnaire about factors having a possible influence on the decision to use immediate invasive ventilation in AECOPD patients.
Patients in Study IV
51 COPD patients on 3 ICUs in Sweden with an ICU stay longer than 24 hours were analysed according to their health-related quality of life at 6, 12 and 24 months after discharge from the ICU. The results were compared to HRQL of two reference groups from the general population, an age- and sex-adjusted reference population, and a reference group with COPD.
Measurements and measuring instruments

**Study I**
The following measurements and measuring instruments were included in Study I.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Measured as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Admissions on the ICU for patients with COPD.</td>
<td>Admissions per hour/ 24 hours.</td>
</tr>
<tr>
<td></td>
<td>Admissions per day in the week.</td>
</tr>
<tr>
<td></td>
<td>Admissions per month.</td>
</tr>
<tr>
<td>2. Age</td>
<td>Years, mean age.</td>
</tr>
<tr>
<td>3. Crude mortality risk within 90 days.</td>
<td>Factors related to mortality within 90 days after admission to ICU.</td>
</tr>
<tr>
<td>4. Discharge time.</td>
<td>Discharge during office hours (07.00-16.00).</td>
</tr>
<tr>
<td></td>
<td>Discharge out of office hours.</td>
</tr>
<tr>
<td></td>
<td>Discharge day of week (Mo-Fri 16.00).</td>
</tr>
<tr>
<td></td>
<td>Discharge day of week (Fri16.00-Sun 12.00).</td>
</tr>
<tr>
<td>5. Gender.</td>
<td>Female/ Male.</td>
</tr>
<tr>
<td>6. Hospital size.</td>
<td>Regional hospital.</td>
</tr>
<tr>
<td></td>
<td>County hospital.</td>
</tr>
<tr>
<td></td>
<td>Local hospital.</td>
</tr>
<tr>
<td>7. ICD-10 diagnostic code.</td>
<td>J.44 Present/ Not present.</td>
</tr>
<tr>
<td>8. Length of stay on the ICU.</td>
<td>Hours, days.</td>
</tr>
<tr>
<td>9. NCR 11 Score.</td>
<td>Score, points.</td>
</tr>
<tr>
<td>10. NEMS.</td>
<td>Score, points.</td>
</tr>
<tr>
<td>11. Severity illness score, APACHE II.</td>
<td>Score, points.</td>
</tr>
<tr>
<td>12. APACHE II, Estimated Mortality Risk</td>
<td>Probability, %</td>
</tr>
<tr>
<td>14. Route of admission, location before admission.</td>
<td>• Admission from emergency room.</td>
</tr>
<tr>
<td></td>
<td>• Admission from regular ward.</td>
</tr>
<tr>
<td></td>
<td>• Admission from other location.</td>
</tr>
</tbody>
</table>
Study II
The following measurements and measuring instruments were included in Study II.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Measured as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute respiratory failure.</td>
<td>PaCO₂ ≥ 7 kPa or PaO₂/ FiO₂ &lt; 26.7 kPa.</td>
</tr>
<tr>
<td>2. Age</td>
<td>Years.</td>
</tr>
<tr>
<td>3. Arterial Base Excess.</td>
<td>mmol/l.</td>
</tr>
<tr>
<td>5. Arterial PaO₂.</td>
<td>kPa.</td>
</tr>
<tr>
<td>6. Arterial PaO₂/FiO₂ ratio.</td>
<td>kPa.</td>
</tr>
<tr>
<td>7. Arterial acid base balance.</td>
<td>pH.</td>
</tr>
<tr>
<td>8. Body Mass Index.</td>
<td>Weight in kilos/ (length in metres)².</td>
</tr>
<tr>
<td>9. Gender.</td>
<td>Female/ Male.</td>
</tr>
<tr>
<td>10. Time with invasive ventilation.</td>
<td>Hours.</td>
</tr>
<tr>
<td>12. Length of stay, ICU.</td>
<td>Days.</td>
</tr>
<tr>
<td>13. NIV failure rate.</td>
<td>Intubation after initiation of NIV.</td>
</tr>
<tr>
<td>15. Respiratory rate.</td>
<td>Breaths per minute.</td>
</tr>
</tbody>
</table>
Study III, Part 1

