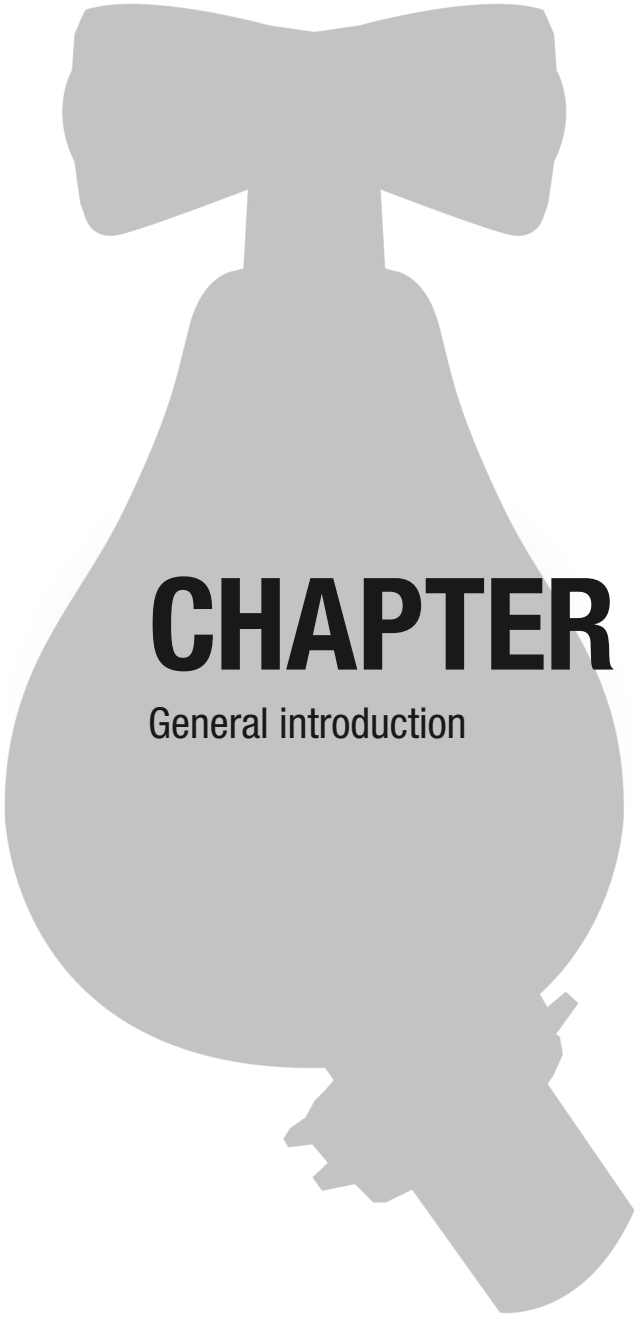

CHAPTER 1

General introduction

COPD

Chronic Obstructive Pulmonary Disease (COPD) is a chronic lung disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases.[1]

It is estimated that 64 million people worldwide have moderate to very severe COPD.[2] Currently it is the fourth leading cause of death but it has been projected to become the leading cause of death worldwide in 2030.[3]

The main risk factor for COPD, certainly in the Western world, is tobacco smoke (including second-hand or passive exposure); other factors are in- and outdoor air pollution and exposure to occupational dusts and chemicals.[3] Characteristic symptoms are chronic and progressive dyspnoea especially on exertion, cough and sputum production that can vary from day-to-day.[4,5] COPD is a complex disease involving more than airway obstruction; in many patients the disease is associated with several systemic manifestations that can effectively result in impaired functional capacity, worsening dyspnoea, reduced health-related quality of life and increased mortality.[6] Common co morbidities include cardiovascular disease, skeletal muscle dysfunction, osteoporosis, pulmonary hypertension and depression.[1]

For the assessment of the disease severity and treatment, airway obstruction (forced expiratory volume in 1 second (FEV_1)) used to play the most important role. However, research has shown that multidimensional indicators, such as the BODE index (body mass index, airflow obstruction, dyspnoea, exercise capacity)[7] and quality of life,[8] are better predictors of morbidity, mortality and health-care utilization than the FEV_1 alone.[9]

Treatment options include smoking cessation, pharmacologic therapies, oxygen therapy, rehabilitation, non-invasive ventilation and surgical treatments.[1,10] Non-invasive ventilation will be described in detail further in this chapter.

