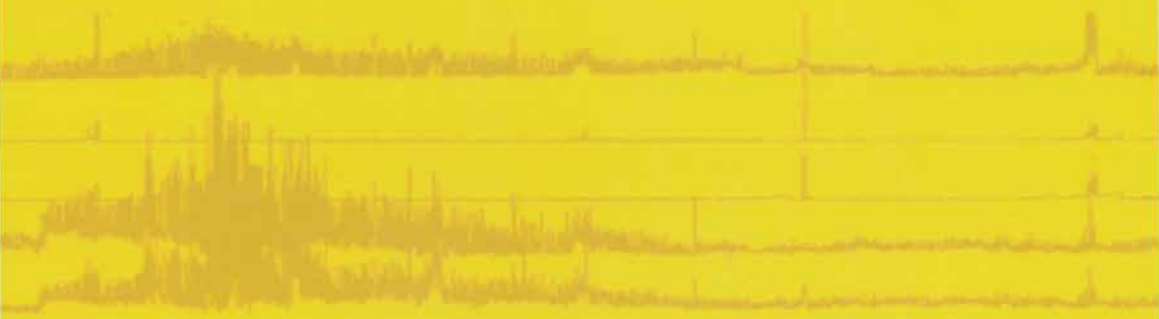
Marieke Duiverman

Severe Chronic Obstructive Pulmonary Disease:

assessment of respiratory muscle activity and the benefits of noninvasive ventilation



Chronic Obstructive Pulmonary Disease is a leading cause of morbidity and mortality worldwide. Therefore, it is important to investigate both underlying physiological mechanisms of breathing in these patients and new therapeutic options to treat these patients effectively.
In the first part of this thesis we investigated inspiratory muscle activity in COPD patients and in healthy subjects with surface electromyography. In the second part of this thesis, we investigated whether noninvasive ventilation is an effective treatment option in patients with severe Chronic Obstructive Pulmonary Disease.

Severe Chronic Obstructive Pulmonary Disease:
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Stellingen

behorende bij het proefschrift:

Severe Chronic Obstructive Pulmonary Disease: assessment of respiratory muscle activity and the benefits of noninvasive ventilation

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1. Oppervlakte elektromyografie is een reproduceerbare en sensitieve techniek waarmee de elektrische activiteit van de ademhalingsspieren gemeten kan worden (*dit proefschrift*).

2. Het patroon waarmee patiënten met COPD hun ademhalingsspieren rekruteren bij een toename van de belasting op het ademhalingssysteem is anders dan bij gezonden (*dit proefschrift*).

3. Er is een relatie tussen de toename in elektrische activiteit van de ademhalingsspieren en de toename van dyspneu sensatie tijdens inspanning (*dit proefschrift*).

4. Een patiënt heeft pas profijt van de therapie als hij effect ervaart.

5. Nachtelijke noninvasieve beademing verbetert de uitkomsten van revalidatie bij patiënten met ernstig COPD en chronisch hypercapnisch respiratoir falen (*dit proefschrift*).

6. Nachtelijke noninvasieve beademing verbetert het adempatroon overdag zich uitend in een hoger ademminuutvolume (*dit proefschrift*).

7. Gebreken zijn altijd minder ernstig wanneer ze duidelijk zichtbaar zijn, en het gevaarlijkst wanneer ze achter een schijn van gezondheid verborgen gaan (*Seneca, 62 AD*).

8. Chronische noninvasieve beademing is meer een verlichting dan een belasting.

9. Het insturen van een artikel voor review is net als het rijden van een dressuurproef: hoe tevreden je zelf ook bent, je blijft toch afhankelijk van een enigszins subjectieve beoordeling.

10. Het verstrekken van chronische beademing is het verkopen van lucht!

ISBN: 978-90-367-3348-9

Lay out: Helga de Graaf, Studio Eye Candy, Groningen (www.proefschrift.info).
Printed by: Ipskamp PrintPartners Enschede, the Netherlands.

RIJKSUNIVERSITEIT GRONINGEN

Severe Chronic Obstructive Pulmonary Disease:
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Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 16 april 2008
om 14.45 uur

door

Marieke Leontine Duiverman
geboren op 7 juli 1981
te Nieuwerkerk aan den IJssel

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Beoordelingscommissie:	Prof. dr. P.N.R. Dekhuijzen Prof. dr. R.S. Goldstein Prof. dr. E.F.M. Wouters

Paranimfen: Sytse Duiverman
Bertine Flokstra-de Blok

The studies described in this thesis were financially supported by:
The Dutch Asthma Foundation, the University of Groningen, de Stichting Astma Bestrijding, GlaxoSmithKline, Astra Zeneca, Boehringer Ingelheim BV, and TEFA-Portanje.

Publication of this thesis was financially supported by:
The University of Groningen, Graduate School for Drug Exploration (GUIDE), Stichting Astma Bestrijding (SAB), Dräger Medical, Emdamed BV, Intelligent Biosignals BV, Novartis Pharma BV, Teva Pharma Nederland, Vivisol Nederland BV, Boehringer Ingelheim BV en Pfizer, GlaxoSmithKline BV, Respironics International, Resmed Nederland BV, Nycomed BV, TMS International BV, Merck Sharp & Dohme BV.

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CHAPTER 1

Introduction

Definition and classification of COPD

Chronic Obstructive Pulmonary Disease (COPD) is defined as:

"a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow obstruction that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases [1]*."*

COPD can be divided in 4 categories of severity according to the degree of airflow obstruction [2]. These disease stages and the prevalence of the different stages of COPD in the Netherlands are shown in Table 1 [3].

The most important risk factor for COPD is cigarette smoking. Although the prevalence of smoking has decreased in most developed countries, -among which the Netherlands-, the number of people with a long history of smoking is still increasing. Therefore the prevalence of COPD will increase over the coming decades [4]. Furthermore, the proportional increase in prevalence of the very severe group is predicted to become the largest over the coming twenty years [4].
The characteristic symptoms of COPD are dyspnoea especially on exertion, cough and sputum production. Patients with severe and very severe COPD often experience severe breathlessness already at rest or during regular daily activities, and experience a substantial reduction in their quality of life [5, 6]. Once chronic respiratory failure develops, prognosis is usually very poor, and many patients die of respiratory failure within five years [7, 8].

Table 1. Classification and prevalence of COPD severity.

	Characteristics	Prevalence
I mild	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ predicted	30 %
II moderate	$FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted	52 %
III severe	$FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 50\%$ predicted	17 %
IV very severe	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure.	2 %

FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; chronic respiratory failure: arterial partial oxygen pressure (PaO_2) less than 8.0 kPa (60 mmHg) with or without arterial partial carbon dioxide pressure ($PaCO_2$) greater than 6.7 kPa (50 mmHg) while breathing air at sea level [2].

Chronic respiratory failure in COPD

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions, i.e. oxygenation and/or carbon dioxide elimination from mixed venous blood. As a result, the partial oxygen pressure in arterial blood (PaO_2) decreases while the partial carbon dioxide pressure in arterial blood ($PaCO_2$) increases [9].

Respiratory failure results from either a problem with the gas-exchanging compartment, i.e. the lungs, or with the pump that ventilates the lungs. The "pump" consists of a controller system (central nervous system) and of the chest wall, including the respiratory muscles [9]. In general, failure of the lung compartment, -ventilation/perfusion mismatching; increased shunt; and/ or diffusion impairment-, leads primarily to hypoxemia (PaO_2<8.0 kPa). Failure of the pump generally leads to hypercapnia ($PaCO_2$>6.0 kPa). Ventilatory pump failure can result from inadequate neural drive of the respiratory controller (for example with drug overdose), from chest wall restrictions (for example with kyphoscoliosis), or from weakness of the respiratory muscles (for example with myopathies).

In COPD, pump failure occurs if the respiratory muscles are unable to overcome the load placed on the respiratory system. The increased load placed on the respiratory system is attributed to several factors related to the main pathophysiological processes in COPD, i.e. airway narrowing and lung parenchyma destruction. Firstly, inspiratory flow resistance is increased more than fourfold in COPD compared to healthy subjects. Secondly, loss of elastic recoil of the lungs causes premature small airway closure during expiration and expiratory flow limitation. As a consequence, inhaled air is incompletely expired, and this leads to the development of hyperinflation. In this situation the respiratory system has not returned to its relaxation volume when inspiration already begins. Therefore the inspiratory muscles have to offset an additional threshold load. Finally, to maintain adequate gas exchange, minute ventilation must increase. This need for increased minute ventilation is caused by ventilation-perfusion mismatching and an increased physiological dead space [10].

On the other hand, the capacity of the respiratory muscles to generate sufficient negative intrathoracic pressure is reduced [11, 12]. Firstly, the reduced capacity of the respiratory muscles is caused by lung hyperinflation. Hyperinflation shortens the diaphragm, and, to a much lesser extent, the intercostal muscles. Shortening places the muscles on an inefficient part of the muscle's length/tension relationship. Furthermore, diaphragmatic tension to pressure conversion is affected by the position the diaphragm is forced into; the diaphragm is flattened and its zone of apposition is reduced. This reduced apposition zone is disadvantageous for the contribution of diaphragm contraction to chest wall expansion. Next to the mechanical disadvantage, generalised muscle weakness caused by electrolyte disturbances, blood gas abnormalities, weight loss, systemic inflammation, and steroid myopathy, can all contribute to respiratory muscle weakness [13].

On the one hand, the increased load placed on the diaphragm induces "diaphragm endurance training", and leads to a beneficial shift to more fatigue resistant type-I

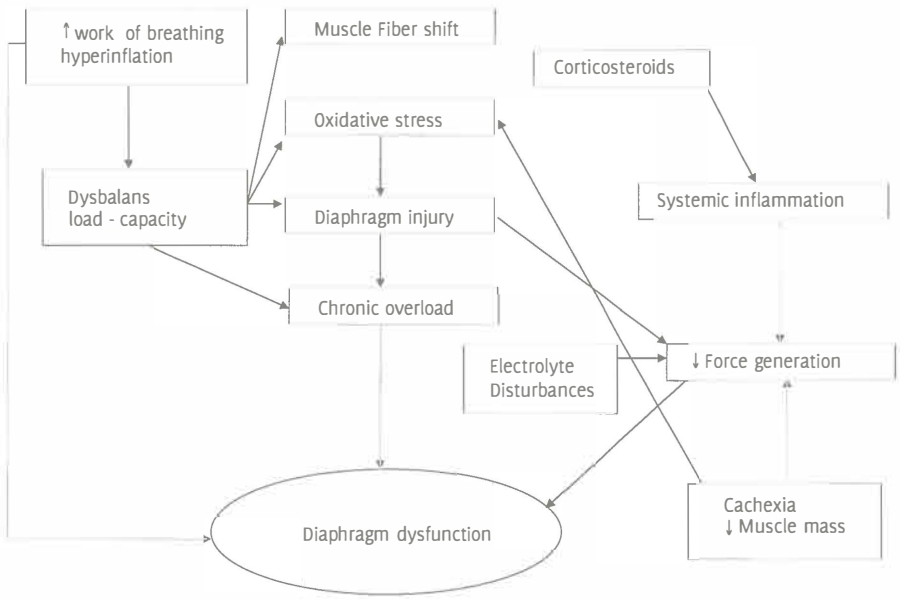

Figure 1. Factors that affect diaphragm function in patients with COPD [adapted from ref 14].

muscle fibres. However, on the other hand, negative effects of chronic overloading of the diaphragm, such as the occurrence of diaphragm injury, reduce the force generating capacity of the diaphragm [14, 15]. Extensive diaphragm muscle injury has not only been demonstrated in patients with very severe COPD [16]. Also in mild to moderate COPD it has been shown that alterations occur within the diaphragm that reduce its force generating capacity [17] (Figure 1).

With increasing severity, some COPD patients develop chronic hypercapnia. Why some patients do and some patients do not develop hypercapnia despite very severe airflow limitation is still incompletely understood. Two hypotheses have been proposed.

The first hypothesis suggests that the respiratory drive to the respiratory muscles is downregulated centrally when the respiratory muscles are overloaded, in order to prevent them from becoming fatigued. However, it has been shown that the central neural drive to the respiratory muscles is increased in severe COPD patients compared to controls, also in patients who are hypercapnic [18, 19]. Although neural drive seems to be high, there are doubts about the adequacy of the chemoresponsiveness of the respiratory controller in chronic hypercapnic COPD patients [20]. Compared to eucapnic patients, with a similar high central drive, hypercapnic patients have lower ventilatory responses [19, 20]. Whether the observed lower ventilatory response in hypercapnic versus eucapnic patients results from impaired chemoresponsiveness or impaired respiratory muscle function remains a subject of controversy. The second hypothesis

suggests that abnormal respiratory mechanics and increased mechanical loads lead to an inability of the respiratory muscles to perform the necessary work to provide adequate ventilation. Initially, it was proposed that the imbalance between the load placed on the system and the capacity of the respiratory muscles lead to respiratory muscle fatigue [21]. With muscle fatigue, the loss of contractile capabilities impairs the ability to develop sufficient pressure swings to maintain adequate alveolar ventilation [9]. However, more recently it was shown that muscle fatigue is not present in stable COPD [22]. Instead, it was suggested that hypercapnic COPD patients in stable condition maintain their inspiratory effort within certain limits by alveolar hypoventilation [23]. Deep breathing would increase ventilation and reduce carbon dioxide levels, but increases the load placed on the system and brings the respiratory muscles close to the fatigue threshold [24]. In order to prevent this, patients adopt a rapid shallow breathing pattern with small tidal volumes [9]. However, small tidal volumes are disadvantageous as the ratio dead space volume/ tidal volume increases. This leads to worsening of hypercapnia [9].

Acute respiratory failure in COPD

Patients with severe COPD often suffer from repeated exacerbations of their disease. An exacerbation of COPD is defined as "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 patients with underlying COPD" [1]. In Figure 2 the central pathophysiological mechanisms of a COPD exacerbation are schematically represented.
A COPD exacerbation is associated with airway inflammation [26].The airway inflammatory response causes airway oedema, bronchospasm and increased sputum production. These changes lead to worsening of airflow limitation and dynamic hyperinflation [25]. Dynamic hyperinflation in turn causes dyspnoea and has deleterious effects on gas exchange, especially in severe disease [25]. In patients with pre-existent chronic respiratory failure, only a small change in condition may lead to a life-threatening episode of severe acute on chronic respiratory failure [26]. The presence of hypercapnia during an acute exacerbation negatively affects survival, both initially and during the subsequent year of follow-up [27]. During exacerbations, mechanical ventilation can be needed to maintain arterial blood gas homeostasis [1]. Mechanical ventilation can be applied via endotracheal intubation. However, invasive mechanical ventilation via an endotracheal tube has disadvantages, such as an increased risk for ventilator associated infections, damage to the airways, and loss of muscle strength leading to a prolonged weaning course. Over the last decades, noninvasive ventilation via face mask has gained popularity as an important alternative to mechanical ventilation. It has been shown that in patients with moderate to severe COPD exacerbations complicated by respiratory failure, noninvasive ventilation decreases the need for endotracheal intubation, reduces the length of hospital stay and decreases mortality [28]. In patients with very severe respiratory failure, invasive mechanical ventilation can still be necessary, although success rates of noninvasive ventilation are also increasing in this group [29,30].

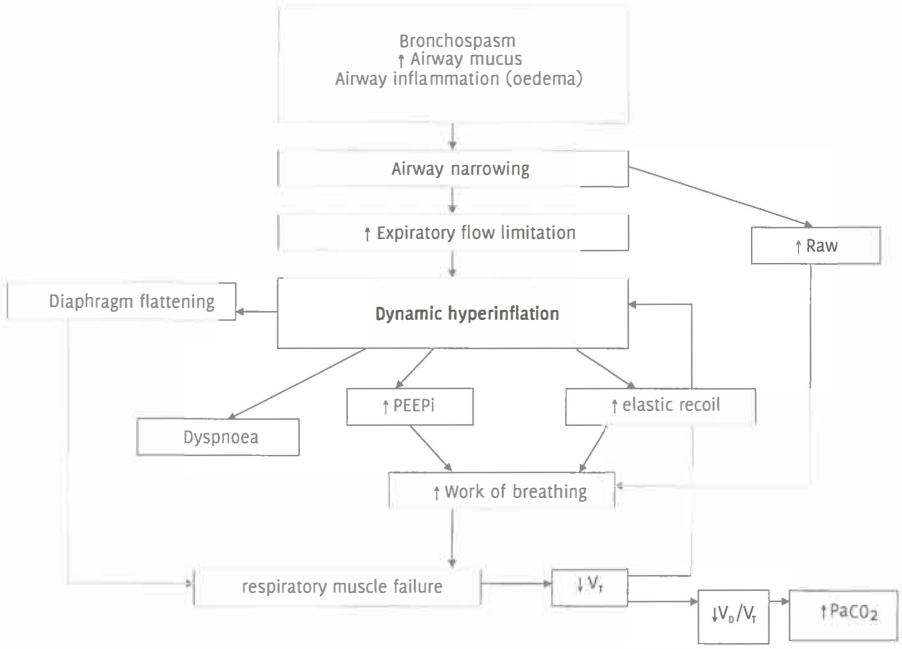

Figure 2: Schematic representation of the pathophysiological mechanisms that occur during a COPD exacerbation.
Raw: airway resistance; PEEPi: intrinsic positive end-expiratory pressure; V_T: tidal volume; V_D/V_T: dead space volume/ tidal volume; $PaCO_2$: arterial carbon dioxide pressure [adapted from ref 25].

Investigating respiratory muscle activity in COPD

The respiratory muscles are the main "motor" of the respiratory system; by contraction they produce the negative pressure needed to allow the lungs to inflate. For the respiratory muscles to contract, electrical activation of the muscles elicited by propagation of the electrical impulses across the muscle membranes is necessary. This electrical activation results from action potentials carried from the brainstem via motor neurons to the muscles [31].

As explained in the first part of this introduction, the respiratory muscles in COPD are subjected to on the one hand an increased load placed on the system, and on the other hand a decreased capacity to produce force. In severe COPD, it has been shown that the neural drive to the intercostal muscles, scalene muscles and diaphragm are increased already at rest [18]. So it seems that COPD patients drive their respiratory muscles as hard as possible to produce sufficient output. If the respiratory system is stressed, for example during exercise or with loaded breathing, hyperinflation increases. This further shortens the respiratory muscles and thereby reduces the production of force, tension, and pressure. The effects of hyperinflation are more pronounced for the diaphragm as it is shortened to a much larger extent compared to

the intercostal muscles. To compensate for the loss in diaphragm capacity it has been shown that COPD patients preferentially increase the pressure contribution of the other respiratory muscles, i.e. the scalene and intercostal muscles [32, 33]. However little is known about whether this is also accompanied by an increased neural drive to the accessory respiratory muscles in comparison to the diaphragm neural drive.
Electromyography (EMG) describes the electrical manifestations of the excitation process elicited by action potentials propagating along muscle fibre membranes and so can be used to assess neural drive [31]. Electromyographic signals can be obtained from electrodes placed on the skin (surface EMG), electrodes placed into the oesophagus, or electrodes inserted into the respiratory muscle of interest (needle electrodes). With surface EMG, signals can be obtained from large number of motor units both from the diaphragm and the accessory respiratory muscles simultaneously, without discomfort to the patient. This technique has been shown to be reproducible and responsive in measuring respiratory muscle activity of the separate respiratory muscle groups both in toddlers, asthmatic children, and young adults [34-36].

Management of severe COPD

COPD management consists of 4 components: disease assessment and monitoring; reduction of risk factors; management of stable COPD; and the management of exacerbations [1]. The aim of effective COPD management is to relieve symptoms, improve exercise tolerance, improve health status, prevent and treat exacerbations and its complications, limit disease progression, and reduce mortality [1].

However, except for oxygen supplementation, no treatment for COPD has been shown to improve survival. Therefore, most treatments aim to relieve symptoms. Patients with advanced COPD often experience substantial disability and reduced quality of life. Individualised multimodal treatment programs including pharmacological and non-pharmacological treatment options reduce this disability and improve quality of life in these patients [37].
As this thesis mainly deals with pulmonary rehabilitation and noninvasive ventilation, we will discuss in more detail these treatment options in the next paragraphs.

Pulmonary rehabilitation

Pulmonary rehabilitation has been shown to improve exercise tolerance, dyspnoea, and health-related quality of life, and reduce health care utilisation in patients with COPD [38-39]. It therefore plays an important role in the management of COPD [37]. It is recommended in the management of all COPD patients with functional and/or physiological deficits [2, 40]. Pulmonary rehabilitation is multimodal and should contain exercise training, patient education, nutritional support, and physiological support.
Improvement of exercise tolerance is the cornerstone of pulmonary rehabilitation, as reduced exercise tolerance limits participation in activities of daily living and consequently health-related quality of life. In moderately severe COPD, high intensity training reduces the rate of rise in lactate levels and subsequently in minute ventilation

during exercise after rehabilitation [41]. However, in patients with severe COPD, because of extreme breathlessness and peripheral muscle weakness, exercise sessions at high intensity for a longer period are often difficult to achieve [42]. Therefore, interval training was introduced in patients with severe COPD. Interval training consists of short periods of high intensity exercise interspaced by short periods of rest. It has been shown that this modality results in lower symptom scores while training effects were maintained [43, 44].

Noninvasive ventilation

Noninvasive ventilation has been used for decades in patients with neuromuscular and chest wall diseases. The first mode of delivering noninvasive ventilation was negative pressure ventilation during the 1950s poliomyelitis epidemic [45]. Negative pressure ventilation inflates the lungs by exposing the chest to subatmospheric pressures during inspiration and allowing expiration by returning the pressure around the chest wall to atmospheric. Negative pressure ventilation was delivered with tank respirators or cuirass devices driven by a negative pressure cycled machine.

The first studies on negative pressure ventilation in COPD used it for short periods in hospital. These studies aimed at resting the respiratory muscles. It was found that negative pressure ventilation was capable of resting the respiratory muscles, as indicated by improvements of respiratory muscle strength, respiratory muscle endurance, and arterial blood gas tensions after assisted ventilation [46, 47]. Furthermore, in 1988, Gutierrez et al. found in a small uncontrolled study that a weekly 8h negative pressure ventilation session for 4 weeks also improved arterial blood gases, exercise tolerance, and quality of life in patients with severe COPD [48].

However, the effects of negative pressure ventilation for a longer period in severe COPD were less positive. Levine et al. found that although negative pressure ventilation rested the respiratory muscles (as assessed by electromyography) and improved respiratory muscle endurance, exercise tolerance did not improve [49]. The first long-term randomised trials on negative pressure ventilation in severe COPD did not find positive effects on respiratory muscle parameters and exercise tolerance, dyspnoea, and quality of life [49-51]. Furthermore, negative pressure ventilation was poorly tolerated [50-52]. Discomfort with the device, but also the size of the device and the limited access to the patient, were important disadvantages [52]. To overcome these disadvantages, negative pressure ventilation was gradually replaced by positive pressure ventilation.

Noninvasive intermittent positive pressure ventilation (NIPPV) delivers a constant predetermined volume (volume-targeted ventilation) or a preset pressure (pressure-targeted ventilation) by means of a mask. A preset high airway pressure is delivered during inspiration to get air into the lungs (IPAP), while during expiration a low pressure can be delivered to maintain airway patency (EPAP). This is called bilevel positive airway pressure [53].

Four main mechanisms have been proposed why NIPPV should be beneficial in patients with COPD and chronic respiratory failure. The first mechanism proposed

is resting of chronically overloaded and fatigued respiratory muscles [54]. The second mechanism is improved lung mechanics, so that patients are able to adopt a slower and deeper more effective breathing pattern [55]. The third mechanism is improved chemosensitivity of the respiratory controller [56]. Finally, improvement of sleep quality could be important in both correction of arterial blood gases as improvement in exercise tolerance and health-related quality of life [57].

Notwithstanding the proposed positive effects of NIPPV in COPD provided above, randomised controlled trials of NIPPV in severe COPD have shown conflicting results [55-65]. These conflicting results can be explained by several factors. First, studies differed in patient selection. Patients with more severe blood gas derangements at daytime seem to benefit most. Secondly, assurance that effective ventilation was achieved in terms of an increase in tidal volumes and an improvement in arterial blood gases during ventilatory assistance is limited. Available studies monitored ventilation in different ways (monitoring of arterial blood gases [63] end-tidal $PaCO_2$ [58], transcutaneous $PaCO_2$ [57], ear lobe gases [62], monitoring by diaphragmatic EMG [61], by visual assessment of respiratory muscle use, dyspnoea and breathing frequency [61], or did not monitor at all [60]). Thirdly, ventilator settings were probably not always high enough to achieve sufficient ventilatory assistance [66]. Finally, compliance might not always have been optimal as the degree of assistance and time available for the patient to get used to the ventilator was very short in some studies [60].

Noninvasive ventilation and pulmonary rehabilitation

Patients with severe COPD were initially found to have little benefit from a home-based rehabilitation program [67]. Later on, however, positive effects from a centre-based program were found in the very severe COPD patients [68], even in COPD patients with chronic respiratory failure [69]. Nevertheless, because of extreme breathlessness and severe deconditioning patients with severe COPD often cannot achieve high exercise intensities.

We hypothesise that noninvasive improves the outcomes of pulmonary rehabilitation in these severe patients for the following reasons. First, nocturnal noninvasive ventilation might rest the chronically overloaded respiratory muscles [54]. Secondly, improved daytime arterial blood gases may lead to a better internal milieu for the peripheral muscles [70]. Thirdly, noninvasive ventilation might improve ventilatory mechanics [64]. Fourthly, nocturnal noninvasive ventilation might improve sleep quality, so that patients feel better during the day [57]. Finally, nocturnal NIPPV might prevent severe COPD exacerbations with severe worsening of respiratory failure leading to prolonged discontinuation of the rehabilitation program [71].

Until now, two studies have investigated the additional value of noninvasive ventilation to pulmonary rehabilitation. Celli et al. investigated the effect of negative pressure ventilation in addition to pulmonary rehabilitation. However, they found no difference in outcomes in comparison with the control group who participated in the rehabilitation program without negative pressure ventilation [50]. Garrod et al. used positive pressure ventilation, and showed that exercise tolerance and quality of

life improved significantly more in patients who additionally used NIPPV at night in comparison to rehabilitation alone [62]. In this study, the magnitude of changes is somewhat surprising, as ventilator use during the night was limited (median only 2.08 h/day).

RECOVER study

The RECOVER study (**RE**search in **CO**PD: the additional effect of noninvasive **VE**ntilation on **R**ehabilitation) was designed to investigate whether short-term (3 months) and long-term NIPPV (24 months) has beneficial effects on top of rehabilitation in chronic hypercapnic COPD patients. Health-related quality of life was chosen as primary outcome parameter. We set up a randomised controlled trial in which nocturnal NIPPV in addition to rehabilitation was compared to rehabilitation as the only intervention.

The patients were investigated at baseline, after 3 months, after 6 months, after 12 months, after 18 months, and after 24 months. In this thesis, we will describe the 3-months outcomes only. The long-term outcomes will follow in 2009.

AIMS OF THE THESIS

Respiratory muscle activity in COPD

To get insight in breathing patterns and neural drive to the respiratory muscles, electromyographic studies have been performed in patients with COPD during breathing against an inspiratory load (chapter 2), and during exercise (chapter 3).

Chapter 2

The purposes of the study were 1) to assess the reproducibility of noninvasive surface electromyography in both COPD patients and healthy subjects; and 2) to assess the responsiveness (sensitivity to change) of this EMG technique by evaluating and comparing respiratory muscle activity and breathing patterns of COPD patients and healthy subjects during breathing against an increasing inspiratory load.

Chapter 3

The purposes of the study were to determine: 1) whether COPD patients preferentially increase the EMG activity to the scalene and intercostal muscles and less to the diaphragm, as compared to healthy subjects, 2) whether increased EMG activity is associated with increased dyspnoea sensation, and 3) whether the ratio between EMG activity and volume displacement by the lungs is increased in COPD compared to healthy subjects. To answer these questions we investigated, by means of noninvasive EMG, the patterns of increase in diaphragmatic, intercostal and scalene EMG activity alone and in relation to the increase in dyspnoea sensation and tidal volume increases in COPD patients and healthy subjects during exercise.

The assessment and treatment of patients with respiratory failure

Chapter 4
In chapter 4 the Groningen experience with restrictive pulmonary disorders treated with home mechanical ventilation from 1956 till 2005 is reported. The aim of the study was: 1) to describe the development of home mechanical ventilation in our hospital, and 2) to assess the effects of negative pressure ventilation, tracheal intermittent positive pressure ventilation, and noninvasive intermittent positive pressure ventilation on pulmonary function, arterial blood gas tensions, and survival and in patients with kyphoscoliosis, post-poliomyelitis or a miscellaneous restrictive ventilatory disorder.

Chapter 5
In chapter 5, we present a review in which we aim to give an evidence-based practical advise why, when, where and how to apply NIPPV in the treatment of COPD exacerbations with secondary respiratory failure.

Chapter 6
In Chapter 6 we commented in a letter to the editor on a review on noninvasive positive pressure ventilation in patients with severe stable COPD.

From chapter 7 on data are presented from the RECOVER study.

Chapter 7
In chapter 7, a study is presented in which we aim to determine whether the Maugeri Respiratory Failure questionnaire (MRF-28) and the Severe Respiratory Insufficiency questionnaire (SRI) are reliable and valid health-related quality of life questionnaires in COPD patients with chronic hypercapnic respiratory failure.

Chapter 8
Chapter 8 contains the results of the first three months treatment in the RECOVER study. In this study we aimed to investigate whether noninvasive intermittent positive pressure ventilation (NIPPV) in addition to pulmonary rehabilitation as compared to pulmonary rehabilitation alone improves health-related quality of life, arterial blood gases, pulmonary function, exercise tolerance, dyspnoea, daily activities, and mood state, in severe COPD patients with chronic hypercapnic respiratory failure.

Chapter 9
In chapter 9, a general summary and discussion are provided, with specific emphasis on future perspectives.

REFERENCES

1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J; Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532-55.
2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of COPD [Internet]. Available from: http://www.goldcopd.org.
3. Hoogendoorn M, Feenstra TL, Schermer TR, Hesselink AE, Rutten-van Mölken M P. Severity distribution of chronic obstructive pulmonary disease (COPD) in Dutch general practice. *Respir Med* 2006; 100: 83-6.
4. Hoogendoorn M, Rutten-van Mölken MP, Hoogenveen RT, van Genugten ML, Buist AS, Wouters EF, Feenstra TL. A dynamic population model of disease progression in COPD. *Eur Respir J.* 2005; 26: 223-33.
5. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax* 2000; 55: 1000-6.
6. Mahler DA, Farynairz K, Tomlinson D, Colice GL, Robins AG, Olmstead EM, O'Conner GT. Impact of dyspnea and physiological function on general health status in patients with chronic obstructive pulmonary disease. *Chest* 1992; 102: 395-401.
7. Sahn SA, Nett LM, Petty TL. Ten year follow-up of a comprehensive rehabilitation program for severe COPD. *Chest* 1980; 77 (2 Suppl): 311-4.
8. Chailleux E, Fauroux B, Binet F, Dautzenberg B, Polu JM. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. *Chest* 1996; 109: 741-9.
9. Roussos C, Koutsoukou A Respiratory failure. *Eur Respir J* 2003; 47 (Suppl): 3-14.
10. Polkey MI. Muscle metabolism and exercise tolerance in COPD. *Chest* 2002; 121 (Suppl): 131-5.
11. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 154: 1310-7.
12. Sinderby C, Spahija J, Beck J, Kaminski D, Yan S, Comtois N, Sliwinski P. Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1637-41.
13. MacIntyre NR. Muscle dysfunction associated with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1654-9.
14. Verheul AJ, Dekhuijzen PN. Diaphragm dysfunction in patients with chronic obstructive pulmonary disease. *Ned Tijdschr Geneeskd* 2003; 147: 855-60.
15. Ottenheijm CA, Heunks LM, Dekhuijzen PN. Diaphragm muscle fiber dysfunction in chronic obstructive pulmonary disease: toward a pathophysiological concept. *Am J Respir Crit Care Med* 2007; 175: 1233-40.
16. Macgowan NA, Evans KG, Road JD, Reid WD. Diaphragm injury in individuals with airflow obstruction. *Am J Respir Care* 2006; 51: 840-7.
17. Ottenheijm CA, Heunks LM, Sieck GC, Zhan WZ, Jansen SM, Degens H, de Boo T, Dekhuijzen PN. Diaphragm dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 200-5.
18. De Troyer A, Leeper JB, McKenzie DK, Gandevia SC. Neural drive to the diaphragm in patients with severe COPD. *Am J Respir Crit Care Med* 1997; 155: 1335-40.
19. Montes de Oca M, Celli BR. Mouth occlusion pressure, CO2 response and hypercapnia in severe chronic obstructive pulmonary disease. *Eur Respir J* 1998 ; 12: 666-71.
20. Scano G, Spinelli A, Duranti R, Gorini M, Gigliotti F, Goti P, Milic-Emili J. Carbon dioxide responsiveness in COPD patients with and without chronic hypercapnia. *Eur Respir J* 1995; 8: 78-85.
21. Grassino A, Macklem PT. Respiratory muscle fatigue and ventilatory failure. *Ann Rev Med* 1984; 35: 625-47.
22. Schönhofer B, Polkey MI, Suchi S, Kohler D. Effect of home mechanical ventilation on inspiratory muscle strength in COPD. *Chest* 2006; 130: 1834-8.

23. Bégin P, Grassino A. Chronic alveolar hypoventilation helps to maintain the inspiratory muscle effort of COPD patients within sustainable limits. *Chest* 2000; 117 (5 Suppl 1): 271-3.
24. Bellemare F, Grassino A. Force reserve of the diaphragm in patients with chronic obstructive pulmonary disease. *J Appl Physiol* 1983; 55: 8-15.
25. O'Donnell DE, Parker CM. COPD exacerbations. 3: Pathophysiology. *Thorax* 2006; 61: 354-6.
26. Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370: 786-96.
27. Calverley PMA. Respiratory failure in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 47 (Suppl): 26-30.
28. Ram FSF, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD004104. DOI: 10.1002/14651858.CD004104.pub3.
29. Crummy F, Buchan C, Miller B et al. The use of noninvasive mechanical ventilation in COPD with severe hypercapnic acidosis. *Respir Med* 2007; 101: 53-61.
30. Scala R, Nava S, Conti G, Antonelli M, Naldi M, Archinucci I, Coniglio G, Hill NS Noninvasive versus conventional ventilation to treat hypercapnic encephalopathy in chronic obstructive pulmonary disease. *Intensive Care Med* 2007; 33: 2101-8.
31. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518-624.
32. Yan S, Kaminski D, Sliwinski P. Inspiratory muscle mechanics of patients with chronic obstructive pulmonary disease during incremental exercise. *Am J Respir Crit Care Med* 1997; 156: 807-13.
33. Mador MJ, Kufel TJ, Pineda LA, Sharma GK. Diaphragmatic fatigue and high intensity exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 118-23.
34. Sprikkelman AB, van Eykern LA, Lourens MS, Heymans HSA, van Aalderen WMC. Respiratory muscle activity in the assessment of bronchial responsiveness in asthmatic children. *J Appl Physiol* 1998; 84: 897-901.
35. Maarsingh EJ, Oud M, van Eykern LA, Hoekstra MO, van Aalderen WM. Electromyographic monitoring of respiratory muscle activity in dyspneic infants and toddlers. *Resp Physiol Neurobiol* 2006; 150: 191-9.
36. Maarsingh EJW, van Eykern LA, Sprikkelman AB, Hoekstra MO, van Aalderen WMC. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. *J Appl Physiol* 2000; 88: 1955-61.
37. Wouters EF. Management of severe COPD. *Lancet* 2004; 364: 883-95.
38. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, Garvey C, Goldstein R, Gosselink R, Lareau S, MacIntyre N, Maltais F, Morgan M, O'Donnell D, Prefault C, Reardon J, Rochester C, Schols A, Singh S, Troosters T; ATS/ERS Pulmonary Rehabilitation Writing Committee. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390-413.
39. Lacasse Y, Wong E, Guyatt GH, et al. Meta-analysis of respiratory rehabilitation in Chronic obstructive Pulmonary disease. *Lancet* 1996; 348: 1115-9.
40. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R, Herrerias C. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* 2007; 131 (5 Suppl): 4-42.
41. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 155: 1541-51.
42. Maltais F, LeBlanc P, Jobin J, Bérubé C, Bruneau J, Carrier L, Breton MJ, Falardeau G, Belleau R. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 155: 555-61.
43. Vogiatzis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J* 2002; 20: 12-9.
44. Puhan MA, Busching G, vanOort E, Zaugg C, Schunemann HJ, Frey M. Interval exercise training versus continuous exercise in patients with moderate to severe chronic obstructive pulmonary disease-

study protocol for a randomised controlled trail. *BMC pulmonary medicine* 2004; 4: 5.
45. Meinesz AF, Wijkstra PJ, Zijlstra JG, Albers MJIJ, Koëter GH. Van de poliomyelitisepidemie naar de oprichting van beademingscentra, intensivecareafdelingen en centra voor thuisbeademing. *Ned Tijdschr Geneesk* 2006; 150: 444-9.
46. Braun N, Marino WD. Effects of daily intermittent rest of Respiratory muscle in patients with severe chronic airflow limitation (CAL). *Chest* 1984; 85 (Suppl): 59-60.
47. Cropp A, DiMarco AF. Effects of intermittent negative pressure ventilation on respiratory muscle function in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1987; 135: 1056-61.
48. Gutiérrez M, Beroiza T, Contreras G, Diaz O, Cruz E, Moreno R, Lisboa C. Weekly cuirass ventilation improves blood gases and inspiratory muscle strength in patients with chronic air-flow limitation and hypercarbia. *Am Rev Respir Dis* 1988; 138: 617-23.
49. Levine S, Levy SF, Henson DJ Effect of negative pressure ventilation on ventilatory muscle endurance in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992; 146: 722-9.
50. Celli B, Lee H, Criner G, Bermudez M, Rassulo J, Gilmartin M, Miller G, Make B. Controlled trial of external negative pressure ventilation in patients with severe chronic airflow obstruction. *Am Rev Respir Dis* 1989; 140: 1251-6.
51. Zibrak JD, Hill NS, Federman EC, Kwa SL, O'Donnell C. Evaluation of intermittent long-term negative-pressure ventilation in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1988; 138: 1515-8.
52. Shapiro SH, Ernst P, Gray-Donald K, Martin JG, Wood-Dauphinee S, Beaupre A, Spitzer WO, Macklem PT. Effect of negative pressure ventilation in severe chronic obstructive pulmonary disease. *Lancet* 1992; 340: 1425-9.
53. Schönhofer B, Sortor-Leger S. Equipment needs for noninvasive mechanical ventilation. *Eur Respir J* 2002; 20: 1029-36.
54. Nava S, Fanfulla F, Frigerio P, Navalesi P Physiologic evaluation of 4 weeks of nocturnal nasal positive pressure ventilation in stable hypercapnic patients with chronic obstructive pulmonary disease. *Respiration* 2001; 68: 573-83.
55. Díaz O, Bégin P, Torrealba B, Jover E, Lisboa C. Effects of noninvasive ventilation on lung hyperinflation in stable hypercapnic COPD. *Eur Respir J* 2002; 20: 1490-8.
56. Elliott MW, Mulvey DA, Moxham J, Green M, Branthwaite MA. Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. *Eur Respir J* 1991; 4: 1044-52.
57. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med* 1995; 152: 538-44.
58. Strumpf DA, Millman RP, Carlisle CC, et al. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 144:1234-9.
59. Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. *Mayo Clin Proc* 1996; 71:533-42.
60. Lin CC. Comparison between nocturnal nasal positive pressure ventilation combined with oxygen therapy and oxygen monotherapy in patients with severe COPD. *Am J Respir Crit Care Med* 1996;154: 353-8.
61. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, Santolaria F. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest* 2000; 118: 1582-90.
62. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1335-41.
63. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, Ambrosino N. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; 20: 529-38.
64. Díaz O, Bégin P, Andresen M, Prieto ME, Castillo C, Jorquera J, Lisboa C. Physiological and clinical effects of diurnal noninvasive ventilation in hypercapnic COPD. *Eur Respir J* 2005; 26: 1016-23.

65. Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. *Eur Respir J* 2007; 30: 293-306.
66. Windisch W, Kostić S, Dreher M, Virchow JC Jr, Sorichter S. Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of Pa(CO2). *Chest* 2005; 128: 657-62.
67. Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized Controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients stratified with the MRC dyspnoea scale. *Eur Respir J* 1998;12: 363-9.
68. Ries AL, Make BJ, Lee SM, Krasna MJ, Bartels M, Crouch R, Fishman AP; National Emphysema Treatment Trial Research Group. The effects of pulmonary rehabilitation in the national emphysema treatment trial. *Chest* 2005; 128: 3799-809.
69. Carone M, Patessio A, Ambrosino N, Baiardi P, Balbi B, Balzano G, Cuomo V, Donner CF, Fracchia C, Nava S, Neri M, Pozzi E, Vitacca M, Spanevello A. Efficacy of pulmonary rehabilitation in chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD): The Maugeri Study. *Respir Med* 2007; 101: 2447-53.
70. Koechlin C, Maltais F, Saey D, Michaud A, LeBlanc P, Hayot M, Préfaut C. Hypoxaemia enhances peripheral muscle oxidative stress in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 834–41.
71. Carr SJ, Goldstein RS, Brooks D. Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) in Subjects Completing Pulmonary Rehabilitation (PR). *Chest* 2007; 132: 127-34.

RESPIRATORY MUSCLE ACTIVITY IN COPD

CHAPTER

2

Reproducibility and responsiveness of a noninvasive EMG technique of the respiratory muscles in COPD patients and in healthy subjects

J Appl Physiol 2004; 96: 1723-9

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ABSTRACT

Purpose: In the present study, we assessed the reproducibility and responsiveness of transcutaneous electromyography (EMG) of the respiratory muscles in patients with chronic obstructive pulmonary disease (COPD) and healthy subjects, during breathing against an inspiratory load.

Methods: In seven healthy subjects and seven COPD patients, EMG signals of the frontal and dorsal diaphragm, intercostal muscles, abdominal muscles, and scalene muscles were derived on 2 different days, both during breathing at rest and during breathing through an inspiratory threshold device of 7, 14, and 21 cm H_2O. For analysis, we used the logarithm of the ratio of the inspiratory activity during the subsequent loads and the activity at baseline [log EMG activity ratio (EMGAR)]. Reproducibility of the EMG was assessed by comparing the log EMGAR values measured at test days 1 and 2 in both groups. Responsiveness (sensitivity to change) of the EMG was assessed by comparing the log EMGAR values of the COPD patients to those of the healthy subjects at each load.

Results: During days 1 and 2, log EMGAR values of the diaphragm and the intercostal muscles correlated significantly. For the scalene muscles, significant correlations were found for the COPD patients. Although inspiratory muscle activity increased significantly during the subsequent loads in all participants, the COPD patients displayed a significantly greater increase in intercostal and left scalene muscle activity compared to the healthy subjects.

Conclusions: In conclusion, the present study showed that the EMG technique is a reproducible and sensitive technique to assess breathing patterns in COPD patients and healthy subjects.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) suffer from an imbalance between an increased load placed on the respiratory system and an impaired capacity of the respiratory muscles [1-3]. We believe that COPD patients, compared with healthy subjects, behave differently in their breathing strategy to achieve adequate ventilation, especially when the load on the respiratory system is further increased. We, therefore, consider it interesting to compare breathing strategies in COPD patients and healthy subjects by measuring the tidal breathing activity and the recruitment of the respiratory muscles during additional loading of the respiratory system.

In the past, various methods have been used to assess respiratory muscle activity [4-7]. One of the methods that may be used to assess respiratory muscle activity is electromyography (EMG). Esophageal electrodes may obtain reliable and valid EMG signals from the diaphragm. However, this technique is unpleasant for the participant and carries risks of regurgitation, aspiration and vagally mediated bradycardia [4]. Another method to obtain EMG recordings is the use of intramuscular electrodes. Although relatively selective EMG recordings can be obtained with this technique, the needles are difficult to place, and it is invasive, unpleasant for the study subject, and carries a risk of pneumothorax [8]. Therefore, transcutaneous EMG techniques are favorable, as they are noninvasive, and there is little to no discomfort for the participant. In addition, it can be used easily for clinical practice to determine the effects of different interventions.

In the past, several investigators have found that, with bilaterally widely separated electrodes placed in the costal spaces and below the costal margin, high-quality EMG recordings, minimally disturbed by unwanted external factors, could be obtained [9-11].