The following measurements and measuring instruments were included in Study III. The study consisted of two parts. Measurements and measuring instruments of Part 1 included:

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Measured as</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age</td>
<td>Years</td>
</tr>
<tr>
<td>2. Acidosis rate among admissions.</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>• Moderate-to-severe acidosis</td>
</tr>
<tr>
<td></td>
<td>(arterial pH&lt;7.35).</td>
</tr>
<tr>
<td></td>
<td>• Severe acidosis</td>
</tr>
<tr>
<td></td>
<td>(arterial pH&lt;7.25).</td>
</tr>
<tr>
<td>3. Arterial Base Excess.</td>
<td>mmol/l</td>
</tr>
<tr>
<td>4. Arterial HCO₃⁻.</td>
<td>mmol/l</td>
</tr>
<tr>
<td>5. Arterial PaCO₂.</td>
<td>kPa</td>
</tr>
<tr>
<td>6. Arterial PaO₂.</td>
<td>kPa</td>
</tr>
<tr>
<td>7. Body Mass Index.</td>
<td>Weight in kilos/ (length in metres)²</td>
</tr>
<tr>
<td>8. Respiratory rate.</td>
<td>Breaths per minute</td>
</tr>
<tr>
<td>9. Gender</td>
<td>Female/ Male</td>
</tr>
<tr>
<td>10. Intubation rate.</td>
<td>% of patients admitted</td>
</tr>
<tr>
<td></td>
<td>• Daytime 07-22.</td>
</tr>
<tr>
<td></td>
<td>• Nighttime 22-07.</td>
</tr>
<tr>
<td>11. Mode of ventilation.</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Non-invasive ventilation started.</td>
</tr>
<tr>
<td></td>
<td>Invasive ventilation started.</td>
</tr>
<tr>
<td>14. Severity illness score. APACHE II.</td>
<td>Score, points</td>
</tr>
<tr>
<td>15. Spirometry available.</td>
<td>% of patients admitted</td>
</tr>
</tbody>
</table>
Study III, Part 2

Part two of the study III was a questionnaire based on 35 items, it was based on constructs and items deemed relevant when choosing between non-invasive ventilation and invasive ventilation.

Questionnaire and related literature search with references

Concepts and items important for the outcome of COPD patients on the ICU were identified in two steps. First, the current Global Initiative for Chronic Obstructive Lung Disease guidelines (GOLD) were studied. Second, an extensive PubMed search was conducted using the following search terms in 11 combinations: chronic, pulmonary, airways OR lung OR pulmonary, disease, prognosis OR outcome OR death, intensive care OR intensive treatment OR intensive therapy, ventilatory OR respiratory OR mechanical ventilation, intubation OR non invasive ventilation, exacerbation, workload, readmission, guidelines, indications.

The instructions to the respondents were as follows:

Please grade them as:

- No or little significance.
- Quite important.
- Of great importance.
- Most important.

The questions in the questionnaire with related references.

1. The patient is suffering from severe dyspnoea.
2. The patient has a severe cough.
3. The patient has copious secretions.
4. The patient is admitted to the ICU from the emergency department.
5. The patient is admitted to the ICU from the ward.
6. At what time of day the patient arrives on the ICU.
7. At what day of the week the patient arrives on the ICU.
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**Study IV**

The following measurements and measuring instruments were included in Study IV.