Respiratory failure

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions, i.e. oxygenation of and/or elimination of carbon dioxide from mixed venous blood. For clinical routine purposes, respiratory failure is usually defined by an arterial oxygen tension (PaO_2) of <8.0 kPa, an arterial carbon dioxide tension ($PaCO_2$) of >6.0 kPa or both.[11] However, a PaO_2 of below 10.0 kPa already reflects hypoxemia. In routine practice, the term hypoxemia is used when PaO_2 is below 10.0 kPa and severe hypoxemia when PaO_2 is lower than 8.0 kPa.

Hypoxemic respiratory failure (type I) is characterized by an arterial oxygen tension (PaO_2) <8.0 kPa (60 mmHg) with a normal or low arterial carbon dioxide tension ($PaCO_2$). This is the most common form of respiratory failure, and it can be associated with virtually all acute diseases of the lung. Following Dutch guidelines, long-term oxygen therapy (LTOT) is indicated in stable COPD patients with severe hypoxemia by day at rest (PaO_2 <8.0 kPa) who receive optimal medication.[12]

Hypercapnic respiratory failure (type II) is characterized by a $PaCO_2$ >6.0 kPa (45 mmHg). Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air. Common etiologies include drug overdose, neuromuscular disease, chest wall abnormalities, and severe airway disorders like COPD. In this thesis we will focus mainly on hypercapnic failure.

Finally, respiratory failure can occur as acute, chronic or acute-on-chronic failure.

Acute respiratory failure in COPD

Acute respiratory failure occurs when the underlying disease deteriorates abruptly within hours. Patients with severe COPD are prone to these exacerbations of respiratory failure, which frequently results in admission to hospital. They are often triggered by infections. In this thesis we define exacerbation as 'an event in the natural course of the disease defined as characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond day-to-day variations, is acute in onset, and which is treated with an antibiotics course and/or prednisolon in patients with underlying COPD'.[13,14] When there is respiratory failure and conventional treatment like oxygenation and pharmacological therapies are insufficient, mechanical ventilation can be started to improve gas exchange.

Invasive and non-invasive mechanical ventilation

With invasive mechanical ventilation, ventilatory support is applied via endotracheal intubation or transtracheal cannulation. Although it is common practice, the treatment is associated with high complication rates[15] like damage to airways, increased risk for ventilator associated infections, loss of muscle strength leading to a prolonged weaning course and also high morbidity in general.[16]

With non invasive ventilation (NIV), ventilatory support is given via a nasal or full-face mask. Over the last decades, it has become an established alternative to invasive mechanical ventilation for those patients with mild-to-moderate- acute respiratory failure as it has been shown to reduce hospital deaths and complications associated with treatment and length of hospital stay.[17]

Chronic respiratory failure in COPD

Many patients with severe or long-standing COPD suffer from chronic respiratory failure. Studies in this group of severely ill patients have shown that they have very poor quality of life in terms of emotional, social, and physical functioning. Therefore, for these patients with severe or end-stage COPD, an effective management program has to center on not only adequate management of symptoms but also maintenance of a reasonable quality of life.[18]

In patients with severe resting hypoxemia, long-term oxygen therapy (>15 hours per day) has been shown to be the only treatment to increase survival.[19,20] The use of nocturnal NIV in stable severe COPD is gradually growing and in some countries in Europe even becoming routine practice [21] despite conflicting results from randomized trials (details further on).

Non-invasive ventilation

Non-invasive positive pressure ventilation refers to the delivery of air or a mixture of oxygen and air through the trachea to the lungs by means of a mask covering the nose and/or mouth.

With bilevel positive airway pressure, the ventilator delivers a preset high airway pressure during inspiration (IPAP) to get air into the lungs, while during expiration a low pressure can be delivered to maintain airway patency (EPAP). The difference between the two levels determines the level of pressure support.[22,23]

Mechanical ventilation can be "controlled" (i.e. the machine determines respiratory frequency), "assisted" (i.e. the machine augments the patients spontaneous breaths), or a combination of the two, "assist/control" (A/C) mode, which is called "spontaneous-timed" (S/T) mode in pressure targeted ventilators.[23]

Rationale of NIV

Competing theories have been described in the last two decades as to how NIV works in COPD. In summary: one theory involves resting of the chronically fatigued muscles (during NIV), leading to recovery of the inspiratory muscle function.[24] The second theory describes the resetting of central chemosensitivity and consequently improving daytime ventilation.[25] The third theory includes decreasing hyperinflation and thereby improving respiratory mechanics.[26] The last hypothesis concerns improving sleep quality by correcting for episodes of nocturnal hypoventilation and desaturation.[27]