Investigators from our center showed that, with this surface EMG technique, good reproducible and high quality signals of the diaphragm and intercostal muscles in both young adults and children can be obtained [12-14]. This EMG technique, however, has never been used in patients with COPD. In the present study, we measured the activity of the diaphragm, the intercostal muscles, and the scalene muscles, as these muscles together determine inspiratory activity and breathing patterns in patients with COPD [15, 16]. Furthermore, we added the scalene muscles, as it is known that these muscles are important in achieving adequate ventilation in patients with COPD [17].

The aim of the present study was: 1) to asses the reproducibility of this EMG technique between test day 1 and test day 2 in both COPD patients and healthy subjects; and 2) to assess the responsiveness (sensitivity to change) of this EMG technique by evaluating and comparing respiratory muscle activity and breathing patterns of COPD patients and healthy subjects during breathing against an increasing inspiratory load.

METHODS

Subjects

Seven healthy subjects and seven COPD patients were included. Baseline characteristics are shown in Table 1. COPD was defined according to the American Thoracic Society criteria [18].The COPD patients were recruited from the outpatient clinic of the University Hospital Groningen or from the affiliated rehabilitation facility Beatrixoord, Haren. Excluded were patients with other lung diseases than COPD. Patients had to be in a stable condition, without signs or symptoms of an exacerbation in the last 12 months before the study. Healthy subjects were defined as having a normal pulmonary function (Tiffeneau index > 75 %).

All participants were informed about the purpose of the study and gave informed consent. The study was approved by the Medical Ethics Committee of the University Hospital Groningen.

Experimental protocol

The EMG recordings were performed twice, on 2 different days, with a time interval from 1 to 4 weeks. Electrical muscle activity of the frontal diaphragm (FD), dorsal diaphragm (DD), intercostal muscles (Int), abdominal muscles (Abd), and scalene muscles (Sc) was derived during breathing at rest (T0) and during breathing through an inspiratory threshold device (Threshold IMT; Respironics Inc., USA) of 7 (T1), 14 (T2) and 21 (T3) cmH_2O for 2 minutes each, with 2 minutes rest between the episodes of breathing through the threshold. During the measurements, the subjects were sitting in a comfortable chair and were asked not to move or talk. During the measurement, the investigator stood at the left of the subjects and held the threshold device.

Table 1. Baseline characteristics.

	COPD patients	Healthy subjects
Number	7	7
Age, years	61 ± 13	53 ± 3
VC, L	4.0 ± 0.9	4.5 ± 0.8 *
FEV_1, L	1.0 ± 0.2	3.8 ± 1.0 ***
FEV_1, % pred	34 ± 6	108 ± 13 ***
TLC, % pred	121 ± 12	-

Values are expressed as mean ± standard deviation (SD). COPD: chronic obstructive pulmonary disease; VC: vital capacity; FEV_1: forced expiratory volume in 1 sec; % pred.: percentage of predicted value; TLC: total lung capacity. Significant differences: * $p < 0.05$ and ***: $p < 0.001$.

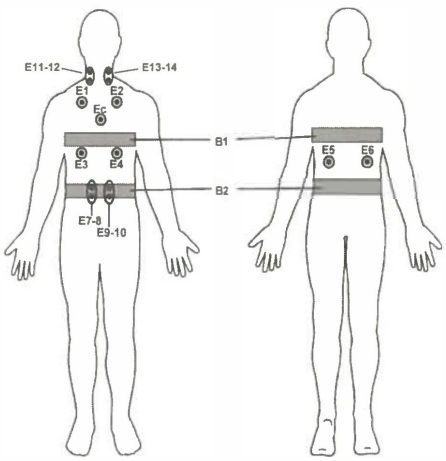

Figure 1. Placement of the 2 MR bands (B1 and B2) and the electrodes.
EC: common electrode, E1-E2: intercostal electrodes, E3-E4: frontal diaphragm electrodes, E5-E6: dorsal diaphragm electrodes, E7-E8 and E9-E10: right and left abdominal electrodes respectively, E11-12 and E13-E14: right and left scalene muscle electrodes.

EMG-recordings

The electrical activity of the FD, DD, Int, and left and right Sc was derived transcutaneously from pairs of electrodes (Neotrode, Conmed, New York, USA) placed as follows: one pair bilaterally at the costal margin in the nipple line; one pair bilaterally on the back at the level of the diaphragm; one pair in the second intercostal spaces, one electrode left and one right, 3 cm parasternal; and bipolar electrodes left and right on the neck over the Sc. The EMG signals of the rectus abdominis muscle were derived from bipolar electrode pairs, one pair on the right and one pair on the left side, 4 cm apart, at the level of the umbilicus. The common electrode was placed at the level of the sternum. The placement of the electrodes is shown in Figure 1.
The electrodes were connected to a Porti-16 front-end (Porti-X, Twente Medical Systems International, Enschede, The Netherlands), which allows for the acquisition of electrophysiological signals [Electro-X-Gram, (EXG)]. The true direct current digital physiological amplifier used for this study has been specially designed for use in the signal hostile clinical setting. The amplifier comprises high impedance (> 2GΩ), low-noise input stages with a low input bias current to minimise movement artifacts, a corresponding low input noise current to minimise the influence of the electrode impedance on the input noise, shielded electrode cables with carbon coated inner wire to prevent cable artifacts caused by tribo-electricity and line interference pick-up, and signal guarding to exclude distortion of the electrode signal by the cable capacitance. Both analogue high- and low-pass filters are excluded to prevent further distortion of the electrode signals by mismatches in their frequency characteristics. The

specific part of the DC electrode signals was amplified with a gain of 20 to increase the signal-to-noise ratio before sampling by means of a sigma-delta ADC with a resolution of 22 bits. The primary sample frequency (fs) of the ADC was 570 kHz, so a simple first order, low-pass filter set at 5 kHz was sufficient to prevent aliazing around 0.5 fs. Digital decimation filters were used to increase the resolution to 22 bits and served as intrinsic anti aliazing filters.

The common mode signal range was 6 V, the differential signal range was 300 mV, and the common mode rejection range was > 100 dB at 50-60 Hz. The converters put out samples with a resolution of 22 bits, resulting in a least significant bit of 71.5 nV for the physiological signal. The total amplifier and ADC noise was < 2 μV at peak power. The AUX channels had an instrumentation amplifier with both common mode and differential signal ranges of 6 V, an input impedance of > 1 GΩ, and a common mode rejection range of > 100 dB. We utilized the same ADC as that used for the EXG channels but with a least significant bit of 1.43 μV. Each AUX input connector was provided with a symmetrical 10-V, 10-mA power supply for powering analogue signal conditioning circuits. Although the maximum sample frequency of the front-end was 2 kHz, we found that, during tidal breathing, the sensitivity for the detection of respiratory muscle activity was optimal at a sample frequency of ~ 400 Hz. At higher sample frequencies, to allow for an increased bandwidth for EMG signals, it appeared that the power of the EMG did not significantly exceed the power of the amplifier and ADC noise in the higher frequency bands. The EXG signal was transformed into an EMG signal by means of a digital first-order high-pass filter (time constant = 0.01 s), as an electrophysiological signal is characterised by the position of the electrodes in relation to the electrically active tissue and its signal properties. For patient safety, the front-end was isolated from the main supply by a highly isolated power supply, and all signals were sent to a computer via fibre optics. All data processing, recording, post-analysis, and reporting was conducted by the POLY data acquisition and processing package (Inspector Research Systems, Amsterdam, The Netherlands).

Substantial heart activity interferes with the diaphragm EMG signals measured at the trunk. The electrical heart activity was removed from the respiratory muscle activity by the following process: the electrical ventricle activity of the heart (QRS) complexes of the ECG were easily detected and stretched into a pulse with a length of 100 ms. A cut was made in the slightly delayed EMG signal to completely filter out the QRS complex (gated EMG). Next the gated EMG was rectified and averaged with a moving time window of 200 ms. Finally the missing signal in the gate was filled with the running average, resulting in a fairly good interpolation during the gate and an almost ECG-free averaged EMG signal.

Magnetometer respiration monitoring

Gross changes in depth of breathing were measured by means of Magnetometer Respiration (MR) bands (Respiband, SensorMedics, Bilthoven, The Netherlands): one placed around the chest and one around the abdomen. The MR bands were connected to and powered by the AUX input. After analogue-to-digital conversion, scaling and

filtering of the data were performed digitally, transforming the AUX input signal into an independent signal to monitor respiration.

Data analysis and statistics

To determine the peak and bottom values of the respiratory EMG we used an inspiration synchronised averager. The chest band signal was used to detect the beginning of an inspiration. The beginning of an inspiration started the collection of samples from the averaged EMG signals in data buffers. Sampling continued until the beginning of the next inspiration was detected. The data in the buffers containing the samples of one inspiration cycle were moved to the interval data buffers and the collection of EMG data from a new inspiration was started. The data in the interval buffers were re-sampled to a normalised interval time and summed to averaging buffers [14]. To calculate the mean peak-to-peak excursion, 6 to 10 breathings were averaged. From the average data, the highest and lowest peak was detected for each signal. The differences between the peak and bottom values were reported as the mean peak-to-peak values.

For the analysis of the EMG signals, we used 6 to 10 successive breaths in the time interval before the first load (T0) and during the 3 increasing loads (T1, T2 and T3). EMG data were reported as the logarithm of the EMG Activity Ratio (log EMGAR). A ratio was calculated of the mean peak-to-peak inspiratory activity during the subsequent loads (T1 to T3), and the mean peak-to-peak value at baseline (T0). The logarithmic transformation for the EMGAR was used to make the relative change in the EMGAR symmetric around unity.

To obtain an EMG signal representing the whole diaphragm, the mean of the activity of the frontal and the dorsal diaphragm was used.

Reproducibility of the EMG technique was assessed by comparing the log EMGAR values of the diaphragm, the intercostal muscles and the left scalene muscle at the subsequent inspiratory loads at test day 1 to the log EMGAR values at test day 2. To assess the reproducibility of a technique, we compared signals over the full range of signal amplitude (T1, T2 and T3). Pearson's correlation coefficients and the method described by Bland and Altman [19] were used to assess reproducibility.

Responsiveness of the EMG technique, defined as sensitivity to change, was determined by evaluating and comparing the mean log EMGAR values of COPD patients with that of the healthy subjects during T1, T2, and T3 of the diaphragm, the intercostal muscles, and the left scalene muscle. The independent t-test was used. A $p < 0.05$ was regarded as significant.

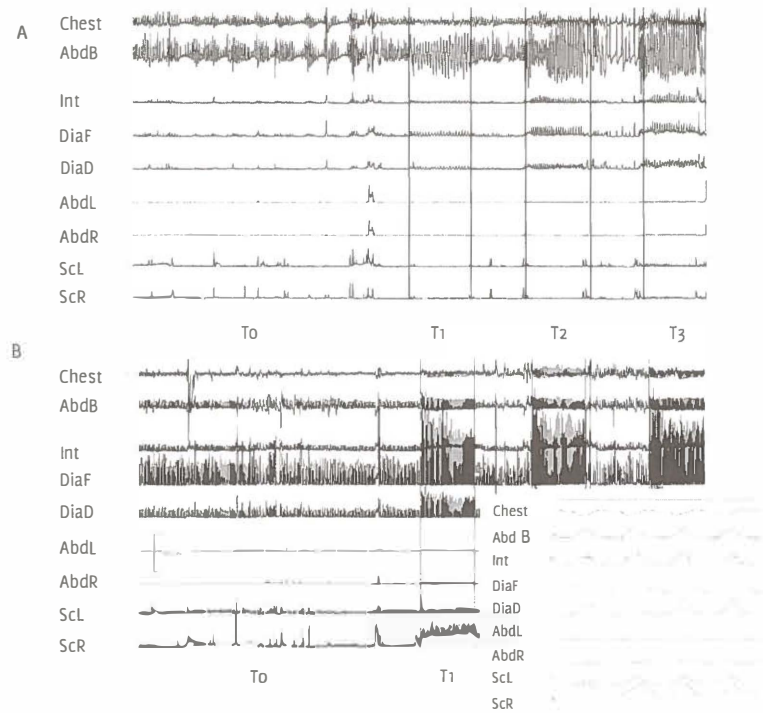

Figure 2. The total recording (time-compressed) and a detailed recording (inlet in Figure 2B) of the averaged EMG signals and MR band signals (top 2 curves) at rest (To) and during breathing against an inspiratory device of 7 (T1), 14 (T2) and 21 (T3) cm H_2O in a healthy subject (A) and in a COPD patient (B). Legend: Chest: chest MR band; AbdB: abdominal MR band; Int: intercostal; DiaF: frontal diaphragm; DiaD: dorsal diaphragm; AbdL: left abdomen; AbdR: right abdomen; ScL: left scalene muscle; ScR: right scalene muscle.

RESULTS

One COPD patient had a respiratory tract infection prior to the second test day and was excluded from the study. Furthermore, one healthy subject was excluded because of technical problems during the first measurement.

In Figure 2, the total recording (time-compressed) and a detailed recording of the averaged EMG signals and MR band signals of a representative healthy subject (Figure 2A) and COPD patient (Figure 2B) at T0 and during the loads (T1 to T3) are presented.

At T0, the healthy subject showed low respiratory activity in the Int and the diaphragm and almost no activity in the Sc. In the COPD patient, at T0, much respiratory activity was present in all but the Abd.

During breathing against the inspiratory loads, the activity of the Int and diaphragm increased in both the COPD patient and the healthy subject. In the COPD patient, however, although the activity of the Int and the diaphragm increased at T1, it seemed

Table 2. Correlation coefficients.

	COPD patients	Healthy subjects
Diaphragm	R = 0.73 **	R = 0.77 **
Int	R = 0.89 **	R = 0.63 *
Left Sc	R = 0.77 **	R = 0.44
Right Sc	R = 0.49	R = 0.32

Correlations (R) are between the log EMG activity ratio values obtained at test day 1 and the log EMG activity ratio values obtained at test day 2 of the COPD patients and the healthy subjects.
Int: intercostal muscles; Left Sc: left scalene muscle; Right Sc; right scalene muscle. Significant correlations: * $p < 0.05$ and ** $p < 0.01$.

to reach a plateau at T2 and T3. In the healthy subject, the activity of the Int and the diaphragm was much lower and did not reach a plateau. The activity of the Sc increased in the COPD patient at all three inspiratory loads, while in the healthy subject a small increase could be observed only at T3. In the COPD patient, a difference in the amplitude of the signal of the right and left Sc was found. This might be explained by the fact that patient turned his head to the investigator, who stood at the left of the participant, holding the threshold device.

Reproducibility between test day 1 and test day 2

The correlation coefficients for the log EMGAR values of the diaphragm, the Int, and the left and right Sc at the subsequent loads at test day 1 and test day 2 of the COPD patients and the healthy subjects are presented in Table 2.
The mean log EMGAR values against the differences between test day 1 and test day 2 of the diaphragm, the Int, and the left Sc during T1, T2, and T3 are shown in Figure 3.

Responsiveness

The mean and 95 % confidence interval of the log EMGAR values of the diaphragm, the Int, and the left Sc of the COPD patients compared with the healthy subjects are shown in Figure 4.

Diaphragm

In the healthy subjects, the mean diaphragm activity was increased with a factor of 2.3 ± 0.8 at T1 (log EMGAR = 0.36; $p < 0.05$), with a factor of 2.4 ± 0.8 at T2 (log EMGAR = 0.38; $p < 0.05$), and with a factor of 2.7 ± 0.7 at T3 (log EMGAR = 0.43; $p < 0.05$), as compared to baseline breathing (T0). In the COPD patients, the activity of the diaphragm increased significantly only during breathing against load T3 with a factor of 2.3 ± 0.7 (log EMGAR = 0.37; $p < 0.05$). At T1 and T2, the activity of the diaphragm in the COPD patients tended to increase with a factor of 1.6 ± 0.7 (log

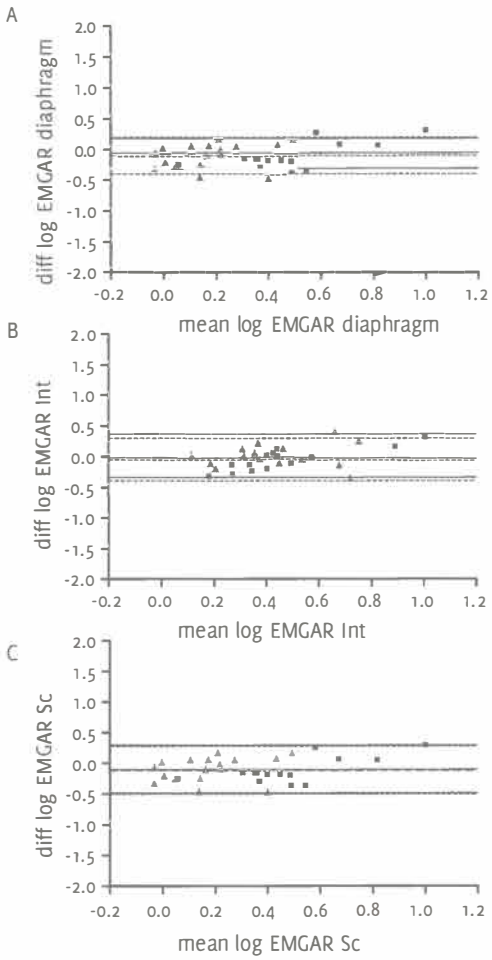

Figure 3.
Bland and Altman plots of the mean differences (diff) between the 2 measurements versus the mean log EMG activity ratio (log EMGAR) of the 2 measurements at day 1 and day 2 of the diaphragm (A), the intercostal muscles (Int, B), and the left scalene muscle (Sc, C) during breathing against an inspiratory device.
The mean differences and the 95 % confidence interval (mean ± 1.96 SD) are shown for the COPD patients (black squares; dashed line) and the healthy subjects (grey triangles; solid line).

EMGAR = 0.20; p = 0.07) at both T1 and T2. However, this was not significant. Although the activity of the diaphragm tended to increase more in the healthy subjects, no significant differences between the increases in activity in the COPD patients and healthy subjects were found.

Intercostal muscles

In the healthy subjects, the mean Int activity increased during breathing against the loads with a factor of 1.9 ± 0.6 ($p < 0.01$) at T1, with a factor of 2.5 ± 0.9 ($p < 0.01$) at T2, and with a factor of 2.9 ± 0.9 ($p < 0.05$) at T3, compared to T0. In the COPD patients, the activity of the intercostal muscles increased with a factor of 3.0 ± 0.6 ($p < 0.01$) at T1, with a factor of 3.3 ± 0.8 ($p < 0.001$) at T2, and with a factor of 4.3

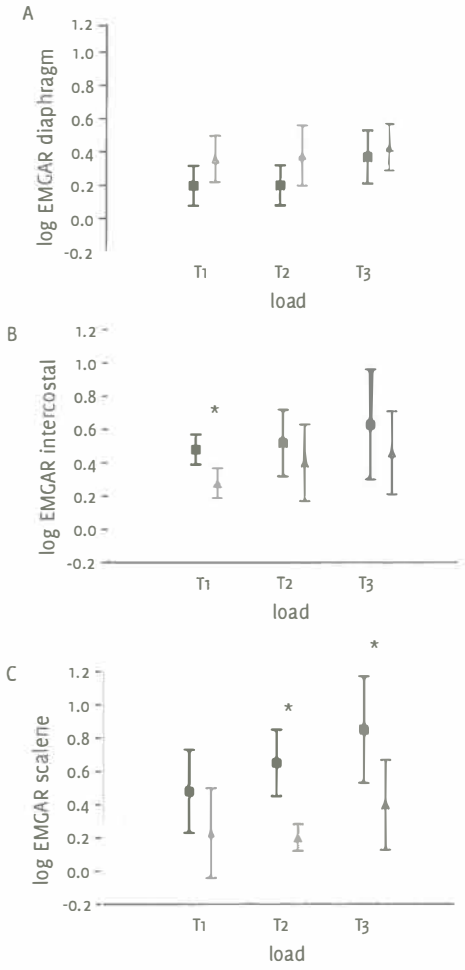

Figure 4.
Plots of the mean and 95% confidence interval of the log EMG activity ratio (log EMGAR) of the inspiratory muscles measured: the diaphragm (A), the intercostal muscles (B), and the left scalene muscle (C) of the COPD patients (black squares) compared to the healthy subjects (grey triangles) during breathing against an inspiratory device at a pressure of 7 (T1), 14 (T2) and 21(T3) cm H_2O. Significant differences: * $p < 0.05$.

$\pm$ 1.0 ($p < 0.001$) at T3, compared to T0.
Log EMGAR values of the intercostal muscles were significantly higher in COPD patients compared to healthy subjects at T1 ($p < 0.01$). At T2 and T3 the log EMGAR values of the intercostal muscles in COPD patients were not different from the healthy subjects.

Left Scalene muscle
In the healthy subjects the mean left Sc activity increased with a factor of 1.7 $\pm$ 1.0 at T1 ($p < 0.01$), with a factor 1.6 $\pm$ 0.6 at T2 ($p < 0.01$), and with a factor of 2.5 $\pm$ 1.0 at T3 ($p < 0.05$), compared to T0. In the COPD patients, the mean left Sc activity increased with a factor of 3.0 $\pm$ 0.9 at T1 ($p < 0.01$), with a factor of 4.5 $\pm$ 0.9 at T2

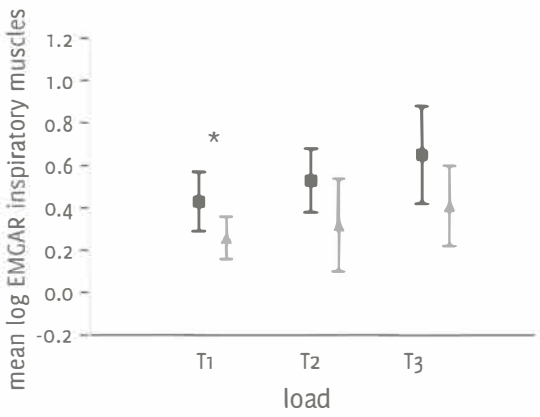

Figure 5.
Plot of the mean and 95 % confidence interval of the sum of the log EMG activity ratio (EMGAR) of the frontal diaphragm, the dorsal diaphragm, the intercostal muscles and the left scalene muscle of the COPD patients (black squares) compared to the healthy subjects (grey triangles) during breathing against an inspiratory device at a pressure of 7 (T1), 14 (T2) and 21(T3) cm H_2O. Significant differences: * $p < 0.05$.

($p < 0.01$), and with a factor of 7.0 ± 1.1 at T3 ($p < 0.01$), compared to T0.
Significant differences between the COPD patients and the healthy subjects were found in the log EMGAR values of the left scalene muscle at T2 ($p < 0.01$) and T3 ($p < 0.05$). At T1, the log EMGAR values of the COPD patients did not differ from those of the healthy subjects.

Total inspiratory activity
The mean and 95 % confidence interval of log EMGAR values of the FD, the DD, the Int, and the left Sc of the COPD patients, as compared to the healthy subjects, are shown in Figure 5.
In the healthy subjects, the mean total inspiratory muscle activity of the healthy subjects was increased with a factor of 1.8 ± 0.6 at T1 ($p < 0.01$), with a factor of 2.1 ± 0.9 at T2 ($p < 0.01$), and with a factor of 2.6 ± 0.8 at T3 ($p < 0.01$), compared to T0. In the COPD patients, the mean total inspiratory muscle activity of the COPD patients was increased with a factor of 2.7 ± 0.7 at T1 ($p < 0.01$), with a factor of 3.4 ± 0.7 at T2 ($p < 0.01$), and with a factor of 4.5 ± 1.0 at T3 ($p< 0.01$), compared to T0.
Although there was a trend towards a higher overall activity in the COPD patients, the only significant difference between the total inspiratory muscle activity of the COPD patients and the healthy subjects was found at T1 ($p < 0.05$).

DISCUSSION

The present study showed that this noninvasive EMG technique has an acceptable reproducibility both in COPD patients and in healthy subjects. Moreover, this technique appeared sensitive to detect different breathing patterns in COPD patients and healthy subjects when breathing against increasing inspiratory loads.
Although this transcutaneous EMG technique could serve as a useful tool in

assessing breathing patterns in healthy subjects and COPD patients, this method is still controversial. Firstly, it has been argued that with this technique, difficulties arise in maintaining electrode orientation with respect to the muscle fibres and in controlling for influences of variable muscle-to-electrode distance (as with variations in the amount of subcutaneous fat) [20]. We minimised these influences by using the ratio of the averaged electrical muscle activity at a given instance in relation to that at baseline (EMGAR). By doing this, constant factors that influence the amount of electrical activity measured at both instances will be reduced to unity. In addition, by logarithmic transformation (log EMGAR) to zero, we corrected the actual value for the baseline value. Furthermore, we used large electrodes (diameter 2.5 cm) for the Int and the diaphragm, and placed them relatively far apart. Thus, electrical activity was measured from an extensive portion of these muscles. Secondly, cross-talk from adjacent muscles may also influence transcutaneous EMG signals [21, 22]. Most sensitive to cross-talk are the Sc (from the sternocleidomastoideus muscles) and the diaphragm (from the Abd). To minimise cross-talk from the sternocleidomastoideus muscles, the electrodes for the scalene muscles have to detect more specific signals. Therefore, we used relatively small bipolar electrodes for these muscles. Cross-talk from the abdominal muscles was ruled out, as almost no activity of the abdominal muscles could be detected during inspiration.

In our study, we measured the activity of both the FD and DD. As no significant differences could be found in activity patterns between the FD and DD, we considered the diaphragm as one single muscle and averaged the FD and DD signals to obtain one single diaphragm signal [3, 23].

We choose to report the left Sc signals only. We believe that tonic activity of the right sternocleidomastoideus muscle disturbed the signals obtained from the right Sc. We asked our participants to look straight ahead, but could not prevent that they turned their heads somewhat towards the investigator. Although it has been shown that most COPD patients showed strong inspiratory contractions of the scalene muscles and not of the sternocleidomastoideus muscle at rest [17], it can not be excluded that in our subjects, the activity of the sternocleidomastoideus muscle increased with inspiratory loading and disturbed the scalene signals. We believe that when more attention is given to a correct position of the head, an acceptable level of reproducibility of the signals of both Sc can be obtained with the presented EMG technique [24].

Reproducibility

A correlation of 0.8 has been reported to be acceptable for EMG measurements [13, 25]. In our study, most correlation's showed this degree of reproducibility. However, the method of Bland and Altman [19] may provide more appropriate information on the level of reproducibility.

As our EMG technique is only used sparsely, the limits of agreement have not been generally accepted yet. Maarsingh et al [13] did use the same Bland and Altman method[19] in assessing reproducibility of their data. However, in their study, the EMG data were presented as raw data and not the logarithmic relative values as we used [13]. So, we

cannot apply their limits of agreement to our results.
It should be noticed that, for the diaphragm and for the left Sc, a systemic deviation in the mean difference was observed in both the healthy subjects and the COPD patients. This suggests that, at test day 2, there was a greater increase in the activity of these muscles compared to day 1. However, these differences between signal amplitude at test day 1 and test day 2 were observed during the 7 cm H_2O load (T1) only.
Furthermore, in the healthy subjects, the increased left Sc activity was caused by a large increase in log EMGAR at day 2 in only one single participant. At day 1, the left scalene muscle activity of this subject showed serious disturbance during tidal breathing (T0), leading to unreliable and low log EMGAR values at day 1. As a consequence, a large, but artificial difference between day 1 and 2 was observed in this subject, leading to a lower correlation coefficient and a remarkable deviation in the mean difference.
The greater increase in respiratory muscle activity the subjects showed at day 2 might be due to deterioration in their clinical condition. However, we included COPD patients who were in a clinical stable condition. Furthermore, the log EMGAR values of the diaphragm at day 2 showed the same increase in six out of seven healthy subjects, which could not be due to a clinical deterioration.
It has been shown that, during successive sessions of breathing through an inspiratory threshold, COPD patients adapt to a different breathing pattern [26]. We noticed that all participants were able to handle the threshold device very soon after initiating the first load. The difference in muscle activity at T1 between test day 1 and day 2 might, therefore, be explained by the fact that both the COPD patients and the healthy subjects had to get used to the threshold during the first load at day 1. We observed that the subjects, when used to the threshold device, adopted a less shallow pattern immediately after T1. Differences in breathing patterns and depth greatly influence the pattern and the degree of recruitment of the different respiratory muscles and, consequently, the EMG signals of the individual respiratory muscles.

Responsiveness

When breathing against increasing inspiratory loads, the COPD patients used a different breathing strategy by showing significantly more increase in activity of their Sc and Int, while they displayed a lower increase in activity of their diaphragm, compared with healthy subjects.
Due to emphysema, the diaphragm works at an unfavourable position causing a decreased inspiratory capacity [1, 27]. Therefore, the relative contribution to force generation of the Int and accessory muscles is necessary to maintain sufficient ventilation. De Troyer et al.[17] found that COPD patients had strong inspiratory contraction of the Sc, even at rest. It seems logical that, during breathing against an inspiratory load, the contribution of the Sc increases further.
At T1, the activity of the Int increased significantly in COPD patients compared to healthy subjects. At T2 and T3, Int activity in COPD patients was still higher, but not significantly. Because the contribution of the Int to pressure generation in COPD

patients is already greatly enhanced at rest, the reserves of the muscles are presumably low [27]. Therefore, the increase in Int activity during incremental loading, as can be observed in the healthy subjects, is lower in COPD patients. This may explain why the differences between the log EMGAR values between the COPD patients and the healthy subjects were only significant at T1 and not at T2 and T3.

We averaged the signals of the FD, DD, Int, and the left Sc to determine whether the EMG technique was a sensitive method to measure changes in overall inspiratory muscle activity. The increase in overall inspiratory muscle activity tended to be higher in the COPD patients than in the healthy subjects at all three loads, with a significantly higher increase in the COPD patients at T1. We found a linear relationship between mean log EMGAR and load, which means that the mean averaged activity ratio of the muscles we measured was exponentially related to the inspiratory load.

In conclusion, the EMG technique showed to be reproducible and sensitive to assess changes in respiratory muscle activity and breathing patterns in healthy subjects and in patients with COPD. This technique can be used to assess the activity of the different respiratory muscles simultaneously both at rest and during inspiratory loading. Its noninvasive and nonintrusive character makes this technique useful in assessing respiratory activity and breathing patterns during different intervention programs.

Acknowledgements

We are grateful to D.J. van Hoogstraten for editorial advice.

REFERENCES

1. Polkey MI. Muscle metabolism and exercise tolerance in COPD. *Chest* 2002; 121 (Suppl): 131–5.
2. Riera HS, Rubio TM, Ruiz FO, Ramos PC, Otero D, Hernandez TE, Gomez JC. Inspiratory muscle training in patients with COPD; effect on dyspnea, exercise performance and quality of life. *Chest* 2001; 120: 748 – 56.
3. Sinderby C, Beck J, Spahija J, Weinberg J, Grassino A. Voluntary activation of the human diaphragm in health and disease. *J Appl Physiol* 1998; 85: 2146-58.
4. ATS/ ERS Comittee. Electrophysiologic techniques for the assessment of respiratory muscle function (Statement on respiratory muscle testing). *Am J Respir Crit Care Med* 2002; 166: 518-624.
5. De Troyer A, Leeper JB, McKenzie DK, Gandevia SC. Neural drive to the diaphragm in patients with severe COPD. *Am J Respir Crit Care Med* 1997; 155: 1335-40.
6. Mador MJ, Kufel TJ, Pineda LA, Sharma GK. Diaphragmatic fatigue and high-intensity exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 118-23.
7. Sinderby C, Spahija J, Beck J, Kaminski D, Yan S, Comtois N, Sliwinski P. Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1637- 41.
8. Saadeh PB, Crisafulli C, Garofalo M. Needle EMG of the diaphragm. *Muscle & Nerve* 1993; 16: 323.
9. O'Brien MJ, van Eykern LA, Prechtl HFR. Monitoring respiratory activity in infants - a non-intrusive diaphragm EMG technique. In: P. Rolfe (ed.). Noninvasive Measurements. Vol. 2. Academic Press, London Ltd., (1983) 131-77.
10. Prechtl HFR, van Eykern LA, O'Brien MJ. Respiratory muscle EMG in newborns: A non-intrusive method. *Early Hum Develop1* 1977; 265-83.
11. Taylor A. The contribution of the intercostal muscles to the effort of respiration in man. *J Physiol* 1960; 151: 390-402.
12. Maarsingh EJW, Eykern van LA, Haan de RJ, Griffioen RW, Hoekstra MO, Aalderen van WMC. Airflow limitation in asthmatic children assessed with a noninvasive EMG technique. *Respir Physiol and Neurobiol* 2002; 133: 89-97.
13. Maarsingh EJW, Eykern van LA, Sprikkelman AB, Hoekstra MO, Aalderen van WMC. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. *J Appl Physiol* 2000; 88: 1955-61.
14. Sprikkelman AB, Eykern van LA, Lourens MS, Heymans HA, Aaalderen van WMC. Respiratory muscle activity in the assessment of bronchial responsiveness in asthmatic children. *J Appl Physiol* 1998; 84: 897-901.
15. Grassino A, Bellemare F, Lapo D. Diaphragm fatigue and the strategy of breathing in COPD. *Chest* 1984; 85 (Suppl): 51-4.
16. Roussos C, Macklem PT. The respiratory muscles. *New Engl J Med* 1982; 307: 786-97.
17. De Troyer A, Peche R, Yernault JC, Estenne M. Neck muscle activity in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994; 150: 41-7.
18. ATS Comittee. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (Statement). *Am J Respir Crit Care Med* 1995; 152 (Suppl): 77-120.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurements. *Lancet* 1986; 1: 307-10.
20. Gandevia SC, McKenzie DK. Human diaphragmatic EMG: changes with lung volume and posture during supramaximal phrenic nerve stimulation. *J Appl Physiol* 1986; 60: 1420-8.
21. De Troyer A, Estenne M, Ninane V, Van Gansbeke D, Gorini M. Transversus abdominis muscle function in humans. *J Appl Physiol* 1990; 68: 1010-6.
22. Sinderby C, Friberg S, Comtois N, Grassino A. Chest wall muscle cross-talk in canine costal diaphragm elektromyogram. *J Appl Physiol* 1996; 81: 2312-27.
23. Beck JC, Sinderby L, Lindstrom L, Grassino A. Effects of lung volume on diaphragm EMG signal strength during voluntary contractions. *J Appl Physiol* 1998; 85: 451-8.
24. Eykern van LA, Geisler HC, Gramsbergen A. A new technique for simultaneously recording EMG and movements in experimental animals. *Brain Research Protocols* 2001; 6: 108-11.

25. Franssen JLM. The measurement. In: Handbook of Surface Elektromyography. Utrecht, the Netherlands: De Tijdboom 1995, p.161-173.
26. Eastwood PR, Hillmann Dr, Morton AR, Finucane KE. The effects of learning on the ventilatory responses to inspiratory threshold loading. *Am J Respir Crit Care Med* 1998; 158: 1190-6.
27. Yan S, Kaminski D, Sliwinski P. Inspiratory muscle mechanics of patients with chronic obstructive pulmonary disease during incremental exercise. *Am J Respir Crit Care Med* 1997; 156: 807-13.

CHAPTER

3

Respiratory muscle activity and dyspnoea during exercise in COPD

Submitted

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ABSTRACT

Background: Little is known regarding inspiratory muscle activity during exercise in COPD. With noninvasive electromyography (EMG), the activity of the different inspiratory muscles as a measure of neural drive can be assessed without discomfort to the patient.

Purposes: To determine whether during exercise: 1) COPD patients preferentially increase scalene and intercostal muscle EMG activity, 2) increased EMG activity is associated with increased dyspnoea, and 3) the ratio between EMG activity and volume displacement is increased in COPD compared to healthy subjects (HS).

Methods: EMG of the diaphragm, scalene, and intercostal muscles was derived transcutaneously during an incremental bicycle test in 17 COPD patients and 10 HS.

Results: COPD patients demonstrated several differences compared to HS: earlier increase in diaphragm, intercostal, and scalene EMG activity; at peak exercise, more marked increases in scalene and intercostal activity. The increased EMG activity was related to increased dyspnoea. In COPD, there was a larger increase in EMG activity relatively to tidal volume increases compared to HS.

Conclusions: Already at lower exercise intensity, COPD patients showed marked increases in scalene and intercostal EMG. We believe that the steeper relationship between increase in EMG activity and dyspnoea in COPD results from a dissociated neuroventilatory drive.

INTRODUCTION

In patients with Chronic Obstructive Pulmonary Disease (COPD), the demand on the respiratory system increases during exercise. As dynamic hyperinflation diminishes the negative-pressure generating capacity of the diaphragm [1, 2, 3], COPD patients increase the contribution of their scalene and intercostal muscles relative to the diaphragm during exercise [4, 5]. The limited increase in diaphragmatic pressure generation has been proposed to result from central inhibition of the neural drive, in order to prevent contractile fatigue of the diaphragm [6]. On the other hand, it has been proposed that the neural drive increases, but that the capacity of the diaphragm to generate sufficient negative pressure is limited [3].

As these studies focussed on the diaphragm, little is known about the other inspiratory muscles when the ventilatory demand increases. Electromyography (EMG) measures the electrical manifestations of the excitation process elicited by action potentials propagating along muscle fibre membranes. As such, it can be used to assess neural drive [7]. With surface EMG, signals can be obtained both from the diaphragm, the intercostals, and scalene muscles simultaneously, without discomfort to the patient [8-11].

An increased neural drive probably influences dyspnoea sensation. In COPD, the motor command from the brain is relatively high compared to the volume displaced by the lungs, as tidal volume expansion is limited by dynamic hyperinflation [12, 13]. The ratio between motor command and volume displacement is known as neuroventilatory coupling (NVC).

The purposes of the present study were to determine: 1) whether COPD patients preferentially increase the EMG activity to the scalene and intercostal muscles and less to the diaphragm, as compared to healthy subjects, 2) whether increased EMG activity is associated with increased dyspnoea sensation, and 3) whether the ratio between EMG activity and volume displacement by the lungs is increased in COPD compared to healthy subjects. To answer these questions, we investigated, by means of noninvasive EMG, the patterns of increase in diaphragmatic, intercostal, and scalene EMG activity alone and in relation to the increase in dyspnoea sensation and tidal volume increase in COPD patients and healthy subjects during exercise.

METHODS

Subjects

Seventeen COPD patients [14] were recruited from the rehabilitation centre of the University Medical Center Groningen. Patients had to be without signs of an exacerbation in the last 4 weeks before the study. Excluded were patients with pulmonary diseases other than COPD, known cardiovascular diseases, and other systemic diseases or conditions that might have influenced exercise tolerance. For controls, ten healthy subjects (HS), matched by age, were recruited by advertisement.

Table 1. Anthropometric and pulmonary function data.

	Patients	Healthy subjects
Number (male)	17 (9)	10 (6)
Age, years	60 (54-64)	55 (53-59)
BMI, kg/m²	22 (21-25)	26 (22-28)
FEV_1, L	0.91 (0.77-1.11)*	3.44 (2.89-3.93)
FEV_1, %predicted	32 (22-39)*	107 (93-117)
IVC, L	3.02 (2.64-3.18)*	4.74 (3.60-5.88)
FRC, %predicted	153 (131-170)	-
TLC, %predicted	124 (106-133)	-

Data are presented as median (IQR). Significant difference: *: $p<0.001$ compared to healthy subjects; FEV_1: forced expiratory volume in 1 second in litres (L); IVC: inspiratory vital capacity; FRC: functional residual capacity; TLC: total lung capacity.

All HS had a $FEV_1/FVC > 70\%$ and FEV_1 %predicted > 80% and no pulmonary complaints (Table 1). Written informed consent was obtained from all participants.

Measurements and study design

Pulmonary function testing

In all participants vital capacity (VC) and forced expiratory volume in 1 second (FEV_1) were measured by spirometry. Lung volumes were assessed only in the COPD patients by body plethysmography (Masterscreen IOS, Viasys, Bilthoven, the Netherlands).

Exercise testing

All subjects performed a maximal incremental cycle ergometry test in a semi-recumbent position, in order to minimise the effects of muscle activity necessary for body stabilisation (Oxycon Pro and Jaeger ER900 LSE, Viasys, Bilthoven, the Netherlands). Furthermore, to minimise muscle activity for head positioning, the subjects were instructed to look straight ahead during the measurements. The measurements started with 5 minutes of rest, followed by the incremental phase (COPD patients: 5 or 10 and HS: 25 Watts per minute increase in order to reach exercise duration of about 10 minutes for each individual). During the test, work load, oxygen uptake (VO_2), minute ventilation (V_E), and tidal volume (V_T) were measured continuously. Furthermore, dyspnoea sensation was quantified using a 10-point modified Borg scale, ranging from zero (no dyspnoea) to 10 (maximal dyspnoea). The scale was displayed in front of the participants during the test. Before the test and then every two minutes during the test, participants were asked to indicate, by pointing, the value on the scale that represented the magnitude of respiratory effort they experienced at that particular moment (Table 2).

Table 2. Cycle ergometry results.

	Patients		Healthy subjects	
	Rest	Peak	Rest	Peak
Exercise time, min	-	6.0 (4.7-8.0)*	-	9.6 (7.4-10.0)
Workload, watt	-	35 (23-60)*	-	225 (169-256)
Workload, % pred	-	31 (22-45)*	-	150 (126-189)
VO_2/ kg, ml/min/kg	3.3 (2.6-3.7)	11.5 (9.2-13.1)*	2.8 (2.4-3.4)	27.4 (23.1-33.7)
V_E, ml/min	9 (7-11)*	27 (21-33)*	7 (6-7)	76 (53-102)
BF, breaths/min	18 (15-23)	29 (25-35)	16 (11-18)	32 (27-47)
V_T, L	0.50 (0.31-0.61)	0.82 (0.72-1.13)*	0.44 (0.38-0.51)	2.15 (1.75-2.56)
PaO_2, kPa	8.7 (7.9-10.7)	7.7 (6.8-9.1)	-	-
$PaCO_2$, kPa	5.4 (4.5-6.4)	5.7 (5.1-6.8)	-	-
Borg dyspnoea	1.0 (0-2.5)	8.0 (6.0-9.0)*	0	3.0 (0.9-5.3)
Borg exertion	0 (0-1.0)	5.0 (3.5-8.5)	0	6.0 (3.3-9.0)

Data are presented as median (IQR). VO_2: oxygen uptake per kg body weight; V_E: minute ventilation; BF: breathing frequency; V_T: tidal volume; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure. Significant difference: *: $p < 0.05$, COPD compared to healthy subjects.

EMG Recordings

Electrical activity of the scalene muscles, intercostal muscles, frontal diaphragm, dorsal diaphragm, and the abdominal muscles was derived transcutaneously during the cycle test from surface electrodes placed on the skin.

Detailed technical aspects of the electrode placement, measurements, measurement devices, and data acquisition and processing are given in the supplementary material.

Data analysis

For analyses, the logarithm of the EMG Activity Ratio (logEMGAR) was used, which is the ratio between the peak inspiratory muscle activity during exercise and the peak activity during quiet breathing at rest (baseline). The logEMGAR shows changes in inspiratory muscle activity during exercise in relation to inspiratory muscle activity at rest. For scalene muscle activity we used the lowest scalene signal of the right and left scalene muscle in order to select the signal with the least possible signal contamination (in 13 subjects this was the left scalene signal, in 14 subjects this was the right scalene signal). For diaphragm activity, we used the mean of the frontal and dorsal diaphragm.

Total exercise time of the test was divided in four stages: the beginning of the exercise test (stage 1, baseline breathing), at 1/3 of the total test time (stage 2), 2/3 of the total test time (stage 3), and at maximal effort (stage 4).

Neuroventilatory coupling (NVC) was calculated as the difference of logEMGAR of the inspiratory muscles [intercostals, diaphragm, and scalene muscle] and the logarithmic

ratio of the tidal volume (V_T) during exercise and the tidal volume at baseline (V_TB), called the logV_TR (NVC= logEMGAR-logV_TR). By doing this, we computed change in NVC from baseline.

Statistics

As they were not normally distributed, anthropometric, pulmonary function, cycle ergometry data, and logEMGAR and NVC data are presented as medians and interquartile ranges (IQR). Differences in anthropometric, pulmonary function and cycle ergometry data, and logEMGAR and NVC ratio's at the stages between COPD patients and HS were compared by Mann-Whitney U tests. For categorical variables, chi-square tests were used. Differences in logEMGAR and NVC between the stages and between the different respiratory muscles were assessed with a Friedman test for multiple dependent samples and, if significant, with Wilcoxon signed rank tests.
The change in Borg dyspnoea scores with the increase in logEMGAR over time was assessed using a mixed effects model taking into account repeated measures within individual subjects. This model assessed both the change in Borg dyspnoea score with increasing logEMGAR in the COPD patients and HS, as well as the differences in change in Borg scores with logEMGAR between the COPD patients and the HS.
Analyses were performed with SPSS 14.0. A $p < 0.05$ was considered to be significant.