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<th>Measurement</th>
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<tbody>
<tr>
<td>1. Age</td>
<td>Years.</td>
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<tr>
<td>2. Charlson co-morbidity index</td>
<td>Score, points.</td>
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<td>3. EuroQoL instrument</td>
<td>EQ-5D, score, points.</td>
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<td></td>
<td>EQ-VAS, score, points.</td>
</tr>
<tr>
<td>4. Gender</td>
<td>Female/ Male</td>
</tr>
<tr>
<td>5. ICD-10 diagnostic code</td>
<td>Present / Not present:</td>
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<tr>
<td></td>
<td>• J44.0 Chronic obstructive pulmonary disease with acute lower respiratory infection.</td>
</tr>
<tr>
<td></td>
<td>• J44.1 Chronic obstructive pulmonary disease with acute exacerbation, unspecified.</td>
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<tr>
<td></td>
<td>• J44.8 Other specified chronic obstructive pulmonary disease.</td>
</tr>
<tr>
<td></td>
<td>• J44.9 Chronic obstructive pulmonary disease, unspecified.</td>
</tr>
<tr>
<td>6. Reason for admission in the ICU</td>
<td>Respiratory: Present / Not present</td>
</tr>
<tr>
<td>7. Severity illness score, APACHE II</td>
<td>Points.</td>
</tr>
<tr>
<td>8. Short Form 36 Health Survey (SF-36)</td>
<td>Score, points.</td>
</tr>
<tr>
<td></td>
<td>• Physical Functioning (PF).</td>
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<td>• Role Physical (RP).</td>
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<td>• Bodily Pain (BP).</td>
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<td>• Role Emotional (RE).</td>
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<td></td>
<td>• Mental Health (MH).</td>
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Statistical Methods used in the studies

<table>
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<td>Mann-Whitney U</td>
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<tr>
<td>Wilcoxon rank-sum test.</td>
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Ethical aspects

There was no need for ethic approval and informed consent for the Studies I-III, as they were observational and included no change in clinical practice. In Study IV the study protocol was approved by the Linköping University Regional Ethics Review board. The patients that answered the questionnaire about Health-related quality of life in Study IV had given an informed consent to use their data in scientific studies.
Results

Results Study I

In Study I we investigated characteristics and long-term outcome of COPD patients admitted to Swedish ICUs. 1009 patients with 1199 admissions were identified (1.3 % of all admissions). 53 % of the patients were admitted to ICUs in a county hospital, 26 % to ICUs in a local hospital and 21 % to a regional hospital. The patients were admitted to the ICU from the emergency department in 49.3 % of cases and from the ward in 44.6 % of cases, leaving 6.1% with other locations prior to ICU admission.

The patients had an mean age of 70.2 years (SD 9.1), the majority were female (61.5 %). The mean APACHE II score was 20.2 (SD 7.0). Admissions were evenly distributed over the year with the highest number admitted in April and the lowest in September.

The resource usage for the COPD patients was higher than the median resource usage for all other patients. A high percentage (15.8 %) of these COPD patients were readmitted. Older patients had less chance of being readmitted.

The mortality in this patient cohort was very high with a ICU mortality of 7.8 %, a 30-day mortality of 26 %, and a 3-year mortality of 70 %. Median survival time was 15 months.

Risk factors for mortality after 90 days were male gender, age, APACHE II probability and discharge at the weekend.

Results Study II

In this study, 93 COPD patients admitted to 9 ICUs in the south-east region of Sweden were stratified according to mode of ventilation. These COPD patients represented 1.6 % of all ICU admissions at this point in time.

The mean age was 70.6 years (SD 9.6), and 57 % were female. Sixteen patients (17 %) were intubated and invasively ventilated and 77 patients (83%) began with non-invasive ventilation. NIV failed in 15 patients (19 %).

The groups with NIV and invasive ventilation differed in body mass index, ICU length of stay and age. Other characteristics were similar including arterial blood gases, acid base status and respiratory rate.

The mortality in both groups was high, with a 5-year survival of 17 % in the NIV group and 6 % in the invasive ventilation group.

Non-invasive ventilation was associated with increased survival, whereas increased APACHE II score and age were associated with decreased survival.

