Monitoring long-term nocturnal non-invasive ventilation for chronic hypercapnic respiratory failure: What are the basic tools?

Sigurd Aarrestad

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Department of Pulmonary Medicine, Oslo University Hospital, Ullevål, Norway.

Institute of Clinical Medicine, University of Oslo, Norway

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Table of content

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
$AHI_{software}$	Apnea-hypopnea index downloaded from ventilator
ALS	Amyotrophic lateral sclerosis
BMI	Body mass index
BPAP	Bi-level positive airway pressure
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
EPAP	Expiratory positive airway pressure
FRC	Functional residual capacity
FVC	Forced vital capacity
ICC	Intraclass correlation coefficient
IPAP	Inspiratory positive airway pressure
ISCD-3	The International Classification of Sleep Disorders 3
LTMV	Long-term mechanical ventilation
NIV	Non-invasive ventilation
NMD	Neuromuscular disorders
ODI	Oxygen desaturation index
ODI3%	ODI with ≥ 3 % oxygen desaturation lasting 10-90 seconds
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
$PaCO_2$	Carbon dioxide tension in arterial blood
PaO_2	Oxygen tension in arterial blood
PSG	Polysomnography
PtcCO2	Transcutaneous CO2
PVA	Patient-ventilator asynchrony
PWA	Photoplethysmographic pulse wave amplitude
RCT	Randomised controlled trials
REM	Rapid eye movement
RPG	Respiratory polygraphy
RTD	Restrictive thoracic disorders
SPO_2	Oxygen saturation
SpO_290	Percentage of time spent with SpO2 < 90%
VC	Vital capacity

Summary

Background

In patients with neuromuscular disorders, obesity or chest wall disorders, chronic hypercapnic respiratory failure may occur. Non-invasive ventilation (NIV) is increasingly being used for long-term treatment of these patients. NIV aims to improve quality of life and to reduce morbidity and mortality. However, during NIV-treatment nocturnal respiratory events may compromise the efficacy of NIV, events like obstructive or central apnea and hypopnea, patient-ventilator asynchrony (PVA), leaks, and sleep hypoventilation. How to monitor patients treated with long-term NIV in order to detect these events, is under debate. Recently, an algorithm for monitoring NIV during sleep has been proposed by the international SomnoNIV group. They suggest that a combination of clinical evaluation, daytime arterial blood gases (ABG), nocturnal pulse oximetry (SpO_2), and a synthesis report from the ventilator software should be used as the first step during follow-up of these patients.

Aims

The aim of this thesis was to evaluate how to monitor nocturnal ventilation in patients treated with long-term NIV. We specifically aimed to evaluate the accuracy of the proposed test panel from the SomnoNIV group for detecting sleep related respiratory events. In addition, we aimed to evaluate the accuracy of specific tests for selected events: nocturnal SpO_2 and daytime ABG, as markers of sleep hypoventilation, oxygen desaturation index (ODI) and apnea-hypopnea index (AHI) from NIV software ($AHI_{software}$), as markers of apnea-hypopnea, and ODI, as a marker of PVA. We also aimed to evaluate the methods used as reference standards for the detection of respiratory events, and the frequency of respiratory events.

Methods

Patients treated with long-term NIV scheduled for a regular follow-up were eligible for inclusion. Transcutaneous CO_2 ($PtcCO_2$), the reference standard used for detecting hypercapnia and sleep hypoventilation, was evaluated by comparing $PtcCO_2$ with $PaCO_2$ obtained from ABG. The overnight instrumental drift of the $PtcCO_2$ sensor was studied by repeated ex vivo measurements (Paper I). Respiratory polygraphy (RPG), the references standard used for detecting PVA and apnea-hypopnea, was evaluated by studying interrater agreement between two scorers (Paper II).The prevalence of sleep hypoventilation was detected by performing overnight $PtcCO_2$ in all patients (Paper III), and the prevalence of

other respiratory events was studied by performing RPG in all patients (Paper II). The diagnostic accuracy of the tests for detecting respiratory events was evaluated by comparing them with the reference standards (Paper III).

Results

Sixty-seven patients were included. We found that $PtcCO_2$ accurately reflects $PaCO_2$ and that overnight instrumental drift of the $PtcCO_2$ sensor is low in most patients. RPG reliably identifies and quantifies apnea-hypopnea and PVA. Sleep hypoventilation was found in 35 % - 76 % of patients depending on the definition used for sleep hypoventilation. AHI was ≥ 10 in 24 % of the patients. Obstructive hypopnea was the most frequent event. Twenty-one per cent of patients spent > 10 % of total recording time with PVA. None of the test evaluated could accurately detect sleep hypoventilation. In addition, overnight SpO_2 could not accurately detect high AHI or PVA. $AHI_{software}$ from the ventilator accurately detected high AHI.