Nocturnal NIV in stable hypercapnic COPD

Although the role of NIV in patients with COPD and acute hypercapnic respiratory failure (HRF) is undisputed,[28] its role in the treatment of chronic HRF in patients with stable COPD is still under debate. Several short term and long term studies and a systematic review comparing nocturnal NIV to standard therapy and LTOT in patients with stable COPD and chronic HRF could not provide clear and unequivocal evidence in favor of NIV.[27,29-32] Many of the studies were of less than perfect quality: no randomization,[33] small numbers of patients, short intervention period of receiving NIV,[34] uncontrolled designs,[35] insufficient ventilatory pressures,[29,30,33] low adherence to the ventilator, lack of monitoring NIV during the night, high drop-out rates[30,31] and/or lack of health-related quality-of-life questionnaires specifically for mechanical ventilation or HRF.[27] As a result, NIV for chronic and stable hypercapnic failure is not recommended in any of the major guidelines.

Nocturnal NIV in hypercapnic COPD patients after acute exacerbation

However, the situation in unstable patients who survived acute respiratory failure treated by ventilatory support might be different. Two early studies are promising in this respect. Firstly, an English uncontrolled study investigated the impact of domiciliary NIV on the need for admission to hospital and its attendant costs.[36] Thirteen patients were identified with recurrent acidotic exacerbations of COPD who tolerated and responded well to NIV.

They concluded that nocturnal NIV for a highly selected group of COPD patients with recurrent admissions requiring NIV was effective at reducing admissions and minimises costs.

The second study showed that NIV after acute respiratory failure could even improve survival. This prospective randomised controlled trial was conducted in mechanically ventilated patients who tolerated a spontaneous breathing trial after extubation.[37] They were either randomised to NIV for 24 hours or to conventional management with oxygen. Overall the 90-days survival did not change significantly between groups. However, patients who were hypercapnic after the spontaneous breathing trial showed a significantly better survival in the NIV group compared to medical treatment only. Fifty percent of this group were patients with COPD.

Although both studies suggest positive effects, there are some methodological problems. The first study is an uncontrolled study and the second is a post-hoc analysis and therefore both studies do not provide the highest level of evidence.

We performed, and report here, the RESCUE trial (REspiratory Support in COPD after acUte Exacerbation), a randomised controlled trial conducted to investigate the benefits of nocturnal NIV alongside standard medical treatment for the period of 1 year in patients who remain hypercapnic after receiving ventilatory support for acute respiratory failure (ARF). During the recruitment and follow-up period of the trial, several other randomised controlled trials investigating nocturnal NIV either in stable hypercapnic,[38] or in acute-on-chronic hypercapnic COPD[39,40] were published and will be discussed in chapter 5.

AIMS OF THIS THESIS

In summary, results from studies investigating nocturnal NIV in stable COPD have been conflicting. The first aim of this thesis is to give an overview of all randomized controlled trials studying the effects of nocturnal NIV in patients with stable COPD. Based on the lack of agreement in previous studies in the field as to which health-related quality-of-life questionnaire is the most appropriate for measuring effects of nocturnal NIV, a second aim is to assess and compare four commonly used questionnaires to determine which is the most appropriate for COPD patients with chronic HRF. Our final aim is to investigate if nocturnal NIV alongside standard treatment will prolong the time to readmission for respiratory causes or death in COPD patients who remain hypercapnic after ventilatory support during acute respiratory failure compared to standard treatment alone.

OUTLINE OF THIS THESIS

In **chapter 2** we present a systematic review on NIV in severe stable COPD which we performed using a meta-analysis based on individual patient data and according to Cochrane guidelines.

In **chapter 3**, we ventilate some concerns considering a systematic review performed by others on NIV in severe stable COPD.

In **chapter 4** we explore the individual patient data of the meta-analysis presented in chapter 2 further by performing sub analyses within the NIV group based on IPAP levels, compliance and levels of hypercapnia.

Chapter 5 presents a study determining whether the Clinical COPD Questionnaire (CCQ), Chronic Respiratory Questionnaire (CRQ), the Maugeri Respiratory Failure-28 (MRF-28) Questionnaire and the Severe Respiratory Insufficiency (SRI) Questionnaire are reliable and valid for measurement of health related quality of life in patients with chronic hypercapnic respiratory failure requiring ventilatory support.

In **chapter 6** the results of the RESCUE trial on nocturnal NIV in patients who remain hypercapnic after ventilatory support during acute respiratory failure compared to standard treatment alone are presented. At the end of this chapter (6B), we respond to a letter that was sent in following publication of the RESCUE trial. In this reply to the authors we discuss certain subgroups of patients who are suggested to respond better to NIV.

The last chapter, **chapter 7** consists of a summary of the results of all chapters and a general discussion including ideas for further research.

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