The mortality in the NIV fail group was not significantly different from survival in the invasive ventilation group.
Results Study III

In this study 95 admissions for acute exacerbation of COPD were analysed according to characteristics associated with invasive ventilation. Thereafter a questionnaire with 35 items was sent to ICU personnel with different professions (doctors, nurses and assistant nurses) in the admitting ICUs to study the relative importance of various factors that possibly influence the decision to use invasive ventilation immediately. Seventy-nine patients (83%) began with NIV on admission, 16 (17%) were intubated immediately. The two groups did not differ in arterial blood gases, acid base status or respiratory rate. The NIV group was significantly younger and had a lower BMI than patients that were intubated immediately. BMI was the only variable remaining associated with increased risk for intubation in a multivariate analysis. The intubation rate day and night-time was similar. The usage of NIV was not correlated to the presence of acidosis. Eighty-three per cent of the patients with pH<7.35 were treated with NIV, and 81% of the patients with severe acidosis pH<7.25 received NIV. Ranking of responses to the questionnaire showed that consciousness, respiratory symptoms and blood gases were powerful factors determining invasive ventilation. Non-patient-related factors (physician in charge, presence of guidelines, ICU workload) were also deemed important for the decision to intubate immediately. There were small differences between professions in ranking of the five most important factors in the questionnaire.

Results Study IV

In this study we examined the health-related quality of life (HRQL) in COPD patients treated on the ICU. Their results were compared to the HRQL of two other groups, a reference group with COPD (COPD-reference), and reference group without COPD from the general population (Non-COPD reference). HRQL was measured using the EuroQol (EQ-5D) and the Short Form 36 Health Survey (SF-36) questionnaires. HRQL in the COPD-ICU group was always markedly lower compared to the Non-COPD reference group from the general population. In COPD-ICU patients where a complete follow-up was done, changes in HRQL over time were minor and did not decline further during 6 to 24 months after discharge. There were differences in EQ-VAS (p<0.05) and PF (p<0.059) between the COPD-ICU group and the COPD-reference group. The SF-36 results in the COPD-ICU group were not statistically different from the COPD-reference group. Patients that died during the study had a poorer HRQL. PF and SF scores were statistically lower in this group of patients. HRQL in COPD patients 24 months after discharge from the ICU was quite similar to that of COPD patients not treated on the ICU.
Figure 1.
SF-36 measurements at 6, 12 and 24 months in patients from the COPD-ICU group providing responses at all three times. There were no statistically significant changes over time (Friedman’s test). The Non-COPD and COPD reference groups are added for comparison. Values are mean.
Discussion

Introduction

When we started our research project, at the beginning of this millennium, on COPD patients in need of ventilatory support admitted to Swedish ICUs, not much was known about this group of patients. All Swedish ICU physicians were familiar with this group of patients and knew of the severity of their disease and that the short-term mortality was high. Available details of admission and treatment were scarce and little was known about outcomes beyond the ICU. The creation of a national registry on ICU patients in Sweden (the Swedish Intensive Care Registry, SIR) in 2001, together with a programme intended to support research and the creation of healthcare networks in the south-east region of Sweden (The Health Research Council in the South-East of Sweden, FORSS), however, made it possible to gather essential information about these patients.

The introduction of international and national healthcare programmes for COPD patients at the beginning of the millennium, with guidelines on the indication for ICU care of these patients, was a further important development.

Much of the research that we have performed during this project is based on the views of attending personnel on the ICU department where COPD patients with respiratory failure are admitted.

The COPD patient before admission to the ICU

When a patient with COPD and respiratory failure arrives at the ICU, some information about the individual that could help in deciding the best possible treatment for that patient is often missing.

We have seen that spirometry, that is obligate for the diagnosis and staging of COPD according to present guidelines, is surprisingly often missing. Information about activities of daily living and the patients opinion regarding advance directives, if any, is very often missing for COPD patients admitted to the ICU in Sweden, as well as information about nutritional status and health-related quality of life prior to admission. The absence of such information could lead to important decision-making becoming arbitrary and dependent on the physician responsible for the patient at admission rather than being objective. Since COPD is a chronic and progressive disease, some patients have reached the endpoint in their disease and will not survive despite ventilatory treatment on the intensive care unit. At present objective information on admission, indicating whether the patient has a treatable acute exacerbation of COPD or has reached an end stage in the disease, is often lacking.