Conclusions

$PtcCO_2$ and RPG can be used to detect sleep respiratory events during NIV. Sleep hypoventilation, obstructive hypopnea and PVA are frequent during long-term NIV treatment. Therefore, overnight efficacy of NIV should be systematically monitored, and $PtcCO_2$ should be implemented in the routine follow up of these patients in order to detect sleep hypoventilation. Also, $AHI_{software}$ should be systematically evaluated. In the presence of a high $AHI_{software}$, obstructive hypopnea should be suspected and a trial with increased EPAP could be implemented. RPG can be limited to non-responders to this adjustment of treatment. RPG is needed if detection of PVA is warranted.

List of papers

Paper I

Validity of transcutaneous PCO_2 in monitoring chronic hypoventilation treated with non-invasive ventilation.
Respiratory Medicine. 2016;112:112-8.
Aarrestad S, Tollefsen E, Kleiven AL, Qvarfort M, Janssens JP*, Skjønsberg OH*.

Paper II

Sleep related respiratory events during non-invasive ventilation of patients with chronic hypoventilation.
Respiratory Medicine. 2017;132:210-6.
Aarrestad S, Qvarfort M, Kleiven AL, Tollefsen E, Skjønsberg OH*, Janssens J-P*.

Paper III

Diagnostic accuracy of simple tools in monitoring patients with chronic hypoventilation treated with non-invasive ventilation; a prospective cross-sectional study.
Respiratory Medicine. 2018;144:30-5
Aarrestad S, Qvarfort M, Kleiven AL, Tollefsen E, Skjønsberg OH*, Janssens J-P*.

*The authors have contributed equally to the conduction of the study

1. Background

The respiratory system delivers oxygen to and removes carbon dioxide (CO_2) from the body. When this system fails, respiratory failure occurs. Respiratory failure may be due to disorders within the lung or due to failure in the transport of air to the lung. A failure of transport of air to the lung is called hypoventilation and leads primarily to accumulation of CO_2: hypercapnic respiratory failure. Hypercapnic respiratory failure can be caused by many disorders, including neuromuscular disorders (NMD), chest wall disorders and disorders of the control of ventilation. Many of these conditions are chronic, without an existing cure and may ultimately lead to death due to respiratory failure. The use of mechanical ventilation has dramatically changed this over the last decades.

With mechanical ventilation the transport of air to the lung is provided with a machine. For most patients this treatment is provided via a mask: non-invasive ventilation (NIV), and for a majority only during sleep. NIV aims to improve the quality of life and reduce mortality and morbidity. However, during NIV a variety of respiratory events may occur, especially during sleep. These events may compromise the efficiency of the treatment. My thesis includes papers where we aimed to describe the frequency of these events and how to detect them. The gap in knowledge in this area is reflected in the variation of recommendations in how to monitor patients during long-term NIV. Our studies provide results that may guide clinicians in how to follow-up these patients in order to individualize the ventilator settings. Hopefully, our contribution to increase the knowledge in the field of long-term NIV-treatment may improve quality of life and reduce mortality in these severely affected patients.

1.1. Chronic hypercapnic respiratory failure

Respiratory failure occurs when the gas-exchange is insufficient, i.e. oxygenation of and/or elimination of carbon dioxide from mixed venous blood.[1] It is conventionally defined by the oxygen tension (PaO_2) and carbon dioxide tension ($PaCO_2$) in arterial blood; $PaO_2 < 8.0$ kPa, PaCO2 > 6.0 kPa, or both. The respiratory system can be seen as a system consisting of two parts: the lung where the gas-exchange occurs and the pump that ventilates the lung.[2] The pump includes the nervous system with the controllers of ventilation and the pathways that connect these centers to the respiratory muscles, the respiratory muscles, and the chest wall. Diseases of the lung will primarily lead to hypoxemia (type 1 respiratory failure), while diseases leading to failure of the ventilator pump will primarily lead to hypercapnia (type II respiratory failure). There are 3 major causes of pump failure:1) Abnormal control of

ventilation due to inadequate output from the respiratory center, 2) reduced capacity of the inspiratory muscles, and 3) excessive mechanical load to the respiratory muscles (chest wall disorders or obesity).[2] Failure of the pump causes hypoventilation, a condition in which alveolar ventilation is insufficient to meet the individual's metabolic demands, resulting in high $PaCO_2$ (hypercapnia).[3] Respiratory failure may occur acutely, insidiously leading to chronic respiratory failure, or acute on chronic respiratory failure. This thesis will focus on patients with diseases leading to chronic hypercapnia primarily due to pump failure, i.e. diseases outside the lung including NMD affecting the respiratory muscles, chest wall disorders, ventilatory control abnormalities, and obesity hypoventilation.