RESULTS

EMG results

A time compressed recording of the EMG signals of a representative COPD patient and a representative healthy subject during exercise are presented in Figure 1. Figure 2 shows the logEMGAR of the inspiratory muscles during the successive stages in both COPD patients and HS.

Diaphragm

Both in the COPD patients and the HS diaphragmatic activity increased progressively from 1/3 of total exercise time (stage 2). Diaphragm activity was more increased in the COPD patients compared to the HS at 1/3 of total exercise time (stage 2). At stage 4 there was a trend towards more increase in diaphragm activity in the HS ($p=0.12$).

Intercostal muscles

In the COPD patients, intercostal activity increased progressively from 1/3 of total exercise time (stage 2). In the HS, intercostal activity was increased significantly just as from 2/3 of total exercise time (stage 3). Intercostal activity was more increased in the COPD patients compared to the HS at 1/3 of total exercise time (stage 2).

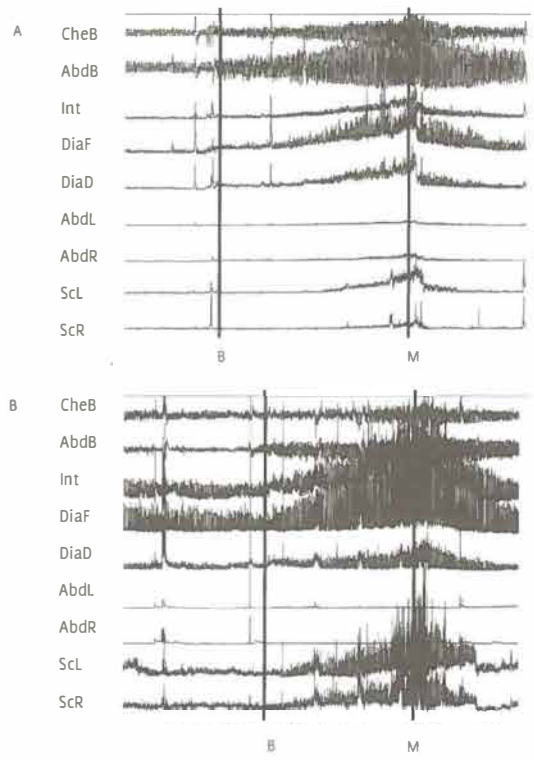

Figure 1.
Total recording (time compressed) of the averaged EMG signals and magnetometer band signals during quiet breathing and during exercise of a representative healthy subject (A) and a representative COPD patient (B).
CheB: chest magnometer band; AbdB: abdominal magnometer band; Int: intercostal muscles; DiaF: frontal diaphragm; DiaD: dorsal diaphragm; AbdL: left abdomen; AbdR: right abdomen; ScL: left scalene muscle; ScR: right scalene muscle. B: Beginning of the exercise test; M: Maximal effort. Before the test, the COPD patient showed higher respiratory activity in the scalene muscles, the intercostal muscles, and the diaphragm compared to the healthy subject. Abdominal activity was low in both subjects. During exercise, respiratory activity increased in both the COPD patient and in the healthy subject. However, the COPD patient showed higher activity in all muscles except for the Abd, where the activity in the healthy subject was higher.

Scalene muscles

In the COPD patients, scalene activity increased progressively as from 1/3 of total exercise time (stage 2). In the HS, scalene activity was increased only at maximum exercise (stage 4). Scalene muscle activity was more increased in the COPD patients compared to the HS at 1/3 (stage 2) and at 2/3 of total exercise time (stage 3).

Respiratory muscles contributions

In the COPD patients, at stage 4, intercostal and scalene activity were increased more than diaphragm activity (median intercostal activity increase by a factor 3.3 (IQR 2.4 - 4.0; $p<0.01$); median scalene activity increase by 3.6 (IQR 2.2 – 5.0; $p<0.01$) vs. median diaphragm activity increase by 2.6 (IQR 2.0 – 3.9)).

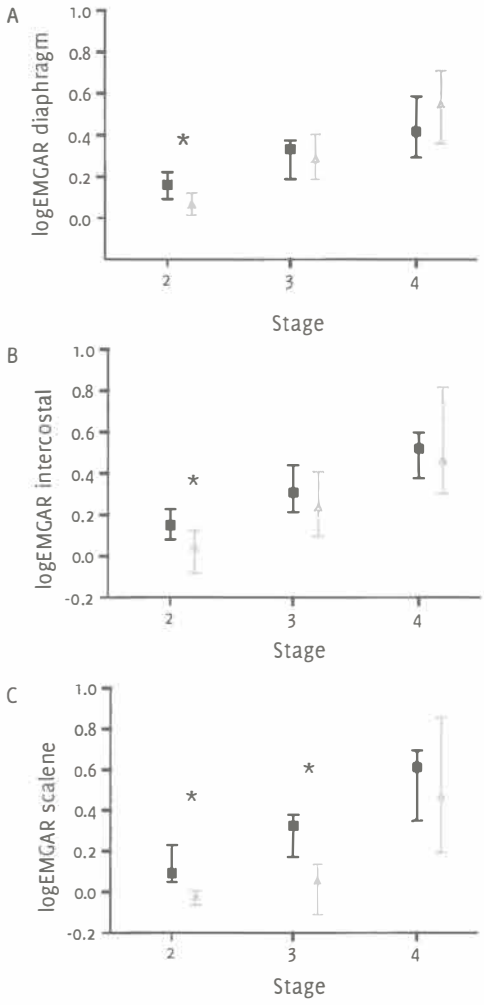

Figure 2.
LogEMGAR diaphragm (A), intercostals muscles (B), and scalene muscles (C) per exercise stage in COPD patients (black squares) and HS (grey triangles). Plots display median and interquartile range. * Significant difference between COPD and HS at the marked stage.

Relationship logEMGAR and dyspnoea

There was a relationship between logEMGAR of the scalene, intercostal muscles, and diaphragm and dyspnoea sensation, both in the COPD patients and HS ($p<0.001$). With a doubling of the scalene, intercostal, and diaphragm logEMGAR, the Borg dyspnoea score increased respectively by 1.7 points (95% CI 0.7-2.7), 2.4 points (95% CI 1.3-3.5) and 3 points (95% CI 1.8-4.4) more in the COPD patients compared to the HS (all $p<0.001$; Figure 3).

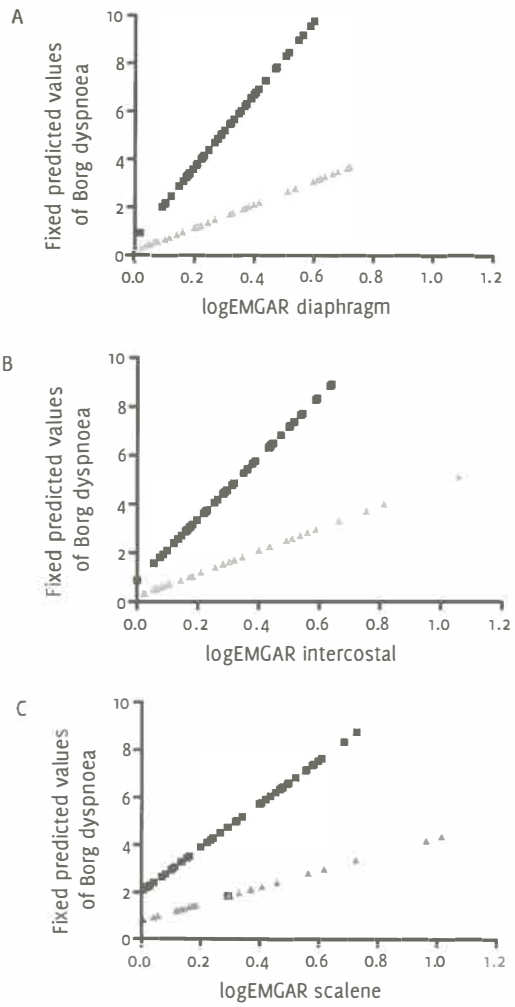

Figure 3.
Changes in Borg dyspnoea scores with logEMGAR diaphragm (A), intercostals (B) and scalene muscles (C) for COPD patients (black) and HS (grey) (results of mixed model for change).
Borg dyspnoea scores increased significantly with increasing logEMGAR and the rate of change was significantly higher in the COPD patients compared to HS.

Neuroventilatory coupling

In the COPD patients, inspiratory activity increased more than V_T during the successive stages compared to baseline. Therefore, the index of NVC for all inspiratory muscles increased during exercise from stage 3. For the intercostal muscles and the diaphragm, the NVC ratio was increased at stage 3 (by a factor 1.3 (IQR 1.0 - 1.4; $p<0.02$) and by 1.2 (IQR 1.0 - 1.5; $p<0.04$) respectively) and stage 4 (by a factor 1.8 (IQR 1.2 - 2.5; $p<0.001$) and by 1.4 (IQR 1.0 - 2.1; $p<0.01$) respectively). For the scalene muscles, the NVC ratio was markedly increased at stage 4 (by 2.0 (IQR 1.2 - 3.2; $p<0.002$)) compared to baseline.
In the HS, inspiratory activity increased but V_T increased much more. Therefore, the

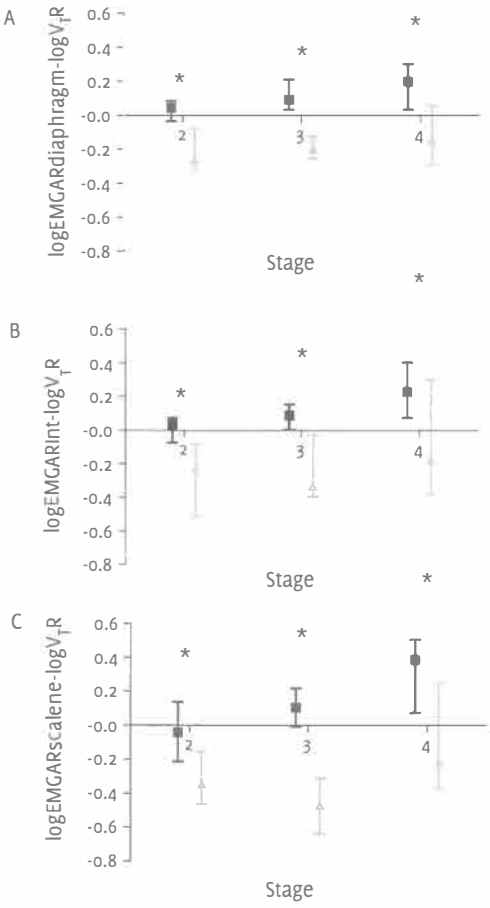

Figure 4.
Change in neuroventilatory coupling index (logEMGAR-logV$_T$R)from quiet breathing per exercise stage in COPD patients (black squares) and HS (grey triangles).
Plots display median and interquartile range. * Significant differences between COPD and HS at the marked stage.

index of NVC decreased during exercise. For both the scalene muscles, the intercostal muscles, and the diaphragm, the NVC ratio was decreased at stage 2 (by a factor 2.0 (IQR 1.1 - 3.3; $p<0.01$), by 1.8 (IQR 0.7 - 3.8; $p<0.02$), and by 1.7 (IQR 0.9 - 2.9; $p<0.01$) respectively), and at stage 3 (by a factor 2.6 (IQR 0.5 - 5.6; $p<0.01$), by 1.8 (IQR 0.7 - 3.0; $p<0.02$), and by 1.5 (IQR 1.2 - 2.0; $p<0.01$) respectively). At stage 4, the decrease was not significantly different from baseline (Figure 4).

DISCUSSION

This study shows that COPD patients increase the EMG activity of the scalene and intercostal muscles early during exercise and, at peak exercise, more than diaphragm activity. In contrast, in healthy subjects, diaphragm EMG activity dominated and recruitment of the intercostals and scalene muscles occurred only at higher exercise

levels. Secondly, this study shows that increased EMG activity was associated with increases in dyspnoea sensation. Finally, this study shows that the ratio between EMG activity and volume displacement by the lungs is increased in COPD compared to healthy subjects.

With the presented surface EMG technique, signals can be obtained easily, without any discomfort to the patient. The technique has been shown to be a sensitive and reproducible method in COPD during breathing though an inspiratory threshold [8]. As far as we know this is the first study assessing activity of the separate inspiratory muscles simultaneously during incremental cycle exercise in COPD.
Inspiratory muscle function in COPD during exercise has been assessed before. However, most studies focussed on diaphragm pressure generation, and not on EMG, which is a measure of neural drive. Two studies that did measure EMG, although only of the diaphragm, showed conflicting results. Sinderby et al. found that diaphragmatic electrical activity, measured with an oesophageal catheter, increased progressively during incremental cycle exercise [3]. In contrast to these results, Luo et al. found that diaphragm EMG reached a plateau after 40% of exercise time [15]. In the study of Luo, participants exercised on a treadmill, probably resulting in different exercise patterns and thus different EMG activity patterns [15]. As we analysed the EMG signals only at three time points (1/3, 2/3 and maximum), finding a true plateau was not possible. We found that the increase in intercostal and scalene activity from stage 3 to peak exercise was much larger compared to the diaphragm. Although diaphragm neural drive kept increasing, it seemed to a lesser extent than the drive directed to the scalene and intercostal muscles. This indicates that inhibition of the neural drive to the diaphragm but not to the other inspiratory muscles indeed occurred.
As most studies focused on the diaphragm, little is known about inspiratory muscle activity of the scalene and intercostal muscles during exercise in COPD. It was shown that the pressure contribution of the scalene and intercostal muscles increases during exercise relative to diaphragm contribution [4]. We found that, during exercise, COPD patients also increase their neural drive directed to the scalene and intercostal muscles more than that directed to the diaphragm.

There was a significant relationship between neural drive and dyspnoea in both groups. Interestingly, in the COPD patients, at similar increases in neural drive, dyspnoea sensation increased more as compared to the HS. Probably, the occurrence of neuroventilatory dissociation in COPD patients contributed to this phenomenon. However, patient expectations, anxiety, changes in breathing pattern, arterial blood gases, and circulatory factors are all known to influence dyspnoea [16].

In patients with COPD, dynamic hyperinflation causes a mechanical limitation to expand V_T so that the outgoing motor command is higher compared to the pressure produced and eventually the volume displaced by the respiratory system. O'Donnell found that the ratio between inspiratory effort and the tidal volume displaced by the lungs was increased in COPD patients compared to age-matched controls throughout

exercise [13]. In line with this study, we found increased NVC ratios in COPD compared to healthy controls. As in COPD patients the motor command is usually higher than the produced inspiratory pressures especially at higher exercise levels [3], we had indeed expected that the increase in NVC ratio was even higher in our study [13].

Surface EMG measurements have been criticised for several reasons. Firstly, there may be a variable muscle-to-electrode distance, caused by a variable amount of subcutaneous fat between the participants. However, constant factors within patients (such as the amount of subcutaneous fat) that influence the amount of electrical activity were reduced to unity by using the ratio between the averaged electrical muscle activity at a given moment during the cycle test and that at baseline (EMG activity ratio). For "baseline" signals we choose the EMG signals measured while the participant was already on the bicycle, just before the participant started to cycle. Most authors relate their EMG signals to the signals obtained during maximal diaphragm activation. However, in inexperienced subjects the maximal manoeuvres have high coefficients of variation between different manoeuvres. This limits the use of values of the signals during these maximal manoeuvres as "baseline" [3]. From our results, many of which showed significant differences between COPD and healthy controls, it is clear that we succeeded in reducing variability to an acceptable degree.
Secondly, the method has been criticised because increases in lung volume (hyperinflation) might artificially increase diaphragmatic and intercostal EMG activity [17]. However, Beck et al. showed that voluntary diaphragmatic EMG activity, although measured with oesophageal electrodes, was not influenced by changes in lung volume at submaximal contraction levels [18]. Next to this, in a study in asthmatic patients employing the same surface EMG method we used, histamine induced increases in lung volumes and thereby increases in tonic activity of the respiratory muscles had only a minor influence on the mean peak-to-bottom EMG activity [19]. The last reason why we believe hyperinflation did not affect our results is that at peak exercise, diaphragmatic EMG activity tended to be increased more in HS compared to the COPD patients. As hyperinflation is expected to occur in the COPD patients and not in HS, the signals are expected to be artificially heightened in the COPD patients. Thus also if artefacts occurred, this would not affect our conclusion that, diaphragmatic activity increases more in the HS compared to the COPD patients at peak exercise.
The third reason why surface EMG measurements has been criticised is that surface EMG signals could be contaminated by electrical activity derived from adjacent muscles, such as abdominal and back muscle activity. We believe signal contamination, especially for the diaphragm and intercostals, was minimal in our study for the following reasons. Firstly, we controlled body posture. The participants were seated a semi-upright position, while the back and head of the patient were supported and the arms were in a steady, constant position. Secondly, tonic activity necessary to maintain body position would not influence the peak-to-bottom electrical activity substantially, as activities are vectorially summed. Therefore, the peak activity would override the tonic activity.

Thirdly, if back muscles and abdominal muscles would influence diaphragm activity, one would have picked up electrical activity in a rhythmic cycle pattern. We did not find such rhythmic activity. Next to postural activity, expiratory abdominal muscle activity increases as a result of dynamic hyperinflation [20]. However, as this activity is expiratory in action [21], we could separate those signals from our inspiratory signals. Scalene muscle activity might be influenced by sternocleidomastoid activity. Although we instructed the participants to look straight forward, and supervised this closely during the test, adjacent neck muscles could possibly have influenced the scalene signals, especially at high exercise levels. This might explain the larger variance in these signals at maximum exercise.

In summary, we found that COPD patients, in contrast to healthy subjects, increase their neural drive to the inspiratory muscles already at very low exercise levels during incremental exercise. While at higher exercise levels healthy subjects mainly increase the drive to their diaphragm, COPD patients recruit their accessory inspiratory muscles. Increases in neural drive were associated with increasing dyspnoea perception. Interestingly, at similar increases in neural drive the increase in Borg score was higher in the COPD patients compared to the healthy subjects. The disproportionately high drives COPD patients generate to achieve (still insufficient) tidal volumes are probably responsible for the exaggerated dyspnoea sensation. Improving insight into the activity patterns of respiratory muscles in an easy noninvasive manner can help us to develop and evaluate therapeutic options in COPD, such as exercise protocols and medication effects.

REFERENCES

1. Polkey MI. Muscle metabolism and exercise tolerance in COPD. *Chest* 2002; 121 (5 Suppl): 131-5.
2. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 154: 1310-7.
3. Sinderby C, Spahija J, Beck J, Kaminski D, Yan S, Comtois N, Sliwinski P. Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1637-41.
4. Yan S, Kaminski D, Sliwinski P. Inspiratory muscle mechanics of patients with chronic obstructive pulmonary disease during incremental exercise. *Am J Respir Crit Care Med* 1997; 156: 807-13.
5. Mador MJ, Kufel TJ, Pineda LA, Sharma GK. Diaphragmatic fatigue and high intensity exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 118-23.
6. Polkey MI, Kyroussis D, Keilty SE, Hamnegard CH, Mills GH, Green M, Moxham J. Exhaustive treadmill exercise does not reduce twitch transdiaphragmatic pressure in patients with COPD. *Am J Respir Crit Care Med* 1995; 152: 959-64.
7. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518-624.
8. Duiverman ML, van Eykern LA, Vennik PW, Koëter GH, Maarsingh EJW, Wijkstra PJ. Reproducibility and responsiveness of a noninvasive EMG technique of the respiratory muscles in COPD patients and in healthy subjects. *J Appl Physiol* 2004; 96: 1723-9.
9. Sprikkelman AB, van Eykern LA, Lourens MS, Heymans HSA, van Aalderen WMC. Respiratory muscle activity in the assessment of bronchial responsiveness in asthmatic children. *J Appl Physiol* 1998; 84: 897-901.
10. Maarsingh EJ, Oud M, van Eykern LA, Hoekstra MO, van Aalderen WM. Electromyographic monitoring of respiratory muscle activity in dyspneic infants and toddlers. *Resp Physiol Neurobiol* 2006; 150: 191-9.
11. Maarsingh EJW, van Eykern LA, Sprikkelman AB, Hoekstra MO, van Aalderen WMC. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. *J Appl Physiol* 2000; 88: 1955-61.
12. Mahler DA. Mechanisms and measurement of dyspnea in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; 3: 234-8.
13. O'Donell DE, Hamilton AL, Webb KA. Sensory mechanical relationships during high intensity constant work rate exercise in COPD. *J Appl Physiol* 2006; 101: 1025-35.
14. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 1995; 152: 77S-121S.
15. Luo YM, Moxham J. Measurement of neural respiratory drive in patients with COPD. *Respir Physiol Neurobiol* 2005; 146: 165-74.
16. Grazzini M, Stendardi L, Gigliotti F, Scano G. Pathophysiology of exercise dyspnea in healthy subjects and in patients with chronic obstructive pulmonary disease. *Respir Med* 2005; 99:1403-12
17. De Troyer A, Leeper B, McKenzie DK, Gandevia SC. Neural drive to the diaphragm in patients with severe COPD. *Am J Respir Crit Care Med* 1997; 155:1335-40.
18. Beck J, Sinderby C, Lindström L, Grassino A. Effects of lung volume on diaphragm EMG strength during voluntary contractions. *J Appl Physiol* 1998; 85: 1123-34.
19. Maarsingh EJW, Eykern van LA, Sprikkelman AB, Aalderen van WMC. Histamine induced airway response in pre-school children assessed by a noninvasive EMG technique. *Respir Med* 2004; 98: 363-72.
20. Ninane V, Yernault JC, de Troyer A. Intrinsic PEEP in patients with chronic obstructive pulmonary disease. Role of expiratory muscles. *Am Rev Respir Dis* 1993; 148: 1037-42.
21. Ninane V, Rypens F, Yernault JC, de Troyer A. Abdominal muscle use during breathing in patients with chronic airflow obstruction. *Am Rev Respir Dis* 1992; 146:16-21.

SUPPLEMENTARY MATERIAL

EMG electrodes

The electrical activity of the intercostal muscles (Int), frontal diaphragm (FD) and dorsal diaphragm (DD) were derived transcutaneously from pairs of single disposable electrodes (Neotrode, Conmed Corporation, New York, USA). For the common or ground electrode the same disposable electrode was used. Electrical activity of the scalene muscles (Sc) and the abdominal muscles (Abd) were derived transcutaneously from reusable bipolar electrodes formed by two narrow rim electrodes housings, each containing a 4 mm Ag-AgCl sintered electrode pallet (In Vivo Metrics, Healdsburg, USA), interconnected with a plastic clip (homemade UMCG, Groningen, The Netherlands) at a distance of 14 mm. After filling the electrode cavity with electrode gel (IVM) the assembly was fixed to the skin by means of double sided adhesive disc washers (IVM). All electrodes were provided with shielded low noise cables.

Electrode placement

To obtain electrical activity of the Int, the electrodes were placed bilaterally in the second intercostal space, about 3 cm parasternal. To obtain frontal diaphragmatic activity, one pair of electrodes was placed bilaterally on the costal margin in the nipple line. Dorsal diaphragmatic activity was obtained by the placement of one pair of electrodes bilaterally on the back at the level of the diaphragm, in the vertical line of the angulus inferior of the scapula. Bipolar electrode pairs were placed on the neck: one pair over the right and one pair over the left scalene. The EMG signals of the rectus abdominis muscle were also derived from bipolar electrode pairs: one pair on the right and one pair on the left side, 4 cm apart, at the level of the umbilicus. A common (ground) electrode was placed at the level of the sternum.

Supplement on Data Acquisition and Pre-processing

Data Acquisition

The electrodes were connected to a Porti-16 front-end (Porti-X, Twente Medical Systems International, Enschede, The Netherlands), which allows for the acquisition of electrophysiological signals (Electro-X-Gram, EXG) and of physical signals (auxiliary, AUX)

The Porti-16 sports an analogue part for conditioning the electrode signals and a digital part for analogue to digital conversion (ADC) connected to a Digital Signal Processor for signal management, local storage and data transport to a Personal Computer. The analogue part contains a Reference Amplifier with an input impedance is > 2 GΩ. The electrode-specific part of the electrode signal is amplified with a gain of 20 and the mean of all electrode signal of the electrode ensemble with unity gain. The true DC analogue data was sampled at 400 Hz by means of a 22 bits Sigma Delta ADC. The over-sampling technique used in this type of converters enables the use of digital anti-aliasing filters before sub-sampling at 400 Hz.

The EXG-signal was transformed into an EMG-signal by means of a digital first order high pass filter (Time Constant TC = 0.01 s), as an electro-physiological signal is characterized by the position of the electrodes in relation to the electrically active tissue and its signal properties. Respiratory movements were obtained by connecting two magnetometer respiration (MR) bands (one placed around the thorax and one around the abdomen) to the AUX-inputs and were used for measuring a reference respiration signal (Respiband, SensorMedic, Bilthoven, The Netherlands).

EMG Pre-processing

Electrical heart activity, which interferes with diaphragm EMG signals, was removed according to the process described in Figure 1 of the data supplement.
All data recording, processing, analysis, and reporting were conducted by the POLY 5.0 data-acquisition and processing package (Inspektor Research Systems, Amsterdam, The Netherlands).

EMG Processing

To determine the peak and bottom values of the respiratory EMG, the averaged EMG signals were re-sampled at 10 Hz in streaming amplitude histograms with a time window of 30 seconds. Every 10 seconds the 5th and 95th percentiles were calculated serving as the bottom (5^{th}) and peak (95^{th}) values of the respiratory EMG during the previous 30 seconds. The differences between the peak and bottom values were reported as the mean peak-to-peak values.

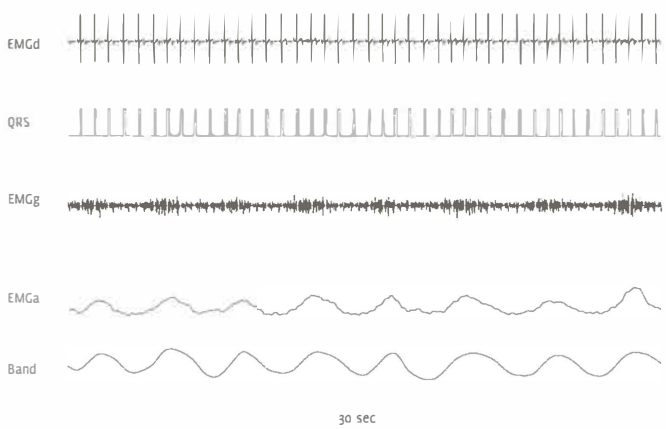

Figure 1 Data supplement. The QRS removal process.
Data supplement: The averaged EMG (EMGa) shows respiratory activity. As control the signal from the abdominal magnetometer band (Band) is shown. From the diaphragmatic EMG signal (EMGd) the QRS complex was detected and stretched into a standard QRS pulse with a duration of 100 ms (QRS). During the QRS pulse a cut was made in the slightly delayed (40 ms) EMG signal, to completely filter out the QRS complex (EMGg). Next, the gated EMG was rectified and averaged with a moving time window of 200 ms. Finally, the missing signal in the gate was filled with the running average resulting in a fairly good interpolation during the gate and an almost QRS-free averaged EMG signal.

THE ASSESSMENT AND TREATMENT OF PATIENTS WITH RESPIRATORY FAILURE

CHAPTER

4

Home mechanical ventilatory support in patients with restrictive ventilatory disorders: a 48-year experience

Respir Med. 2006; 100: 56-65

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ABSTRACT

Purpose and methods: We performed a retrospective analysis to the effects of negative pressure ventilation (NPV), tracheal intermittent positive pressure ventilation (TIPPV), and nasal intermittent positive pressure ventilation (NIPPV, volume or pressure-controlled ventilatory mode), in 114 patients with restrictive ventilatory disorders instituted in our hospital from 1956 until 2005. The patients were assigned on "ad hoc" basis to NPV, TIPPV, or NIPPV.

Results: All patients were subdivided in an idiopathic kyphoscoliosis group (IK, n = 64), post-poliomyelitis syndrome group (PP, n = 30), or a miscellaneous group (M, n = 20). The patients in the PP group had higher survival rates compared to the IK patients ($p<0.05$), while the M patients had the lowest survival rates ($p<0.01$). Both NPV ($p<0.01$) and TIPPV ($p<0.05$) lead to a decrease in $PaCO_2$ after nine months compared to baseline. This decrease in $PaCO_2$ was still present after five years NPV ($p<0.001$) and TIPPV ($p<0.05$). NIPPV resulted in significant improvements in pulmonary function ($p<0.05$) and arterial blood gases ($p<0.001$) after 9 months compared to baseline. After five years NIPPV, arterial blood gases were still significantly improved compared to baseline ($p<0.01$). Both volume-controlled and pressure-controlled ventilation improved pulmonary function and arterial blood gases.

Conclusions: Long-term home mechanical ventilatory support by both negative pressure ventilation and positive pressure ventilation is effective in patients with idiopathic kyphoscoliosis, post-poliomyelitis syndrome, and a miscellaneous group, even after a period of five years.

INTRODUCTION

Restrictive ventilatory disorders are characterised by a reduced chest wall compliance and mechanical disadvantage of the respiratory muscles, leading to a decrease in respiratory function and an increase in the work of breathing. Therefore, patients with restrictive ventilatory disorders will adopt a pattern of rapid, shallow breathing, which may result in chronic alveolar hypoventilation. During sleep, there is a progressive fall in minute ventilation exaggerating the hypoventilation. As a consequence, these patients develop hypercapnia, firstly during sleep, and finally in wakefulness [1]. Eventually, respiratory failure may occur, which makes chronic ventilatory support necessary [2].

Home mechanical ventilation (HMV) has been used for more than sixty years now in a variety of disorders. Several methods have been used: firstly only negative pressure ventilation (NPV) was available, later on tracheal intermittent positive pressure ventilation (TIPPV) appeared, and finally nasal intermittent positive pressure ventilation (NIPPV) became available.

NPV devices are cumbersome to use and may lead to insufficient ventilation due to an inadequate covering of the chest wall surface and the abdomen. In our hospital we solved this problem by using a specially designed tailor made shell [3]. Despite the disadvantages of NPV, it has shown beneficial effects in patients with a variety of pulmonary disorders, including patients with restrictive ventilatory disorders [4-8].

TIPPV has been shown to be effective in patients with restrictive ventilatory disorders [9-10]. Although the use of TIPPV is limited by drawbacks such as disfigurement, difficulties associated with phonation, risk of infection, and the burden of tracheotomy care, this therapy is nowadays still prescribed to obtain adequate ventilatory support.

NIPPV is nowadays the most frequently used mode of ventilatory support in patients with restrictive ventilatory disorders. Several studies have shown the benefits of NIPPV in terms of improvement in daytime arterial blood gas tensions, relief of nocturnal hypoventilation and its symptoms, improvement of health-related quality of life, and improved survival [11-28]. At the introduction of NIPPV, only volume-controlled ventilators were available. Later, pressure-controlled and bilevel pressure-controlled ventilation became available as well. Only a few studies have compared the effects of volume-controlled versus pressure-controlled ventilation [19, 30, 31].

However, a number of issues are remarkable from the above mentioned studies. Firstly, many of them only monitored the effects of noninvasive ventilatory support, while invasive ventilation is still being used in a considerable number of patients. Secondly, most studies assessed the effect of ventilatory support for a short period. Finally, patients with a variety of different disorders were placed and analysed in the same group to increase the number of patients in the study groups.

In our hospital we have been using HMV since 1956 in a variety of disorders. For this study, we selected the patients with kyphoscoliosis, post-poliomyelitis syndrome, and other restrictive ventilatory disorders for analysis of the effects of HMV, as we have been able to build up long-term experience with HMV in a large number of patients with restrictive ventilatory disorders.

Therefore, the aim of the study was: a) to describe the development of HMV in our hospital, and b) to assess the effects of NPV, TIPPV, and NIPPV on pulmonary function, arterial blood gas tensions, and survival in patients with kyphoscoliosis, post-poliomyelitis and miscellaneous restrictive ventilatory disorders. Therefore, we set up a retrospective analysis including all 114 patients with restrictive ventilatory disorders who received ventilatory support in our hospital from 1956 until 2005.

METHODS

Patients

Data were collected from all patients who received HMV initiated at our department of HMV from 1956 until 2005. From this population we selected patients with idiopathic kyphoscoliosis (IK), post-poliomyelitis syndrome (PP), and other restrictive ventilatory disorders (miscellaneous (M)) for analysis of the effects of HMV.

Ventilatory equipment and monitoring

Patients were ventilated by NPV, TIPPV, or NIPPV. NPV was delivered by means of a chest respirator with tailor made shell [3]. TIPPV was delivered by means of volume or pressure ventilation. NIPPV was delivered via nasal or full face mask, either by a volume-controlled ventilator (Monnal D, Taema, Antony Cedex, France; Lifecare PLV 100, Respironics, Murrysvile, USA; Breas PV 501, Breas Medical, Mölndal, Sweden), or a pressure-controlled ventilator (bilevel pressure (BilevelPAP; Puritan Bennet PB 335, Respironics, Murrysville, USA; Respironics Synchrony, Respironics, Murrysville, USA) or pressure-controlled (PCV; Airox VP 2000, Beaumont, Migennes, France; Breas 401, Breas Medical, Mölndal, Sweden)). Although nowadays we have the choice between volume-controlled or pressure-controlled ventilators, in the past, the decision to implement a particular mode of ventilation was dependent on the availability of the ventilator in the market at the moment patients were instituted.

All patients were instituted on ventilatory support in the hospital. The indication for chronic ventilatory support was either chronic stable or progressively deteriorating respiratory failure unresponsive to other treatment options, both in combination with symptoms such as increasing shortness of breath on exertion, tiredness, and sleepiness.

Ventilator settings were determined at baseline and adjusted depending on arterial blood gas tensions. Before 1990, we measured arterial blood gas tensions at rest during the day. Since 1990, we performed an arterial blood gas registration in the hospital during the night, initially without the ventilator, and after the patients were able to tolerate the ventilation for at least 6 hours a night, with the ventilator. Thereafter they were discharged and followed at the outpatient clinic. After two months we performed another overnight arterial blood gas registration while on the ventilator and adjusted ventilator settings as necessary. Furthermore the patients were monitored every six

months, including pulmonary function tests, daytime arterial blood gas levels (ABG), and end-tidal CO_2 measurements.
Supplemental oxygen was provided in patients in whom arterial oxygen saturation remained low (saturation < 90%) despite optimal ventilator settings.

Data collection and analysis

We collected the following data: birth date, sex, primary and secondary diagnoses, indication for initiating ventilatory support, date of starting and ending ventilatory support, mode of ventilatory support, oxygen need, and prescribed hours of ventilatory support. Furthermore, we collected data on pulmonary function, nocturnal and daytime arterial blood gas analyses, and dependency in activities of daily living just before ventilatory support was initiated (baseline) and after 9 months, 1 ½ year, 3 years, and then every two years after initiating ventilatory support. Arterial blood gas tensions were obtained while the patients were breathing room air without ventilation.

Statistical analysis

Survival rates were calculated and compared between the three diagnostic groups by using the method of Kaplan-Meier and log rank tests. Differences in the age at start between the diagnostic groups (IK, PP, and M) were assessed by a Kruskal Wallis test; differences in baseline arterial blood gases and pulmonary function were assessed by one way analysis of variance.
We compared baseline arterial blood gases and pulmonary function with the values obtained after nine months (short-term effects) and to those after five years (the long-term effects) by multiple linear regression of repeated measurements. Patients who dropped out and patients from whom only incomplete data could be collected were excluded from these analyses.
Differences in baseline parameters between patients ventilated by volume-controlled and pressure-controlled NIPPV were assessed by Wilcoxon sign rank tests. In the patients receiving volume-controlled and pressure-controlled ventilation, we compared baseline arterial blood gases and pulmonary function with the values obtained after nine months by Mann-Whitney U tests.

RESULTS

HMV at the University Medical Center Groningen

From 1956 until January 1, 2005, we instituted 433 patients with a wide variety of disorders on HMV at our hospital. We instituted patients with restrictive ventilatory disorders (idiopathic kyphoscoliosis, post-poliomyelitis complicated by kyphoscoliosis, post-tuberculosis); pure neuromuscular disorders (morbus Duchenne,

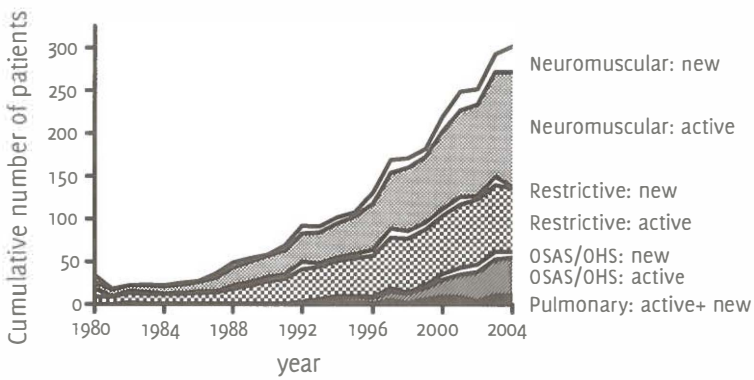

Figure 1. Annual number of patients with pulmonary disorders (pulmonary), restrictive ventilatory disorders (restrictive), neuromuscular disorders (neuromuscular), and patients with the obstructive sleep apnoea syndrome or obesity hypoventilation syndrome (OSAS/ OHS) subdivided into "already active users" (solid area) and "new users" (hatched area) of home mechanical ventilation (HMV) at the University Medical Center Groningen from 1980 until January 1, 2005.

amyotrophic lateral sclerosis (ALS)); pulmonary disorders (COPD patients, cystic fibrosis patients); and patients with an obstructive sleep apnoea syndrome (OSAS) or obesity hypoventilation syndrome (OHS). The treatment prevalence of HMV in the region of the HMV Center Groningen was 5/ 100.000 on January 1, 2000, and 8.5/ 100.000 on January 1, 2005. This increase was mainly caused by a more than 5-fold increase in the number of patients with ALS (2000; 6 active users; 2005: 41 active users) and a more than twofold increase in the number of patients with OSAS or OHS (2000: 20; 2005: 44) (Figure 1).

Characterisation of the study subjects

We selected the patients with IK, the PP syndrome, and other restrictive ventilatory disorders for analysis of the effects of HMV. We subdivided these patients in three groups according to their primary diagnosis. The first group included 64 patients (25 men, 39 women) with IK. The second group included 30 patients (15 men, 15 women) with the PP syndrome. A third group included 20 patients with a miscellaneous restrictive ventilatory disorder. This group consisted of twelve patients (3 men, 9 women) who underwent a thoracoplasty and/or (partial) lung resection for tuberculosis (performed between 1939 and 1953), five patients (3 men, 2 women) who experienced spondylitis tuberculosa, two women with bronchiectasis (one of them underwent a thoracoplasty in 1939), and a woman with atelectase as a result of radiotherapy for lung metastases. This group was called the miscellaneous (M) group. Baseline characteristics of the three diagnostic groups are shown in Table 1.

A total of 48 patients started ventilatory support because of acute on chronic respiratory

Table 1. Number of patients and baseline characteristics all patients per diagnostic group.

Diagnosis	number, n	Acute patients, %	Age at start, years	FEV_1, L	VC, L	PaO_2, kPa	$PaCO_2$, kPa
IK	64	39	56 ± 13.4	0.77 ± 0.27	1.10 ± 0.44	7.44 ± 2.04	7.77 ± 1.72
PP	30	43	50 ± 15.8	0.76 ± 0.35	1.16 ± 0.61	8.33 ± 1.56	7.33 ± 1.34
M	20	50*	64 ± 10.2 **	0.64 ± 0.15	1.09 ± 0.43	8.88 ± 1.81 ***	8.01 ± 2.19

Values are expressed as mean ± SD. FEV_1: forced expiratory volume in 1 sec; VC: vital capacity; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure; IK: idiopathic kyphoscoliosis; PP: post-poliomyelitis syndrome; M: miscellaneous group.
Significant differences: *: M higher than IK ($p< 0.001$); **: M higher than IK ($p< 0.05$) and PP ($p< 0.01$); ***: M higher than IK ($p< 0.05$).

failure (acute patients). For the other patients, ventilatory support was initiated non-emergently because of chronic ventilatory failure with symptoms like shortness of breath on exertion, tiredness, sleepiness, and morning headache (chronic patients). The proportion of patients instituted acutely was higher in the M group than in the IK group. At baseline, the chronic patients had a significantly higher vital capacity (VC; $p< 0.05$), higher daytime PaO_2 ($p< 0.003$), and lower daytime $PaCO_2$ ($p< 0.001$) compared to the acute patients.

Survival and causes of death in three different groups of patients

Figure 2 shows the cumulative survival of patients from the three diagnostic groups receiving ventilatory support. The PP patients had higher survival rates than the IK patients ($p< 0.05$). The M patients group experienced the lowest survival rates ($p< 0.01$) of all groups.

Of the 64 IK patients, 40 patients were still being ventilated at our hospital at the time of the analysis with a median duration 4.5 years (interquartile range 5.4). Twenty IK patients had died after a median duration of 6.3 years HMV (interquartile range 6.6); eleven patients died from respiratory failure, one patient died from esophageal cancer, one patient died from a malignant sarcoma, one patient got a fatal accident, and six patients died from unknown causes. Furthermore, three IK patients were lost from follow-up and one patient decided to end the HMV after one month because of coping problems. We found no significant differences in age at start of ventilation, baseline pulmonary function and arterial blood gas tensions between the IK patients who had died and the IK patients who were still alive at the time of the analysis. However, the IK patients who had died had more frequently been ventilated by TIPPV (25%) or NPV (30%) compared to the IK patients who were still alive at the time of the analysis (TIPPV: 7.5%, NPV: 5%).

Of the 30 PP patients, 21 patients were still being ventilated at the time of the analysis after a median duration of 11.3 years (interquartile range 11.0). Nine PP patients had

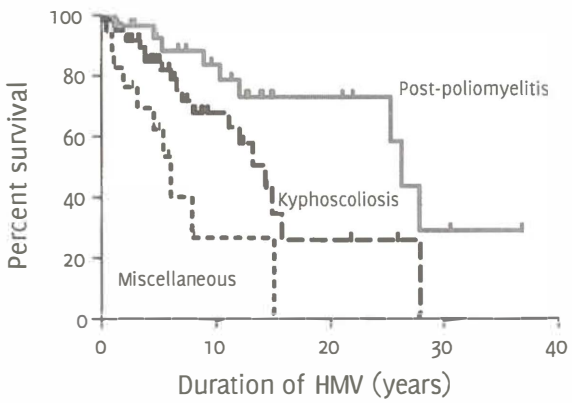

Figure 2. Cumulative survival of idiopathic kyphoscoliosis patients, post-poliomyelitis patients, and patients with miscellaneous restrictive ventilatory disorders, treated by home mechanical ventilation (HMV).

died after a median duration of 10.3 years ventilatory support (interquartile range 20.8); four patients died from respiratory failure, two patients died after surgery for a hip fracture, one patient died from a cerebral haemorrhage, and two patients died from unknown causes. We found no significant differences in age at start of ventilation, pulmonary function, arterial blood gas tensions, or type of ventilatory support at baseline between the PP patients who had died and the PP patients who were still alive at the time of the analysis.

Of the 20 M patients, five patients were still being ventilated at the time of the analysis after a median duration of 5.1 years HMV (interquartile range 3.4). Eleven M patients had died after a median duration of 4.7 years HMV (interquartile range 5.5); three M patients died from respiratory failure, one patient died from a heart attack, two patients died after they became severely depressed and quitted the assisted ventilation voluntarily, and four patients died from unknown causes. Furthermore, three M patients ended the ventilatory support (two NIPPV ventilated patients, one NPV ventilated patient) because of coping problems after a median duration of fourteen months ventilatory support (interquartile range 40), and one patient was lost from follow-up. We found no significant differences in age at start of ventilation, pulmonary function, and arterial blood gas tensions at baseline between the M patients who had died, the M patients who were still alive and the M patients who had stopped because of coping problems. The M patients who were still being ventilated at the time of the analysis were all instituted non-emergently. In contrast, the M patients who had died were more frequently instituted acutely (nine patients instituted acutely, two patients non-emergently).

At baseline, a significantly higher proportion of IK patients (73%) compared to the PP patients (47%) and M patients (40%) was independent in activities of daily living (ADL) ($p < 0.01$). After five years HMV, significantly less IK patients were ADL independent (54%) compared to baseline. In the PP group the proportion of ADL

Table 2. Long-term changes in pulmonary function and arterial blood gases in patients ventilated by NPV, TIPPV or NIPPV.