The COPD patient in need of ventilatory support on admission to the ICU

Our studies have increased our knowledge of the characteristics of COPD patients admitted to the ICU in need of ventilatory support. We now know that these patients have a mean age of about 70 years, and that the proportion of women is higher. COPD patients have a high severity illness score on admission according to their APACHE II scores. The main route of admission is via the emergency department and the ward in about equal proportions.
A large proportion of the patients have acute respiratory failure on arrival with a high respiratory rate and severe life-threatening disturbances in their acid base status and blood gases.

**Non-invasive ventilation in patients with COPD on the ICU**

Despite its long history NIV is a quite new treatment modality for patients with COPD in need of ventilatory support admitted to the ICU. When we started these studies there were no data on the usage and results of NIV on Swedish ICUs. The correct way of using NIV in COPD patients in the intensive care setting is stated in the current national and international guidelines. However this treatment is not always easy to apply, and is dependent of the skill and education of the attending personnel. As COPD patients are admitted to the ICU at any time, night and day, all year, NIV-treatment must be understood by all personnel on the ICU and not just a few skilled and interested individuals. Our data show that NIV is now well-established in Sweden, its usage is high even in patients with severe respiratory derangement, and the failure rate is low and in line with current international experience.

**The choice between NIV and invasive ventilation in patients with COPD on the ICU**

The advantages of NIV compared to invasive ventilation are better short-term survival, fewer complications, and a shorter length of stay on the ICU. It also gives the attending personnel time to gather important information in order to proceed with optimal care of the patient. The indications for NIV and invasive ventilation are stated in the current national and international guidelines for the treatment of COPD patients. Our studies show that in Sweden some COPD patients with very severe respiratory derangements that fulfil the criteria for invasive ventilation may successfully be treated with NIV. This is probably due to the evolution of this treatment modality following the development of special facemasks, ventilators, and the extensive experience and education of ICU personnel. The decision to start treatment with invasive ventilation in a patient with acute exacerbation of COPD, where it is presumed that the patient will recover and return to a state with good health-related quality of life, is an easy decision. The decision to treat a patient with terminal disease with invasive ventilation, on the other hand, is very demanding. Unfortunately we lack objective criteria indicating when a patient has end-stage disease and where ICU treatment is futile. Our questionnaire revealed the importance of NIV in providing the personnel time to gather information considered important when deciding whether or not to intubate the patient. The questionnaire also showed that information other than that present in current healthcare programmes was important for this decision. We are not quite sure why overweight patients (BMI>25kg/m²) were more likely to be intubated immediately in Study III.

**Treatment on the ICU**

In these studies we did not have information about treatment of the patients before being admitted to the ICU apart from the absence of ventilatory support. We did not use a formal
treatment protocol on the ICU stating pharmacological treatment or the use of different pressure levels or levels of positive end-expiratory pressures during ventilation. We measured the resource use among the personnel, which was slightly higher for COPD patients than the median value for all ICU patients. In the answers to our questionnaire, the presence of guidelines and ongoing inhalational treatment were ranked 15 and 16 of the 35 items important for the decision to intubate immediately, other factors associated with pharmacological treatment of the patients on the ICU were ranked low. The length of stay on the ICU was much shorter for patients treated with NIV than patients that were intubated and invasively ventilated, and was shorter than in previous international studies.

**Mortality on the ICU**

The ICU mortality in our studies varied between 7.8 % in Study I and 15 % in Study II. These numbers are lower than previously reported results from the UK and US (23.1 % and 9.3 %) 144,187.

**Readmission after ICU treatment**

In Study I, 15.8 % of all COPD patients were readmitted to the ICU during this 5-year study. In Study III 11 % of the patients in the NIV group were readmitted. This is a high proportion of patients with regard to our finding that readmission is less likely in older patients. We do not know if this is preventable. The readmission rate in previous studies in mixed ICU populations is 4-14 % 167 and 2.56 % in COPD patients readmitted to the ICU 188.

**Short-term mortality after treatment on the ICU**

The 30-day mortality in Study I was 26 %. Most studies do not present 30-day mortality, but the hospital mortality in studies from the US 144 is 23.8 %, and in the UK 38.3 % 187. The 90-day mortality rate in Study I was dependent on male gender, higher age, increased APACHE II probability and discharge during the weekend. We do not know if the increased mortality related to discharge at the weekend can be reduced. Theoretically this is due either to premature discharge or the presence of an advance directive indicating reduced level of care.

**Long-term mortality after treatment on the ICU**

The long-term mortality rate in our studies was high; 49.4 % of the patients treated with NIV in Study II died within a year, and 70 % of the patients in Study I died within 3 years. In Study II five-year survival rates of 17 % in the NIV group and 6 % in the invasive ventilation group were found. In Study IV which included survivors after ICU care, the 4-year mortality rate was 60 %. There are only a few other diseases with such a pessimistic prognosis after treatment on the ICU.
Health-related quality of life in COPD patients after ICU care

There is a growing interest in studies of health-related quality of life after ICU care. I do believe that all personnel involved in the care of patients with severe diseases in need of intensive care are interested in getting feedback about the recovery and subsequent life of their patients. It is also important to study HRQL to avoid the notion that ICU treatment of COPD patients is futile and a burden for the patient and society. The study of HRQL is challenging as the methods used are quite new, HRQL in COPD patients is dependent on several factors such as dyspnoea, depression, anxiety and exercise tolerance. Clinically important differences in HRQL scores are not unanimously defined, there are floor and ceiling effects in the methods used and there is no clear consensus about the use of statistics and how to deal with missing data. Nevertheless it is important to describe the patient’s situation after ICU care using objective measurements not restricted to just age, disease or treatment group. The findings in Study IV were to some extent surprising to us. In view of the fact that COPD is a chronic and progressive disease, we expected to see a decline in HRQL over time in these patients. This was not the case. The HRQL in this group of patients was low compared to the general population, but did not decline further during the 24-month period after discharge. After 24 months it was similar to the HRQL of COPD patients not treated in the ICU. Patients that died during the study had a poorer HRQL. PF and SF scores were statistically lower in this group of patients.

Strengths and limitations

This thesis has some major strengths. The data source is multi-center in all four studies. Secondly, the Swedish 12-digit personal number made it possible to ascertain almost complete vital status for all the patients. The randomised controlled trial is the gold standard for evaluation of medical methods. There is however one major limitation with randomised trials, they have difficulty in detecting rare or late adverse effects of treatment. Observational studies are better in detecting the benefits and harms of medical interventions. The quality of observational studies is dependent on appropriate selection of participants, appropriate measurement of variables and appropriate control of confounding. Non-invasive ventilation has been shown to be beneficial in the treatment of AECOPD on the ICU in randomised trials. Observational studies may thus be the only way to investigate several aspects of the usage of NIV in COPD patients in need of ventilatory support. We believe that the selection of participants in our studies was correct. We have confirmed the diagnosis COPD in several ways, from the local databases at different ICUs in the southeast region of Sweden, by the APACHE II system on admission, with the ICD-10 code and with help of the Swedish Cause-of-death register. The diagnosis was made with the help of clinical signs and not by spirometry in many patients, but this is inevitable in patients in need of ventilatory support admitted to the ICU from the emergency department. The proportion of COPD patients in the ICUs in Sweden is lower than in other countries. We believe that this is dependent on the smoking habits, or rather lack of, in Sweden rather than selection bias.

The measurement of most variables used is defined in the guidelines of the Swedish intensive care registry (SIR) and we believe they are appropriate and precise.
The questionnaire in Study III was designed with a systematic approach including a pilot test run and reliability and validity testing. We do not have a complete control of confounding factors in our studies as the treatment of COPD patients in and outside the ICU has many components apart from those we can measure on the ICU. The group of patients for example, is not uniform and COPD has several phenotypes and genetic factors that also influence the outcome not least when mortality is used as end-point. Acute exacerbations of COPD are poorly defined and possibly heterogeneous in their pathophysiology and biomarkers for AECOPD are lacking. The treatment COPD patients receive is not standard neither outside nor on the ICU. Co-morbidity scores are not always present in the data from COPD patients in Sweden. Furthermore the cause of death was not separately analysed in all studies included.
Conclusions