Ventilatory mode		Baseline	9 months	5 years
NPV	FEV_1, L (n = 7)	0.78 ± 0.49	0.96 ± 0.46	0.93 ± 0.37
	VC, L (n = 7)	1.06 ± 0.66	1.16 ± 0.68	1.23 ± 0.55
	PaO_2, kPa (n = 9)	6.97 ± 1.98	8.79 ± 1.82	8.26 ± 1.76
	$PaCO_2$, kPa (n = 9)	8.58 ± 1.08	6.54 ± 0.88**	6.52 ± 0.69***
TIPPV	FEV_1, L (n = 4)	0.69 ± 0.18	0.74 ± 0.21	0.70 ± 0.24
	VC, L (n = 5)	0.95 ± 0.36	1.08 ± 0.32	1.10 ± 0.43
	PaO_2, kPa (n = 4)	6.89 ± 1.63	9.14 ± 1.73	9.36 ± 1.86
	$PaCO_2$, kPa (n = 6)	9.71 ± 1.97	5.85 ± 0.76*	6.00 ± 0.53*
NIPPV	FEV_1, L (n = 27)	0.81 ± 0.28	0.91 ± 0.31*	0.87 ± 0.27
	VC, L (n = 29)	1.29 ± 0.58	1.42 ± 0.63*	1.39 ± 0.64
	PaO_2, kPa (n = 22)	7.86 ± 1.95	9.60 ± 1.45**	9.39 ± 1.30**
	$PaCO_2$, kPa (n = 29)	7.46 ± 1.37	5.96 ± 0.75***	6.23 ± 0.73***

Values are expressed as mean ± SD. NPV: negative pressure ventilation; TIPPV: tracheal intermittent positive pressure ventilation; NIPPV: noninvasive positive pressure ventilation; FEV_1: forced expiratory volume in 1 second; VC: vital capacity; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure
Significant differences: *: p< 0.05 (compared to baseline); **: p< 0.01 (compared to baseline); ***: p< 0.001 (compared to baseline).

independent patients was not changed (47%) after five years HMV compared to baseline. In the M group only 25% of the M patients was independent in activities of daily living after five years HMV compared to baseline (not significant).

Different types of ventilatory support

NPV

Twenty patients received NPV (nine IK patients, eight PP patients, and tree M patients). Sixteen patients were ventilated with NPV for at least five years (80%). NPV significantly improved $PaCO_2$ after nine months and even after five years HMV (Table 2).
Only one IK patient and one PP patient changed from NPV to TIPPV after 30 and 279 months respectively. One PP patient received 48 months cuirass followed by 32 months NIPPV before he eventually switched to TIPPV. The reason for switching to invasive ventilatory support was deterioration into respiratory failure in all three patients. We found no significant differences in baseline lung function parameters

and baseline daytime or overnight arterial blood gas values between the patients who switched to TIPPV and the patients who remained receiving ventilatory support by NPV.

TIPPV

Sixteen patients received TIPPV (nine IK patients, four PP patients, three M patients). Eleven patients were ventilated by TIPPV for at least five years (69%). TIPPV improved $PaCO_2$ after nine months compared to baseline, and this effect was still evident after five years (Table 2).

Two patients were instituted on TIPPV because of chronic respiratory failure. One of those patients got TIPPV in 1975 while he already received a tracheostoma in 1968 for reducing dead space area of the lungs, while in the other patient TIPPV was used after NIPPV failed because of severe apnoeas during NIPPV. Fourteen patients were instituted on TIPPV after a period of severe acute respiratory failure. This group consisted of six patients in whom NIPPV was tried but failed repeatedly because no improvement in gas exchange could be obtained or because of severe sputum clearance problems, four patients who were set on TIPPV directly after a period of intubation because of expected weaning problems, two patients instituted on TIPPV before NIPPV was available, and two patients who were already tracheostomised in another hospital.

Later on, three patients changed from TIPPV to NIPPV (one patient from the IK group after four months (in 2000) and two patients from the PP group after nine months (in 1993) and fifty-two months respectively (in 1999)). In one other patient an attempt was made to switch to NIPPV, unsuccessful due to anxiety. The other twelve patients stayed on TIPPV. Half of them died before 1986 when NIPPV was not available yet at our hospital. In the other half, because the patients had no complaints about the TIPPV, the decision was made not to change a successful treatment.

NIPPV

Seventy-eight patients received NIPPV (46 IK patients, 18 PP patients, 14 M patients). Thirty-four patients received NIPPV for at least five years (48.6%). NIPPV improved pulmonary function and ABG after nine months compared to baseline, and the improvement in arterial blood gases was still evident after five years NIPPV (Table 2). Only one IK patient switched from NIPPV to TIPPV after twenty-five months because NIPPV could not give a satisfactory relief of his clinical condition.

Volume or pressure support

Of the 78 patients on NIPPV, 27 patients received volume-controlled ventilation (11 IK patients, 12 PP patients, 4 M patients), 17 patients pressure-controlled ventilation (11 IK patients, 2 PP patients, 4 M patients), and 28 patients BilevelPAP (21 IK patients, 4 PP patients, 3 M patients). Data regarding the type of NIPPV were lost in six patients and these patients were excluded from the analyses.

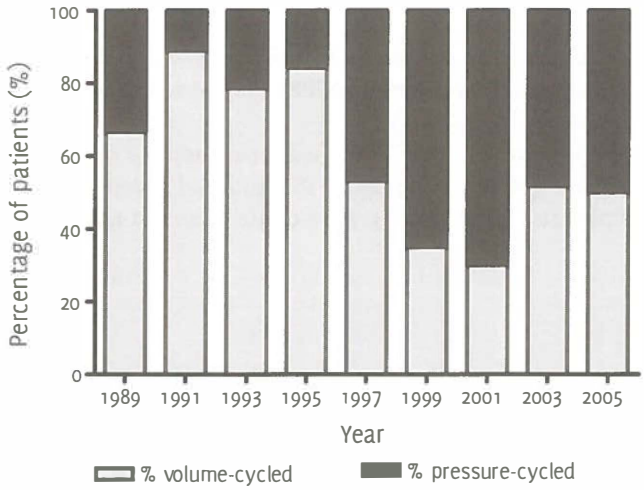

Figure 3. Changes in ventilatory support mode of NIPPV from 1989 until 2005 in the University Medical Center Groningen

Table 3. Changes in pulmonary function and arterial blood gases in patients ventilated by NIPPV by means of the volume-controlled mode or pressure-controlled mode.

		Baseline	9 months
Volume-controlled (n=27)	FEV_1, L	0.59 ± 0.16	0.73 ± 0.29*
	VC, L	1.00 ± 0.47	1.09 ± 0.51
	PaO_2, kPa	8.67 ± 1.96	9.12 ± 1.22
	$PaCO_2$, kPa	7.43 ± 1.49	6.06 ± 0.94***
Pressure-controlled (n= 45)	FEV_1, L	0.88 ± 0.26 ##	0.95 ± 0.26*
	VC, L	1.27 ± 0.47 #	1.39 ± 0.50***
	PaO_2, kPa	7.83 ± 2.07	9.53 ± 1.41***
	$PaCO_2$, kPa	7.38 ± 1.31	5.89 ± 0.44***

Values are expressed as mean ± SD. FEV_1: forced expiratory volume in 1 second; VC: vital capacity; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure. Significant differences: *: p< 0.05 (compared to baseline); ***: p< 0.001 (compared to baseline); #: p< 0.05 (pressure versus volume-controlled); ##: p< 0.001 (pressure versus volume controlled).

Changes in home mechanical ventilatory support modes are shown in Figure 3. The first patients who received NIPPV were instituted in 1989. In the first years mostly volume-controlled ventilation was available. As a relatively large percentage of the patients instituted on NIPPV in the first years were diagnosed with post-poliomyelitis syndrome, most of these patients were instituted on volume-controlled ventilation. These days, there is an almost equal proportion of volume-controlled and pressure-controlled ventilation in our hospital.

The effects on pulmonary function and gas exchange are presented in Table 3. Both volume and pressure-controlled ventilation improved pulmonary function and arterial blood gas tensions.

Daily ventilator use

All the patients used their ventilator during the night. At baseline, several patients used the ventilator during the day as well (10 patients on NIPPV (13%), seven patients on TIPPV (44 %) and three patients on NPV (16%)).
After 1 ½ year, significantly more patients on NIPPV used their ventilator during the day next to overnight use (34% ($p < 0.05$)). In the TIPPV ventilated patients (36%), and in the NPV ventilated patients (27%) the degree of daytime use did not change significantly.

DISCUSSION

The present study illustrates that both invasive and noninvasive HMV are effective in terms of short-term and long-term improvement of pulmonary function and arterial blood gas tensions in patients with kyphoscoliosis, post-poliomyelitis syndrome, and miscellaneous restrictive ventilatory disorders. Furthermore, the study demonstrates that volume-controlled ventilation and pressure-controlled ventilation are equally effective in improving pulmonary function and arterial blood gas tensions in patients with restrictive ventilatory disorders.

In this study, we selected the patients with restrictive ventilatory disorders to analyse the effects of HMV. Last years, the number of patients on HMV in the area covered by the department of HMV of the University Medical Center Groningen has increased. These data agree with data from Sweden [32]. This increase in prevalence is mainly due to an increase in the number of patients with neuromuscular disorders, such as ALS, and patients with OSAS/ OHS that were instituted on HMV. However, because the restrictive ventilatory disorder group has remained relatively constant over several years now, we have been able to build up long-term experience with HMV in a large number of patients.

The idiopathic kyphoscoliosis patients and the post-poliomyelitis patients showed survival rates of 84% and 93% after five years respectively. These survival rates are comparable to previous studies in these patients [16-18]. The miscellaneous group showed a significantly worse survival rate of 62% after five years compared to the IK and PP patients. The worse survival rate of the M patients can partly be explained by the older age at the start of HMV in these patients compared to the IK and PP patients. Furthermore, it is important to note that the M patients were mainly patients who experienced tuberculosis and therefore had an underlying intrinsic lung disease [33 35]. In the study of Jackson et al [6], patients who underwent a thoracoplasty had a 5-years survival rate of 64%, which is comparable to the survival of our M group.
Two patients in our M group suffered from bronchiectasis. Although it has been shown that patients with bronchiectasis have very low survival rates [17, 18], the two bronchiectasis patients of the M group in our study had a moderate survival rate. One

patient who initiated cuirass at age forty-seven died after sixteen years of ventilatory support, the other patient who initiated NIPPV at age seventy died after nine years ventilatory support. The long survival of these patients tells us that not all patients with bronchiestasis are bad candidates for chronic ventilatory support.

NPV

Several studies have shown benefits from long-term home NPV in patients with restrictive ventilatory disorders [4-7]. However, direct comparisons between NPV and NIPPV are rare. Baydur et al. described the outcomes of seventy-nine patients receiving home ventilation by NPV or NIPPV. They found that in twenty-five patients with poliomyelitis, VC and $PaCO_2$ did not change significantly on body ventilation (tank or shell) and that NIPPV resulted in better outcomes in terms of a decreased number of tracheotomies and a better survival rate compared to NPV [24]. We did find an improvement of pulmonary function and ABG and, although in the IK group there seemed to be a survival benefit for the NIPPV ventilated patients, we did not find a difference in overall survival rates between the patients on NPV and those on NIPPV. Furthermore, in our study only two patients on NPV switched to TIPPV (10%) compared to 56% in the study of Baydur.

However, patient characteristics and diagnoses of the patients were different in the study of Baydur and in our study. Secondly, as more than half of Baydur's patients was instituted on ventilatory support during the primary phase of poliomyelitis at a young age, the duration of NPV in the study of Baydur (mean 24 years) was far longer than in our study (mean 12.5 years). This might explain the high number of tracheostomies in the study of Baydur, compared to our study.

On the basis of outcomes in terms of physical effects, no conclusion can be drawn about superiority of NPV or NIPPV. However, because of the difficult and cumbersome use of NPV, nowadays NIPPV tends to be the first choice. Our study again shows that NPV can be effective in restrictive ventilatory disorders. This supports the idea that NPV remains a second choice to be used in patients whom, for technical or other reasons, can not be offered NIPPV [36].

TIPPV

In our study, twenty patients started with TIPPV. Most of our patients on TIPPV required this type of ventilation because of acute on chronic respiratory failure which could not be controlled by NIPPV or because of uncontrollable sputum clearance problems. However, with the availability of a variety of nasal and mouth interfaces, coughing techniques and machines, it became increasingly possible to use NIPPV instead of TIPPV, even in acute situations. In the period from 1997-2005, only one post-poliomyelitis patient eventually required chronic TIPPV, because of deteriorating blood gasses and a deteriorating clinical condition on NIPPV.

Three of the patients on TIPPV changed successfully to NIPPV. In two other patients, severe sputum clearance problems and anxiety for not being adequately ventilated

at night, hindered a successful switch to NIPPV. The patients required TIPPV in the acute situation but were in a stable condition at the time of the switch. In the future, we should try to switch more tracheostomal ventilated patients to NIPPV when their condition has stabilised, as NIPPV has many advantages over TIPPV. Nevertheless, as TIPPV has shown a high degree of effectiveness in patients with a restrictive ventilatory disorder, it still remains a good alternative for some patients.
Our results agree with the study of Zaccaria et al, who found that in patients with respiratory insufficiency who were treated by TIPPV arterial blood gasses improved to a same degree than in patients treated by NIPPV. Furthermore, they found that these effects were still evident after one year of ventilation [10].

NIPPV

Several studies have shown that NIPPV is effective in patients with restrictive ventilatory disorders [11-28]. In our study, NIPPV improved ABG and pulmonary function, and these positive effects were significant even after of five years ventilatory support. Only one patient with chronic hypoxia, pulmonary hypertension, and heart failure changed to TIPPV after twenty-five months of NIPPV because severe air leakage hindered an adequate oxygenation.
Several potential mechanisms are postulated to explain the effects of NIPPV. It may improve the mechanical properties of the thorax, it may "rest" the respiratory muscles, and it may improve respiratory drive [31, 37]. We can only suggest that, in our patients, NIPPV worked through improving the mechanical properties of the thorax (as we did find a small improvement in VC and FEV_1), probably in combination with another mechanism mentioned above. However, we did not measure respiratory muscle strength, respiratory muscle activity, or CO_2 sensitivity.
According to the Conference Consensus of 1999, daytime hypercapnia in combination with symptoms of shortness of breath on exertion, tiredness, sleepiness, and ankle swelling is the primary indication for starting NIPPV [38]. Furthermore, we found that the success of home mechanical ventilation seems to be linked to the clinical condition of patients at the time they were instituted. The patients who were instituted acutely had worse baseline arterial blood gases and pulmonary function, and seemed to have a worse survival rate on HMV than the patients instituted non-emergently. Furthermore, more patients suffering from acute respiratory failure had to be trachestomised. Therefore, it seems better to initiate ventilator support before patients deteriorate into acute respiratory failure. Recently it has been suggested that starting NIPPV at the stage of nocturnal hypoventilation before daytime hypercapnia ensues can prevent ventilatory decompensation [39], which suggests that it is a good policy to initiate NIPPV even earlier in the course of the disease, maybe even before daytime hypercapnia develops.
In summary, NPV, TIPPV, and NIPPV have a positive effect on pulmonary function and arterial blood gas tensions both at short-term and long-term. If patients receive NIPPV, the mode of ventilation did not show different effects on pulmonary function and ABG. Patients with idiopathic kyphoscoliosis and post-poliomyelitis syndrome

showed a significantly better survival rate compared to the miscellaneous group. As the underlying disorder determines survival and probably the course of the disease, we think it is important to assess the effects of HMV in patients with different disorders separately.

REFERENCES

1. Sawicka EH, Branthwaite MA. Respiration during sleep in kyphoscoliosis. *Thorax* 1987; 42: 801-8.
2. Sheerson JM, Simonds AK. Series "Noninvasive ventilation in acute and chronic respiratory failure": Noninvasive ventilation for chest wall and neuromuscular disorders. *Eur Respir J* 2002; 20: 480-7.
3. Wiers P W, Le Coultre R, Dallinga OT, van Dijl W, Meinesz AF, Sluiter HJ. Cuirass respirator treatment in chronic respiratory failure in scoliotic patients. *Thorax* 1977; 32: 221-8.
4. Schiavina M, Fabiani A. Intermittent negative pressure ventilation in patients with restrictive respiratory failure. *Monaldi Arch Chest Dis* 1993; 48(2): 169-75.
5. Hill NS. Today's practice of cardiopulmonary medicine: Clinical applications of body ventilators. *Chest* 1986; 90: 897-905.
6. Jackson M, Smith I, King M, Shneerson J. Long term non-invasive domiciliarly assisted ventilation for respiratory failure following thoracoplasty. *Thorax* 1994; 49: 915-9.
7. Goldstein RS, Molotiu N, Skrastins R et al. Reversal of sleep-induced hypoventilation and chronic respiratory failure in patients with restrictive ventilatory impairment. *Am Rev Respir Dis* 1987; 135: 1049-55.
8. Jackson M, Kinnear W, King M, Hockley S, Shneerson J. The effects of five years of nocturnal cuirass-assisted ventilation in chest wall disease. *Eur Respir J* 1993; 6: 630-5.
9. Splaingard ML, Frates RC, Harrison GM, Carter RE, Jefferson LS. Home positive pressure ventilation: twenty years experience. *Chest* 1983; 84: 376-82.
10. Zaccaria S, Ioli F, Lusuardi M, Ruga V, Spada EL, Donner CF. Long-term nocturnal ventilation in patients with kyphoscoliosis. *Monaldi Arch Chest Dis* 1995; 50: 433-7.
11. Goldstein RS, De Rosie JA, Avendano MA, Dolmage TE. Influence of non-invasive positive pressure ventilation on inspiratory muscles. *Chest* 1991; 99: 408-15.
12. Masa JF, Celli BR, Riesco JA, Sánchez de Cos J, Disdier C, Sojo A. Non-invasive positive pressure ventilation and not oxygen may prevent overt ventilatory failure in patients with chest wall diseases. *Chest* 1997; 112; 207-13.
13. Bach JR, Alba AS. Management of chronic alveolar hypoventilation by nasal ventilation. *Chest* 1990; 97: 52-7.
14. Smith IE, Laroche CM, Jamieson SA. Kyphosis secondary to tuberculosis osteomyelitis as a cause of ventilatory failure. Clinical features, mechanisms and management. *Chest* 1996; 110(4): 1105-10.
15. Gay PC, Patel AM, Viggiano RW, Hubmayer RD. Nocturnal nasal ventilation for treatment of patients with hypercapnic respiratory failure. *Mayo Clin Proc* 1991; 66: 695-703.
16. Criner GJ, Brennan K, Travaline JM, Kreimer D. Efficacy and compliance with non-invasive positive pressure ventilation in patients with chronic respiratory failure. *Chest* 1999; 116: 667-75.
17. Leger P, Bedicam JM, Cornette A et al. Nasal intermittent positive pressure ventilation. Long term follow-up in patients with severe chronic respiratory insufficiency. *Chest* 1994; 105: 100-5.
18. Simonds AK, Elliott MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. *Thorax* 1995; 50: 604-9.
19. Janssens JP, Derivaz S, Breitenstein E et al. Changing patterns in long-term non-invasive ventilation. *Chest* 2003; 123: 67-79.
20. Annane D, Chevrolet JC, Chevret S, Raphael JC. Nocturnal mechanical ventilation for chronic hypoventilation patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev. 2000; (2): CD001941.
21. Gonzalez C, Ferris G, Diaz J, Fontana I, Nunez J, Marín J. Kyphoscoliotic ventilatory insufficiency: effect of long-term intermittent positive pressure ventilation. *Chest* 2003; 124: 857-62.
22. Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation. *Eur Respir J* 2003; 22: 525-8.
23. Chu CM, Yu WC, Tam CM, Lam CW, Hui DS, Lai CK. Home mechanical ventilation in Hong Kong. *Eur Respir J* 2004; 23: 136-41.
24. Baydur A, Layne E, Aral H et al. Long term non-invasive ventilation in the community for patients with musculoskeletal disorders: a 46 year experience and review. *Thorax* 2000; 55: 4-11.

25. Brooks D, De Rosie J, Mousseau M, Avendo M, Goldstein RS. Long term follow-up of ventilated patients with thoracic restrictive or neuromuscular disease. *Can Respir J* 2002; 9: 99-106.
26. Nauffal D, Domenech R, Martinez Garcia MA, Compte L, Macian V, Perpina M. Noninvasive positive pressure home ventilation in restrictive disorders: outcome and impact on health-related quality of life. *Respir Med* 2002; 96: 77-83.
27. Schönhofer B, Barchfeld TM, Wenzel M, Köhler D. Long term effects of non-invasive mechanical ventilation on pulmonary haemodynamics in patients with chronic respiratory failure. *Thorax* 2001; 56: 524-8.
28. Hill NS, Eveloff SE, Carlisle CC, Goff SG. Efficacy of nocturnal ventilation in patients with restrictive thoracic disease. *Am Rev Respir Dis* 1992; 145: 365-71.
29. Shneerson JM. Respiratory failure in tuberculosis: a modern perspective. *Clin Med* 2004; 4: 72-6.
30. Meecham-Jones D, Wedzicha J. Comparison of pressure and volume-preset ventilator systems in stable chronic respiratory failure. *Eur Respir J* 1993; 6: 1060-4.
31. Schönhofer B, Sonneborn M, Haidl P, Böhrer H, Köhler D. Comparison of two different modes for non-invasive mechanical ventilation in chronic respiratory failure. *Eur Respir J* 1997; 10: 184-91.
32. Laub M, Berg S, Midgren B. Home mechanical ventilation in Sweden- inequalities within a homogenous health care system. *Respir Med* 2004; 98: 38-42.
33. Philips MS, Kinnear WJM, Shneerson JM. Late sequelae of pulmonary tuberculosis treated by thoracoplasty. *Thorax* 1987; 42: 445-51.
34. O'ConnerTM, O'Riordan DM, Stack M, Bredin CP. Airways obstruction in survivors of thoracoplasty: reversibility is greater in non-smokers. *Respirology* 2004; 9: 130-3.
35. van Kesteren RG, Teding van Berkhout F, Rutgers MR. Respiratoire insufficientie en het postpoliosyndroom. *Ned Tijdschr Geneeskd* 1991 ; 138 : 1282-3.
36. Corrado A, Gorini M. Negative-pressure ventilation: is there still a role? *Eur Respir J* 2002; 20: 187-97.
37. Dellborg C, Olofson J, Hamnegård CH, Skoogh BE, Bake B. Ventilatory response to CO2-rebreathing before and after nocturnal nasal intermittent pressure ventilation in patients with chronic alveolar hypoventilation. *Respir Med* 2000; 94: 1154-60.
38. Consensus Conference. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung diseases, COPD, and nocturnal hypoventilation- A Consensus Conference Report. *Chest* 1999; 116: 521-34.
39. Ward S, Heather S, Simonds AK. Randomized controlled trial of non-invasive ventilation (NIV) in congenital neuromusculo-skeletal disease (CNMD) patients with nocturnal hypoventlation but daytime hypercapnia. ERS Congress Glasgow 2004.

CHAPTER

5

Noninvasive ventilation for acute respiratory failure in COPD: where do we stand?

International Journal of Respiratory Care 2007; 3: 23-32

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ABSTRACT

Several randomised controlled trials have shown that noninvasive positive pressure ventilation (NIPPV) improves gas exchange, decreases the need for endotracheal intubation (ETI), reduces length of hospital stay, and decreases mortality in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD).
Recent studies have shown that NIPPV can also be effective in COPD exacerbations with severe respiratory failure. In these patients, NIPPV was shown to be comparable to invasive mechanical ventilation in terms of survival, with, importantly, fewer complications. A favourable approach seems to be to start the NIPPV shortly after the patient's arrival in the hospital, as success rates increased when NIPPV was initiated early in the course of the exacerbation.
NIPPV is traditionally being implemented on the intensive care unit. In experienced centres, more severely ill patients can also be treated effectively on general wards with experienced staff. However, because failure rates are higher in this group with severe respiratory failure, good monitoring facilities and rapid access to ETI are obligatory.
Although most studies used bilevel pressure support ventilation (BiPAP), in addition, pressure- and volume-controlled ventilation can be effective in COPD exacerbations. The choice of the interface used is largely individual with great emphasis on patient comfort.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an irreversible disabling disease with increasing incidence worldwide. Patients with COPD often suffer from acute exacerbations (AECOPD) with secondary respiratory failure [1]. The usual approach to care consists of treatment with oxygen to achieve adequate oxygenation, and bronchodilators, corticosteroids, and antibiotics to treat the underlying cause. Mechanical ventilation may be necessary in case of severe respiratory failure. However, endotracheal intubation, invasive mechanical ventilation itself, and a prolonged weaning process all increase morbidity and mortality. Therefore the development of noninvasive mechanical ventilation has been welcomed.

Several randomised, controlled trials (RCTs) have shown that noninvasive positive pressure ventilation (NIPPV) in addition to standard therapy is effective in the management of respiratory failure in patients with AECOPD [2-14].

However, in daily practice, failure rates are often higher than those reported in the literature. In our intensive care unit (ICU), failure rate of NIPPV in an unselected population of patients admitted with AECOPD during 1998-2004 was 37% [15]. Differences in patient selection, location where NIPPV is applied, ventilation mode, ventilator settings, type of interface, and degree of experience of the caregivers may be important factors responsible for the differences in success rates. However, for quality assurance, we have to rely on an adequate implementation of NIPPV.

In this review we aim to give evidence-based practical advice as to why, when, where and how we should apply NIPPV in the treatment of COPD exacerbations with secondary respiratory failure.

Why should we add NIPPV to usual treatment?

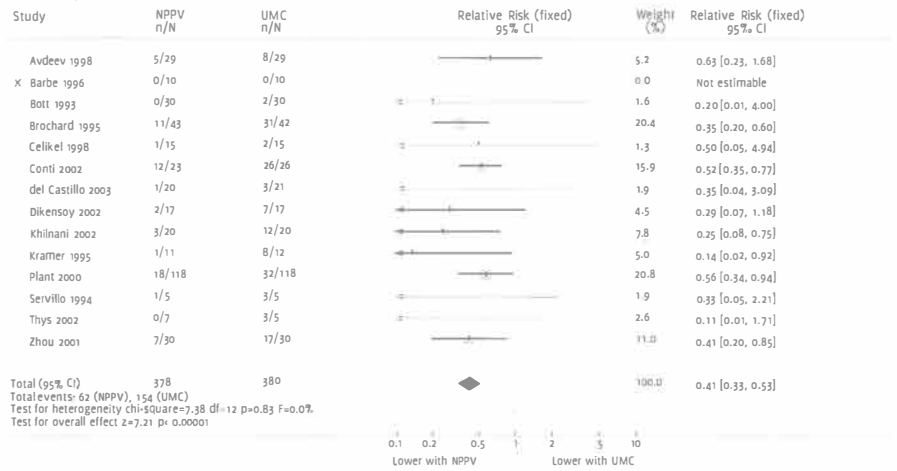
High level (grade A) evidence has shown that adding NIPPV to standard therapy with oxygen and medication for patients withAECOPD improves pH, $PaCO_2$, and respiratory rate more effectively; decreases the need for endotracheal intubation (ETI); reduces length of hospital stay; and decreases mortality (Figure 1A-C) [2-5, 8, 10, 13, 14, 16]. Above all, fewer complications were observed in the NIPPV-treated group compared to the standard therapy group [16].

In which patients with AECOPD should we apply NIPPV?

The RCTs that demonstrated effectiveness of NIPPV in AECOPD included patients with severe dyspnoea, signs of respiratory distress such as a high breathing frequency with use of accessory muscles, mild to severe acidosis (pH <7.35), hypercapnia and hypoxaemia [3-5, 9, 10, 14].

Setting aside obvious exclusion criteria such as moribund patients, circulatory instability, and facial deformity, there are still some patients in whom the use of NIPPV is debatable. NIPPV does not improve outcomes and is poorly tolerated in mild exacerbations compared to usual care alone [17, 18]. Otherwise, in patients with severe

A



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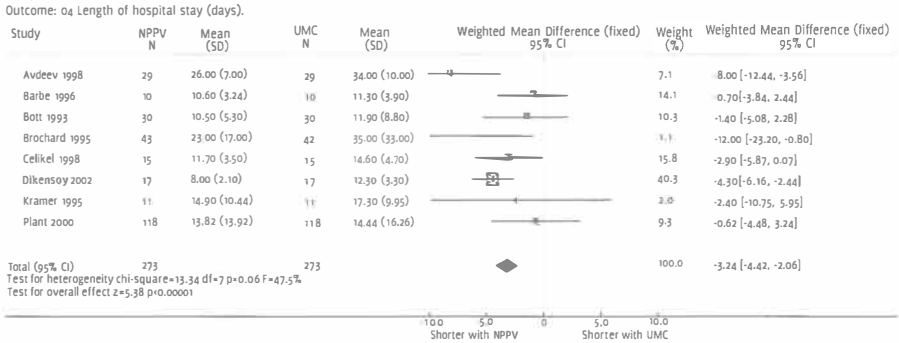

Figure 1. Effect of NIPPV on intubation rate (A), length of hospital stay (B), and mortality (C) in patients presenting with acute respiratory failure.

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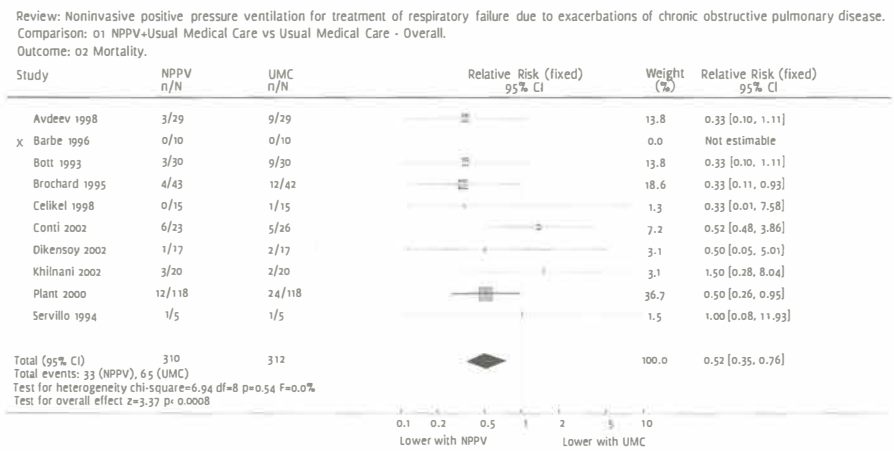
A: effect of NIPPV on intubation rate in patients presenting with acute respiratory failure.

B: effect of NIPPV on length of hospital stay in patients presenting with acute respiratory failure.

C: effect of NIPPV on mortality in patients presenting with acute respiratory failure.

C



respiratory failure (pH< 7.25), NIPPV is less successful. Studies comparing NIPPV to invasive mechanical ventilation via ETI in patients failing to respond to standard therapy showed that a large proportion of patients in the NIPPV group eventually needed ETI (52-62.5%) [19, 20]. Although failure rates were high, postponing ETI did no harm, as no difference was observed in mortality or complication rate between those who failed on NIPPV and were intubated thereafter and those patients who were intubated immediately [19, 20]. Furthermore, NIPPV was shown to be of benefit in patients in whom it succeeded, with fewer complications, lower mortality, and shorter ICU and hospital lengths of stay compared to the patients who were treated with ETI from the start [19, 20].

Recent data suggest that failure rates are improving, even in severe AECOPD. A recent small uncontrolled trial showed that NIPPV instituted at the emergency department (ED) shortly after arrival improved gas exchange to a similar extent without the need for ETI both in severely acidotic patients (pH <7.25; mean pH 7.19) and in mildly acidotic patients (pH 7.25-7.35; mean pH 7.30) [21]. In an uncontrolled study NIPPV had success rates of > 86% in comatose COPD patients (mean Glasgow coma score 6.5±1.7) [6]. In another study, with decreasing levels of consciousness, intubation rates increased but were acceptable, with the only significant increase in intubation rate to 45% in the most severe comatose patients compared to a 15% intubation rate in patients with a normal level of consciousness [12]. It was recently shown, in a case-control study comparing NIPPV with invasive ventilation in patients with a decreased level of consciousness, that NIPPV has similar mortality rates with lower occurrence of ventilator-associated pneumonia, and reduced length of hospital stay [22].

In conclusion, we recommend that NIPPV should not be applied in patients with mild

AECOPD (pH >7.35). In moderate AECOPD (pH 7.25-7.35) NIPPV should certainly be applied. In severe AECOPD (pH <7.25) NIPPV should be tried with potential benefit. However, because of the increased likelihood of failure, precautions should be taken such as ensuring good monitoring capabilities and rapid access to endotracheal intubation.

Can the failure rate be predicted?

NIPPV has lower success rates in severe exacerbations, as indicated by high Acute Physiology and Chronic Health Evaluation II Scores (APACHE II) [23, 25], low pH values on admission [9, 25, 26], and impaired levels of consciousness on admission [25, 26]. A trial in a large unselected group of patients with acute exacerbations, in different care settings, confirmed these results, showing that, on admission, APACHE II score ≥ 29, Glasgow Coma Score <14, pH <7.25, and respiratory rate >30 all significantly increased the probability of NIPPV failure (Figure 2A) [27]. Furthermore, improvement in these variables after two hours also significantly predicted NIPPV success rates, with pH <7.25 after 2 hours having an odds ratio for failure of 21.02 (Figure 2B) [27]. Consensus reports therefore recommend the use NIPPV in severely acidotic patients (pH <7.25) and in patients with impaired levels of consciousness only if good monitoring facilities (on an ICU) are available [28, 29, 30].

When should we start NIPPV?

Although we expect intuitively that starting a treatment early is better, in this case there are only sparse data to support this approach.

In patients with moderate AECOPD, treatment with medication and oxygen may lead to a significant improvement in arterial blood gases, making NIPPV unnecessary. In the study by Barbé it was shown that initiation of NIPPV on the ward, 12-48 hours after arrival at the emergency department, did not facilitate recovery from acute respiratory failure in COPD [17]. However, in the period of usual treatment between arrival at the emergency department (ED) and initiation of NIPPV, both patient groups showed already significant improvements in pH, leaving less space for improvement by NIPPV [17].

In patients with severe AECOPD, starting early is important to increase success rates. In the study by Crummy et al. [21], the high success rate they found in severely acidotic patients was explained by the fact that NIPPV was instituted shortly after arrival on the ED, and not, as in the studies by Conti and Squadrone [19, 20], only after medical treatment has failed. The same was found in the study by Celikel, where early NIPPV after initial randomisation in severely acidotic patients (pH 7.27) had a success rate of 93% [4]. If NIPPV was applied later, after failure of standard therapy, the success rate decreased to 67% [4].

Therefore, we recommend starting NIPPV in patients with moderate COPD if 1-2 hours of medication and oxygen treatment does not lead to improvement in arterial blood gases. In patients with severe AECOPD, we advise initiation of NIPPV immediately after arrival at the hospital, as it seems that such a policy increases success rates in these patients.

A

		pH admission < 7.25		pH admission 7.25-7.29		pH admission >7.30	
	RR	APACHE ≥29	APACHE <29	APACHE ≥29	APACHE <29	APACHE ≥29	APACHE < 29
GCS 15	<30	29	11	16	6	17	6
	30-34	42	18	29	11	27	10
	≥35	52	24	37	13	35	14
GCS 12-14	<30	48	22	33	13	32	12
	30-34	63	34	48	22	46	21
	≥35	71	42	57	29	55	27
GCS ≤ 11	< 30	64	35	49	23	47	21
	30-34	78	49	64	35	62	33
	≥35	82	59	72	44	70	42

B

		pH after 2 h <7.25		pH after 2 h 7.25-7.29		pH after 2 h >7.30	
	RR	APACHE ≥29	APACHE <29	APACHE ≥29	APACHE < 29	APACHE ≥29	APACHE< 29
GCS 15	<30	72	35	27	7	11	3
	30-34	88	59	49	17	25	7
	≥35	93	73	64	27	38	11
GCS 12-14	<30	84	51	41	13	19	5
	30-34	93	74	65	28	39	12
	≥35	96	84	78	42	54	20
GCS ≤ 11	< 30	93	74	65	28	39	12
	30-34	97	88	81	51	63	26
	≥35	99	95	90	66	80	40

Figure 2. Failure risk chart of noninvasive positive pressure ventilation at admission (A) and after 2 h (B). Picture reprinted from Confalonieri M et al, with permission from Eur Respir J 2005.
The values in the table correspond to the percentage of patients who fail in each category. Green: 0-24%; yellow: 25-49%; orange: 50-74%; red: 75-100%. RR: respiratory rate; APACHE: acute physiology and chronic health evaluation II score; GCS: Glasgow Coma Scale.

In what location should NIPPV be applied?

Intensive care unit (ICU)

Initial RCTs were all performed in the ICU [2-5]. Although these studies showed positive results in favour of NIPPV, no comparative studies were performed comparing success rates in the ICU with other locations. The ICU environment can guarantee sufficient personnel, adequate surveillance, and rapid access to rescue therapy in case of failure. However, most ICUs do not provide a quiet and comfortable surrounding for a patient in distress. This might be disadvantageous for the application of NIPPV.
Probably, as long as good monitoring possibilities and rapid access to ETI are available, other locations can be equally or even more suitable.

Emergency Department

The results of RCTs investigating NIPPV for AECOPD in the ED are heterogeneous. Kramer et al. showed that, in 31 patients with acute respiratory failure (ARF), NIPPV initiated on the ED reduced the need for intubation from 73 to 31% and improved heart rate, respiratory rate, PaO_2, maximal inspiratory pressure and dyspnoea scores [13]. Among the 23 COPD patients included in this study, the need for intubation decreased

even more substantially from 67 to 9% [13]. In another group of patients with acute respiratory failure, the need for intubation was not decreased compared to standard treatment (44% and 46% respectively) and the NIPPV patients even had higher mortality rates (25% and 0% respectively) [31]. This unexpected finding was explained by a delay in the application of ETI in some patients receiving NIPPV [31]. Only six out of 27 included patients had AECOPD with only two COPD patients receiving NIPPV [31]. Therefore these results may not apply for AECOPD.

General ward

NIPPV has been effectively applied on the general respiratory ward [8-10]. The first study performed on the general ward concluded that NIPPV did not improve outcomes, as all patients were discharged successfully. However, this high rate of success is rather unusual in patients who suffer COPD exacerbations. The patients in this study were probably suffering from a mild COPD exacerbation and therefore NIPPV was unnecessary [17].

A multicentre RCT on the respiratory ward of 14 hospitals in the UK showed that NIPPV reduced the need for intubation, reduced in-hospital mortality, and led to a more rapid correction of acidosis and relief of dyspnoea [9]. Strikingly, the staff had no prior experience with NIPPV in 22 out of the 25 wards participating. The study regarded severe acidosis or a Glasgow Coma Scale < 8 as contraindications for NIPPV and thus as exclusion criteria, since on a general ward there is usually no rapid access endotracheal intubation [9].

However, a recent study showed that even patients who are lethargic or stuporous can be effectively ventilated on a general respiratory ward [12]. Although these outcomes might broaden the application of NIPPV on the general ward, there are several comments to be made about this study. Firstly, it was designed to compare patients with a normal level of consciousness to patients with an altered level of consciousness. Thus, its design was not appropriate for it to be considered alongside those RCTs comparing NIPPV treatment addition to standard treatment alone. Secondly, it was conducted on the special respiratory monitoring unit of a general ward with very experienced staff. Finally, in the group of comatose patients, who had a mean pH < 7.25, both the need for ETI and mortality rates were higher (45%) [12].

The overall conclusion may be that NIPPV is an appropriate procedure to be carried out in multiple locations provided that there is adequate experience, monitoring and access to ETI.

How should NIPPV be applied?

Pressure controlled or volume controlled ventilation

Most studies in acute respiratory failure due to COPD used bilevel positive airway pressure (BiPAP) ventilation [3, 5, 6, 9, 10, 12-14]. However, pressure-controlled ventilation (PCV) [2, 4, 7] and volume-controlled ventilation (VCV) [8] were also effective in acute COPD exacerbations.

Girault et al. compared noninvasive VCV with PCV (in pressure support mode) via nasal mask in 15 COPD patients with acute respiratory failure. Both modes decreased inspiratory muscle effort, improved breathing pattern and improved gas exchange. Although the inspiratory workload was lower with VCV, PCV was found to be more comfortable for the patients [32].

Ventilator settings

Ventilator settings should be titrated in such a way that satisfactory blood gas equilibrium exists while the patient can tolerate the NIPPV. In the RCTs in which NIPPV was shown to be superior to standard treatment, IPAP levels were titrated to the maximum levels patients could tolerate (range 11-20 cm H_2O) and EPAP levels were fixed or adjustable on 3-7 cm H_2O (Table 1).

Within certain ranges it seems that variation in inspiratory pressures thus do not influence NIPPV outcomes such as the need for endotracheal intubation or mortality. However, in two studies it was found that a significantly higher level of inspiratory pressure support was applied in responders to NIPPV compared to non-responders (15 ± 4 cm H_2O versus 12 ± 2 cm H_2O) [7]; (12 ± 2 cm H_2O versus 10 ± 4 cm H_2O) [33]. It is unclear whether the non-responders were non-responders because they did not tolerate sufficiently high pressures [7, 33].

Unfortunately, more subtle differences in respiratory mechanics with different ventilator settings are not investigated in noninvasively ventilated patients. In invasively ventilated patients acceptable oxygen saturation (SaO_2 >93%), adequate tidal volumes (8-10 ml/kg) and pH (≥ 7.32) could be maintained within a range of 10 cm H_2O pressure level of the initial inspiratory pressure level that was titrated on patient comfort (baseline pressure support (Pb)). Increasing or decreasing the inspiratory pressure level in this range did indeed not significantly change arterial blood gas values. However, too low (more than 5 cm H_2O decrease from Pb) or too high levels (more than 5 cm H_2O increase from Pb) seem to be undesirable, as excessively low levels of pressure support increase inspiratory muscle effort, while excessively high pressure levels lead to further increase in ineffective efforts, and consequently also increased inspiratory muscle effort [34].

Expiratory pressure, EPAP, or with PSV the addition of extrinsic positive expiratory pressure (PEEPe), can have a benefit in COPD as it may improve exhalation in the presence of intrinsic PEEP (PEEPi), may eliminate ineffective efforts, and may reduce respiratory muscle effort. However, the addition of PEEPe remains controversial as PEEPe higher than dynamic PEEPi in patients with an airflow limitation may lead to further increase in functional residual capacity.

The 1994 study by Meecham Jones compared a trial of one hour each of NIPPV with inspiratory pressure support (IPAP) 18 cm H_2O, IPAP 18 cm H_2O with the addition of expiratory pressure support (EPAP) 6 cm H_2O, continuous positive airway pressure (CPAP) 8 cm H_2O, and volume cycled NIPPV. Pressure support, CPAP and volume-cycled NIPPV improved significantly PaO_2, while with the combined IPAP + EPAP mode the improvement in PaO_2 did not reach statistical significance. None of the modes produced significant changes in mean $PaCO_2$. They concluded that the

Table 1. Mode of ventilation, settings, interfaces and complications related to NIPPV and results of the RCT's with positive results of NIPPV in AECOPD.

Author	Mode	IPAP/ EPAP	Duration	Mask	Complications	Important results (ST → ST+NIPPV)
RCT's comparing standard therapy with NIPPV added to standard therapy						
Brochard [2]	PSV	20*/-	4 ± 4 days (6–22) h/day	ONM	Facial skin necrosis: 2%	ETI: 74 %→ 26% LHS: 35→23 days M: 29% → 9%
Adveev [3]	BiPAP	30 /4-6	29 ± 25 u	NM FM	Mask intolerance: 10%	ETI: 28 %→ 12% LHS: 34→26 days M: 31% → 8%
Celikel [4]	PSV	15.4 ± 3/ 5	26.7 ± 16.1 h Continuously	FFM	Facial skin necrosis: 46% Gastric distension: 7%	LHS: 15 →12 days SR: 60% → 93%
Kramer [13]	BiPAP	11.3 ± 0.9/ 2.6 ± 0.3	3.8 ± 1.4 days 14.4 ± 2.2 h/ day	NM	Nasal ulcerations: 18%	ETI 67% → 9%
Thys [14]	BiPAP	17.5 ± 2.9/ 7 ± 1.6	95 ± 29 min	ONM	No skin damage or gastric distension	SR: 0% → 100%
Bott [8]	VCV	-	6.0 (2-9) days 7.63 (1-23) h/day	NM	1 patient (3 %) unable to breath through his nose.	Improvement blood gases and dyspnoea M: 9/30→ 3/30(NS)
Plant [9]	BiPAP	10- 20*/4	Median 3 days (0-26)	ONM/FFM	7.2% used ventilator < 1 hour on day 1	ETI: 27 →15% M: 20 →10%
Dikensoy[10]	BiPAP	15.3 ± 4.3/ 1	11.2 ± 9.5 h	FFM	NIPPV intolerance: 12%	LHS 12.3 →8 days
RCT comparing NIPPV with invasive mechanical ventilation						
Conti [19]	PSV	16±2/ 5	Non-responders vs. responders: 7 ± 9 h vs. 28 ± 11 h	FFM	VAP: 9 → 3 (NS) Sepsis: 13 → 6 (NS) Mask intolerance: 13% *All complications in NIPPV group developed after intubation*	NIPPV comparable in terms of mortality rate ETI: 52%

Ventilator settings and duration presented as mean ± SD; range between brackets. NS: not significant. ST: standard therapy, ST+NIPPV: standard therapy + NIPPV. BiPAP: bilevel positive airway pressure, PSV: pressure support ventilation; PEEP: positive end-expiratory pressure; CPAP: continuous airway pressure. NM: nasal mask; ONM: oronasal mask; FFM: full face mask. VAP: ventilator associated pneumonia. ETI: endotracheal intubation; LHS: length of hospital stay; M: in-hospital or in-ICU mortality; SR: success rate, defined as not needing invasive mechanical ventilation in the NIPPV group and not needing NIPPV or invasive ventilation in the standard treatment group.