- The mortality of COPD patients with respiratory failure admitted to Swedish ICUs is high in the short- and long-term perspectives despite ICU care.
- Non-invasive ventilation (NIV) is used as first-line treatment in a very high proportion of COPD patients with respiratory failure admitted to the ICU in Sweden.
- Non-invasive ventilation had a better long-term outcome compared to immediate invasive ventilation in COPD patients in need of ventilator support admitted to the ICU in our observational study.
- A failed NIV-trial does not increase the long-term mortality compared to immediate invasive ventilation in COPD patients in need of ventilatory support on the ICU.
- Factors other than those deemed most important in guidelines appear to have an inappropriate influence on the choice between NIV and immediate intubation of patients with an acute exacerbation of COPD.
- The health-related quality-of-life (HRQL) of COPD patients admitted to the ICU in Sweden is lower than in the general population, but does not decline further during the period 6 to 24 months after discharge.
- HRQL in COPD patients 24 months after discharge from the ICU was quite similar to that of COPD patients not treated on the ICU.
Populärvetenskaplig sammanfattning på svenska

Kroniskt obstruktiv lungsjukdom (KOL) är ett växande hälsoproblem över hela världen. Idag är det den femte vanligaste dödsorsaken, men sjukdomen kommer att bli än mer vanlig som dödsorsak de närmaste årtiondena. WHO räknar med att dödligheten i KOL kommer att öka med 30 % de närmaste 10 åren. 5 % av alla dödsfall tros bero på KOL. KOL sjukdomen är lömsk då det är en kronisk sjukdom som progredierar, det finns i nuläget ingen bot för sjukdomen, bara lindring i form av läkemedelsbehandling och syrgasbehandling. Sjukdomen karakteriseras av en försämrad lungfunktion samt andnöd, ökad slemproduktion och hosta. Efterhand påverkas hela kroppen av den kroniska inflammation som finns i luftvägarna. Den vanligaste orsaken till KOL är rökning. Diagnosen KOL ställs med hjälp av en spirometriundersökning. Tyvärr ställs diagnosen oftast sent och ett rökstopp i det skedet av sjukdomen ger bara en viss bättring, men ingen bot. Många patienter med KOL är inte medvetna om sin sjukdom. I Sverige har ca 500 000 personer sjukdomen. Ca 2500 avlider av sjukdomen i Sverige varje år.

Sjukdomen har ett ojämnt förlopp. KOL-patienter kan drabbas av plötsliga försämringar, såsom exacerbationer. En exacerbation kan bero på en infektion, men orsaken är inte alltid känt. Försämringen i hosta, slemproduktion och andnöd kan kräva sjukhusvård och de svårast sjuka patienternas andning kan vara så påverkad att de kan behöva intensivvård.

Intensivvårdsavdelningen kan erbjuda ventilationsstöd där man stöttar eller tar över patientens andningsarbete med hjälp av en respirator.

Respiratorbehandling har sedan 1960 talet genomförs med hjälp av sövning av patienten varefter man för ner en endotrachaltub i patientens luftrör och stöttar andningen, detta kallas invasiv ventilatorbehandling.


Syftet med denna avhandling var att studera de KOL patienter som var så svårt sjuka att de behövde intensivvård.

Vi ville veta mer om dessa patienter och studera deras överlevnad efter intensivvård. Vi ville också se hur deras vårdresultat påverkades av vilken ventilatorbehandling (non-invasiv eller invasiv) de behandlades med. Vi ville också veta mer om hur personalen valde mellan non-invasiv och invasiv ventilatorbehandling till KOL-patienter på intensivvårdsavdelningarna. Vidare ville vi se vilken hälsorelaterad livskvalitet dessa KOL patienter hade efter intensivvård och hur den förändrade sig över tid efter intensivvården, samtidigt som vi jämförde deras hälsorelaterade livskvalitet med personer ur befolkningen utan KOL och dessutom med KOL-patienter som inte hade genomgått intensivvårdsbehandling.