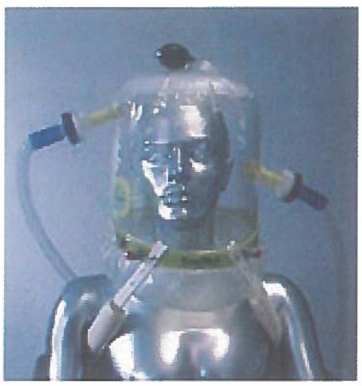


Figure 3. Helmet ventilation (picture obtained from website of CaStar; Starmed; Mirandola, Italy).

addition of EPAP had no advantage. However, one hour might be too short to achieve sufficient ventilation [35].
In conclusion, research into optimal ventilator modalities and optimal ventilator settings is needed. Until otherwise proven, ventilator settings should be titrated according to blood gases and the patient's tolerance.

The choice of the interface

The choice of the interface used influences patient acceptance with the NIV because the interfaces differ in terms of dead space, the amount of leaks, risk of pressure sores, risk of claustrophobia, and the ability to communicate and take oral foods.
Success rates appear to be approximately equivalent for oronasal masks compared to nasal masks [36]. The 2003 study by Antón et al. showed that, in patients recovering from acute respiratory failure, similar improvements in arterial blood gases were achieved with oronasal and nasal mask ventilation, although respiratory rate decreased more with the oronasal mask [37]. In terms of patient tolerance results were heterogeneous, showing equal or better tolerance with oronasal masks compared to nasal masks [36-37]. This might be explained by different circumstances at the moment NIPPV was applied in the different studies: for patients in acute distress oronasal masks may be more comfortable [36].
Helmets were designed in an attempt to improve NIPPV tolerance, as pressure sores are prevented. However, because of their large volume, helmets influence trigger sensitivity and therefore might increase the work of breathing in comparison to facial mask ventilation (Figure 3) [38-40]. Moerer et al. found that during inspiration the effort was similar for the helmet and the full-face mask [39]. They explain this by the fact that patients utilise the large gas reservoir in the helmet during the beginning of the inspiration, so that during the initial phase of inspiration the work of breathing was less compared to face mask ventilation. By increasing pressure support and PEEP the delay times were reduced [39].

However, although no difference in the need for ETI, length of ICU stay, or mortality has been found, helmet NIPPV may decrease trigger sensitivity leading to patient-machine dyssynchrony and thus may reduce hypercapnia less efficiently than face mask NIPPV. Therefore, it was advised not to use helmet NIPPV in patients with severe AECOPD who require a rapid increase of alveolar ventilation and to monitor closely [39]. On the other hand tolerance was much better with helmet ventilation: in the helmet group all patients could tolerate NIPPV, whereas in the mask group five out of 14 patients (38%) failing to improve on NIPPV did so because of mask intolerance [40].

CONCLUSION

NIPPV effectively reduces the need for intubation and decreases mortality compared to standard treatment alone in AECOPD. Except for a few exceptions, such as facial deformations, NIPPV should be used when there is respiratory acidosis ($PaCO_2$ >6.0 kPa, pH <7.35), which persists despite maximal medical treatment and appropriate controlled oxygen therapy [30].

In severe AECOPD, with pH <7.25, failure rates are higher especially after medical treatment has failed. However, as complication rates are lower compared to ETI, NIPPV should be applied also in these patients. Therefore, NIPPV should be tried as soon as possible after arrival at the hospital, for one to two hours, and only if good monitoring facilities and access to ETI are available.

NIPPV can be applied in multiple locations provided that adequate monitoring, rapid access to rescue intubation, and sufficient experience are available. Interface and ventilator mode and settings can be chosen depending on local experience and patient preferences.

REFERENCES

1. Chu CM, Chan VL, Lin AWN. Readmission rates and life threatening events in COPD survivors treated with noninvasive ventilation for acute hypercapnic respiratory failure. *Thorax* 2004; 59; 1020-5.
2. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, Isabey D, Harf A. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *New Eng J Med* 1995; 333: 817-22.
3. Avdeev SN, Tret'iakov AV, Grigor'iants RA, Kutsenko MA, Chuchalin AG. Study of the use of noninvasive ventilation of the lungs in acute respiratory insufficiency due exacerbation of chronic obstructive pulmonary disease. *Anesteziol Reanimatol* 1998; 3: 45-51. *Abstract*
4. Celikel T, Sungur M, Ceyhan B, Karakurt S. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic respiratory failure. *Chest* 1998; 114: 1636-42.
5. Martin TJ, Hovis JD, Costantino J P. A Randomized, Prospective evaluation of Noninvasive Ventilation for Acute Respiratory Failure. *Am J Respir Crit Care Med* 2000; 161; 807-13.
6. Díaz GG, Alcaraz AC, Talavera JC, Pérez PJ, Rodriguez AE, Cordoba FG, Hill NS. Noninvasive positive-pressure ventilation to treat hypercapnic coma secondary to respiratory failure. *Chest* 2005; 127: 952-60.
7. Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E. Noninvasive positive pressure ventilation via facial mask. First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. *Chest* 1996; 109:179-93.
8. Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, Paul EA, Elliott MW, Godfrey RC, Wedzicha JA. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993; 341: 1555-7.
9. Plant PK, Owen JL, Elliot MW. Early use of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000; 355: 1931-5.
10. Dikensoy O, Ikidag B, Filiz A, Bayram N.Comparison of noninvasive ventilation and standard medical therapy in acute hypercapnic Respiratory failure: a randomised controlled study at a tertiary health centre in SE Turkey. *Int J Clin Pract* 2002; 56: 85-8.
11. González Barcala FJ, Zamarrón Sanz C, Salgueiro Rodríguez M, Rodríguez Suárez JR. Noninvasive ventilation in chronic obstructive pulmonary disease patients with acute respiratory hypercapnic failure in a conventional hospital ward. *An Med Interna* 2004; 21: 373-7. *Abstract*
12. Scala R, Naldi M, Archinucci I. Noninvasive positive pressure ventilation in patients with acute exacerbations of COPD and varying levels of consciousness. *Chest* 2005; 128: 1657-66.
13. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995; 151: 1799-1806.
14. Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein DO. Noninvasive ventilation for acute Respiratory failure: a prospective randomised placebo-controlled trial. Eur Respir J 2002; 20: 545-55.
15. Zijlstra GJ, Postma DS, Wijkstra PJ, Ligtenberg JJM., Tulleken JE, Van der Werf TS. Acute Respiratory failure in COPD: evaluation of an ICU policy. *Intensive Care Med* 2006; 32 [S1]: S248. *Abstract.*
16. Ram FSF, Picot J, Lightowler J, Wedzicha JA. Noninvasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD004104. DOI: 10.1002/14651858.CD004104.pub3.
17. Barbé F, Togores B, Rubí M, Pons S, Maimó A, Agustí AG. Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. *Eur Respir J* 1996; 9:1240-5.
18. Keenan SP, Powers CE, McCormack DG. Noninvasive Positive-Pressure Ventilation in Patients with Milder Chronic Obstructive Pulmonary Disease Exacerbations: A Randomized Controlled Trial. *Respir Care* 2005; 50: 610-6.

19. Conti G, Antonelli M, Navalesi P, Rocco M, Bufi M, Spadetta G, Meduri GU. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. *Intensive Care Med* 2002; 28:1701-7.
20. Squadrone E Frigerio P, Fogliati C, Gregoretti C, Conti G, Antonelli M, Costa R, Baiardi P, Navalesi P. Noninvasive vs. invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. *Intensive Care Med* 2004; 30:1303-10.
21. Crummy F, Buchan C, Miller B, Toghill J, Naughton MT. The use of noninvasive mechanical ventilation in COPD with severe hypercapnic acidosis. *Respir Med* 2007; 101: 53-61.
22. Scala R, Conti G, Nava S, et al. Noninvasive ventilation (NIV) versus conventional ventilation (ETI-MV) to treat moderate-to-severe hypercapnic encephalopathy (EI) in COPD patients: a case-control study. P4726 ERS Munchen 2006
23. Putinati S Ballerin L, Piattella M, Panella GL, Potena A. Is it possible to predict the success of noninvasive positive pressure ventilation in acute respiratory failure due to COPD? *Respir Med* 2000; 94: 997-1001.
24. Phua J, Kong K, Lee KH, Shen L, Lim TK. Noninvasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs other conditions: effectiveness and predictors of failure. *Intensive Care Med* 2005; 31: 533-9.
25. Antón A, Güell R, Gómez J, Serrano J, Castellano A, Carrasco JL, Sanchis J. Predicting the result of Noninvasive Ventilation in Severe Acute Exacerbations of patients with Chronic Airflow Limitation. *Chest* 2000; 117:828-33.
26. Plant PK, Owen JL, Elliot MW. Noninvasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long tem survival and predictors of in-hospital outcome. *Thorax* 2001; 56: 708-12.
27. Confalonieri M, Garuti G, Cattaruzza MS, Osborn JF, Antonelli M, Conti G, Kodric M, Resta O, Marchese S, Gregoretti C, Rossi A; Italian noninvasive positive pressure ventilation (NPPV) study group. A chart of failure risk for Noninvasive ventilation in patients with COPD exacerbation. *Eur Respir J* 2005; 25: 348-55.
28. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management and prevention of Chronic Obstructive pulmonary Disease. Based on April 1998 NHLBI/WHO workshop, updated version 2005. Online.
29. American Thoracic Society. International Consensus Conference in Intensive Care Medicine: Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure. *Am J Respir Crit Care Med* 2001; 163: 283-91.
30. British Thoracic Society Standards of Care Committee. BTS Guideline: Noninvasive ventilation in acute respiratory failure. *Thorax* 2002; 27:192-211.
31. Wood KA, Lewis L, Von Harz B, Kollef MH. The use of noninvasive positive pressure ventilation in the emergency department: result of a randomized clinical trial. *Chest* 1998; 113: 1339-46.
32. Girault C, Richard JC, Chevron V, Tamion F, Pasquis P, Leroy J, Bonmarchand G. Comparative effects of noninvasive assist-control and pressure support ventilation in acute respiratory failure. *Chest* 1997; 11(6): 1639-48.
33. Poponick JM, Renston JP, Bennett RP, Emerman CL. Use of Ventilatory Support System (BiPAP) for Acute Respiratory Failure in the Emergency Department. *Chest* 1999; 116: 166-71.
34. Nava S, Bruschi C, Rubini F, Palo A, Iotti G, Braschi A. Respiratory response and inspiratory effort during pressure support ventilation in COPD patients. *Intensive Care Med* 1995; 21: 871-9.
35. Meecham Jones DJ, Paul EA, Grahame-Clarke C, Wedzicha JA. Nasal ventilation in acute exacerbations of chronic obstructive pulmonary disease: effect of ventilator mode on arterial blood gas tensions. *Thorax* 1994; 49: 1222-4
36. Kwok H, McCormack J, Cece R, Houtchens J, Hill NS. Controlled trial of oronasal versus nasal mask ventilation in the treatment of acute respiratory failure. *Crit Care Med* 2003; 31: 468-73.
37. Antón A, Tárrega J, Giner J, Güell R, Sanchis J. Acute physiologic effects of nasal and full-face masks during noninvasive positive-pressure ventilation in patients with acute exacerbations of chronic pulmonary disease. *Respir Care* 2003; 48: 922-5.
38. Chiumello D, Pelosi P, Carlesso E, Severgnini P, Aspesi M, Gamberoni C, Antonelli M, Conti G,

Chiaranda M, Gattinoni L. Noninvasive positive pressure ventilation delivered by helmet vs. standard face mask. *Intensive Care Med* 2003; 29: 1671-9.

39. Moerer O, Fischer S, Hartelt M, Kuvaki B, Quintel M, Neumann P. Influence of two different interfaces for noninvasive ventilation compared to invasive ventilation on the mechanical properties and performance of a respiratory system: a lung model study. *Chest* 2006; 129: 1424-31.
40. Antonelli M, Pennisi MA, Pelosi P. Noninvasive positive pressure ventilation using a helmet in patients with acute exacerbations of chronic obstructive pulmonary disease. *Anesthesiology* 2004; 100: 16-24.

CHAPTER

6

Noninvasive ventilation severe stable COPD: is it effective, and if so, in what way?

Eur Respir J 2008; 31(5): 1-2 (In press)

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To the editors:

We have read with interest the systematic review of Kolodziej about noninvasive positive pressure ventilation (NIPPV) in severe stable chronic obstructive pulmonary disease (COPD) [1]. First of all, we would like to complement the authors with their excellent review. It is extremely important that good quality reviews are published in the field of noninvasive positive pressure ventilation in severe stable COPD. The development of new therapeutic options in these patients is increasingly being recognised as urgently needed [2].

However, we would like to make some comments about the conclusion Kolodziej et al. draw in their review. They conclude that bilevel noninvasive positive pressure ventilation used in a select proportion of patients with severe stable COPD can improve gas exchange, exercise tolerance, dyspnoea, work of breathing, frequency of hospitalisation, health-related quality of life and functional status. Following this, they suggest an adjunctive role for the use of bilevel NIPPV in the management of chronic respiratory failure due to COPD.

The first remark we would like to make is that their conclusions were based mostly on non-randomised controlled trails. Combined analysis of the results of the randomised controlled trials (RCTs) did not show effects on arterial blood gases, exercise tolerance, work of breathing, or hospitalisations. Evidence for an improved health-related quality of life was derived from only two studies [3, 4]. Furthermore, in the study of Garrod, the NIPPV group had very low baseline Chronic Respiratory Questionnaire scores, which may have influenced their positive outcome [4].

Secondly, Kolodziej pooled studies of different study length, different kind of control interventions and different type of ventilation (daytime and nocturnal). They did assess their data on heterogeneity in study quality, patients, interventions, and measurement of outcomes and indeed they showed that heterogeneity was evident in many parameters. This prohibits strong conclusions that NIPPV is as effective in severe stable COPD.

In our opinion, in the review by Kolodziej et al.[1], there is only little discussion about the importance of achieving effective ventilation. It is discussed that with more hours of ventilatory use, a greater reduction in hypercapnia can be achieved. Although this might be true for nocturnal ventilation, with daytime ventilation large effects might be reached with less hours of NIPPV use. From the RCTs included, a significant reduction in hypercapnia during spontaneous breathing at room air was shown only in the study of Díaz [5]. This study, and also the more recent study of the same group [6], showed that large effects can be achieved with 3 hours of NIPPV during daytime. During the night, increased upper airway resistance, decreased respiratory drive, and less supervision might lead to the deliverance of less volume to the patient. Therefore, correct monitoring of whether or not effective ventilation is achieved is very important, especially during the night. Kolodziej et al. do address this point of more dynamic monitoring of effectiveness of NIPPV. However, they imply that dynamic monitoring by transcutaneous measurements is preferred above arterial blood gases

alone. However, transcutaneous measurement of CO_2 with current techniques tends to drift overnight [7]. In our opinion, measuring multiple arterial blood gas samples during NIPPV is the golden standard. Unfortunately, until now, no randomised controlled trial has monitored the effectiveness of their intervention in this way.

The second remark relates to the importance of using high inspiratory pressures. Even higher pressures than used in most RCTs might be necessary to achieve normocapnia [8], although no clear evidence exists on how high pressures exactly should be.

The third remark relates to the selection of appropriate patients. Patients with very severe COPD seem to benefit most. Kolodziej et al emphasise that patients with severe hyperinflation probably benefit most. However, too little evidence currently exists to make a clear statement about whether patients should be selected on basis of the severity of chronic respiratory failure, hyperinflation, or maybe the height of the work of breathing.

To conclude, we do find that the review of Kolodziej is et al. is timely and a major contribution, but we feel the strength of the conclusions is overstated. With this review in hand, some of the gaps in our knowledge are carefully uncovered and should lead to well designed RCTs of sufficient power. Some are undoubtedly underway.

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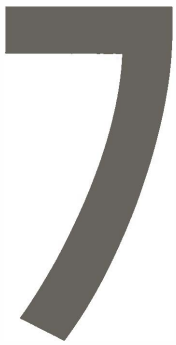
REFERENCES

1. Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. *Eur Respir J* 2007: 30: 293-306.
2. Ambrosino N, Goldstein R. Series on comprehensive management of end-stage COPD. *Eur Respir J* 2007; 30: 828-30.
3. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, Ambrosino N. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; 20: 529-38.
4. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1335-41.
5. Díaz O, Bégin P, Torrealba B, Jover E, Lisboa C. Effects o f noninvasive ventilation on lung hyperinflation in stable hypercapnic COPD. *Eur Respir J* 2002; 20: 1490-8.
6. Díaz O, Bégin P, Andresen M, Prieto ME, Castillo C, Jorquera J, Lisboa C. Physiological and clinical effects of diurnal noninvasive ventilation in hypercapnic COPD. *Eur Respir J* 2005; 26: 1016-23.
7. Storre JH, Steurer B, Kabitz HJ, Dreher M, Windisch W. Monitoring of transcutaneous PCO_2 during initiation of noninvasive positive pressure ventilation NPPV. *Chest* 2007; 132; 1810-6.
8. Windisch W, Kosti S, Dreher M, Virchow JC Jr, Sorichter S. Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of Pa(CO2). *Chest* 2005; 128: 657-62.

CHAPTER



Health-related quality of life in COPD patients with chronic respiratory failure

Submitted

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ABSTRACT

Background: The Maugeri Respiratory Failure (MRF-28) and Severe Respiratory Insufficiency (SRI) questionnaire were recently developed to assess health-related quality of life (HRQoL) in patients with chronic respiratory failure, although not exclusively in COPD patients.

Questions: Whether the MRF-28 and SRI are reliable and valid HRQoL questionnaires in COPD patients with chronic hypercapnic respiratory failure.

Patients and methods: Seventy two COPD patients with chronic hypercapnic respiratory failure underwent pulmonary function testing; exercise testing; and filled in the MRF-28, SRI, the Chronic Respiratory Questionnaire (CRQ), the Hospital Anxiety and Depression Scale, the Groningen Activity and Restriction Scale, and two dyspnoea indexes.

Results: Physical domain scores of the questionnaires correlated with exercise tolerance, dyspnoea, and daily activities, while psychological domains correlated strongly with anxiety and depression. Anxiety scores accounted for 51% and 56% of the total explained variance in total CRQ and SRI scores respectively. The emphasis of the MRF-28 was restrictions in activities of daily living (52% of total variance).

Answer: The MRF-28 and SRI are reliable and valid questionnaires in COPD patients with chronic hypercapnic respiratory failure. While the emphasis in the MRF-28 is on activities of daily living, the SRI, like the CRQ, is more related to anxiety and depression.

ABBREVIATIONS

HRQoL: health-related quality of life
COPD: chronic obstructive pulmonary disease
CHRF: chronic hypercapnic respiratory failure
MRF-28: maugeri respiratory failure questionnaire
SRI: severe respiratory insufficiency questionnaire
CRQ: chronic respiratory questionnaire
FEV_1: forced expiratory volume in the first second
$PaCO_2$: arterial carbon dioxide pressure
PaO_2: arterial oxygen pressure
MRC: medical research counsel
BDI: baseline dyspnoea index
GARS: groningen activity and restriction scale
HADS: hospital anxiety and depression scale
ICC: intraclass correlation coefficient

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide [1]. As COPD is a progressive disease, the number of COPD patients with severe disease and chronic respiratory failure will increase the coming decades. It has been shown that patients with chronic respiratory failure have poor survival. A 5-year mortality of 70-100% was reported [2]. Survival rates are difficult to improve once patients have become respiratory insufficient. Despite treatment with long-term oxygen or home mechanical ventilation median survival was still only three years [3]. Although survival rates are difficult to improve, therapeutic interventions in severe COPD might nevertheless improve health-related quality of life (HRQoL) [4, 5]. The Chronic Respiratory Questionnaire (CRQ) is a widely used disease specific questionnaire which has been shown to be reliable, valid, and responsive in COPD patients [6]. It has also been used in more severe patients [7-9]. However, it was not designed for patients with chronic respiratory failure and might not include items specifically important for these patients. Therefore, a need was felt for questionnaires specific for patients with respiratory failure [10]. The Maugeri Respiratory Failure questionnaire (MRF-28) and the Severe Respiratory Insufficiency Questionnaire (SRI) were developed especially for these patients [11, 12]. Both questionnaires contain items on problems that patients with chronic respiratory failure experience. However, both questionnaires were developed in a group of patients with respiratory failure of different origin, already treated with home mechanical ventilation for a longer period. Reliability and validity of the MRF-28 and SRI have not been investigated in a homogeneous group of patients with COPD who actually suffer from chronic respiratory failure.

The purpose of the present study was to determine whether the MRF-28 and SRI are reliable and valid HRQoL questionnaires in COPD patients with chronic hypercapnic respiratory failure (CHRF). We therefore evaluated: 1) reliability of the 3 questionnaires, amongst others by assessing reproducibility, 2) concurrent validity by comparing SRI and MRF-28 scores to CRQ scores; 3) construct validity of the 3 questionnaires by correlating the scores with relevant physiological parameters, dyspnoea ratings, and psychological status, in COPD patients with CHRF.

METHODS

Patients

All participants were in stable condition, out of rehabilitation at least 18 months, and were treated with medication and long-term oxygen if necessary. None of them was or had been on long-term ventilation. Inclusion criteria were COPD GOLD stage III or IV [13] with chronic hypercapnic respiratory failure (FEV_1<50% predicted, $PaCO_2$ >6.0 kPa, at rest while breathing room air)[14]. Exclusion criteria were cardiac or musculoskeletal diseases limiting exercise performance, or obstructive sleep apnoea syndrome (apnoea/hypopnoea index ≥ 10 episodes/ hour). Details are given in the

online supplement.
The study was approved by the local Medical Ethical Committee. All participants gave written informed consent to participate. The study is registered at ClinicalTrials.Gov.

Measurements

Patients underwent pulmonary function testing [15-17], a maximal incremental cycle ergometry, and a 6-minute walking test [18, 19]. HRQoL was measured by the Maugeri Respiratory Failure questionnaire (MRF-28) [11], the Severe Respiratory Insufficiency questionnaire (SRI) [12], and the Chronic Respiratory Questionnaire (CRQ) [6]. The MRF-28 contains 3 subscales related to daily activities, cognition, and invalidity, and a total score with additional items related to fatigue, depression and problems with treatment. MRF-28 scores range from 0-100; higher scores indicate worse HRQoL [11]. The SRI contains 7 subscales related to respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being, social functioning, and a summary scale. SRI scores range from 0-100; higher scores indicate better HRQoL [12].
Dyspnoea was assessed with the Medical Research Counsel (MRC) [20] and the Baseline Dyspnoea Index (BDI) [21, 22]. Activities of daily living were assessed by the Groningen activity and restriction scale (GARS) [23], and mood state by the hospital anxiety and depression scale (HADS) [24]. Additional information about the tests and questionnaires is presented in the supplementary material.

Study design

Tests were performed on 3 different days. On day 1, first the CRQ was administered. Patients filled in the MRF-28, SRI, MRC, BDI, HADS and GARS by themselves in random order. The 6-minute walking test and cycle ergometry were performed on 2 different days, to allow the patients to rest sufficiently. Pulmonary function testing was performed at least 3 hours before or after an exercise test. After 12 weeks, the tests were repeated in similar order.

Analysis and statistics

Reliability was assessed by internal consistency, distribution of the scores, and test-retest reproducibility. Internal consistency was determined by Cronbach's alpha coefficient. Test-retest reproducibility was approximated by intraclass correlation coefficients (ICC) in 23 patients who completed the questionnaires for a second time after 12 weeks and who had no exacerbations in those 12 weeks [25]. Reproducibility could not be tested in 36 patients who did have an exacerbation, in 7 patients who changed in therapy, in 3 patients because they withdrew, and in 3 patients who died in this 12-week period.
To evaluate construct validity of the questionnaires, we investigated whether the HRQoL scores correlated with other measures that assessed the same construct [26].

Physical domains should correlate with related physical parameters, while psychological domains should correlate with psychological parameters. The construct was further scrutinized by backward multiple regression analysis identifying patterns in parameters that could best explain the variance in the questionnaires total scores. Variables entered in the backward model were chosen on basis of existing literature together with a $p < 0.10$ in the univariate regression analyses. Because a strong correlation was found between the HADS anxiety and HADS depression score (rho 0.69), and between the GARS score and the six minute walking test (rho 0.77), we entered only one variable of these respective parameters. For the final model, as independent variables were chosen gender, exacerbation frequency during the previous year; FEV_1, GARS scores, lactate at rest, HADS anxiety score, and BDI score. Exacerbation frequency was divided by the median into two categories (few exacerbations: ≤3/ year versus frequent exacerbations: >3/ year). Dependent variables were MRF-28, SRI and CRQ total scores.
SPSS 14.0 was used for all analyses. A p-value < 0.01 was considered significant.

RESULTS

Patients

Baseline measurements were performed in 86 patients. Fourteen patients were excluded from the analyses as they were not hypercapnic (9 patients), had an apnoea/ hypopnoea index ≥10 (3 patients), or an FEV_1 >50% predicted (1 patient). One patient was unable to fill in questionnaires. Therefore, a total of 72 patients was included for the present study (Table 1). All patients were hypercapnic as per protocol. Thirty-one of them were also hypoxemic (PaO_2<8.0 kPa at room air at rest). Thirty-three patients were on long-term oxygen therapy. We found no significant differences in pulmonary function, exercise tolerance, and any of the questionnaire scores between the patients who were or were not hypoxemic, except for a significantly lower pH and higher $PaCO_2$ in the hypoxemic patients. All patients were treated with inhaled β_2-agonists or anticholinergic medication; 60 patients used inhaled corticosteroids; 33 patients were treated with oral corticosteroids. We found no significant differences in any of the questionnaire scores between the patients who were or were not on steroids (inhaled and/ or oral).

Reliability

Scores were obtained over a large range for the MRF-28, SRI, and CRQ (Table 2, Figure 1). The MRF-28 cognition domain showed obvious floor and ceiling effects, with 11 patients (15%) scoring the maximum (=worst possible score), and 19 patients (26%) scoring the minimal (=best possible score). Floor and ceiling effects were also observed for the daily activities and invalidity domain. For the CRQ and SRI no obvious floor and ceiling effects were observed.

Table 1. Patient characteristics.

	Mean ± SD
Gender, male/ female	39/ 33
Age, years	62 ± 8.6
Number on long-term oxygen	33
Number on oral/ inhaled steroids	33/ 60
Exacerbations, number/ yr	4.0 ± 3.2
BMI, kg/m²	27.1 ± 6.2
FEV_1, L	0.80 ± 0.31
FEV_1, % predicted	30 ± 11
VC, L	2.60 ± 0.77
FEV_1/VC, %	31 ± 9
TLC, % predicted	125 ± 18
RV%TLC	64.8 ± 8.4
$P_I$max, kPa	5.3 ± 2.1
pH	7.39 ± 0.03
PaO_2, kPa (room air)	8.1 ± 1.2
$PaCO_2$, kPa (room air)	6.8 ± 0.6
HCO_3, mmol/ L	28.8 ± 2.4
BE, mmol/ L	4.1 ± 2.0
6-MWD, m	284 ± 119
GARS score	42 ± 11
HADS depression	7.5 ± 5
HADS anxiety	7.2 ± 4
BDI total score	3.6 ± 1.8
MRC	3.5 ± 0.9

Footnote: Data are presented as mean ± SD. Exacerbations: the number of patient-reported exacerbations over the previous year; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; VC: vital capacity; TLC: total lung capacity; RV%TLC: residual volume as percentage of total lung capacity; $P_I$max: maximal inspiratory pressure; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure; HCO_3: bicarbonate; BE: base excess; 6-MWD: 6-minute walking test distance; GARS: Groningen Activity and Restriction Scale (score range from best (18) to worst (72)); HADS: Hospital Anxiety and Depression Scale (separate scores for anxiety and depression, score range best (0) to worst (21)); BDI: baseline dyspnoea index (score range best (12) to worst (0)); MRC: Medical Research Counsel dyspnoea scale (score range best (1) to worst (5)).

Internal consistency of the MRF-28 was high for the daily activity domain, but lower for the cognition and invalidity domain (Table 2). Internal consistency of the CRQ was high for all domains; while for the SRI domains it was good except for the attendant symptoms and sleep domain for which internal consistency was lower (0.66). Test-retest reproducibility was good for the MRF-28 (ICC 0.92), SRI (ICC 0.81), and CRQ (ICC 0.87).

Table 2. MRF-28, SRI and CRQ scores and internal consistency.

	Items (n)	Patients with minimum score (n)	Patients with maximum score (n)	Mean ± SD	α
Maugeri Respiratory Failure Questionnaire					
Daily activities (0-100)	11	3	6	60.6 ± 28.9	0.83
Cognition (0-100)	4	19	11	44.1 ± 35.2	0.69
Invalidity (0-100)	5	4	15	63.1 ± 29.6	0.60
Total (0-100)	27	0	0	55.5 ± 22.0	
Severe Respiratory Insufficiency Questionnaire					
Respiratory complaints (0-100)	8	0	0	46.7 ± 15.5	0.73
Physical functioning (0-100)	6	0	0	38.5 ± 18.5	0.73
Attendant symptoms and sleep (0-100)	7	0	0	59.7 ± 16.9	0.66
Social relationships (0- 100)	6	0	0	63.2 ± 18.0	0.78
Anxiety (0-100)	5	1	0	48.2 ± 19.8	0.70
Well-being (0-100)	9	0	0	57.0 ± 18.3	0.84
Social functioning (0-100)	8	1	0	46.2 ± 17.5	0.73
Summary score (0-100)	49	0	0	51.3 ± 13.6	
Chronic Respiratory Questionnaire					
Dyspnoea (5-35)	5	1	0	16.2 ± 5.5	0.73
Fatigue (4-28)	4	1	0	13.8 ± 4.9	0.82
Emotion (7-49)	7	1	0	30.3 ± 7.7	0.78
Mastery (4-28)	4	1	0	17.6 ± 5.4	0.80
Total (20-140)	20	0	0	78.1 ± 19.3	

Footnote: Shown are respectively the domains (minimal and maximal scores which can be obtained), number of items, number of patients with minimum and maximum score, mean scores ± SD, and α: Cronbach's alfa for internal consistency.

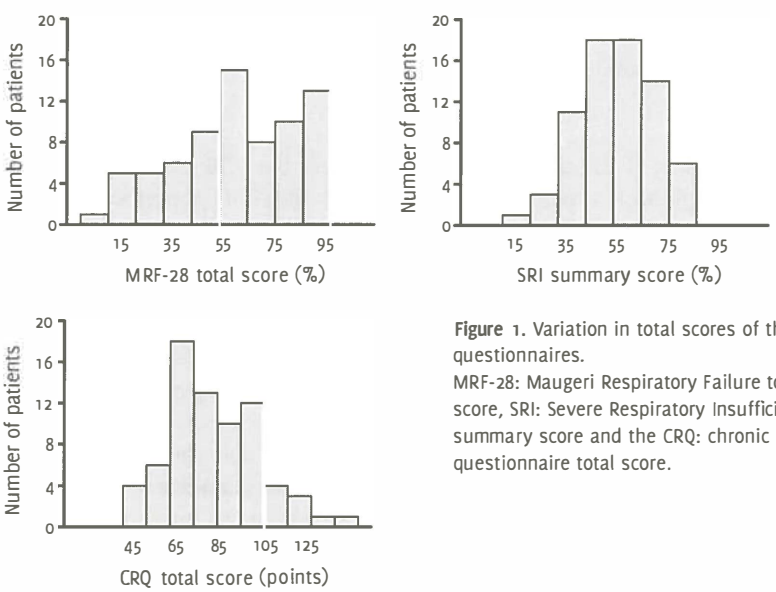


Figure 1. Variation in total scores of the questionnaires.
MRF-28: Maugeri Respiratory Failure total score, SRI: Severe Respiratory Insufficiency summary score and the CRQ: chronic respiratory questionnaire total score.

Table 3. Spearman's rank correlations between MRF-28, SRI, and CRQ.

	Chronic Respiratory Questionnaire				
	Dyspnoea	Fatigue	Emotion	Mastery	Total
Maugeri Respiratory Failure Questionnaire					
Daily activities	-0.44	-0.51	-0.33	-0.25	-0.45
Cognition	-	-	-	-	-
Invalidity	-0.44	-0.49	-0.45	-0.41	-0.54
Total	-0.52	-0.61	-0.49	-0.36	-0.60
Severe Respiratory Insufficiency Questionnaire					
Respiratory complaints	0.57	0.59	0.40	0.34	0.54
Physical functioning	0.46	0.61	0.47	0.42	0.59
Attendant symptoms and sleep	-	0.39	0.38	0.27	0.39
Social relationships	0.44	0.57	0.59	0.45	0.63
Anxiety	0.35	0.57	0.65	0.60	0.67
Well-being	0.38	0.60	0.79	0.70	0.79
Social functioning	0.42	0.57	0.51	0.41	0.60
Summary score	0.53	0.74	0.73	0.62	0.81

Footnote: only significant correlations are shown.

Validity

Concurrent validity

The MRF-28 and SRI total score correlated significantly with all CRQ domains (Table 3). The best correlations for both questionnaires were found with the CRQ fatigue domain. The anxiety and well-being domain of the SRI correlated highest with the CRQ emotion domain. The MRF-28 cognition domain did not correlate with any of the CRQ domains. The SRI attendant symptoms and sleep did not correlate with the CRQ dyspnoea domain.

Construct validity

The physical domains of the questionnaires, which are the MRF-28 daily activities domain, the SRI physical functioning domain, and the CRQ dyspnoea domain, correlated strongly with GARS (rho=0.75, rho=0.86, rho=0.42 respectively), and with dyspnoea scores and the 6-minute walking distance. The highest correlations with these physical parameters were found for the SRI domain. Emotional domains, which are the SRI anxiety and SRI psychological wellbeing domain, and the CRQ emotion and mastery domain, correlated strongly with both HADS anxiety and depression. Again the highest correlations were found for the SRI psychological well-being domain.

Only the MRF-28 daily activities and invalidity domains and three SRI domains correlated weakly to moderately with pulmonary function parameters, while none of the CRQ domains did. The MRF-28 invalidity domain contains questions on effort and social activities. It correlated moderately both with physical and psychological parameters. However, no MRF-28 domain correlated as strongly with mood state as

Table 4. Spearman's rank correlations between physiological parameters and MRF-28, SRI, and CRQ scores.

	MRF-28				SRI								CRQ				
	daily	*cog*	*inv*	*total*	*RC*	*PF*	*AS*	*SR*	*AX*	*WB*	*SF*	*SS*	*dys*	*fat*	*em*	*mas*	*total*
Exacerbations	0.36	-	0.30	***0.40***	0.37	0.43	-	0.43	0.35	-	0.45	***0.46***	0.35	0.33	0.31	0.27	***0.37***
FEV_1% pr	0.27	-	0.40	***0.33***	-	0.33	-	-	0.26	0.27	0.26	***0.27***	-	-	-	-	-
VC, L	0.39	-	0.27	***0.30***	-	0.27	0.33	-	-	0.28	0.35	***0.32***	0.28	-	-	-	***0.26***
RV%TLC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
$P_I$max, kPa	0.34	-	-	-	-	0.26	-	-	-	-	0.25	-	-	-	-	-	-
VO_2max, ml/min/kg	0.31	-	0.40	***0.26***	-	0.38	-	-	-	-	0.25	-	-	-	-	-	-
6-mwd, m	0.53	-	0.50	***0.50***	0.38	0.60	-	0.48	0.29	0.25	0.58	***0.49***	0.33	0.39	0.30	0.23	***0.36***
PaO_2, kPa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
$PaCO_2$,kPa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
pH	-	0.27	-	-													
HCO_3	-	-	-	-	-	-	-	0.32	-	-	-	-	-	-	-	-	-
Lactate, mmol/L	-	0.24	-	***0.26***	-	0.30	-	0.33	-	0.29	0.36	***0.30***	-	0.26	0.36	0.29	***0.33***
GARS	0.75	-	0.59	***0.70***	0.49	0.86	-	0.53	0.40	0.36	0.66	***0.65***	0.42	0.52	0.39	0.33	***0.47***
HADS depression	0.52	-	0.48	***0.57***	0.41	0.54	0.26	0.61	0.54	0.68	0.58	***0.68***	0.29	0.61	0.60	0.56	***0.65***
HADS anxiety	0.43	-	0.56	***0.56***	0.50	0.51	0.39	0.56	0.69	0.79	0.54	***0.75***	0.30	0.54	0.75	0.72	***0.74***
BDI	0.67	-	0.58	***0.68***	0.57	0.67	-	0.43	0.41	0.40	0.51	***0.59***	0.53	0.63	0.40	0.32	***0.54***
MRC	0.49	-	0.50	***0.47***	0.43	0.59	-	0.30	0.26	-	0.43	***0.41***	0.41	0.33	-	-	***0.27***

Footnote: Only significant correlations ($p<0.01$) are shown. Correlations with total scores are shown in bold italics.
MRF-28 domains: daily activities (daily), cognition (cog), invalidity (inv); SRI domains: respiratory complaints (RC), physical functioning (PF), attendant symptoms and sleep (AS), social relationships (SR), anxiety (AX), psychological well-being (WB), social functioning (SF) and a summary scale (SS); CRQ domains: dyspnoea (dys), fatigue (fat), emotion (em), and mastery (mas).
VO_2max: maximal oxygen uptake during cycle ergometry; Lactate: lactate levels from arterial blood sample. For the remaining abbreviations see footnote Table 1.

Table 5. Backward multiple regression analyses.

	MRF-28 total score (%)		SRI total score (%)		CRQ total score (points)	
	B	R^2	*B*	R^2	*B*	R^2
GARS, points*	0.7 (0.3 to 1.1)	0.52	-0.4 (-0.6 to -0.3)	0.13	-	-
HADS anxiety, points†	1.2 (0.3 to 2.1)	0.05	-1.7 (-2.2 to -1.2)	0.56	-2.3 (-3.0 to -1.5)	0.51
BDI, points‡	- 4.1 (-6.4 to -1.7)	0.08	-	-	2.5 (0.7 to 4.2)	0.06
Gender, female	6.0 (0.8 to 12.7)	0.01	-	-	-8.6 (-14.6 to 2.5)	0.03
Exacerbations, frequent (›3/yr)	-	-	-4.9 (-8.7 to -1.1)	0.03		
Lactate, mmol/L	-	-	-	-	-6.7 (-12.0 to -1.4)	0.03
Cumulative R^2		0.66		0.72		0.63

Footnote: Included as independent variables in the models were gender, exacerbation frequency, FEV_1% predicted, lactate, GARS score, HADS anxiety score and BDI. Only variables that were included into the final models are shown. B: unstandardised regression coefficient (95% CI), which indicates predicted increase in questionnaire total scores for 1 unit increase in the given variable. R^2: proportion of explained variance for independent variables included in the backward model. * GARS: score from best to worst: 18 to 72 points; HADS anxiety score from 0 to 21 points; BDI score from 12 to 0 points; Gender: 0=male; 1= female; exacerbation frequency: few exacerbations (coded as zero; ,≤3 exacerbations/year) vs. frequent exacerbations (coded as 1; ›3/year). For the remaining abbreviations see footnote table 1 and footnote table 4.

did the psychological domains of the other questionnaires. The cognition domain did not correlate with any parameters at all, also not with arterial blood gases. Overall, the SRI contains domains that correlated most strongly both with physical and psychological parameters. Interestingly, several domains of the SRI correlated with bicarbonate levels (Table 4).

Determinants of HRQoL

Of the variance in the MRF-28 total score, 66% was explained by gender, GARS score, HADS anxiety score, and BDI. The largest part of the variance in MRF-28 total score was explained by the GARS score (52%). Of the total variance in SRI summary score 72% was explained by HADS anxiety, GARS, and exacerbation frequency. The largest part of the total explained variance (56%) was attributable to the HADS anxiety score. Of the total variance in CRQ total score, 63% was explained by gender, lactate at rest, HADS anxiety, and BDI scores, with the largest part (51%) explained by HADS anxiety score (Table 5).

To strengthen our conclusions based on the present model with seven variables, we tested the model with only GARS and HADS anxiety included. For the CRQ and SRI, this model was again dominated by the HADS anxiety, while for the MRF-28 it was dominated by the GARS.

DISCUSSION

The present study shows for the first time that the recently developed MRF-28 and SRI are reliable and valid HRQoL questionnaires in a homogeneous group of COPD patients with CHRF. Overall, the MRF-28 total score was more related to activities of daily living, and less to psychological functioning. The SRI total score, like the CRQ total score, was most strongly related to anxiety and depression. In addition, the SRI total score was also substantially related to daily activity level.

Two results from the present study advocate the use of the MRF-28 and/or SRI in addition to or instead of the CRQ in patients with chronic respiratory failure. First, the MRF-28 and SRI contain items on specific problems that patients with CHRF might encounter that are not included in the CRQ. Secondly, we showed that construct validity was slightly better for the MRF-28 and especially the SRI compared to the CRQ in these patients. The version of the CRQ as used in the present study necessitates an interviewer, while the MRF-28 and SRI are self-administrated. The MRF might be more attractive in the practical sense as it contains 28 items and took the patients about 10 minutes to complete, while the SRI contains 49 items and takes 20 minutes to complete. However, as answer possibilities were clearly indicated both questionnaires were easy to complete for the patients.

The importance of addressing the care for patients with end-stage COPD is increasingly recognised [27]. Once chronic respiratory failure develops, a patient often becomes limited by specific symptoms and complaints that negatively influence HRQoL [28]. Patients might experience severe breathlessness at minimal effort or already at rest. High carbon dioxide levels might cause headaches or concentration problems. These problems reduce the ability to perform activities of daily living. Social relationships and activities become problematic and patients might become depressed or anxious.

A good HRQoL questionnaire should include all the items that are considered to be important for HRQoL in these patients [10]. Because the CRQ was not designed in patients with respiratory failure, a need was felt for a HRQoL questionnaire that included items about complaints and symptoms specific for patients with chronic respiratory failure [10]. However, the MRF-28 and SRI were designed in a mixed group of patients with chronic respiratory failure, not exclusively in patients with COPD [11,12].The present study investigated these questionnaires in a homogeneous group of COPD patients with chronic hypercapnic respiratory failure. We suggest that in the future, the MRF-28 and SRI could probably be added to or even substitute the CRQ in the assessment of HRQoL in COPD patients with C(H)RF.

The MRF-28 and SRI add the following items that are considered to be important in these patients. The MRF-28 adds the cognition domain, which contains 4 items on the effects of impaired memory, attention and concentration on daily living. It

has been shown that neurophysiological functioning is impaired in COPD patients, especially in patients who were hypoxemic [29]. In our hypercapnic COPD patients, 74% answered at least 1 and 56% at least 2 out of 4 questions of the cognition domain as being true. So, cognitive problems are frequently encountered by patients with CHRF. Still, we did not find a relationship with resting blood gases. However, the cognition domain is very short and probably too limited to find this relationship. In addition, an obvious floor and ceiling effect was observed for this domain (Table 2). These limitations advocate the addition of more items in the cognition domain.

The SRI (physical functioning) domains correlated with bicarbonate levels, the most robust parameter for the severity of CHRF. As only the SRI seemed to be able to pick up the influence of bicarbonate levels on physical functioning and social activities, we advocate the use of the SRI in intervention studies aimed at improving the degree of respiratory failure. This is in line with a previous study that showed a high correlation between a reduction in bicarbonate level following establishment of home mechanical ventilation and an increase in the SRI summary scale [30].

Construct validity of the MRF-28 and SRI was better compared to construct validity of the CRQ in this patient group. MRF-28 and especially the SRI scores correlated more strongly with other measures that assessed the same construct. As compared to the CRQ dyspnoea and fatigue domains, the MRF-28 daily activity domain and SRI physical functioning domain correlated more strongly with daily activities, dyspnoea, and exercise tolerance. In addition, the SRI psychological domains correlated more strongly with mood state as compared to the respective CRQ domains. The MRF-28 contains no psychological domain. The invalidity domain contains items both on feeling of invalidity, effort, and social activities. Therefore, it was also unsurprising that correlations with psychological parameters were only moderate.
The MRF-28, SRI, and CRQ emphasize different aspects of HRQoL. For the CRQ, anxiety accounted for a large part of the total explained variance in total score. This is in line with the study of Haijro et al who found that HADS anxiety next to BDI scores accounted for a large percentage of variance in CRQ [31]. For the SRI, as for the CRQ, anxiety also accounted for a large part of the total variance in the summary scale. In addition, for the SRI, restrictions in activities of daily living accounted for a substantial part (13%). However, in the MRF-28, the emphasis was on restrictions in activities of daily living. HADS anxiety, on the contrary, explained only 5% of the total variance in MRF-28 score. As mood state was shown to have substantial effects on HRQoL in patients with chronic hypercapnic respiratory failure [32], the underexposure of psychological aspects is a disadvantage of the MRF-28. Therefore, we recommend using the MRF-28 in addition to the SRI and not as a substitute. Now that we evaluated reliability and validity of the two new questionnaires in a homogeneous group of COPD patients with CHRF not on mechanical ventilation, responsiveness of the different questionnaires should be evaluated in intervention studies on for example pulmonary rehabilitation and home mechanical ventilation.

The MRF-28 and SRI are not widely used yet, which makes it difficult to compare our scores with previous studies. We found somewhat higher MRF-28 scores (indicating worse HRQoL) compared to Carone [11]. This can be explained by the fact that our patients had more severe airflow obstruction. Janssens et al investigated the MRF-28 in a group of patients treated with HMV, but included only 15% COPD patients [33]. Clini et al used the MRF-28 as an outcome measure in their study on HMV in COPD, however, they mentioned only change in scores and no absolute scores [34]. Recently, Carone et al showed that pulmonary rehabilitation increases MRF-28 scores in COPD patients with chronic respiratory failure. Scores were comparable except for a better (lower) cognition domain score in our study, which might be explained by a lower age in our patients [5]. Our SRI scores were comparable to the scores found by Windisch [12].

In conclusion, to include the most extensive measurement of HRQoL in COPD patients with CHRF, we recommend using the SRI. The emphasis in the MRF-28 is mostly on restrictions in activities of daily living, but it underscores the importance of psychological aspects in these patients. However, the MRF-28 adds the cognition domain with which prevalent and relevant problems in these patients are addressed. Therefore the addition of this domain might be a reason to add the MRF-28 in intervention studies.

Acknowledgements

The authors would like to thank Désirée Jansen (Department of Epidemiology, University Medical Center Groningen, University of Groningen) for statistical advice.

REFERENCES

1. Devereaux G. Definition, epidemiology, and risk factors. *BMJ* 2006; 332: 1142-1144.
2. Sahn SA, Nett LM, Petty TL. Ten year follow-up of a comprehensive rehabilitation program for severe COPD. *Chest* 1980; 77 (Suppl): 311-314.
3. Chailleux E, Fauroux B, Binet F, Dautzenberg B, Polu JM. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. *Chest* 1996; 109: 741-749.
4. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F et al. Factors in maintaining long-term improvements in health-related quality of life after pulmonary rehabilitation for COPD. *Qual Life Res* 2005: 14: 2315-2321.
5. Carone M, Patessio A, Ambrosino N, Baiardi P, Balbi B, Balzano G, Cuomo V, Donner CF, Fracchia C, Nava S, Neri M, Pozzi E, Vitacca M, Spanevello A. Efficacy of pulmonary rehabilitation in chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD): The Maugeri study. *Respir Med* 2007; 101: 2447-2453.
6. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; 42: 773-778.
7. Harper R, Brazier JE, Waterhouse JC, Walters SJ, Jones NM, Howard P. Comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. *Thorax* 1997; 52: 879-887.
8. Güell R, Resqueti V, Sangenis M, Morante F, Martorell B, Casan P et al. Impact of pulmonary rehabilitation on psychosocial morbidity in patients with severe COPD. *Chest* 2006; 129: 899-904.
9. Wijkstra PJ, TenVergert EM, van Altena R, Otten V, Postma DS, Kraan J et al. Reliability and validity of the Chronic Respiratory Questionnaire. *Thorax* 1994; 49: 465-467.
10. American thoracic Society/ European Respiratory Society Statement on Pulmonary Rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390-1413.
11. Carone M, Bertolotti G, Anchisi F, Zotti AM, Donner CF, Jones P W on behalf of the Quality of Life in Chronic Respiratory Failure Group. Analysis of factors that characterise health impairment in patients with chronic respiratory failure. *Eur Respir J* 1999; 13: 1293-1300.
12. Windisch W, Freidel K, Schucher B, Baumann H, Wiebel M, Matthys H et al. The severe Respiratory Insufficiency (SRI) Questionnaire. A Specific measure of health-related quality of life in patients receiving home mechanical ventilation. *J Epidemiol* 2003; 56: 752-759.
13. Lenfant C, Khaltaev N. Global Strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop. Executive summary 2005.
14. Roussos C, Koutsoukou A. Respiratory Failure. *Eur Respir J* 2003; 222 (47 Suppl): 3s-14s
15. M. R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C. P. M. van der Grinten, P. Gustafsson, R. Jensen, D. C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O. F. Pedersen, R. Pellegrino, G. Viegi, and J. Wanger. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319-338.
16. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Hankinson J, Jensen R, Johnson D, MacIntyre N, McKay R, Millere MR, Navajas D, Pellegrino R, Viegi G. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511-522.
17. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969; 99: 692-702.
18. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J.* 1985 Apr 15;132: 919-23
19. Steele BRN. Timed walking tests of exercise capacity in chronic cardiopulmonary illness. *J Cardiopulm Rehab* 1996; 16: 25-33.
20. Fletcher, CM, Elmes, PC, Wood, CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959; 1: 257-266
21. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnoea. *Chest* 1988; 93: 580-586.

22. Mahler DA. The measurement of dyspnea: contents, interobserver agreement and physiological correlates of two new clinical indexes. *Chest* 1984; 85: 751-758.
23. Kempen GIJM, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen activity restriction scale: conceptual framework and psychometric properties. *Soc Sci Med* 1996; 11: 1601-1610.
24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-370.
25. Schuck P. Assessing reproducibility for interval data in health-related quality of life questionnaires: which coefficient should be used? *Qual Life Res* 2004; 13: 571-586.
26. Curtis JR, Patrick DL. The assessment of health status among patients with COPD. *Eur Respir J* 2003; 21 (41 Suppl): 36s-45s.
27. Ambrosino N, Golstein R. Series on comprehensive management of end-stage COPD. *Eur Respir J* 2007; 30: 828-30.
28. Simonds AK. Care of end-stage lung disease. *Breathe* 2006; 4: 315-20.
29. Grant I, Prigatano GP, Heaton RK, McSweeny AJ, Wright EC, Adams KM. Progressive neuropsychological impairment and hypoxaemia. *Arch Gen Psychiatry* 1987; 44: 999-1006.
30. Windisch W, Dreher M, Storre JH, Sorichter S. Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. *Respir Physiol Neurobiol* 2006; 150: 251-260.
31. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 785-790.
32. Lacasse Y, Goldstein R. Health status and psychological effects. *Eur Respir J* 2007; (in Press)
33. Janssens JP, Héritier-Praz A, Carone M, Burdet L, Fitting JW, Uldry C et al. Validity and Reliability of a French version of the MRF-28 health-related quality of Life questionnaire. *Respiration* 2004; 71: 567-574.
34. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; 20: 529-358.

SUPPLEMENTARY MATERIAL

Patients

Exclusion because of OSAS

A polygraphy (Embletta pds, Medcare Automation BV, Amsterdam, the Netherlands) was performed in patients with a body mass index >30 kg/m^2 and/or complaints of frequent sleep disturbances, snoring, or excessive daytime sleepiness. Patients were excluded if the polygraphy revealed an apnoea/hypopnoea index ≥ 10 episodes/hour.

Measurements

Pulmonary function testing

All patients performed lung function testing post bronchodilatation with 400 microgram salbutamol. Vital capacity (VC) and forced expiratory volume in 1 second (FEV_1) were measured according to ERS criteria [1]. From a least 3 technical correct measurements, the highest value of at least 2 reproducible values was used (with ≤150 ml difference between those 2 measurements). Lung volumes, total lung capacity, functional residual capacity and residual volume, were analysed by body plethysmography [2]. Furthermore, maximal inspiratory pressure ($P_I$max) was measured at residual volume after maximal expiration. The manoeuvre was repeated at least 5 times with 1 minute rest between the measurements until 3 readings were obtained with less than 10% variance between the measurements. Pressures had to be maintained at least 1 second [3] (Masterscreen PFT, Viasys, Houten, the Netherlands).

Exercise tests

All exercise tests were performed post bronchodilatation with 400 micrograms salbutamol.

Cycle ergometry

All patients performed a maximal incremental cycle ergometry [4]. During the test, oxygen uptake (VO_2) was measured continuously (Oxycon Pro, Viasys, Bilthoven, the Netherlands). Furthermore, a catheter was placed in the radial artery in order to obtain an arterial sample at rest, every other minute during the incremental phase, and after 2 minutes of recovery. The measurements started with 5 minutes of rest, followed by 1 minute unloaded pedalling, followed by the incremental phase with an increase with 5 Watt per minute until the patient reached volitional exhaustion.

6-minute walking test

A 6-minute walking test was performed indoors, along a 40-meter flat, straight corridor, with the turnaround point marked with a cone. Patients used their usual walking aids and, if applicable, their usual ambulatory oxygen therapy during the test. The test assistant gave standardised encouragements every 30 seconds [5, 6].

Maugeri Respiratory Failure Questionnaire

The MRF-28 consists of 3 separate domains and a total score [7]. The daily activities domain contains 11 items related to dyspnoea during daily activities and impairments in daily activities. The cognition domain contains 4 items related to memory function, attention and concentration tasks. The invalidity domain contains 5 items on self-image, social functioning and relationships. Furthermore, the total score contains additional items related to fatigue, depression and problems with treatment, giving a total of 28 items. Scores are coded as 1 (patient agrees with the item) or 0 (patient does not agree). Scores are than recalculated as a percentage of items with which the patient agrees. MRF-28 scores range from 0-100, with higher scores indicating worse HRQoL [7].

Severe Respiratory Insufficiency Questionnaire

The SRI contains 49 items divided in 7 subscales related to respiratory complaints (8 items), physical functioning (6 items), attendant symptoms and sleep (7 items), social relationships (6 items), anxiety (5 items), psychological well-being (9 items), social functioning (8 items), and a summary scale. Items are scores from 1 to 5, 35 items are then recoded, and the mean score is calculated to a percentage. SRI scores on each domain and the summary scale range from 0-100, with higher scores indicating better HRQoL [8].

Chronic Respiratory Questionnaire

We used the interviewed version of the Chronic Respiratory Questionnaire (CRQ). It contains 20 items divided into four dimensions: dyspnoea, fatigue, emotion, and mastery. The CRQ total scores range from 20 to 140, with higher scores indicating better HRQoL [9]. Physical function is assessed by asking the patients to quantify their dyspnoea during 5 frequently performed activities in daily life. They are asked to choose 5 activities from a list of 25 activities or they can mention activities not on the list. The CRQ dyspnoea domain scores range from 5 to 35. In previous studies in patients with COPD, CRQ dyspnoea values were reported ranging from 14.5 to 26.0 [10,11]. Physical function is also assessed by 4 items related to fatigue and energy level. The CRQ fatigue domain scores range from 4 to 27. Reference values reported for the fatigue domain ranged from 13.0 to 19.7 [10,11]. Emotional function, including the emotion and mastery dimensions, includes questions about frustration, depression, anxiety, panic, and fear for dyspnoea. The CRQ emotion domain scores range from 7 to 49, those of the mastery domain range from 4 to 28. Reference values reported in patients with COPD for the emotion domain ranged from 29.2 to 39.5 [10,12], for the mastery domain from 17.9 to 22.9 [10,12].

Medical Research Counsel (MRC)

The MRC is a 5-point scale (1: only dyspnoeic during heavy exercise; 5: too dyspnoeic to leave the house) containing items on various physical activities that precipitate dyspnoea [13]. Patients were instructed to read the descriptive statements and then select the statement which fitted best.

Baseline Dyspnoea Index (BDI)

The BDI consists of 3 domains (functional impairment, magnitude of task and magnitude of effort) containing items that precipitate dyspnoea [14, 15]. The score for each domain ranges from 0 to 4 (0: maximal impairment because of dyspnoea, 4: no impairment); with the baseline total score ranging from 0 to 12. Patients were instructed to read the descriptive statements and then select 1 item from each domain which fitted best.

Activities of daily living

The Groningen activity and restriction scale (GARS) was used to assess disability in personal care and domestic activities. It consists of 18 items covering different domains of daily living, with each item score ranging from 1 (yes, I can do that independently without effort) to 4 (no, I can only do that with help from others) [16].

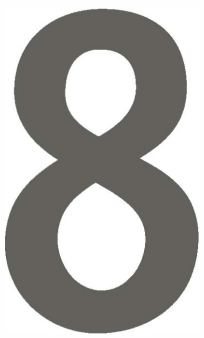
Mood state

The hospital anxiety and depression scale (HADS) was used to assess mood state. It contains 7 items assessing anxiety and 7 items assessing depression [17]. Scores per item range from 0 (no anxiety/ no depression) to 3 (maximal anxiety/ depression). Separate anxiety and depression scores (ranging from 0-21) were obtained.

SUPPLEMENT: REFERENCES

1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur. Respir.* J 2005; 26: 319 - 338.
2. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Hankinson J, Jensen R, Johnson D, MacIntyre N, McKay R, Millere MR, Navajas D, Pellegrino R, Viegi G. Standardisation of the measurement of lung volumes. *Eur Respir* J 2005; 26: 511-522.
3. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969; 99: 692-702.
4. American Thoracic Society/ American College of Chest Physicians. ATS/ ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211-277.
5. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc* J 1985; 132: 919-923
6. Steele BRN. Timed walking tests of exercise capacity in chronic cardiopulmonary illness. J *Cardiopulm Rehab* 1996; 16: 25-33.
7. Carone M, Bertolotti G, Anchisi F, Zotti AM, Donner CF, Jones PW on behalf of the Quality of Life in Chronic Respiratory Failure Group. Analysis of factors that characterise health impairment in patients with chronic respiratory failure. *Eur Respir* J 1999; 13: 1293-1300.
8. Windisch W, Freidel K, Schucher B, Baumann H, Wiebel M, Matthys H et al. The severe Respiratory Insufficiency (SRI) Questionnaire. A Specific measure of health-related quality of life in patients receiving home mechanical ventilation. *J Epidemiol* 2003; 56: 752-759.
9. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; 42: 773-778.
10. Harper R, Brazier JE, Waterhouse JC, Walters SJ, Jones NM, Howard P. Comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. *Thorax* 1997;52: 879-887.
11. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med.* 2003; 167: 544-549.
12. González E, Herrejón A, Inchaurraga I, Blanquer R. Determinants of health-related quality of life in patients with pulmonary emphysema. *Respir Med* 2005; 99: 638-644.
13. Fletcher, CM, Elmes, PC, Wood, CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. BMJ 1959; 1: 257-266
14. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnoea. *Chest* 1988; 93: 580-586.
15. Mahler DA. The measurement of dyspnea: contents, interobserver agreement and physiological correlates of two new clinical indexes. *Chest* 1984; 85: 751-758.
16. Kempen GIJM, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen activity restriction scale: conceptual framework and psychometric properties. *Soc Sci Med* 1996; 11: 1601-1610.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-370.

CHAPTER



Nocturnal noninvasive ventilation in addition to rehabilitation in hypercapnic COPD patients

Submitted

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ABSTRACT

Rationale: Patients with chronic obstructive pulmonary disease (COPD) and chronic respiratory failure experience limitations in daily and social activities and poor health-related quality of life. Although pulmonary rehabilitation has been shown to improve outcomes in COPD, in the most severe patients positive results of pulmonary rehabilitation have been difficult to demonstrate. Long-term noninvasive positive pressure ventilation (NIPPV) might improve the outcomes of pulmonary rehabilitation in patients with severe COPD and chronic respiratory failure.

Objective: To investigate whether nocturnal NIPPV in addition to pulmonary rehabilitation as compared to pulmonary rehabilitation alone improves health-related quality of life, arterial blood gases, pulmonary function, exercise tolerance, dyspnoea, and daily activities in COPD patients with chronic hypercapnic respiratory failure.

Measurements: Seventy-two COPD patients were randomly assigned to nocturnal NIPPV in addition to rehabilitation (n=37) or rehabilitation alone (n=35). Before and after the 3-months intervention period outcome measures were assessed.

Main results: The Chronic Respiratory Questionnaire total score improved 15.1 points with NIPPV + rehabilitation, compared to 8.7 points with only rehabilitation. The difference of 7.5 points was not significant ($p=0.08$). However, compared to rehabilitation alone, the difference in the fatigue domain was greater with NIPPV + rehabilitation (mean difference 3.3 points, $p<0.01$), as was the improvement in the Maugeri Respiratory Failure questionnaire total score (mean difference -10%, $p<0.03$) and its cognition domain (mean difference -22%, $p<0.02$). Only one of the eight domains of the Severe Respiratory Insufficiency questionnaire improved without NIPPV, while with the addition of NIPPV six domains improved. Furthermore, NIPPV improved daytime arterial carbon dioxide pressure (mean difference -0.3 kPa; $p<0.01$), and daily step count (mean difference 1269 steps/ day, $p<0.02$). This was accompanied by an increased daytime minute ventilation (mean difference 1.4 L; $p<0.001$).

Conclusions: Nocturnal NIPPV augments the benefits of pulmonary rehabilitation in COPD patients with chronic hypercapnic respiratory failure.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide [1]. Due to the progressive nature of the disease, many patients will develop severe COPD and chronic respiratory failure [2]. Once chronic respiratory failure is present, patients are often severely dyspnoeic at low exercise levels, and their quality of life is reduced [3]. Furthermore, mortality is high in these patients [4].

Pulmonary rehabilitation has been shown to improve exercise tolerance, dyspnoea, and health-related quality of life, and to reduce health care utilization [5,6]. Patients with severe COPD were initially found to have little benefit from a home-based rehabilitation program [7]. Later on, however, positive effects of a centre-based program were found in very severe COPD patients [8], even in COPD patients with chronic respiratory failure [9]. Nevertheless, because of extreme breathlessness and severe deconditioning, patients with severe COPD often cannot achieve high exercise intensities. Therefore, for these severe COPD patients, additive therapies, like noninvasive ventilation, are needed.

Trials on noninvasive ventilation in stable COPD have yielded conflicting results [10-18]. A recent meta-analysis did not show beneficial effects on daytime blood gases, lung function, respiratory muscle function, exercise tolerance and mortality [19]. The studies differed considerably in patient selection, the mode and duration of ventilation, ventilatory settings, and the degree of assistance and time to adjust to the ventilator.

Of all studies on noninvasive ventilation, only two studies have investigated it as an additional therapy next to pulmonary rehabilitation [15,20]. One of these studies used negative pressure ventilation [20]. In the other study, in patients with mild respiratory failure, despite poor compliance with the ventilator, improvements in exercise tolerance and health-related quality of life were found with the addition of noninvasive positive pressure ventilation [15].

We hypothesize that noninvasive intermittent positive pressure ventilation (NIPPV) augments the benefits of pulmonary rehabilitation in severe COPD patients with chronic hypercapnic respiratory failure. Therefore, we investigated in a randomised, parallel group, controlled clinical trial, whether noninvasive intermittent positive pressure ventilation (NIPPV) in addition to pulmonary rehabilitation as compared to pulmonary rehabilitation alone improves health-related quality of life, arterial blood gases, pulmonary function, exercise tolerance, dyspnoea, daily activities, and mood state, in severe COPD patients with chronic hypercapnic respiratory failure.

METHODS

Patients

Patients were recruited from hospitals in the northern part of the Netherlands. Inclusion criteria were: stable clinical condition (no exacerbation in the four weeks prior to study participation); severe COPD (GOLD stage III or IV [21] (forced expiratory volume in 1 second (FEV_1) / forced vital capacity < 70% and FEV_1 < 50%

predicted); hypercapnia at rest (arterial carbon dioxide pressure ($PaCO_2$) > 6.0 kPa while breathing room air); and age between 40 and 76 years. Exclusion criteria were: cardiac or neuromuscular diseases limiting exercise tolerance; previous exposure to chronic NIPPV or to a pulmonary rehabilitation program during the previous 18 months; or an apnoea/ hypopnoea index ≥ 10 / hour (supplementary material).
The study was approved by the local Medical Ethical Committee. All participants gave written informed consent to participate. The study is registered at ClinicalTrials.Gov (ID NCT00135538).

Study design

The design of the study was parallel-group, randomised, controlled. Patients were randomly assigned to nocturnal NIPPV in addition to rehabilitation (NIPPV + PR) or to rehabilitation alone (PR). Randomisation was computerised and performed by an independent statistician. To achieve an equal distribution of these parameters between the two groups, the randomisation was performed with the minimisation method with factors for FEV_1 (≤ 1.2 L or > 1.2 L), arterial carbon dioxide pressure ($PaCO_2$) (≤ 7.0 kPa or > 7.0 kPa) and body mass index (≤ 30 kg/m² or > 30 kg/m²) [22].
After randomisation, patients were maintained on their usual medication for a 12-week run-in period. Thereafter, the patients commenced a 12-week multidisciplinary rehabilitation program, in either an in-patient or out-patient setting. The program consisted of strength training, cycling, walking, inspiratory muscle training, education, and psychological and/or nutritional support if necessary. Patients trained 3 times a week for 1 hour each session fully supervised (for details: supplementary material).
In the PR + NIPPV group, immediately before starting the rehabilitation program, patients were instituted on nocturnal bilevel NIPPV (bilevel positive airway pressure (BiPAP), spontaneous/ timed mode (S/T), via nasal or full face mask). Patients were admitted to the hospital to get instituted on NIPPV. Inspiratory airway pressure (IPAP) was increased up to maximal tolerated pressure titrated towards an optimal correction of nocturnal arterial blood gases ($PaCO_2$<6.0 kPa and arterial oxygen pressure (PaO_2)>8.0 kPa). Effectiveness of NIPPV was monitored by means of nocturnal blood gas registrations at baseline before institution on NIPPV, at the end of the in-hospital period, and after the rehabilitation program of three months.
Within one week before and after the intervention period the following measurements were performed: arterial blood gases; lung function; exercise testing (6-minute walking test [23, 24], incremental shuttle walk test [25], endurance shuttle walk test [26]); and assessments of dyspnoea (Medical Research Counsel [27], Borg scale [28]), health-related quality of life (Chronic Respiratory Questionnaire (CRQ) [29], Maugeri Respiratory Failure questionnaire (MRF-28) [30], and Severe Respiratory Insufficiency questionnaire (SRI) [31]), daily activity level (daily step count [32-34]), and mood state (Hospital Anxiety and Depression Scale (HADS) [35]).
Details of the rehabilitation program, institution on NIPPV, and measurements used are given in the supplementary material.

Sample size

The primary outcome parameter was health-related quality of life as measured by the CRQ. To detect a clinically relevant change in CRQ score of 10 points with 80% power, at least 40 patients per group were needed for the study [36]. Considering a probability of 20% drop-out of randomised patients, the target sample size was 50 patients per group.

Analyses and Statistics

Results were expressed as mean ± SD or median (range) according to the distribution of the data. Baseline data of the two groups were compared with independent t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables.

The main outcome parameters were evaluated in terms of patient completers. Outcomes were assessed in terms of changes from baseline (paired t-test or Wilcoxon signed rank test for separate groups according to the distribution of the data) and differences in changes from baseline between the two groups corrected for baseline values (linear regression analysis). For the Medical Research Counsel dyspnoea score, a chi-square test was used to assess differences in changes between groups. Overnight blood gas registration results were assessed by repeated measures ANOVA with post-hoc Bonferoni corrections.

SPSS 14.0 was used for all analyses. A p-value < 0.05 was considered significant.

RESULTS

Patients

Two hundred twenty seven patients with severe COPD who were hypercapnic in stable condition in the past six months were asked to participate in the study between September 2004 and January 2007. Of them, 87 patients agreed to participate in the study. As 15 patients did not satisfy the inclusion criteria, 72 patients were randomised.

During the run-in period, six patients randomised to the NIPPV + PR group dropped out (Figure 1). At baseline, there were no significant differences between groups in terms of patient demographics, lung function, arterial blood gases, walking distance, and CRQ scores (Table 1).

Patients who did not complete the study and treatment compliance

In the NIPPV + PR group, seven patients did not complete the study. Five patients could not adapt to the NIPPV (16%). One patient withdrew because of rheumatic complaints. One patient died of progressive respiratory failure due to a severe acute

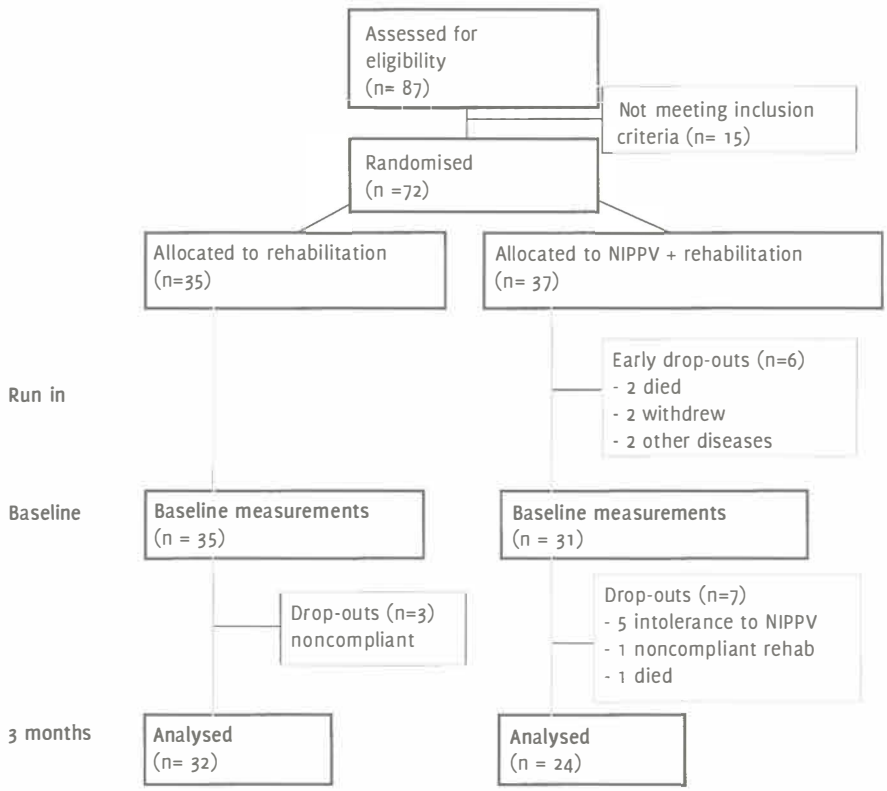


Figure 1. Flow diagram of the study progress.

COPD exacerbation after 69 days on NIPPV, despite initial blood gas improvements. The completers used the NIPPV on average 96% of the days with a median daily NIPPV use of 7.7 h (IQR 5.8 to 8.5 h/ day). In the NIPPV + PR group, the patients who did not complete the study had a lower FEV_1 (0.59 ± 0.17 versus 0.90 ± 0.38; $p<0.05$), and vital capacity (2.20 ± 0.61 versus 2.89 ± 0.82; $p<0.05$) and were more hyperinflated (residual volume % of total lung capacity 69 ± 6 versus 62 ± 8; $p<0.05$) compared to completers.

In the PR group, three patients did not complete the study because of non compliance (9%).The patients who did not complete the study in the PR group had a higher total lung capacity (144 ± 3% versus 122 ± 19%) and residual volume (255 ± 10% versus 220 ± 64%) compared to the completers in this group ($p<0.01$).

The number of rehabilitation sessions attended was not different between the groups (NIPPV + PR group: 39 ± 4 versus PR group: 40 ± 4 sessions (87% versus 89% of the prescribed sessions)). In both groups, the target peak workload as prescribed in the rehabilitation protocol (140% of the peak work load at baseline cycle ergometry) was achieved (NIPPV + PR: 140 (57-500) % versus in the PR group: 140 (63-350) %).

Table 1. Baseline characteristics.

Characteristics	NIPPV + rehabilitation	Rehabilitation
Subjects, n	31	35
Gender, M:F	18: 13	17: 18
Age, yrs	63 ± 10	61 ± 7
Patients on LTOT, n	14	16
In-hospital rehabilitation, n (%)	12 (39%)	17 (49%)
BMI, kg/m²	27.1 ± 6.4	27.5 ± 6.3
Pack years, yrs, median (IQR)	42 (31-57)	43 (24-58)
CRQ dyspnoea	16 ± 4	17 ± 5
CRQ fatigue	14 ± 3	13 ± 5
CRQ emotion	32 ± 7	30 ± 8
CRQ mastery	19 ± 4	17 ± 5
CRQ total score	81 ± 15	78 ± 19

Means ± SD or median (interquartile range, IQR) as indicated. There were no differences between the 2 groups at baseline. Baseline blood gases, exercise tolerance, and lung function data are presented in Table 2-4. LTOT: long-term oxygen therapy; BMI: body mass index; CRQ: chronic respiratory questionnaire (points).

NIPPV settings and overnight arterial blood gasses

Mean IPAP in the completers was 20 ± 4 cm H_2O. Mean expiratory airway pressure (EPAP) was 6 ± 2 cm H_2O. Respiratory rates on NIPPV were 18 ± 3 breaths/min, with an inspiration time of 0.9 ± 0.2 seconds and a rise time of 1.2 ± 0.6 seconds. Ventilator settings used in the drop-outs were not different (IPAP 18 ± 1 and EPAP 5 ± 1). Most patients were ventilated through a full face mask (70%), the remaining through a nose mask. Mask choice was also not different between the completers and non-completers. Using NIPPV, mean nocturnal $PaCO_2$ improved from 7.4 ± 1.1 kPa to 6.6 ± 0.7 kPa ($p<0.05$) at the end of the in-hospital institution. After three months mean nocturnal $PaCO_2$ was 6.4 ± 0.6 kPa (not significantly different from the latter). Mean nocturnal pH also improved significantly (7.36 ± 0.03 at baseline to 7.39 ± 0.03 at the end of the in-hospital institution to 7.40 ± 0.02 after three months; $p<0.05$). Additional oxygen was titrated to achieve oxygen saturation ≥ 90%. Mean nocturnal PaO_2 remained unchanged.

Health-related quality of life, mood state and dyspnoea

The CRQ total score improved significantly in both treatment groups (Figure 2; Table 5 supplementary material). However, the difference in change was not significant (mean difference 7.5 points (i.e. 0.4 point/ question), 95% CI -1.0 to 16.0, $p=0.08$). The CRQ fatigue domain improved significantly more in the NIPPV + PR group as compared to the PR group (Figure 2). The MRF-28 total score and the MRF-28 cognition domain also improved significantly more with the addition of NIPPV (Figure 2). The NIPPV group improved significantly on the SRI summary score as well as on five out of seven SRI subscales whereas the PR group improved significantly

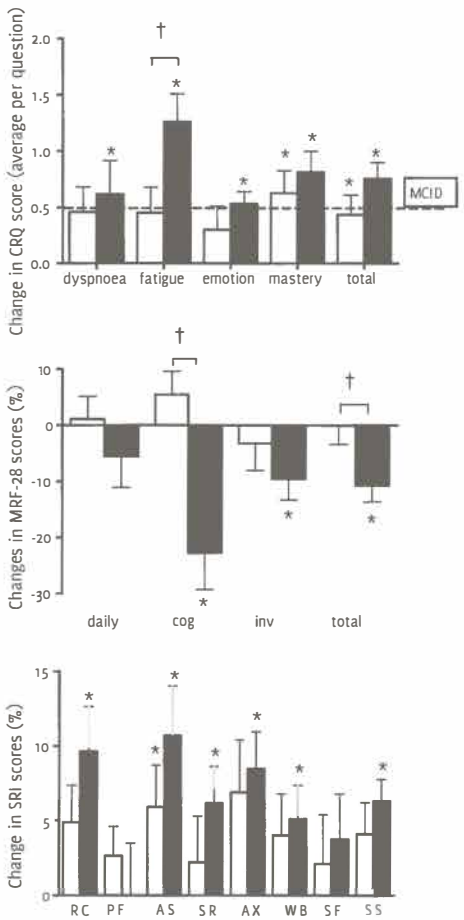


Figure 2. mean changes (+ SEM) in health-related quality of life scores after 3 months therapy in the NIPPV + rehabilitation group (black bars) versus the rehabilitation group (white bars). Chronic Respiratory Questionnaire (CRQ) contains the domains dyspnoea, fatigue, emotion, and mastery; Maugeri Respiratory Failure questionnaire (MRF-28) contains the domains: daily activities (daily), cognition (cog), invalidity (inv); Severe Respiratory Insufficiency (SRI) questionnaire contains the domains respiratory complaints (RC), physical functioning (PF), attendant symptoms and sleep (AS), social relationships (SR), anxiety (AX), psychological well-being (WB), social functioning (SF). MCID: minimal clinically important difference. * denotes significant change from baseline to 3 months within the group; †: denotes significant difference in change between groups (CRQ fatigue: mean difference in change between groups 3.3 points or 0.8 point/ question, 95% CI 0.8 to 5.7; MRF-28 cognition mean difference in change between groups 22%, 95% CI 9 to 35; MRF-28 total score mean difference in change between groups 10%, 95% CI -18 to -1).

only on the SRI attendant symptoms and sleep domain. Changes in SRI scores were not different between the two groups (Figure 2).

The Hospital Anxiety and Depression Scale (HADS) improved significantly in the NIPPV + PR group (depression: median change -1 points (IQR -4 to 0); anxiety: -2 points (-4 to 0)), whereas it did not in the PR group (depression: 0 points (-3 to 1); anxiety: 0 points (-3 to 1)). However, the difference was not significant between the groups ($p>0.05$). The MRC dyspnoea score improved in both groups (NIPPV + PR: median change -0.5 (IQR -1 to 0); PR: -1 (-1 to 0); $p = 0.13$).

Daytime arterial blood gases

After three months therapy, the $PaCO_2$ in the NIPPV + PR group improved significantly more compared to the PR group (Table 2 and Figure 3). The improvements in PaO_2,

Table 2. Changes in arterial blood gases after 3 months therapy.

		Baseline	After 3 months	Change within group	Between group difference in change (95% CI)
$PaCO_2$, kPa	N+R	6.89 ± 0.68	6.44 ± 0.69*	-0.45	-0.32 (-0.6 to -0.1) †
	R	6.81 ± 0.81	6.71 ± 0.58	-0.10	
PaO_2, kPa	N+R	7.82 ± 1.03	8.26 ± 1.20*	0.44	0.25 (-0.2 to 0.7)
	R	8.33 ± 1.25	8.33 ± 0.93	0.01	
HCO_3,mmol/L	N+R	29.2 ± 2.3	28.4 ± 2.4	-0.9	-0.7 (-1.8 to 0.4)
	R	29.4 ± 2.7	29.1 ± 1.8	-0.3	
BE, mmol/L	N+R	4.6 ± 2.0	3.6 ± 1.9*	-1.0	-0.52 (-1.4 to 0.3)
	R	4.4 ± 2.1	4.1 ± 1.4	-0.4	
pH	N+R	7.39 ± 0.03	7.40 ± 0.02	0.01	0.01 (-0.01 to 0.02)
	R	7.40 ± 0.03	7.40 ± 0.03	0.00	

Means ± SD. N+R: NIPPV + rehabilitation group; R: rehabilitation group; $PaCO_2$: arterial carbon dioxide pressure; PaO_2: arterial oxygen pressure; HCO_3: bicarbonate; BE: base excess. All assessments at daytime on room air at rest without NIPPV. * denotes significant change from baseline to 3 months within the group; †: denotes significant difference in change between groups.

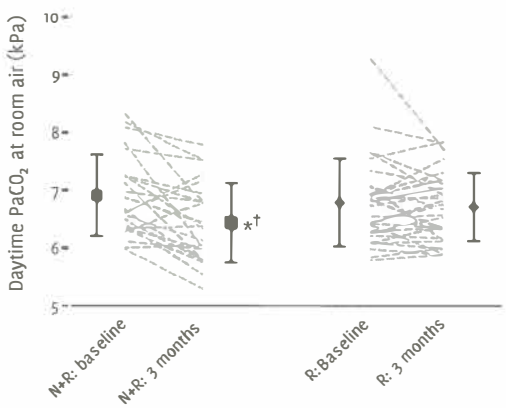


Figure 3. Individual changes (dotted grey lines) and mean ± SD of the changes in $PaCO_2$ in NIPPV + rehabilitation group (N+R, left ■) and rehabilitation (R, right ◆) group after 3 months therapy.

N+R: NIPPV + rehabilitation group; R: rehabilitation group; * denotes significant difference in change within the NIPPV + rehabilitation group. †: the improvement in $PaCO_2$ in the NIPPV +rehabilitation group was also significantly different from the change in the rehabilitation group.

HCO_3, pH, and base excess were not significantly different between the two groups (Table 2). The change in $PaCO_2$ after three months correlated with the baseline $PaCO_2$ ($r = 0.58$, $p<0.001$). Furthermore, the change in $PaCO_2$ correlated with the number of hours use of NIPPV/ day (rho = 0.44, p=0.04).

Exercise tolerance

Patients in both groups generally improved their exercise tolerance. There was no significant difference between the groups in change in 6-minute walking test,

endurance shuttle walking test, and incremental cycle ergometry. However, daily step count as measured at home increased significantly more with NIPPV+ PR compared to PR (Table 3).

Changes in lung mechanics and breathing patterns

Daytime resting minute ventilation improved significantly more with NIPPV + PR compared to PR. The increased minute ventilation was mainly attributable to an increase in tidal volume, as breathing frequency did not change. The NIPPV+ PR group improved significantly in $P_I$max, but the difference between the groups was not significant (Table 4). The other lung function parameters remained unchanged in both groups.

DISCUSSION

The present study shows that, although nocturnal NIPPV in addition to pulmonary rehabilitation as compared to rehabilitation alone did not improve our primary outcome (the CRQ total score (mean difference 7.5 points; 0.4 point/ question; p=0.08)), it did improve the CRQ fatigue domain, the MRF-28 cognition domain and the MRF-28 total health-related quality of life score, daytime arterial $PaCO_2$, and daily activity level in severe COPD patients with chronic hypercapnic respiratory failure. These improvements were accompanied by an increase in resting minute ventilation during the day in the patients in the NIPPV group. We found no significant improvements in pulmonary function, paced exercise testing, dyspnoea scores, anxiety and depression with the addition of NIPPV to pulmonary rehabilitation.

We did find an improvement in $PaCO_2$ in the NIPPV group, which is in contrast to results from Garrod and colleagues who also studied NIPPV added to PR [15]. The lack of effect on blood gases in their study could very well be due to a low compliance in their study; NIPPV was used a median 2.08 h/day. Secondly, a lower median IPAP of 16 was used. Thirdly, COPD patients with mild chronic respiratory failure were included (mean $PaCO_2$ 6.0 kPa, mean PaO_2 8.5 kPa). Finally, the effects of NIPPV on arterial blood gases were not carefully monitored and no target was defined for improvement in blood gases under NIPPV. Large positive effects were found on exercise tolerance and health-related quality of life which is unexplained by the arguments provided above.
Patients with more severe blood gas derangements seem to benefit more from NIPPV [11, 16, 17]. The present study included only patients with severe COPD and chronic hypercapnic respiratory failure. However, we had difficulty to include extremely severe COPD patients, as many of them believed rehabilitation would be too strenuous. Compared to others, we included a patient group with a slightly higher PaO_2 [11, 16, 17] which might explain our lack of significant effect of NIPPV on PaO_2. We adjusted ventilator settings based on nocturnal arterial blood gas registrations. On average, it turned out

Table 3. Changes in exercise tolerance after 3 months therapy.

		Baseline	After 3 months	Change within group	Between group difference in change (95% CI)
6MWD, m	N+R	318 ± 131	340 ± 119*	22	2 (-19 to 23)
	R	304 ± 112	325 ± 108*	22	
ESWT, m	N+R	260 (125-518)	375 (240-973)*	100	129 (-24 to 282)
	R	240 (120-585)	383 (150-693)	0	
Borg max	N+R	5.7 ± 2.3	4.4 ± 2.0*	1.3	-0.8 (-1.8 to 0.1)
	R	5.3 ± 2.0	5.0 ± 2.2	0.3	
PWR, watt	N+R	30 ± 21	35 ± 22*	5	1.3 (-3 to 6)
	R	27 ± 16	31 ± 20*	4	
Daily step count, steps/ day	N+R	1893 (591-3773)	2799 (891 - 6135)*	391	1269 (242-2296)†
	R	1680 (699-3538)	2093 (914-3155)	93	

Means ± SD for 6MWD, Borg max, and PWR and median (IQR) and median changes for ESWT, and daily step count. N+R: NIPPV + rehabilitation group; R: rehabilitation group. 6MWD: 6-minute walking distance, ESWT: endurance shuttle walk test, Borg max: maximum Borg score at ESWT; PWR: peak work load achieved at cycle ergometry. * denotes significant change from baseline to 3 months within the group; †: denotes significant difference in change between groups.

Table 4. Changes in lung function and breathing patterns after 3 months therapy.

		Baseline	After 3 months	Change within group	Between group difference in change (95% CI)
FEV_1, L	N+R	0.90 ± 0.38	0.89 ± 0.39	-0.01	-0.04 (-0.1 to 0.1)
	R	0.78 ± 0.30	0.81 ± 0.29	0.03	
VC, L	N+R	2.89 ± 0.82	2.98 ± 0.89	0.09	-0.07 (-0.3 to 0.2)
	R	2.47 ± 0.73	2.62 ± 0.86	0.15	
RV%TLC	N+R	62 ± 8	62 ± 10	-0.1	1 (-3 to 5)
	R	66 ± 10	64 ± 9	-2.2	
Air-trapping, L	N+R	0.98 ± 0.75	0.96 ± 0.67	-0.03	-0.02 (-0.3 to 0.3)
	R	0.94 ± 0.76	0.95 ± 0.65	0.01	
$P_I$max, kPa	N+R	5.0 ± 2.6	6.4 ± 2.3*	1.44	0.8 (-0.2 to 1.8)
	R	5.3 ± 2.2	5.9 ± 2.3	0.5	
V_E, L/ min	N+R	9.8 ± 3.0	10.6 ± 3.1	0.8	1.4 (0.3 to 2.4) †
	R	9.0 ± 1.9	8.6 ± 2.3	-0.4	
V_T, ml	N+R	506 ± 144	560 ± 135*	54	53 (-9 to 116)
	R	524 ± 129	519 ± 147	-6	
BF, breaths/ min	N+R	20 ± 5	19 ± 5	0.6	0.5 (-1.4 to 2.3)
	R	18 ± 4	17 ± 5	0.2	

Means ± SD. N+R: NIPPV+ rehabilitation versus; R: rehabilitation alone. FEV_1: forced expiratory volume in 1 second; VC: vital capacity; RV%TLC: residual volume as a percentage of total lung capacity; $P_I$max: maximal inspiratory pressure. V_E: minute ventilation during quiet breathing, V_T: tidal volume during quiet breathing, BF: breathing frequency during quiet breathing. * denotes significant change from baseline to 3 months within the group; †: denotes significant difference in change between groups.

that we used higher inspiratory pressures than previous randomised controlled trials have reported. However, in our study, there was no relationship between the height of the IPAP (r=-0.04) or the inspiratory pressure difference (IPAP-EPAP; r=0.01) and the change in $PaCO_2$ after three months.This was consistent with our nocturnal registrations where we noticed that although a certain IPAP level is necessary to achieve effects, further increasing the IPAP does not always result in improvement in blood gases. This emphasizes the importance of careful and reliable monitoring during institution of NIPPV. Our patients were instituted in hospital and carefully monitored during the first week. Only 2/31 (6%) dropped out during the training period, and three patients (10%) dropped out during the 3-months period at home during outpatient rehabilitation. This is an acceptable drop-out rate compared to other studies [11, 12]. In the patients who reached the 3 months measurement point, ventilator use was high with a median of 7.7 h/d. Only three patients used the ventilator less than five hours a day. The fact that compliance is important is confirmed by the relationship we found between the number of hours the NIPPV was used per night and the improvement in daytime arterial blood gases.