I delarbete 1 studerades 1009 KOL-patienter som vårdats på 42 intensivvårdsavdelningar i hela Sverige. Vi fann att KOL-patienterna utgjorde 1.3 % av samtliga intensivvårdspatienter, patienterna kom till IVA från akutmottagningen och vårdavdelningar i lika stora proportioner. De var kring 70 år gamla, andelen kvinnor var högre än andelen män. De var svårt sjuka när de kom till intensivvårdsavdelningarna. Dödligheten hos KOL patienter var betydande både på kort och lång sikt trots intensivvård. Många patienter (15.8 %) blev återinlagda. Äldre patienter hade färre återinläggningar. Risken för att dö inom 90 dagar efter inläggningen
påverkades av patientens kön, ålder och sjuklighet vid inläggningen. Det fanns en ökad risk för död om man skrevs ut från IVA under en helg.

I delarbete 2 studerades 93 KOL-patienter som kommit till 9 intensivvårdsavdelningar och behandlats med ventilatorstöd. Vi jämförde patienterna utifrån vilket ventilatorstöd (invasivt eller non-invasivt) de fick direkt när de kom till intensivvårdsavdelningen. Även bland dessa patienter var dödligheten hög. De patienter som behandlades med non-invasiv ventilation hade en bättre långtidsöverlevnad jämfört med de som fick invasiv ventilation direkt i denna grupp patienter. De patienter som började med non-invasiv ventilation för att sedan gå över till invasiv ventilation hade inte sämre överlevnad än de som behandlades med invasiv ventilation direkt. En hög andel av patienterna behandlades med non-invasiv ventilation.

I delarbete 3 studerades 95 inläggningar vid 9 intensivvårdsavdelningar pga KOL och andningssvikt. Vi försökte identifiera faktorer som var kopplade till att patienterna behandlades med invasiv ventilatorbehandling direkt när de kom till intensivvårdsavdelningen. Vidare analyserades en enkät som skickats till personalen vid intensivvårdsavdelningarna i sydöstra Sverige. Frågorna i enkäten berörde i vilken mån olika faktorer påverkade beslutet att använda invasivt eller non-invasivt ventilatorstöd direkt när KOL patienter kommer till intensivvårdsavdelningen. I analysen av patienterna skilde de sig åt i BMI men inte i värden i blodgasanalyser, syra-bas status eller i andningsfrekvens. Resultatet från enkäten visade att faktorer som finns med i riktlinjer för ventilatorbehandling i vårdprogram för KOL är viktiga för beslutet kring valet av metod, men flera andra faktorer i vårdmiljön som till exempel bemanningen, vem som är ansvarig för patienten och förekomst av vårdprogram på avdelningen, påverkar också beslutet.

I delarbete 4 studerades den hälsorelaterade livskvaliteten (HRLK) efter intensivvård hos en grupp patienter som vårdats på IVA för KOL. HRLK mättes vid tre tillfällen vid 6, 12 och 24 månader efter intensivvård. Dessutom jämfördes HRLK hos de KOL patienter som fått intensivvård med två andra patientgrupper. Dels en ålders och könsmatchad grupp ur befolkningen utan diagnosen KOL och dels en grupp KOL-patienter som inte vårdats med intensivvård.

KOL patienterna som hade vårdats med intensivvård hade lägre värden för HRLK än gruppen ur befolkningen. Värdena för de KOL patienter som fått intensivvård och överlevde var stabila från 6 till 24 månader efter intensivvårdsbehandlingen. De hade efter 24 månader värden som var jämförbara med KOL patienterna som inte hade fått intensivvård.

En sammanfattning av resultaten i dessa fyra studier är att: KOL-patienter i Sverige som behöver intensivvård och respiratorstöd är mycket sjuka då de anländer till intensivvårdsavdelningarna. Trots att de behandlas med intensivvård och respiratorstöd är dödligheten hög både på kort och lång sikt. Non-invasiv ventilatorbehandling bör vara förståndsval till de KOL patienter som behöver respiratorstöd. Den hälsorelaterade livskvaliteten hos de KOL patienter som överlever efter intensivvård och återhämtar sig är lägre än för befolkningen i allmänhet, men stabil och jämförbar med den hälsorelaterade livskvaliteten hos KOL patienter som inte vårdats på IVA.
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