Improvement in health-related quality of life was the primary goal of our study. Although we did not find a significant effect on CRQ total score (our primary end-point), we did find significant improvements in the CRQ fatigue domain, the MRF-28 total score, and the MRF-28 cognition domain. Therefore we judge our study to show that adding NIPPV to pulmonary rehabilitation improves health-related quality of life. Only a few studies investigated the effects of NIPPV on health-related quality of life [11, 15, 16].When comparing our study to previous ones, one important aspect deserves attention. Our control group treated with pulmonary rehabilitation alone also improved (on CRQ mastery and total score, 6-minute walking distance, and incremental cycle workload). In contrast, in two other studies the control group deteriorated [11, 16]. We found a comparable difference in change in the CRQ fatigue score (3.2 points) compared to Garrod et al. [15], but did not find a significant difference in CRQ total score (7.5 points). However, baseline CRQ scores in the study of Garrod were very low, despite the fact that the patients did not have very severe COPD. In our study, on average, the NIPPV group had a clinically relevant improvement (minimal clinical relevant difference of >0.5 point/item [36]) on all CRQ domains and the CRQ total score, while the rehabilitation group improved clinically relevant only on the mastery domain. Improvements in health-related quality of life are frequently attributed to improved sleep quality. We did not objectively measure sleep quality. There was a relationship between the change in bicarbonate levels and the change in both the SRI (r= 0.46; p=0.001) and CRQ total score (r= -0.30; p=0.03), indicating that the degree of improvement in respiratory failure is associated with changes in health-related quality of life [37].
We found that NIPPV improved the cognition domain of the MRF-28. Probably improvement in daytime carbon dioxide contributes to the improvement in cognition, as there was a moderate correlation between the change in $PaCO_2$ at daytime and the change in the MRF-28 cognition score in the NIPPV group (r =0.51 (p=0.01)). Other factors, such as improved sleep quality, might also be important.

Although exercise tests did not significantly improve more with NIPPV, there was a trend towards an improvement in endurance capacity in the NIPPV group. Unsupervised daily step count did improve significantly more with NIPPV + PR compared to PR alone. An increase in daily step count was found before by Schönhofer, though in a mixed group of patients with chronic respiratory failure [38]. The increase in daily step count did not correlate with $PaCO_2$ change, nor did it correlate with change in breathlessness scores, formal exercise test scores, or activity domains of the quality of life questionnaires. This reflects the fact that the pedometer assesses different aspects of exercise tolerance, for example it might provide a reflection of daily submaximal activity, not measured with exercise test or questionnaires. These aspects might be more clinically relevant for the individual patient.

The mechanisms why nocturnal NIPPV might improve the outcomes of rehabilitation include: resting of the respiratory muscles [15, 39, 40]; improvement in internal milieu of the respiratory muscles [41]; improved lung mechanics [17, 42]; improved ventilation during the day [43, 44]; and improved sleep quality [11]. As this study was not designed to elucidate exact underlying mechanisms, we can only speculate about the mechanisms. We did not find evidence for the first three mechanisms. On the other hand, we, like others, did find an improvement in ventilation with higher minute ventilation during the day [43, 44]. We speculate that this was either caused by increased ventilatory response to CO_2 [42], or by improved endurance capacity of the respiratory muscles. Furthermore, we do believe that improved sleep quality is an important mechanism, as the patients in the NIPPV +PR group improved more on the CRQ fatigue domain and consequently were more active during the day.

The present study has some limitations. We did not use sham-ventilation in our control group, and so patients and investigators were not blinded to the therapy. We believe sham-ventilation is difficult to implement at home during the long period of this study. Secondly, we only included 72 patients while power calculation had provided that 40 versus 40 patients were needed to find a 10-point change in CRQ total score. However, recruitment was tedious and due to financial constraints we were unable to further extend the inclusion period. This might have influenced our results due to a type-II error for false negative outcomes. Effects that were already significant in our study with lower numbers of patients, however, remain valid (type I error unchanged set at 0.05).

In conclusion, noninvasive ventilation augments the benefits of pulmonary rehabilitation in COPD patients with chronic hypercapnic respiratory failure as it shows improvements in several measures of health-related quality of life, daytime gas exchange, ventilation and daily activity level. Furthermore, we found that the NIPPV acceptance rates were high as was the median number of hours use when careful assistance and monitoring were applied.

REFERENCES

1. Devereux G. Definition, epidemiology, and risk factors. *BMJ* 2006; 332: 1142-4.
2. Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J* 2003; 22: 47: 3s-14s.
3. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax* 2000; 55: 1000-6
4. Chailleux E, Fauroux B, Binet F, Dautzenberg B, Polu JM. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. *Chest* 1996; 109: 741-9.
5. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R, Herrerias C. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* 2007; 131: 4s-42s
6. Lacasse Y, Wong E, Guyatt GH, et al. Meta-analysis of respiratory rehabilitation in Chronic obstructive Pulmonary disease. *Lancet* 1996; 348: 1115-9.
7. Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized Controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients stratified with the MRC dyspnea scale. *Eur Respir J* 1998; 12: 363-9.
8. Ries AL, Make BJ, Lee SM, Krasna MJ, Bartels M, Crouch R, Fishman AP; National Emphysema Treatment Trial Research Group. The effects of pulmonary rehabilitation in the national emphysema treatment trial. *Chest* 2005; 128: 3799-809
9. Carone M, Patessio A, Ambrosino N, Baiardi P, Balbi B, Balzano G, Cuomo V, Donner CF, Fracchia C, Nava S, Neri M, Pozzi E, Vitacca M, Spanevello A. Efficacy of pulmonary rehabilitation in chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD): The Maugeri Study. *Respir Med.* 2007; 101: 2447-53
10. Strumpf DA, Millman RP, Carlisle CC, Grattan LM, Ryan SM, Erickson AD, Hill NS. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1991; 144:1234-9.
11. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med.* 1995; 152: 538-44.
12. Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. *Mayo Clin Proc* 1996; 71: 533-42.
13. Lin CC. Comparison between nocturnal nasal positive pressure ventilation combined with oxygen therapy and oxygen monotherapy in patients with severe COPD. *Am J Respir Crit Care Med.* 1996; 154: 353-8
14. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, Santolaria F. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest* 2000; 118: 1582-90.
15. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary non-invasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2000; 162: 1335-41.
16. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, Ambrosino N. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J.* 2002; 20: 529-38.
17. Díaz O, Bégin P, Torrealba B, Jover E, Lisboa C. Effects of noninvasive ventilation on lung hyperinflation in stable hypercapnic COPD. *Eur Respir J.* 2002; 20: 1490-8
18. Díaz O, Bégin P, Andresen M, Prieto ME, Castillo C, Jorquera J, Lisboa C. Physiological and clinical effects of diurnal noninvasive ventilation in hypercapnic COPD. *Eur Respir J.* 2005; 26: 1016-23.
19. Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. *Eur Respir J.* 2007: 30: 293-306.
20. Celli B, Lee H, Criner G, Bermudez M, Rassulo J, Gilmartin M, Miller G, Make B. Controlled trial of external negative pressure ventilation in patients with severe chronic airflow obstruction. *Am Rev Respir Dis.* 1989; 140: 1251-6
21. Lenfant C, Khaltaev N. Global Strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop. Executive summary 2005.

22. Pocock SL. Clinical Trials: a practical approach. Chichester, England: Johan Wiley, 1983: 84-7
23. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J.* 1985;132: 919-23
24. Steele BRN. Timed walking tests of exercise capacity in chronic cardiopulmonary illness. *J Cardiopulm Rehab* 1996; 16: 25-33.
25. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA. Comparison of the oxygen uptake during a conventional treadmill test and the shuttle walk test in chronic airflow limitation. *Eur Respir J* 1994; 7: 2016-20.
26. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 1999; 54: 213-22.
27. Mahler DA. The measurement of dyspnea: contents, interobserver agreement and physiological correlates of two new clinical indexes. Chest 1984; 85: 751-8.
28. Fletcher CM, Elmes PC, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959; 1: 257-66
29. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; 42: 773-8.
30. Carone M, Bertolotti G, Anchisi F, Zotti AM, Donner CF, Jones PW on behalf of the Quality of Life in Chronic Respiratory Failure Group. Analysis of factors that characterise health impairment in patients with chronic respiratory failure. *Eur Respir J* 1999; 13: 1293-1300.
31. Windisch W, Freidel K, Schucher B, Baumann H, Wiebel M, Matthys H, Petermann F. The severe Respiratory Insufficiency (SRI) Questionnaire: a Specific measure of health-related quality of life in patients receiving home mechanical ventilation. *J Epidemiol* 2003; 56: 752-9.
32. Schneider PL, Crouter SE, Bassett DR. Pedometer measures of free-living physical activity: comparison of 13 models. Med Sci Sports Exerc 2004; 36(2):331-335.
33. Tudor-Locke C, Williams JE, Reis JP, Pluto D. Utility of pedometers for assessing physical activity: construct validity. Sports Med 2004; 34(5):281-291.
34. Schneider PL, Crouter SE, Lukajic O, Bassett DR Jr. Accuracy and reliability of 10 pedometers for measuring steps over a 400-m walk. Med Sci Sports Exerc 2003; 35 (10):1779-1784.
35. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361-370.
36. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* 1989; 10: 407-15.
37. Windisch W, Dreher M, Storre JH, Sorichter S. Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. *Respir Physiol Neurobiol.* 2006; 150: 251-260.
38. Schönhofer B, Ardes P, Geibel M, Köhler D, Jones PW. Evaluation of a movement detector to measure daily activity level in patients with chronic lung disease. *Eur Respir J.* 1997; 10: 2814-19.
39. Renston JP, DiMarco AF, Supinski GS. Respiratory muscle rest using nasal BiPAP ventilation in patients with stable severe COPD. *Chest* 1994; 105: 1053-60.
40. Nava S, Fanfulla F, Frigerio P, Navalesi P. Physiologic evaluation of 4 weeks of nocturnal nasal positive pressure ventilation in stable hypercapnic patients with chronic obstructive pulmonary disease. *Respiration* 2001; 68: 573-83.
41. Koechlin C, Maltais F, Saey D, *et al.* Hypoxaemia enhances peripheral muscle oxidative stress in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 834–841.
42. Elliott MW, Mulvey DA, Moxham J, Green M, Branthwaite MA. Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. *Eur Respir J.* 1991; 4:1044-52
43. Schönhofer B, Dellweg D, Suchi S, Kohler D. Exercise Endurance before and after Long-Term Noninvasive Ventilation in Patients with Chronic Respiratory Failure. *Respiration.* 2007 Jul 12: [Epub ahead of print]
44. Windisch W, Kostić S, Dreher M, Virchow JC Jr, Sorichter S. Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of Pa(CO2). *Chest* 2005; 128: 657-62

SUPPLEMENTARY MATERIAL

Patients

An overnight polygraphy (Embletta pds, Medcare Automation BV, Amsterdam, the Netherlands) was performed in patients with a body mass index ≥ 30 kg/m^2, in patients who snored or had complaints of disrupted sleep, excessive daytime sleepiness, or morning headache. Patients were excluded if the apnoea/ hypopnoea index was ≥ 10 episodes / hour.

Patients were excluded if medical history revealed significant cardiac diseases limiting exercise tolerance.

Rehabilitation program

The participants followed a centre-based rehabilitation program of twelve weeks. The program could be followed in-hospital or as an out-patient, depending on travel distance to the centre. Nine rehabilitation centers in the northern part of the Netherlands participated. The program started with a 3-week period of upper and lower limb strength exercises (Enraf- Nonius, Rotterdam, the Netherlands), three times a week [1]. Thereafter, the program continued with nine weeks cycling (Lode medical technology, Groningen, the Netherlands; Tunturi, Almere, the Netherlands), walking, and inspiratory muscle training (Threshold® IMT, Respironics, Murrysville, PA, US). The cycling was performed two times a week for thirty minutes according to an interval-based protocol [2, 3]. This cycling protocol consisted of alternating 1 minute loaded cycling (aimed at 140% of a patients initial peak work rate on cycle ergometry), and 1 minute unloaded cycling, during a total of thirty minutes. Walking was performed twice a week. Initially patients walked ten minutes per session. Walking time was increased with five to ten minutes every week until the patients were able to walk thirty minutes per session. The speed of walking was adjusted in order to achieve a maximum Borg score of approximately 80% of the maximum Borg score at the initial six minute walking test. Inspiratory muscle training was performed on an inspiratory threshold device thirty minutes a day on an interval basis (2 minutes loaded breathing, followed by 1 min rest). The aim was to start with the threshold resistance on 30% of baseline maximal inspiratory pressure ($P_I$max). The resistance was increased with 5-10% per session until 70% $P_I$max was reached [4, 5]. Oxygen was used during training to maintain arterial oxygen saturation >92%. Twenty-nine patients used oxygen during the training (16 in PR group and 13 from NIPPV+PR group). The patients also participated in group education sessions where information was given about the disease, various strategies of treatment, use of medication, ways of coping with the disease, the role of rehabilitation, and how to recognise an exacerbation. Next to this, patients were taught breathing exercises, e.g. training lip-pursing techniques, expiratory abdominal augmentation, and synchronisation of thoracic and abdominal movement. Finally, patients received nutritional counselling by a dietician and, if necessary, psychosocial support.

NIPPV

Patients randomised to the NIPPV + rehabilitation group were instituted on NIPPV at the University Medical Center Groningen. They were hospitalized within a week after the baseline measurements and before the rehabilitation program started.

Noninvasive ventilation was supplied through a pressure cycled ventilator, applying both inspiratory and expiratory pressure to the patient (BiPAP; Synchrony, Respironics, INC., Murrysville, PA, USA). A nasal or full face mask (Mirage mask, ResMed Ltd, UK) of the proper size was used. The ventilator was set in a spontaneous/ timed mode (S/T), with a backup frequency. We started with an inspiratory positive airway pressure (IPAP) of 12 cm H_2O and an expiratory positive airway pressure (EPAP) of 4 cm H_2O. IPAP was increased until the maximal tolerated pressure was achieved and titrated towards an optimal correction of arterial blood gases during the night ($PaCO_2$<6.0 kPa and a PaO_2>8.0). EPAP was titrated on patient comfort. Ventilator breathing frequency was adjusted to the patient's own spontaneous breathing frequency. If needed, O_2 was added to the ventilatory circuit to obtain a saturation of ≥ 90%. A humidifier (HC 150 Fisher & Paykel Healthcare, Australia) was used if needed.

To monitor effectiveness of the NIPPV, nocturnal arterial blood gas registrations were performed in the intensive care unit at baseline before institution on NIPPV, after the practice period, and after three months. An arterial canula was placed in the a. radialis and arterial blood gas samples were taken every two hours. For analyses we used the mean of at least three samples taken when patients were asleep.

Initially, patients were hospitalised to practice NIPPV use under close supervision of a nursing consultant specialised in home mechanical ventilation. The in-hospital practice period lasted until patient could sleep at least six hours with the NIPPV (mean number a days necessary in our patients 5 ± 0.6 days). When a patient was able to sleep at least 6 hours per night with the ventilator, the second arterial blood gas registration was performed. If this gave satisfactory results, the patient went home with their ventilator. On the first day a home visit was done by a specialised nursing consultant of the home mechanical ventilation centre, who supervised the ventilatory support during the whole study period. Ventilator compliance was determined from the ventilator counter readings.

Measurements

The following measurements were performed at baseline and after the 3-months intervention period.

Health-related quality of life

The primary outcome parameter was health-related quality of life, assessed by the interviewed version of the Chronic Respiratory Questionnaire (CRQ) [6]. The dyspnoea domain was individualised. In addition, health-related quality of life was measured with the Maugeri Respiratory Failure questionnaire (MRF-28) [7], and the Severe Respiratory Insufficiency questionnaire (SRI) [8].

Pulmonary Function

All patients performed lung function testing post bronchodilatation with 400 microgram salbutamol. Vital capacity and forced expiratory volume in 1 second (FEV_1) were obtained by spirometry according to ERS criteria [9]. Out of a least three technically correct measurements, the highest value of at least two reproducible values was used (with ≤150 ml difference between those two measurements). Lung volumes, total lung capacity, functional residual capacity and residual volume, were measured by body plethysmography [10]. Furthermore, maximal inspiratory pressure ($P_I$max) was measured at residual volume after maximal expiration. The $P_I$max manoeuvre was repeated at least five times with one minute rest between the measurements until 3 readings were obtained with less than 10% variance between the measurements. Pressures had to be maintained at least 1 second [11] (Masterscreen PFT, Viasys, Houten, the Netherlands).

Exercise tests

Cycle ergometry

The bicycle tests were performed between 4 to 8 hours after switching from NIPPV to spontaneous breathing. Prior to the bicycle test, all patients received 400 microgram salbutamol to achieve optimal bronchodilatation.

First, daytime resting arterial blood gases on room air were taken from all patients while lying (Rapid lab type 865, Siemens, U.S.A.).

An incremental bicycle ergometry was performed using a 1-min incremental protocol. Patients were seated on the bicycle, respired through a mouthpiece and wore a nose clip during the test. During the whole test minute ventilation, tidal volume, breathing frequency, and oxygen uptake were measured continuously (Oxycon Pro, Viasys, Bilthoven, the Netherlands). First, recordings were made during breathing at rest for five minutes. The average values of these five minutes were used to analyse resting breathing patterns.

The exercise test started with 1 min unloaded pedalling at 60 cycles/min. This was followed by a 1-min incremental protocol at five watt load increment/min, until the patient reported exhaustion. The maximum workload was defined as the highest work level reached and maintained for a least thirty seconds. Prior to and during the exercise training the subjects were asked to estimate leg effort and dyspnoea intensity, using a 10-point modified Borg scale [12].

6-minute walking distance

A 6-minute walking test was performed indoors, along a 40-meter flat, straight corridor, with the turnaround point marked with a cone. All patients had performed a practice test during the run-in period. Patients used their usual walking aids and, if applicable, their usual ambulatory oxygen therapy during the test. The test assistant gave standardised encouragements every 30 seconds and told the patient after 2 and after 4 minutes that he/she was 2 and 4 minutes on his/her way [13, 14].

Shuttle walk tests

All patients first performed an incremental shuttle walk test [15]. From this, endurance shuttle walk speed was determined according to the protocol of Revill [16]. First, maximal oxygen uptake (VO_2max) was calculated (VO_2max= (0.85*(4.19+0.025*incremental shuttle walk distance [15]). Thereafter, the correct endurance walking speed was read from the graph of endurance walking speed against VO_2max as presented by Revill [16].
For both tests, a practice walk was done during the run-in period. Both tests were performed on a 10 m shuttle course on a quiet flat corridor, demarcated by cones inset 0.5 m from either end to compensate for turning points. Patients were instructed to walk along the course, turning around the cones at either end in synchronization with the audio signals from the cassette player. Prior to the test, patients were given standardized instructions about the tests and instructions to continue walking until too tired or breathless to continue. During the tests, the test operator sat alongside the course and no encouragements were given. Before and after the test patients were asked to estimate dyspnoea intensity on a 10-point modified Borg scale.

For the incremental shuttle walk test the modified protocol of Singh was used [15]. Each minute the walking speed was increased by 0.17 m/s, so that the patient was required to walk progressively faster. The end of the test was determined by a) the patient, when to exhausted to maintain the required speed; b) the operator, if the patients failed to reach the cone by > 0.5 m for a second time [15].
For the endurance shuttle walk test, the same course was used. The test started with a "warm up" slower pace, which lasted for approximately 100 s, preceded the endurance speed to enable the patient to practice walking around the shuttle course. Thereafter the actual endurance speed started and remained constant for the whole test. The test ended if the patient indicated that he was too tired or too breathless to continue or if the cut off time at 20 minutes, chosen for practical reasons, was reached. However, patients were unaware of any time limit and were discouraged from estimating how long they had been walking. The patients performed the endurance shuttle walk test twice at baseline to exclude learning effects [16]. The best of these two tests was used for analyses.

Dyspnoea and mood state

Dyspnoea was assessed by the Medical Research Council [17]. The hospital anxiety and depression scale was used to assess mood state [18].

Activities of daily living

Daily physical activity was assessed on a performance basis by the Digiwalker SW-200 (Yamax; Tokyo, Japan) [19-21]. This pedometer has proved to accurately detect steps taken, as an indication of volume of daily physical activity [19, 20, 22]. It has also shown evidence of reliability and convergent and discriminative validity [21]. In this study, patients were instructed to wear the pedometer during ten days (until going to bed), and to record the number of steps per day. Steps/day was expressed as step equivalents.

Table 5. Changes in health-related quality of life scores after 3 months therapy.

		Baseline	After 3 months	Change within group	Between group difference in change (95% CI)
Chronic Respiratory Questionnaire					
Dyspnoea, points	N+R	16.0 ± 4	19.1 ± 6	3.1*	0.2 (-3.2 to 3.2)
	R	17.2 ± 5	19.5 ± 6	2.3	
Fatigue, points	N+R	13.8 ± 4	18.8 ± 4	5.0*	3.3 (0.8 to 5.7) †
	R	13.6 ± 5	15.4 ± 6	1.8	
Emotion, points	N+R	32.6 ± 7	36.3 ± 6	3.7*	2.4 (-0.9 to 5.5)
	R	30.7 ± 8	32.8 ± 8	2.1	
Mastery, points	N+R	19.3 ± 5	22.5 ± 4	3.3*	1.5 (-0.4 to 3.4)
	R	17.8 ± 5	20.3 ± 5	2.5*	
Total, points	N+R	81.7 ± 16	96.8 ± 15	15.1*	7.5 (-1.0 to 16.0)
	R	79.3 ± 19	87.9 ± 20	8.7*	
Maugeri Respiratory Failure Questionnaire					
Daily activities, %	N+R	58.9 ± 35	53.4 ± 29	-5.5	-5.3 (-17 to 6)
	R	55.7 ± 30	56.8 ± 27	1.1	
Cognition, %	N+R	50.0 ± 33	28.3 ± 25	-21.7*	-22.0 (-35 to -9) †
	R	35.2 ± 39	40.6 ± 38	5.5	
Invalidity, %	N+R	67.0 ± 33	57.4 ± 33	-9.6*	-6.1 (-19 to 7)
	R	65.0 ± 30	61.9 ± 36	-3.1	
Total, %	N+R	55.3 ± 24	44.6 ± 22	-10.7*	-9.7 (-18 to -1) †
	R	52.2 ± 24	52.1 ± 24	-0.1	
Severe Respiratory Insufficiency Questionnaire					
Respiratory complaints, %	N+R	49.0 ± 17	58.7 ± 13	9.6*	6.0 (-0.6 to 12.0)
	R	48.1 ± 17	52.1 ± 17	-4.1	
Physical functioning, %	N+R	40.9 ± 18	40.9 ± 21	0	-2.3 (-9.7 to 5.1)
	R	39.3 ± 17	42.0 ± 18	2.6	
Attendant symptoms and sleep, %	N+R	60.4 ± 19	71.1 ± 16	10.7*	7.4 (-0.6 to 15.3)
	R	54.6 ± 18	60.2 ± 20	5.5*	
Social relationships, %	N+R	58.4 ± 17	64.5 ± 13	6.1*	1.0 (-5.6 to 7.6)
	R	63.3 ± 16	65.5 ± 14	2.2	
Anxiety, %	N+R	54.8 ± 23	63.3 ± 17	8.5*	3.1 (-5.1 to 11.3)
	R	50.7 ± 20	56.9 ± 22	6.1	
Well-being, %	N+R	63.0 ± 19	68.1 ± 14	5.1*	4.2 (-2.5 to 10.9)
	R	54.9 ±20	58.8 ±19	3.9	
Social functioning, %	N+R	50.3 ± 21	54.1 ± 16	3.7	1.1 (-6.4 to 8.6)
	R	51.6 ± 20	53.6 ± 18	2.0	
Summary score, %	N+R	53.8 ± 15	60.1 ± 11	6.3*	3.1 (-2.0 to 8.2)
	R	51.8 ±14	55.7 ±15	3.8	

Means ± SD. N+R: NIPPV + rehabilitation group; R: rehabilitation group. * denotes significant change from baseline to 3 months within the group; †: denotes significant difference in change between groups.

REFERENCES SUPPLEMENT

1. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance versus endurance training in patients with COPD and pheripheral muscle weakness. *Eur Respir J* 2002; 19: 1072-8
2. Vogiatzis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J* 2002; 20: 12-9.
3. Puhan MA, Busching G, vanOort E, Zaugg C, Schunemann HJ, Frey M. Interval exercise training versus continuous exercise in patients with moderate to severe chronic obstructive pulmonary disease- study protocol for a randomised controlled trail. *BMC pulmonary medicine* 2004; 4: 5.
4. Dekhuijzen PN, Folgering HT, van Herwaarden CL. Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD. *Chest* 1991; 99:128-33.
5. Lötters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J* 2002; 20: 570-6.
6. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; 42: 773-8.
7. Carone M, Bertolotti G, Anchisi F, Zotti AM, Donner CF, Jones PW on behalf of the Quality of Life in Chronic Respiratory Failure Group. Analysis of factors that characterise health impairment in patients with chronic respiratory failure. *Eur Respir J* 1999; 13: 1293-1300.
8. Windisch W, Freidel K, Schucher B, Baumann H, Wiebel M, Matthys H, Petermann F. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. *J Clin Epidemiol* 2003 ; 56: 752-9.
9. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319-38.
10. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Hankinson J, Jensen R, Johnson D, MacIntyre N, McKay R, Millere MR, Navajas D, Pellegrino R, Viegi G. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511-22.
11. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969; 99: 692-702.
12. Fletcher CM, Elmes PC, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959; 1: 257-66
13. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132: 919-23
14. Steele BRN. Timed walking tests of exercise capacity in chronic cardiopulmonary illness. *J Cardiopulm Rehab* 1996; 16: 25-33.
15. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA. Comparison of the oxygen uptake during a conventional treadmill test and the shuttle walk test in chronic airflow limitation. *Eur Respir J* 1994; 7: 2016-20.
16. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 1999; 54: 213-22.
17. Mahler DA. The measurement of dyspnea: contents, interobserver agreement and physiological correlates of two new clinical indexes. *Chest* 1984; 85: 751-8.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-70.
19. Crouter SE, Schneider PL, Karabulut M, Bassett DR Jr. Validity of 10 electronic pedometers for measuring steps, distance, and energy cost. *Med Sci Sports Exerc* 2003; 35:1455-60.
20. Schneider PL, Crouter SE, Bassett DR. Pedometer measures of free-living physical activity: comparison of 13 models. *Med Sci Sports Exerc* 2004; 36: 331-35.
21. Tudor-Locke C, Williams JE, Reis JP, Pluto D. Utility of pedometers for assessing physical activity: construct validity. *Sports Med* 2004; 34: 281-91.
22. Schneider PL, Crouter SE, Lukajic O, Bassett DR Jr. Accuracy and reliability of 10 pedometers for measuring steps over a 400-m walk. *Med Sci Sports Exerc* 2003; 35: 1779-84.

CHAPTER 9

Summary, discussion and future persepectives

This thesis deals with two main topics. First, we investigated respiratory muscle function in Chronic Obstructive Pulmonary Disease (COPD) by surface electromyography. Second, we focused on the benefits of noninvasive ventilation in patients with respiratory failure, both in restrictive pulmonary disorders and in COPD, in acute respiratory failure, and in chronic stable condition.

Respiratory muscle activity in COPD

The respiratory system consists of two parts: a gas-exchanging compartment,- the lungs-, and the "pump" that ventilates the lungs. The pump consists of the chest wall, the respiratory muscles that displace the lungs, and the neural system that controls these muscles [1]. In patients with COPD, pump failure is caused by abnormalities of respiratory muscle function, which are multifaceted. Furthermore, in different conditions (stable COPD at rest, during exercise, or with an added increased external load; or during an acute COPD exacerbation), and in different patients, respiratory muscle dysfunction and its consequences differ.

At rest, because of abnormalities of gas exchange and increased mechanical load, patients with COPD have to generate more negative intrathoracic pressure than healthy people to achieve adequate ventilation [2]. On the other hand, lung hyperinflation, a characteristic feature of COPD, decreases the capacity of the respiratory muscles to generate pressure [2]. Initially it was believed that this imbalance causes respiratory muscle fatigue [3]. In the last decades, there has been increasing interest in adaptive changes occurring in the respiratory muscles of COPD patients [4]. Muscle remodelling, i.e. changes in muscle fibre type [5], renders the inspiratory muscles less susceptible to task failure. However, it has also been shown that the force generating capacity of the diaphragm is decreased due to changes occurring within the individual muscle fibres [6, 7]. The final balance between impairment because of an increased load and decreased capacity and adaptive changes within a muscle group varies between patients [4]. To generate pressure, the respiratory muscles have to be driven by the respiratory controller. Within the concept of fatigued respiratory muscles, it was believed that the respiratory centres decrease their output in response to fatigue of the respiratory muscles [3]. However, later on, it was found that patients with COPD have a higher resting neural drive to the respiratory muscles compared to healthy subjects [8, 9]. Apparently, COPD patients drive their respiratory muscles as hard as possible to achieve as much ventilation as possible. With electromyography (EMG) the electrical manifestation of the excitation process elicited by action potentials propagating along muscle fibre membranes can be described [10]. EMG signals are detected by electrodes, either on the skin (surface EMG), swallowed into the oesophagus, or inserted into the muscle (needle electrodes). A great advantage of surface EMG is that it is noninvasive and gives little or no discomfort to the patient. Furthermore, because the different respiratory muscles, -i.e. the diaphragm, intercostal muscles, and the scalene muscles-, can be assessed simultaneously, surface EMG can help to assess respiratory muscle activity of the complete respiratory system during various conditions and interventions.

In **chapter 2**, the activity of the different respiratory muscles was assessed in both COPD patients and in healthy subjects by noninvasive surface EMG. We investigated the reproducibility and responsiveness of the technique. We showed that:

1. The noninvasive EMG technique has an acceptable reproducibility in both COPD patients and healthy subjects.
2. The EMG technique is a responsive tool to detect changes in the recruitment of the different inspiratory muscles in COPD patients and healthy subjects when breathing against an inspiratory load.
3. During inspiratory loading, COPD patients preferentially direct their neural drive towards the accessory respiratory muscles, instead of to the diaphragm.

From this, we concluded that the noninvasive EMG technique is a good tool to study the activity of the different respiratory muscles simultaneously during inspiratory loading.

In **chapter 3**, we extended our EMG measurements to a study performed during a cycle ergometer test. During exercise, end-expiratory lung volume increases because of increased lack of time to exhale (dynamic hyperinflation). This dynamic hyperinflation both progressively reduces the capacity of the respiratory muscles and increases the mechanical load [11]. During exercise, the contribution of the diaphragm in generating negative intrathoracic pressures becomes less, and the rib cage muscles become more important [12].

In this study we found that:

1. COPD patients, compared to healthy subjects, show early recruitment of their accessory muscles during exercise. At peak exercise, they preferentially direct their neural drive to these accessory muscles.
2. There is a relationship between the magnitude of increase in neural drive, as measured with the noninvasive EMG, and dyspnoea sensation. This relationship is more pronounced in COPD patients as compared to healthy subjects.

An explanation for the second finding might be that with larger increases in neural drive, in COPD patients, as compared to healthy controls, less output was achieved (neuromechanical dissociation). This implies that interventions, for example training programs, that would reduce neural drive, or would increase the output, should reduce dyspnoea sensation. With the noninvasive EMG technique the neural drive part and consequently its relationship with the achieved output would be easy to quantify.

Surface EMG measurements have been criticised for several reasons. First, the technique has been criticised because of variability of the measurements. In our study, variable muscle-to-electrode distance was corrected for by using the EMG activity ratio (EMGAR), so that after log transformation constant factors were reduced to zero. By doing so, we could quantify the change in EMG activity compared to baseline. Furthermore, surface EMG signals could be contaminated by electrical

activity derived from adjacent muscles. By controlling carefully for body position, we minimised signal contamination. Scalene muscle activity might be influenced by sternocleidomastoid activity. Although we instructed the participants to look straight forward, and supervised this closely during the test, adjacent neck muscles could possibly have influenced the scalene signals, especially at high inspiratory loading and at high exercise levels. This might explain the poorer reproducibility in the scalene signals, especially at high inspiratory loading.
In both studies, we observed from the raw recordings that neural drive was increased to all respiratory muscles at rest in COPD compared to healthy subjects. However, due to the use of the EMG activity ratio (EMGAR), it was impossible to compare the absolute EMG values between groups. We could quantify the increase in electrical activity within subjects. The pattern we observed in both studies was that with increasing loads COPD patients preferentially direct their neural drive towards the accessory respiratory muscles (the intercostals and the scalene muscles), instead of to the diaphragm. This might be a protective mechanism in response to heavy diaphragm loading. As compared to the intercostal muscles, the diaphragm is at higher mechanical disadvantage as it is more shortened, and therefore compromised, with increasing hyperinflation. As such, the reserve capacity of the intercostals to generate force during heavy loading is greater.

The assessment and treatment of patients with respiratory failure

Home ventilatory support in restrictive pulmonary disorders

Patients who develop chronic respiratory failure may need (intermittent) mechanical ventilation. Initially, mechanical ventilation was applied by means of negative pressure ventilation, through an iron lung or body ventilator (for example a chest cuirass). From the 1960s, the use of invasive mechanical ventilation, especially for patients with acute respiratory failure, increased. As tracheostomal ventilation has risks and difficulties with its administration especially when used for a longer period at home, noninvasive ventilation is preferable in patients with chronic respiratory failure. Because negative pressure ventilation is very cumbersome to use, this mode was gradually replaced by noninvasive positive pressure ventilation (NIPPV) through a mask in the early 1980s [13].
In the Netherlands, the largest group of patients on home mechanical ventilation is currently compromised of patients with neuromuscular diseases, followed by a group of patients with thoracic restrictions (chapter 4). The large majority of patients is now ventilated with NIPPV through a mask. The prevalence of use of home mechanical ventilation varies between countries (estimated prevalence of 0.1/100,000 in Poland to 17/100,000 of the population in France) [14]. The prevalence in the Netherlands has been estimated to be 5.6/100,000 [14]. We found that the estimated prevalence in the region of the Home Mechanical Ventilation Centre Groningen in 2005 (estimated prevalence of 7.2/100,000 of the population) was higher than the estimated

prevalence throughout the Netherlands.
It has been shown that in patients with neuromuscular diseases or restrictive pulmonary diseases, home mechanical ventilatory support reverses respiratory failure and extends survival [15-17]. In patients with stable chronic obstructive pulmonary disease, long-term noninvasive ventilation has been tested, but the results of randomised trials did not shown uniform benefits [18]. Despite this, home mechanical ventilation use in COPD is relatively high throughout Europe, as it was found that 34% of the users had lung diseases, mainly being COPD [14]. Especially in the southern European countries, a high prevalence of patients with lung diseases on home mechanical ventilation was found. This in contrast to the situation in the Netherlands, were the majority of patients on home mechanical ventilation had neuromuscular diseases and only a minority lung diseases (chapter 4). These differences might reflect different attitudes towards long-term home mechanical ventilation in COPD, which are probably driven by the limited evidence of the long-term effects of noninvasive ventilation in COPD.

In **chapter 4**, we present the results of 46-years experience of the Home Mechanical Ventilation Centre Groningen in patients with restrictive pulmonary disorders. Data were retrospectively collected from all patients with a restrictive pulmonary disorder that received home mechanical ventilatory support, initiated at the Home Mechanical Ventilation Centre Groningen between 1956 and 2002. Patients were ventilated by negative pressure ventilation, tracheal intermittent positive pressure ventilation, or noninvasive positive pressure ventilation. We showed that all tree modalities were effective in patients with restrictive pulmonary disorders in terms of both short-term and long-term improvement of pulmonary function and arterial blood gases.

Noninvasive ventilation in acute respiratory failure in COPD

Patients with COPD might develop acute respiratory failure when their condition deteriorates due to an acute exacerbation. When the patients start to retain carbon dioxide and develop respiratory acidosis, specific management strategies are required. Noninvasive positive pressure ventilation (NIPPV) is proven effective when applied for acute respiratory failure due to severe COPD exacerbations. It improves vital signs and dyspnoea scores, avoids intubation, reduces mortality rates, and reduces hospital length of stay [19].

In **chapter 5**, we present a review on noninvasive ventilation in acute respiratory failure. Although the results of most randomised clinical trials rendered positive effects of NIPPV for acute COPD exacerbations, patient selection and location of the ventilatory support might affect outcomes in clinical settings. The most important aspects we discussed were:

1. Recent studies have shown that NIPPV can also be effective in COPD exacerbations with severe respiratory failure.
2. In these patiens, it seems to be favourable to start the NIPPV shortly after arrival in the hospital, as success rates increased when NIPPV was initiated early in the course of the exacerbation.
3. In experienced centres, more severe patients can not only be treated effectively

in the intensive care unit but also on trained general wards. However, because failure rates are higher in this group with severe respiratory failure, good monitoring facilities and rapid access to endotracheal intubation are mandatory.

4. Although most studies used bilevel pressure support ventilation, also volume-controlled ventilation can be effective in COPD exacerbations.
5. The choice of the interface (mask) used is largely individual with great emphasis on patient comfort.

Nocturnal noninvasive ventilation in COPD patients with chronic hypercapnic respiratory failure

The results of studies about long-term NIPPV in patients with severe COPD were conflicting [18]. Some studies did show positive effects on daytime arterial blood gases [20-22], pulmonary function [22], sleep [20], dyspnoea [21,22], health-related quality of life [20,21,23], and/ or exercise tolerance [22,23]. On the other hand, other studies did not show any of these effects [24-27]. In severe stable COPD patients who received NIPPV, a 2-year survival rate of 72% was found, compared to 42% in patients not on NIPPV [28]. However, this study was not randomised but prospective observational. Patients who could not get used to NIPPV at institution were analysed as controls [28].

There are several factors that might have accounted for the diversity in the results of the trials performed. First, it seems that patients with more severe blood gas derangements benefit more from NIPPV [20,22]. Second, studies that did show positive effects used higher inspiratory pressures [20,22,29]. Third, patients need sufficient time and careful assistance to adjust to the ventilation, especially if NIPPV is applied at night [26]. Fourth, the effectiveness of the NIPPV was monitored in different ways in the different studies. Correct and preferentially dynamic monitoring of the effectiveness of the ventilation is very important, especially during the night. Monitoring of end-tidal CO_2 is unreliable in COPD [30]. Monitoring of transcutaneous CO_2 is more reliable, but tends to drift over night [31]. In our opinion, measuring multiple arterial blood gas samples during NIPPV is the golden standard. Unfortunately, no randomised controlled trial except for the RECOVER trial has monitored the effectiveness of their intervention in this way **(chapter 8)**.

In **chapter 6**, we comment upon the most recent review about noninvasive positive pressure ventilation in severe stable COPD [18]. While we do find that the review is a major contribution, we feel that the strength of the conclusions is overstated as it was based on non-randomised controlled trials. Furthermore, we feel that the authors do not place enough emphasis on the factors that are necessary for NIPPV to be effective in severe stable COPD, such as the selection of patients with severe blood gas derangements, the use of higher inspiratory pressures, and good monitoring facilities.

In **chapter 7** and **chapter 8**, data of the RECOVER trial are presented.
In **chapter 7**, the results of a validation study of two new health-related quality of life questionnaires that were developed especially for patients with chronic respiratory failure are presented.

Patients with COPD who develop chronic respiratory failure represent the end-stage of the disease spectrum. These patients are greatly disabled in daily, social, and other activities as extreme dyspnoea limits them to perform even the slightest effort. Because they experience difficulties at multiple levels, it is not surprising that health-related quality of life is also impaired [32, 33]. Furthermore, mortality rates are high in these severe patients [34, 35]. Health-related quality of life specifically represents patient's needs and problems. Therefore, interventions in these patients should include assessment of health-related quality of life, with a good questionnaire.

Measuring quality of life in patients with severe COPD is increasingly recognised as important, but questionnaires have not been specifically designed or validated in this group. Two new questionnaires (the Maugeri Respiratory Failure questionnaire (MRF-28) [36, 37] and the Severe Respiratory Insufficiency questionnaire (SRI) [38]), were recently designed to cover the specific needs and problems in patients with chronic respiratory failure.

We identified that both questionnaires add new important domains and outperform on the traditional Chronic Respiratory Questionnaire (CRQ)in severe COPD patients with chronic respiratory failure. While the emphasis of the MRF-28 is more on activities of daily living, the SRI seems to focus more on psychological aspects. Therefore, the questionnaires cannot be used interchangeably. We recommend using the SRI for the most extensive assessment of health-related quality of life, while the addition of the MRF-28 can be especially useful to assess cognition.

In **chapter 8**, we present the results of the RECOVER trial, in which we compared 3-months noninvasive ventilation in addition to pulmonary rehabilitation (NIPPV +PR) to pulmonary rehabilitation (PR) alone. Therefore, we randomised seventy-two patients to one of both treatment arms. We found that noninvasive ventilation in addition to pulmonary rehabilitation as compared to rehabilitation alone:

1. Improves health-related quality of life, as measured by the Maugeri Respiratory Failure questionnaire.
2. Improves fatigue, as measured by the Chronic Respiratory Questionnaire fatigue domain.
3. Improves cognition, as measured by the Maugeri Respiratory Failure cognition domain.
4. Improves daytime arterial carbon dioxide tension ($PaCO_2$), measured at rest while breathing room air.
5. Improves daily step count, as measured with a pedometer.

These improvements were accompanied by enhanced daytime minute ventilation in the NIPPV + rehabilitation group, caused by increasing tidal volumes.

However, we did not find an improvement in pulmonary function, inspiratory muscle strength, exercise tolerance tested with formal tests, dyspnoea sensation, or mood state with the addition of NIPPV to pulmonary rehabilitation as compared to rehabilitation alone.

There are several theories about why NIPPV might be effective and why it should improve the outcomes of pulmonary rehabilitation [39]. At home, for practical purposes,

noninvasive ventilation is usually applied intermittently during the night. Why can a therapy applied at night have a sustained effect even during the day?
In COPD, the first studies about noninvasive ventilation relied on the concept of resting chronically overloaded fatigued respiratory muscles [40-44]. Resting of the respiratory muscles would enable COPD patients to sustain their ventilatory task more easily. This would lead to better arterial blood gases and probably better exercise performance, less dyspnoea, and maybe eventually even better health-related quality of life (Figure 3). Resting of the respiratory muscles was advocated by Nava et al. They showed that maximal transdiaphragmatic pressure was increased in COPD patients that responded to the noninvasive ventilation [45]. This was not related to a change in hyperinflation or respiratory mechanics. Studies that measured maximal inspiratory pressures ($P_I$max) to assess respiratory muscle fatigue, showed conflicting results [21-23]. However, respiratory muscle strength measurements such as the $P_I$max reflect short-lasting high frequency respiratory muscle fatigue and do not measure respiratory muscle endurance. Recently, Schönhofer et al contradicted the concept of respiratory muscle fatigue [46]. They showed that although NIPPV did result in an improvement in arterial blood gases, low frequency fatigue of the diaphragm as measured by twitch diaphragmatic pressure was not improved by NIPPV [46].
A second mechanism especially related to the additional effect of NIPPV on pulmonary rehabilitation relates to the following. If nocturnal NIPPV improves daytime arterial blood gases, this leads to a better internal milieu for the peripheral muscles [47]. As so the patient should be able to achieve higher trainings intensities.
A third mechanism proposed to explain the mechanism of NIPPV in severe stable COPD is related to improvement of ventilatory mechanics. Recently, Díaz et al showed that daytime noninvasive ventilation reduces lung hyperinflation, thus reducing inspiratory loads [48]. Improved lung mechanics might improve arterial blood gases, but also exercise tolerance. The reduction in lung hyperinflation was explained by an increase in expiratory time during NIPPV which favours lung emptying and leads to volume recruitment [48].
A fourth mechanism might relate to the achievement of increased minute ventilation during the day, attributed to increased tidal volumes [49, 50]. Also, a similar finding was observed when NIPPV was used during exercise. Pressure support of 10 cm H_2O resulted in a significant increase in tidal volume and a decrease in respiratory rate [51]. In our RECOVER study, the increased minute ventilation might have resulted in better blood gases and probably would have enabled patients to be more active during the day. While it seems logical that the ventilator is capable of inducing a more effective breathing pattern, it is interesting that patients were able to continue their more effective breathing pattern during the day in our study, when not on the NIPPV. Furthermore, in our study, like other studies, more effective ventilation was achieved without a clear improvement in hyperinflation. Therefore, additional mechanisms must be present. Probably improved chemosensitivity of the respiratory controller mediates the increased daytime minute ventilation [52]. During ventilation, $PaCO_2$ values are improved. Thereby, the respiratory controller "adapts to" lower $PaCO_2$ levels. As a consequence, during spontaneous breathing, the respiratory controller increases

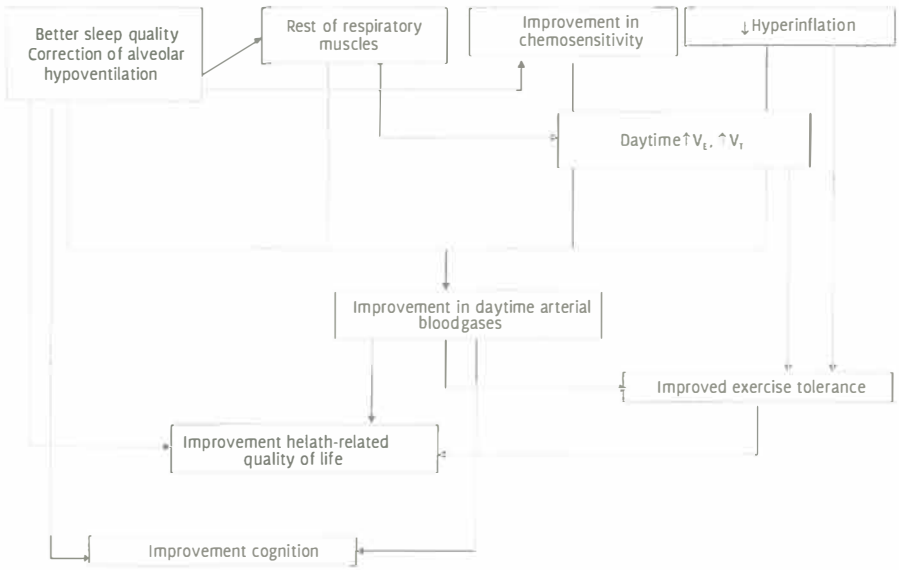


Figure 1. Mechanisms of NIPPV in COPD.
Different mechanism might co-act and interact in individual patients. V_E: minute ventilation, V_T: tidal volume.

its output to maintain those low $PaCO_2$ levels. Elliot et al. found that the change in daytime $PaCO_2$ after a period of nocturnal noninvasive ventilation correlated with the increase in ventilation at an end-tidal CO_2 of 8 kPa [52]. This might indicate that the central chemoreceptors become more sensitive as they adapt to a nocturnal reduction in $PaCO_2$. As the increased minute ventilation we found in the RECOVER study was not accompanied by improved lung mechanics, we speculate that this was either caused by increased ventilatory response to CO_2, or by improved endurance capacity of the respiratory muscles.

A last but important mechanism proposed can be improvement of sleep quality [20]. During sleep, ventilation is reduced, especially during rapid eye movement sleep [53]. Furthermore, during sleep, there is a reduction in CO_2 responsiveness and an increase in upper airway resistance, resulting in a worsening of respiratory failure. Hypoxemia may induce sleep disruptions, with arousals during periods of oxygen desaturation. Although hypoxemia can be reversed by supplemental oxygen, this may worsen hypercapnia. Furthermore, it has been shown that acute elevations in $PaCO_2$ can also induce arousals from sleep [53]. With NIPPV, sleep quality can be improved. As a consequence, patients may feel and may perform better during the day. We do believe this is an important mechanism in our study, as the patients in

the noninvasive ventilation + rehabilitation group improved more on the Chronic Respiratory Questionnaire (CRQ) fatigue domain as compared to the rehabilitation group. Perhaps, as a consequence, they were more active during the day as assessed by the pedometer.
The RECOVER study was not designed to elucidate the exact mechanisms why NIPPV is effective in stable COPD. We did find that with the addition of NIPPV to pulmonary rehabilitation health-related quality of life, fatigue, and cognition improves, as did daytime arterial blood gases and physical activity levels, as compared to rehabilitation alone. We believe several mechanisms might explain why NIPPV is effective in COPD and why it might improve the outcome of rehabilitation (Figure 1). We believe that the improvement in daytime minute ventilation with increasing tidal volumes is an important mechanism for improvement in arterial blood gases. Furthermore, improved sleep quality might have contributed importantly to improved cognition and improved health-related quality of life. It would be interesting to design a study to investigate these effects simultaneously, over a short, but also a longer term.

SUMMARY OF MAIN FINDINGS

Respiratory muscle activity in COPD

1. Noninvasive (surface) electromyography is a reproducible and responsive technique to assess respiratory muscle activity in COPD patients, both during inspiratory loading and during exercise.
2. COPD patients preferentially direct the neural drive towards the intercostal and scalene muscles as compared to the diaphragm, especially at high inspiratory loading and at high exercise levels.
3. The magnitude of increase in respiratory muscle activity is related to the magnitude of increase in dyspnoea sensation. This relationship is steeper in COPD patients as compared to healthy controls.
4. COPD patients, as compared to healthy controls, have a relatively large increase in neural drive, while relatively low output is achieved. This might be an important underlying mechanism causing increased dyspnoea sensation during exercise in COPD.

The assessment and treatment of patients with respiratory failure

1. Home mechanical ventilation is effective in terms of improvement in pulmonary function and arterial blood gases in patients with restrictive pulmonary disorders, also at long-term.
2. Most patients in the northern part of the Netherlands who receive home mechanical ventilation have a neuromuscular disorder.
3. Very few patients with lung diseases were ventilated noninvasively during the past forty-six years in the Netherlands. On contrast, in some other

European countries the prevalence of noninvasively ventilated COPD patients is much larger. This might reflect different attitudes towards NIPPV in COPD. Furthermore, it stresses the need for well performed studies on long-term NIPPV in COPD.

4. Two new health-related quality of life questionnaires (the Maugeri Respiratory Failure questionnaire (MRF-28) and the Severe Respiratory Insufficiency questionnaire (SRI) were developed especially for patients with chronic respiratory failure. We found that in COPD patients with chronic respiratory failure both the MRF-28 and SRI add new important domains.
5. The emphasis of the MRF-28 is more on activities of daily living, while the SRI is directed more to psychological aspects. Therefore, these questionnaires cannot be used interchangeably.

6. Nocturnal noninvasive ventilation for 3-months in addition to pulmonary rehabilitation as compared to rehabilitation alone improves health-related quality of life, daytime $PaCO_2$, and daily activity level in severe COPD patients with chronic hypercapnic respiratory failure.
7. In addition, NIPPV + rehabilitation as compared to rehabilitation alone increases daytime minute ventilation, by increasing tidal volumes.

FUTURE PERSPECTIVES

Following the outcomes being discussed in this thesis, there are a number of studies of great interest for the future:

1. The EMG technique can be used to assess the recruitment of the different respiratory muscles during different interventions. Strategies that will minimise EMG activity will most likely decrease dyspnoea sensation. Furthermore, changing patterns in recruitment of the different respiratory muscles could be indicative of the function of the respiratory muscle system. For example, with EMG one can objectively measure excessive accessory respiratory muscle use when a patient is in need, for example during acute respiratory failure or during weaning failure on the intensive care unit. Secondly, it is interesting to investigate whether the EMG technique can be used to monitor the effects of noninvasive ventilation. Probably EMG measurements can be used to achieve optimal settings of noninvasive ventilation in COPD; i.e. to achieve the optimal breathing frequency, inspiratory and expiratory pressures.

2. The health-related quality of life questionnaires tested in our patient group, the Maugeri Respiratory Failure questionnaire and the Severe Respiratory Insufficiency questionnaire, should be tested further for responsiveness to different interventions in patients with COPD and chronic respiratory failure.

3. (Long-term) noninvasive ventilation in COPD would benefit from further studies.
   - ❖ While we showed that 3-month NIPPV in addition to rehabilitation is effective, we await the long-term (24 months) results of the RECOVER study. We speculate that improved chemosensitivity might take longer time to develop fully. In that case, improvements in arterial blood gases will be more obvious at long-term. Furthermore, effects on exacerbation frequency, hospital and intensive care unit admissions, and survival will become clear only at long-term.
   - ❖ It would useful to execute a study assessing the proposed mechanisms why NIPPV should be effective in COPD: assessing respiratory muscle strength, endurance, and activity; chemosensitivity to CO_2; lung mechanics; and sleep quality by polysomnography. As it seems that it matters considerably whether the NIPPV is applied at daytime or during the night, both situations should be examined head to head in a study.
   - ❖ As little is known about the optimal settings of noninvasive ventilation in COPD, more studies should be performed to investigate this. This can be investigated by comparing different heights of inspiratory and expiratory pressure support, while both monitoring the effectiveness of the ventilation properly and assessing problems that could arise with high pressures (such as aerophagia).
   - ❖ It would be interesting to explore the effects of NIPPV on cognition more extensively (with more extensive psychological and cognitive tests). We found that a substantial proportion of patients with COPD experience problems with attention and concentration. Furthermore we found that 3-months NIPPV improved these aspects. Improved cognition in turn might have contributed to better health-related quality of life.

REFERENCES

1. Roussos C, Koutsoukou A Respiratory failure. *Eur Respir J* 2003; 47 (Suppl): 3-14.
2. Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003; 168: 10-48.
3. Roussos C, Macklem PT. The respiratory muscles. *N Engl J Med* 1982; 307: 786-97
4. Orazco-Levi M. Structure and function of the respiratory muscles in patients with COPD: impairment or adaptation? *Eur Respir J* 2003; 46 (Suppl): 41-51.
5. Levine S, Nguyen T, Kaiser LR, Rubinstein NA, Maislin G, Gregory C, Rome LC, Dudley GA, Sieck GC, Shrager JB. Human diaphragm remodelling associated with chronic obstructive pulmonary disease: clinical implications. *Am J Respir Crit Care Med* 2003; 168: 706-13.
6. Macgowan NA, Evans KG, Road JD, Reid WD. Diaphragm injury in individuals with airflow obstruction. *Am J Respir Crit Care Med* 2006; 51: 840-7.
7. Ottenheijm CA, Heunks LM, Sieck GC, Zhan WZ, Jansen SM, Degens H, de Boo T, Dekhuijzen PN. Diaphragm dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 200-5.
8. De Troyer A, Leeper B, McKenzie DK, Gandevia SC. Neural drive to the diaphragm in patients with severe COPD. *Am J Respir Crit Care Med* 1997; 155:1335-40.
9. Gandevia SC, Leeper JB, McKenzie DK, De Troyer A. Discharge frequencies of parasternal intercostal and scalene motor units during breathing in normal and COPD subjects. *Am J Respir Crit Care Med* 1996; 153: 622-8.
10. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518-624.
11. Sinderby C, Spahija J, Beck J, Kaminski D, Yan S, Comtois N, Sliwinski P. Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1637-41.
12. Yan S, Kaminski D, Sliwinski P. Inspiratory muscle mechanics of patients with chronic obstructive pulmonary disease during incremental exercise. *Am J Respir Crit Care Med* 1997; 156: 807-13.
13. Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med* 2001;163: 540-77.
14. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Faroux B, Robert D, Schönhofer B, Simonds AK, Wedzicha JA. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J* 2005; 25: 1025-31.
15. Simonds AK, Elliott MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. *Thorax* 1995; 50: 604-9.
16. Annane D, Chevrolet JC, Chevret S, Raphael JC. Nocturnal mechanical ventilation for chronic hypoventilation patients with neuromuscular and chest wall disorders. *Cochrane Database Syst Rev.* 2000; (2): CD001941.
17. Gonzalez C, Ferris G, Diaz J, Fontana I, Nunez J, Marín J. Kyphoscoliotic ventilatory insufficiency: effect of long-term intermittent positive pressure ventilation. *Chest* 2003; 124: 857-62.
18. Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. *Eur Respir J* 2007; 30: 293-306.
19. Ram FSF, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD004104. DOI: 10.1002/14651858.CD004104.pub3.
20. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med* 1995; 152: 538-44.
21. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, Ambrosino N. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; 20: 529-38.
22. Díaz O, Bégin P, Andresen M, Prieto ME, Castillo C, Jorquera J, Lisboa C. Physiological and clinical effects of diurnal noninvasive ventilation in hypercapnic COPD. *Eur Respir J* 2005; 26: 1016-23.
23. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive

pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1335-41.
24. Strumpf DA, Millman RP, Carlisle CC, Grattan LM, Ryan SM, Erickson AD, Hill NS. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 144: 1234-9.
25. Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. *Mayo Clin Proc* 1996; 71: 533-42.
26. Lin CC. Comparison between nocturnal nasal positive pressure ventilation combined with oxygen therapy and oxygen monotherapy in patients with severe COPD. *Am J Respir Crit Care Med* 1996;154: 353-8.
27. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, Santolaria F. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest* 2000; 118: 1582-90.
28. Budweiser S, Hitzl AP, Jörres RA, Heinemann F, Arzt M, Schroll S, Pfeifer M. Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. *Int J Clin Pract* 2007; 61: 1516-22.
29. Windisch W, Kostić S, Dreher M, Virchow JC Jr, Sorichter S. Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of Pa(CO2). *Chest* 2005; 128: 657-62.
30. Poppius H, Korhonen O, Viljanen AA, Kreus KE. Arterial to end-tidal CO2 difference in respiratory disease. *Scand J Respir Dis* 1975; 56: 254-62.
31. Storre JH, Steurer B, Kabitz HJ, Dreher M, Windisch W. Monitoring of transcutaneous PCO_2 during initiation of noninvasive positive pressure ventilation NPPV. *Chest* 2007; 132; 1810-6.
32. Anderson KL. The effect of chronic obstructive pulmonary disease on quality of life. *Res Nurs Health* 1995; 18: 547-56.
33. Ambrosino N, Simonds A. The clinical management in extremely severe COPD. *Respir Med* 2007; 101: 1613-24.
34. Salın SA, Nett LM, Petty TL. Ten year follow-up of a comprehensive rehabilitation program for severe COPD. *Chest* 1980; 77: 311s-4s.
35. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease, a clinical trial. *Ann Intern Med* 1980; 93: 391-8.
36. Carone M, Bertolotti G, Anchisi F, Zotti AM, Donner CF, Jones PW on behalf of the Quality of Life in Chronic Respiratory Failure Group. Analysis of factors that characterise health impairment in patients with chronic respiratory failure. *Eur Respir J* 1999; 13: 1293-1300.
37. Janssens JP, Héritier-Praz A, Carone M, Burdet L, Fitting JW, Uldry C, Tschopp JM, Rochat T. Validity and reliability of a French version of the MRF-28 health-related quality of life questionnaire. *Respiration* 2004; 71: 567-74.
38. Windisch W, Freidel K, Schucher B, Baumann H, Wiebel M, Matthys H, Petermann F. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. *J Clin Epidemiol* 2003 ; 56: 752-9.
39. Hill NS. Noninvasive ventilation. Does it work, for whom, and how? *Am Rev Respir Dis* 1993; 147: 1050-5.
40. Braun N, Marino WD. Effects of daily intermittent rest of respiratory muscle in patients with severe chronic airflow limitation (CAL). *Chest* 1984; 85: 59s-60s.
41. Cropp A, DiMarco AF. Effects of intermittent negative pressure ventilation on respiratory muscle function in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1987; 135: 1056-61.
42. Gutierrez M, Beroiza T, Contreras G, Diaz O, Cruz E, Moreno R, Lisboa C. Weekly cuirass ventilation improves blood gases and inspiratory muscle strength in patients with chronic air-flow limitation and hypercarbia. *Am Rev Respir Dis* 1988; 138: 617-23.
43. Levine S, Levy SF, Henson DJ. Effect of negative pressure ventilation on ventilatory muscle endurance in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992; 146: 722-9.

44. Renston JP, DiMarco AF, Supinski GS. Respiratory muscle rest using nasal BiPAP ventilation in patients with stable severe COPD. *Chest* 1994; 105: 1053-60.
45. Nava S, Fanfulla F, Frigerio P, Navalesi P. Physiologic evaluation of 4 weeks of nocturnal nasal positive pressure ventilation in stable hypercapnic patients with chronic obstructive pulmonary disease. *Respiration* 2001; 68: 573-83.
46. Schönhofer B, Polkey MI, Suchi S, Köhler D. Effect of home mechanical ventilation on inspiratory muscle strength in COPD. *Chest* 2006; 130: 1834-8.
47. Koechlin C, Maltais F, Saey D, Michaud A, LeBlanc P, Hayot M, Préfaut C. Hypoxaemia enhances peripheral muscle oxidative stress in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 834-41.
48. Díaz O, Bégin P, Torrealba B, Jover E, Lisboa C. Effects of noninvasive ventilation on lung hyperinflation in stable hypercapnic COPD. *Eur Respir J* 2002; 20:1490-8.
49. Windisch W, Dreher M, Storre JH, Sorichter S. Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. *Respir Physiol Neurobiol* 2006; 150: 251-60.
50. Schönhofer B, Dellweg D, Suchi S, Kohler D. Exercise Endurance before and after Long-Term Noninvasive Ventilation in Patients with Chronic Respiratory Failure. *Respiration* 2007 Jul 12: [Epub ahead of print].
51. van 't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Acute effects of inspiratory pressure support during exercise in patients with COPD. *Eur Respir J* 2004; 23: 34-40.
52. Elliott MW, Mulvey DA, Moxham J, Green M, Branthwaite MA. Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. *Eur Respir J* 1991; 4: 1044-52.
53. McNicholas WT. Impact of sleep in respiratory failure. *Eur Respir J* 1997; 10: 920-33.

NEDERLANDSE SAMENVATTING
(summary in Dutch)

INLEIDING

De longen zijn een gepaard orgaan waarin gaswisseling plaatsvindt tussen lucht en bloed. De longen zorgen ervoor dat er zuurstof (O_2) uit de ingeademde lucht wordt opgenomen in de bloedbaan, waarna het vervoerd kan worden naar de spieren. Daarnaast zorgen de longen ervoor dat het afvalproduct wat vrijkomt in het lichaam, koolzuurgas (CO_2), wordt "uitgeademd".
Bij de mens is de rechterlong wat groter en heeft drie longkwabben, de linker twee. De ingeademde lucht stroomt door de luchtpijp via een uitgebreid systeem van vertakkingen naar de longblaasjes, waarin de uiteindelijke gaswisseling plaatsvindt. Om de long liggen de longvliezen, met daaromheen de borstkas met de ribben. De belangrijkste spieren van de ademhaling zijn het middenrif en de spieren gelegen tussen de ribben (tussenribspieren). Als hulpademhalingsspieren kunnen verder nog nekspieren dienen (Figuur 1).

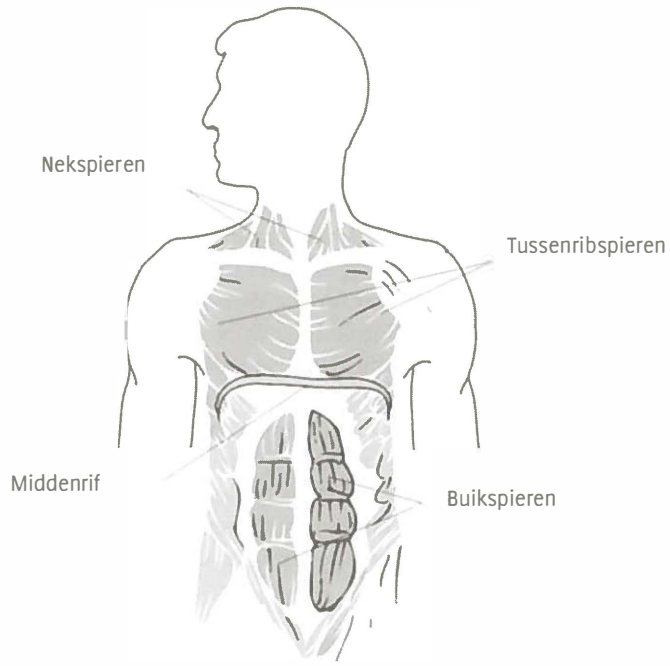
Bij de inademing wordt de borstholte vergroot doordat de tussenribspieren de ribben naar voren en omhoog trekken en doordat het middenrif minder bol wordt. Hierdoor stroomt er lucht de longen in. Als de spieren dan weer verslappen, veert de borstkas weer terug in haar oorspronkelijke stand en veren de longen in elkaar: de lucht wordt uitgeademd.
Ademhalen is meestal onbewust, we hoeven nooit te denken: ik moet ademhalen. De ademhaling wordt geregeld vanuit het ademhalingscentrum gelegen in de hersenstam. Dit centrum reguleert op basis van de koolzuurconcentratie in het bloed de ademhaling en houdt zo het koolzuurgehalte in het bloed vrijwel constant. Daarmee wordt tegelijkertijd de zuurstofconcentratie in het bloed op peil gehouden. Voor een effectieve ademhaling, en dus gaswisseling, is een goede werking van zowel het ademhalingscentrum, de longen, en de ademhalingsspieren, als ook een goed beweeglijke borstkas van belang.

COPD

Eén van de belangrijkste aandoeningen van de longen en de luchtwegen is COPD.
De Engelse afkorting COPD staat voor Chronic Obstructive Pulmonary Disease (chronische obstructieve longaandoeningen). COPD is de verzamelnaam voor chronische bronchitis en longemfyseem. Bij COPD zijn de luchtwegen vernauwd door ontsteking en bij ernstige vormen zijn ook de longen zelf beschadigd.

Roken is meestal de belangrijkste oorzaak van deze beschadiging. COPD uit zich door hoesten, al dan niet met het ophoesten van slijm, kortademigheid en/of een piepende ademhaling bij inspanning.

In Nederland heeft 2% van alle mensen COPD. De ziekte komt vooral veel voor bij ouderen (17% van de mensen boven de 80 jaar heeft COPD). De prevalentie van COPD is in Nederland, net zoals in de rest van de wereld, nog steeds stijgende. Dit



Figuur 1.

komt omdat het aantal mensen dat een lange tijd gerookt heeft, vooral bij vrouwen, sterk stijgt.

De ernst van COPD wordt wereldwijd ingedeeld volgens de GOLD classificatie. Hierbij wordt de mate van vernauwing van de luchtwegen gebruikt om aan te geven hoe ernstig de COPD is. De mate van vernauwing van de luchtwegen wordt gemeten met een longfunctietest, waarbij wordt gekeken hoeveel iemand maximaal kan in- en uitademen.

COPD is een progressieve aandoening, dat wil zeggen dat de luchtwegvernauwing en meestal daarmee ook de klachten, in de loop der tijd toenemen. Als de hoeveelheid lucht die een persoon in 1 seconde kan uitademen minder is dan 50% van wat een gezond persoon van dezelfde leeftijd kan uitademen, spreekt men van ernstig tot zeer ernstig COPD.
Patiënten met ernstig tot zeer ernstig COPD ervaren veelal ernstige beperkingen in hun dagelijks leven omdat zij snel kortademig zijn (soms ook in rust).

Problemen met de gaswisseling bij COPD: de rol van de ademhalingsspieren

Zeer ernstig COPD kan gepaard gaan met problemen met de gaswisseling. Dit wordt veroorzaakt door problemen in de longen zelf, die immers beschadigd zijn bij COPD, maar ook doordat de ademhalingspieren bij COPD de extra belasting die ontstaat niet goed kunnen volbrengen. Deze extra belasting op de ademhalingsspieren bij COPD wordt veroorzaakt door verscheidene factoren. Ten eerste leidt vernauwing van de luchtwegen tot meer weerstand bij het in- en uitademen. Daarnaast blijft er door deze luchtwegvernauwing meer loze lucht achter in de longen bij de uitademing (dit noemt men hyperinflatie). Dit leidt er toe dat de patiënt extra werk moet verzetten aan het begin van de inademing. Tenslotte leidt beschadiging van het longweefsel ertoe dat de gaswisseling minder efficiënt is waardoor de patiënt meer lucht moet verplaatsen om een zelfde uitwisseling van zuurstof en koolzuurgas te verkrijgen. Terwijl bij COPD de belasting op de ademhalingspieren dus groter is dan bij gezonde mensen, is de capaciteit van de ademhalingsspieren afgenomen. Dit komt doordat hyperinflatie er voor zorgt dat de ademhalingsspieren in een minder gunstige positie moeten werken. Verder zijn bij sommige patiënten de spieren verzwakt door de aandoening zelf en soms ook door de bijwerkingen van medicijnen.

Behandeling van COPD

De behandeling van COPD bestaat uit vier componenten. Allereerst moet COPD gediagnostiseerd worden en vervolgens moet een patiënt adequaat begeleidt worden. Risicofactoren moeten zoveel mogelijk worden teruggedrongen (bijvoorbeeld stoppen met roken). Verder onderscheidt men in de behandeling van COPD de behandeling in stabiele fase en de behandeling van plotselinge verergeringen (exacerbaties) van de COPD. COPD is een progressieve aandoening die op dit moment niet te genezen is. Het doel van de COPD behandeling is om symptomen te verlichten, het inspanningsvermogen te optimaliseren, de ervaren gezondheidstoestand te verbeteren, exacerbaties te voorkomen en als deze optreden te behandelen, voortgang van de aandoening zoveel mogelijk te vertragen en eventuele bijkomende problematiek effectief te behandelen.

Longrevalidatie

Longrevalidatie is bij uitstek een behandeling die tot doel heeft meerdere aspecten van de COPD te behandelen. De hoeksteen van een longrevalidatieprogramma is het vergroten van het inspanningsvermogen door middel van fysieke training. Echter daarnaast wordt ook aandacht besteedt aan juiste medicatie, voorlichting over de aandoening, de voedingsstatus van de patiënt, en psychologische aspecten van de aandoening.

Longrevalidatie is een bewezen effectieve behandeling voor mensen met COPD. Echter patiënten met zeer ernstig COPD, vooral de patiënten met een stoornis in de gaswisseling, kunnen soms al ernstig kortademig zijn in rust en bij zeer geringe inspanning. Hierdoor is het voor hen moeilijk effectieve training te volbrengen.

Nieuwe behandeling: noninvasieve beademing
Bij patiënten met ernstig COPD en een stoornis in de gaswisseling zou ondersteuning van de ademhaling gedurende de nacht door middel van beademing wel eens een positief effect kunnen hebben overdag.
Beademing is onder te verdelen in 2 soorten: de invasieve beademing (door middel van een buisje in de luchtpijp), en de noninvasieve beademing. Noninvasieve beademing werd vroeger toegepast door middel van een ijzeren long waar de patiënt in lag. De ijzeren long ondersteunde de inademing door een negatieve druk te creëren rondom de patiënt (dit noemen we negatieve drukbeademing). Omdat dit veel nadelen heeft, is deze ijzeren long later vervangen door positieve druk beademing door middel van een (mond)neusmasker. Met noninvasieve positieve drukbeademing wordt bij iedere inademing een hoeveelheid lucht door het masker de longen in geblazen.

DOEL VAN DIT PROEFSCHRIFT

In het eerste deel van dit proefschrift beschrijven wij onderzoek met als doel meer inzicht te krijgen in de werking van de ademhalingsspieren bij patiënten met ernstig COPD. In het tweede deel van dit proefschrift beschrijven wij het onderzoek naar de effecten van noninvasieve beademing bij COPD.

Samenvatting van de hoofdstukken

Activiteit van de ademhalingsspieren
In **hoofdstuk 2** werd de activiteit van de ademhalingspieren gemeten bij patiënten met COPD tijdens het ademen door een opgelegde extra weerstand bij de inademing. Ademhalingsspieractiviteit kan op verschillende manieren gemeten worden. Een van deze manieren is de oppervlakte elektromyografie (EMG), waarbij met elektrodes geplakt op de huid de elektrische activiteit gemeten kan worden die een spier produceert als hij wordt aangestuurd. Het grote voordeel van deze techniek is dat de activiteit gemeten kan worden met relatief weinig ongemak voor de proefpersoon.
Het doel van deze studie was om de reproduceerbaarheid en de gevoeligheid van deze EMG techniek te onderzoeken bij patiënten met COPD. We vonden dat de techniek een acceptabele reproduceerbaarheid heeft wanneer de metingen worden herhaald over twee verschillende dagen. Daarnaast was de EMG techniek voldoende gevoelig om verschillen in ademhalingsspieractiviteit op te pikken tussen COPD patiënten en gezonde proefpersonen. We zagen dat COPD patiënten tijdens het ademen door een identieke extra weerstand, veel meer activiteit vertonen van hun tussenribspieren en hun nekspieren vergeleken met gezonde proefpersonen, die de ademhaling vooral reguleerden door meer activiteit van het middenrif.

In **hoofdstuk 3** herhaalden we de EMG metingen, maar nu tijdens een maximale fietstest. Het doel van de studie was opnieuw te kijken naar de ademhalingsspieractiviteit, nu tijdens inspanning. Daarnaast onderzochten we de relatie tussen een toename van de ademhalingsspieractiviteit en de ervaren mate van kortademigheid. Er zijn namelijk aanwijzingen dat een hoge ademhalingsspieractiviteit gemeten met EMG, wat een reflectie is van de aansturing van de ademhalingspieren vanuit de hersenen, leidt tot kortademigheid. Tenslotte beoogden we te kijken naar de relatie tussen de ademhalingsspieractiviteit en de daadwerkelijke ventilatie die een persoon bereikt, om zo een uitspraak te kunnen doen over de effectiviteit van het ademhalingssysteem.
In deze studie vonden we allereerst dat COPD patiënten vroeg tijdens de inspanningstest, en dus bij geringe inspanning, al veel activiteit van hun tussenribspieren en nekspieren laten zien in vergelijking met gezonde controlepersonen. Er was een relatie tussen de ademhalingsspieractiviteit en ervaren kortademigheid zowel bij de COPD patiënten als bij de gezonde personen. Deze relatie was meer uitgesproken bij de COPD patiënten. Wij verklaren dit uit een afgenomen efficiëntie van het ademhalingssysteem; met meer ademhalingsactiviteit bereikten de COPD patiënten minder ventilatie.

(Non)invasieve beademing

Langdurige nachtelijke beademing wordt reeds jaren toegepast bij patiënten met aandoeningen die de borstkas en zijn inhoud slechter beweeglijk maken (restrictieve longaandoeningen). In **hoofdstuk 4** analyseerden we de uitkomsten van nachtelijke beademing thuis van alle 114 patiënten met een restrictieve longaandoening die vanaf 1956 tot 2002 zijn beademend vanuit het centrum voor thuisbeademing Groningen. Met een retrospectieve analyse vonden we dat langdurige nachtelijke beademing bij deze patiënten de gaswisseling ook overdag behoorlijk verbetert, waarbij ook de longfunctie blijkt te verbeteren. Met deze studie ondersteunen wij het gebruik van langdurige nachtelijke, bij voorkeur noninvasieve beademing, bij patiënten met een restrictieve longaandoening.

Noninvasieve beademing is een bewezen effectieve therapie bij COPD patiënten die een acute verergering van hun ziekte doormaken (exacerbatie), die gepaard gaat met stoornissen in de gaswisseling. Echter het succespercentage van deze behandeling kan in de praktijk nogal variëren. In **hoofdstuk 5** beogen we aan de hand van de voorhanden zijnde studies een praktische leidraad te geven voor de toepassing van noninvasieve beademing bij COPD exacerbaties en de punten te benoemen die het succes van deze therapie bepalen. Noninvasieve beademing is een bewezen effectieve therapie bij COPD exacerbaties gepaard gaande met stoornissen in de gaswisseling. De kans van slagen van deze therapie wordt vergoot bij vroegtijdig starten van de noninvasieve beademing. De plaats waar de noninvasieve beademing gegeven wordt lijkt niet veel uit te maken mits goede faciliteiten en voldoende ervaring voorhanden zijn. De wijze van beademen en het soort gezichtsmasker dat gebruikt wordt zijn in grote mate patiënt afhankelijk.

Voor COPD patiënten met een stoornis in de gaswisseling die ook bestaat in de stabiele situatie, is noninvasieve beademing niet bewezen effectief. In **hoofdstuk 6** reageren

we op een overzichtsartikel dat recent gepubliceerd is. De conclusies zoals die in dit overzichtsartikel worden gepresenteerd zijn vooral gebaseerd op onderzoeken zonder controlegroep, waardoor men geen goede uitspraak kan doen of noninvasieve beademing nu daadwerkelijk effectief is in de stabiele situatie of niet. Onderzoeken die wel een controlegroep omvatten lieten soms positieve, soms negatieve effecten zien. Dit kan echter veroorzaakt zijn doordat niet aan de basisvoorwaarden voor een effectieve beademing werd voldaan. In hoofdstuk 6, bespreken we deze aspecten, zoals de selectie van patiënten met voldoende ernstige stoornissen in de gaswisseling, het gebruik van voldoende hoge beademingsdrukken, en het correct monitoren van de effecten van de beademing.

RECOVER onderzoek

Het RECOVER onderzoek (**RE**search in **CO**PD: the additional effect of noninvasive **VE**ntilation on **R**ehabilitation) werd in 2004 opgezet om de effecten van nachtelijke noninvasieve beademing als aanvulling op longrevalidatie te onderzoeken in vergelijking met alleen longrevalidatie bij patiënten met ernstig COPD en een stoornis in de gaswisseling in de stabiele situatie. Daarbij hebben we gekeken naar de effecten op korte termijn (3 maanden) en lange termijn (24 maanden). Als belangrijkste uitkomstparameter werd de kwaliteit van leven gekozen. De RECOVER studie is een gerandomiseerd onderzoek met een controlegroep.
Alle patiënten ondergingen een aantal testen om de effecten te evalueren aan het begin van het onderzoek, na 3, 6, 12, 18 en 24 maanden. In dit proefschrift presenteren we de gevonden effecten na 3 maanden. De langere termijn resultaten zullen volgen in 2009. *In Hoofdstuk 7 en 8 zijn de data van het RECOVER onderzoek beschreven.*

Ziekte gerelateerde kwaliteit van leven is een concept dat de laatste jaren als steeds belangrijker wordt gezien en dus ook steeds meer wordt gemeten in onderzoeken naar nieuwe behandelingen. De kwaliteit van leven die een persoon ervaart kan gemeten worden met behulp van speciaal daarvoor ontworpen vragenlijsten. Patiënten met dusdanig ernstig COPD dat de gaswisseling in het gedrang komt kunnen specifieke problemen ervaren die gerelateerd zijn aan deze gestoorde gaswisseling, zoals bijvoorbeeld een slecht concentratievermogen. Deze aspecten hebben dan weer een effect op de ervaren kwaliteit van leven. Echter omdat de meeste kwaliteit-van-leven vragenlijsten ontworpen zijn voor patiënten met minder ernstig COPD, bevatten deze meer conventionele vragenlijsten vaak niet deze specifieke items. In **hoofdstuk 7** onderzochten we in het cohort gerekruteerd voor het RECOVER onderzoek of twee nieuwe vragenlijsten, speciaal ontworpen voor mensen met een stoornis in de gaswisseling, maar dan niet specifiek patiënten met COPD, betrouwbare en valide vragenlijsten zijn bij patiënten met COPD en een stoornis in de gaswisseling. Dit onderzoek resulteerde erin dat we inderdaad vonden dat deze twee nieuwe vragenlijsten een completer beeld geven van de kwaliteit van leven bij deze patiënten. Echter beide vragenlijsten hadden hun eigen specifieke punten van nadruk waardoor ze niet door elkaar heen gebruikt mogen worden.

In **hoofdstuk 8** presenteren we de resultaten van de RECOVER studie. Tweeënzeventig patiënten met ernstig COPD werden gerandomiseerd over twee groepen; de ene groep werd gedurende de nacht noninvasief beademd en volgde overdag een longrevalidatieprogramma, terwijl de nadere groep hetzelf de longrevalidatieprogramma volgde maar daarbij 's nachts niet werd beademd. Na drie maanden therapie onderzochten we of noninvasieve beademing gedurende de nacht additionele effecten had bovenop longrevalidatie alleen. We vonden dat noninvasieve beademing als aanvulling op longrevalidatie: 1) de gaswisseling overdag verbetert (dus ook als de patiënten van de beademing af zijn); 2) de ervaren kwaliteit van leven verbetert, -met name de aspecten aandacht, concentratie, het geheugen, en vermoeidheid overdag -; 3) en het activiteitenniveau verbetert; dit alles ten opzichte van alleen longrevalidatie. Uit deze studie kunnen we concluderen dat nachtelijke noninvasieve beademing als aanvulling op longrevalidatie een positief effect heeft bij patiënten met ernstig maar stabiel COPD en een stoornis in de gaswisseling. Dit is erg belangrijk omdat nieuwe effectieve behandelopties dringend gewenst zijn voor deze patiënten die forse beperkingen ervaren en daardoor een forse achteruitgang van hun kwaliteit van leven.

Conclusie

Door het onderzoek dat in dit proefschrift beschreven is werd vooruitgang geboekt op het gebied van het meten van ademhalingsspieractiviteit bij patiënten met ernstig COPD. Daarnaast hebben we aangetoond dat naast de meer bekende en geaccepteerde toepassingen van noninvasieve beademing, nachtelijke noninvasieve beademing een positief effect heeft bij patiënten met zeer ernstig COPD die in stabiele situatie toch een gestoorde gaswisseling hebben.

DANKWOORD

HET IS AF! Vele, vele mensen wil ik bedanken voor hun inzet, hulp en steun gedurende de afgelopen jaren. Ik vond het geweldig leuk en interessant om de afgelopen jaren het RECOVER project te mogen doen, al had ik tevoren nooit gedacht dat RECOVER zoveel organisatorische voeten in aarde zou hebben.

Allereerst wil ik alle mensen die meegedaan hebben met het RECOVER onderzoek hartelijk danken, evenals familie, vrienden en bekenden die vaak het vervoer van en naar Beatrixoord en het UMCG verzorgden. Ik heb het als zeer bijzonder ervaren dat patiënten die dusdanig ernstig beperkt zijn door hun longaandoening toch zoveel testen en onderzoeken hebben willen doen en steeds opnieuw alle vragenlijsten wilden invullen. Voor sommigen onder u was de reis alleen al een hele onderneming!

Mijn eerste co-promotor, Dr. P.J.Wijkstra
Peter, al een aardig poosje werken we nu samen. Bedankt voor alles wat je me tot dusver op onderzoeks- maar ook op het gebied van de patiëntenzorg hebt geleerd. Ik heb bewondering voor de toewijding en het enthousiasme voor alles wat je doet. Jij gaf me steeds opnieuw het vertrouwen en de ondersteuning die ik nodig had. Ik hoop dat ik in de toekomst, tijdens de opleiding en in de verdere toekomst, nog veel van je mag leren!

Mijn promotor, Prof. Dr. H.A.M. Kerstjens.
Beste Huib, ik had het genoegen tussentijds als promovendus bij jou aan tafel te mogen schuiven. Ik heb genoten van onze maandelijkse uurtjes. Altijd zeer nuttig en inspirerend. Jij wist me steeds uit te dagen net weer even op een andere manier naar de data te kijken en dan alles net wat scherper op te schrijven.

Mijn 2de co-promotor, Dr. J.B.Wempe
Beste Johan, mijn steun en toeverlaat in Beatrixoord. Achter de schermen regelde jij vele organisatorische zaken in Beatrixoord. Jouw ideeën en kijk op het onderzoek waren steeds opnieuw verfrissend!

Beste Gerrie, in de loop der tijd ben jij mij tot steeds grotere steun geworden. Altijd verzorg jij je taken met uiterste precisie. Ik heb zeer veel van je geleerd op het gebied van beademing. De rust en het vertrouwen die jij uitstraalt naar de patiënten zijn immens groot. Ik wens je veel succes met de studie van Fransien.

Prof. Dr. G.H. Koëter, bedankt voor uw waardevolle ondersteuning in het eerste deel van het onderzoek.

I would like to thank Prof. Dr. R. Goldstein, Prof. Dr. E.F.M.Wouters and Prof. Dr. P.N.R Dekhuijzen, for their willingness to be a member of the review committee of this thesis and for their comments on my thesis. I would like to thank Prof. Dr.

R. Goldstein and Prof. Dr. P.N.R Dekhuijzen for their presence at the thesis defence ceremony.

Daarnaast dank ik de longartsen en longartsen in opleiding voor hun hulp en inzet bij het includeren van patiënten voor het RECOVER onderzoek.

De medewerkers van het centrum voor thuisbeademing wil ik bedanken voor hun begeleiding van de RECOVER patiënten.

De medewerkers van de intensive care beademing van het UMCG wil ik bedanken omdat deze afdeling het mogelijk maakte dat wij bij alle beademingspatiënten maarliefst 3 keer een nachtelijke bloedgasregistratie konden verrichten, wat absoluut uniek is bij het onderzoek naar noninvasieve beademing!

Alle co-auteurs wil ik bedanken voor hun bijdrage aan de artikelen. Eric, bedankt voor je hulp met het opzetten van de EMG. Désirée, bedankt voor jouw statistische hulp! Jan Zijlstra wil ik danken voor zijn leerzame, nuttige en altijd zeer snelle commentaren op de artikelen over beademing. Leo van Eykern wil ik bedanken voor zijn hulp bij de EMG metingen en de data-analyse. Fijn dat u steeds weer even tijd had als ik een probleem had met portilab of polybench.

Beste Peter Vennik, bedankt voor alle support bij het overtuigen van patiënten, het prikken van al te lastige bloedgassen en alle andere praktische hulp die u me de afgelopen jaren geboden hebt.

Beste René, u deed alle fietsergometrieën altijd met uiterste precisie. Soms moesten patiënten hiervoor een poosje op de fiets zitten, maar u haalde altijd eruit wat erin zat. Dank hiervoor!

Het longrevalidatieteam van Beatrixoord:
Etta, Hanneke, Thijs, Gonnie, Ria, Marieke, Silwia, verpleegkundigen, diëtistes, psychologen en alle anderen van het team, bedankt voor jullie hulp. Zonder jullie inzet was dit alles niet mogelijk geweest.
De longfunctieafdeling van Beatrixoord: Monica, Therese, Henk, Door, Ellie, Gea, Maria, Margrietha, bedankt voor al jullie metingen. Bij jullie kon altijd allles!
De fysiotherapie: Mariëlle, Hendrie, Indra, Bea, Paulien en alle anderen. Bedankt voor het enthousiasme waarmee jullie zelfs de meest ernstig zieke patiënten laten revalideren.

Collega's van het GRIAC. Ik heb genoten van de dinsdagmiddag bijeenkomsten. Het commentaar is altijd kritisch maar zeker opbouwend. Graag fietste ik op de dinsdagmiddag heen en weer vanuit Haren. Beste Renske, Naomi, Wouter, Emmy, Fransien, Sandra en Linda, ik vond het heerlijk het laatste half jaar bij jullie op de kamer te kunnen zitten. Gewoon even lekker kletsen maar ook serieus overleg en advies over het laatste staartje van het onderzoek.

Beste Bertine, in de loop van de tijd werden we goede vriendinnen. Ik wens je veel succes met jouw onderzoek en hoop dat we nog vele gezellige uurtjes zullen beleven. Ik vind het helemaal top dat je mijn paranimf wilt zijn.

Mijn vader, moeder, broer en zusje wil ik bedanken voor alle steun die de totstandkoming van dit proefschrift überhaupt mogelijk heeft gemaakt. Mam, bedankt dat jij gedurende al die jaren Lets hebt willen verzorgen, waardoor het mogelijk was dat ik minstens 4 keer per week 's avonds zo even op zijn rug kon kruipen. Een betere ontspanning bestaat er voor mij niet! Pap, bedankt voor je hulp. Ik heb van het voordeel mogen genieten dat jij wist hoe de onderzoekswereld in elkaar zat! Sytse, bedankt dat je vandaag mijn paranimf wilt zijn. Kun je alvast een beetje voorproeven...

Lieve, lieve Ap, jij verzon de naam achter de noninvasieve beademingsstudie (RECOVER). En hier bleef het niet bij. Juist doordat jij niet in de medische wereld zit, zijn jouw ideeën altijd verfrissend. Maar bovenal mag ik zo gelukkig zijn dat jij altijd naast me staat, en jij me altijd weer weet te overtuigen, "t komt wel goed"...
Lieve....., je maakte het laatste half jaar behoorlijk roerig en hebt mijn promotiedatum wel aardig weten te versnellen. Ook heeft jouw aankondiging mijn relativeringsvermogen vergroot: een "reject decision" is nog steeds altijd erg balen (en natuurlijk onterecht.....), maar één schopje van jou maakt mijn hele dag weer goed.
Lieve Ap en lieve kleine...., jullie zijn het allerbelangrijkste!

CURRICULUM VITAE

The author of this thesis, Marieke Leontine Duiverman, was born in Nieuwerkerk aan den IJssel on July 7th, 1981. In 1999 she graduated secondary school cum laude at the Goudse Waarden in Gouda.

Thereafter she started to study medicine at the University of Groningen. From 2002 she participated in research under supervision of Dr. P.J. Wijkstra, pulmonologist at the University Medical Center Groningen. From 2004 she started a MD/PhD program facilitated by the Junior Scientific Masterclass. In this program, she combined doing research on the RECOVER project under supervision of Dr. P.J. Wijkstra, Prof. Dr. G.H. Koëter, Prof Dr. H.A.M. Kerstjens and Dr. J.B.Wempe, with her medical internships. RECOVER was designed to investigate nocturnal noninvasive ventilation in addition to rehabilitation in patients with severe chronic obstructive pulmonary disease. In august 2006 she obtained her medical degree cum laude.

In 2008 Marieke will start her residency at the pulmonary department of the University Medical Center Groningen. She is married with Ap van der Bas and they expect their first child in June.