1.2. Sleep and breathing

Pathophysiological mechanisms related to breathing during sleep plays an important role in the diseases insidiously leading to chronic hypercapnic respiratory failure. The International Classification of Sleep Disorders 3 (ISCD-3) classifies four main groups of *sleep related breathing disorders*: 1) obstructive sleep apnea- 2) central sleep apnea- 3) sleep related hypoventilation- and 4) sleep related hypoxemia- disorders. [4] Also, four main types of *respiratory events* that can occur during sleep are described: obstructive events, central events, sleep hypoventilation and sleep hypoxemia.[4] Main characteristic of these events are described in Table 1.

Table 1. Main characteristic of sleep related respiratory events[4]

Event	Characteristics
Obstructive event	Upper airway narrowing or closure during sleep while effort to breath continues
Central event	Reduction of or cessation of airflow due to absent or reduced effort to breath
Sleep hypoventilation	Insufficient ventilation resulting in abnormally elevated $PaCO_2$ during sleep
Sleep related hypoxemia	Sustained periods of significantly reduced oxyhemoglobin saturation during sleep

For the definitions of obstructive, central and sleep hypoventilation events, ISCD-3 refers to the most recent version of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events.[5] These criteria are described later. Sleep hypoxemia is defined in the ISCD-3 as arterial oxygen saturation (SPO_2) during sleep $\leq 88\% \geq 5$ minutes. The individual clinical characteristic of the patient combined with the respiratory events present during sleep guide further classification within each group of sleep related breathing disorders. This is described in details in ISCD-3 and will not be further outlined here.

Sleep hypoventilation disorders are further classified in the following groups: (Table 2.)

Table 2. Classification of sleep hypoventilation disorders according to ISCD-3[4]

Sleep hypoventilation disorders:
Obesity hypoventilation syndrome
Congenital central alveolar hypoventilation syndrome
Late-onset central hypoventilation with hypothalamic dysfunction
Idiopathic central alveolar hypoventilation
Sleep related hypoventilation due to a medication or substance
Sleep related hypoventilation due to a medical disorder

The general criteria for all sleep related hypoventilation disorders is the presence of one or more sleep hypoventilation events. Daytime hypercapnia may or may not be present, except for obesity hypoventilation syndrome (OHS), in which daytime hypoventilation is required for the diagnosis. If hypoventilation is present during wakefulness, it worsens during sleep.[4] Strictly speaking, chronic hypercapnic respiratory failure refers to chronic elevated daytime $PaCO_2$. For sleep hypoventilation disorders, on the other hand, it is only required that one or several sleep hypoventilation events are present during sleep. This reflects the knowledge of the natural history of many of the disorders ultimately leading to hypercapnic respiratory failure: Hypoventilation typically first occur during sleep, gradually leading to symptoms due to disturbed sleep, often preceding daytime abnormality of gas exchange. Daytime gas exchange is first evident by an increase in daytime $PaCO_2$ before severe respiratory failure with severe hypoxemia occurs (Figure 1).[6]

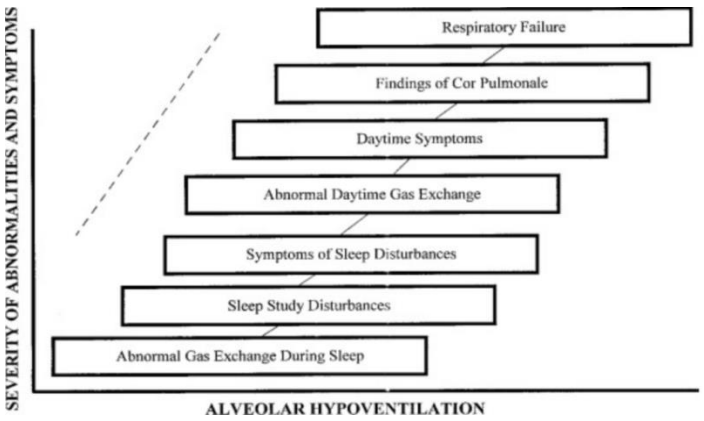

Figure 1. Progression of severity of gas-exchange abnormalities and symptoms of hypoventilation over time. Hypoventilation and symptoms increase from abnormalities during sleep, to daytime symptoms, and finally to symptoms of overt respiratory failure. (Used with permission by Elsevier: Previously published in Chest[6])

Several common and rare disorders are associated with the development of sleep hypoventilation and chronic hypercapnic respiratory failure (Table 3).[7-13]

Table 3. Disorders associated with the development of sleep hypoventilation and chronic hypercapnic respiratory failure

Disorders
Neuromuscular disorders
Hereditary neuromuscular disorders
• Duchenne muscular dystrophy
• Myotonic dystrophy
• Other muscular dystrophies and myopathies: Limb girdle muscular dystrophy, Facioscapulohumeral muscular dystrophy, Becker, Nemaline myopathy, central core, Emery-Dreifuss muscular dystrophy and others
• Spinal muscular dystrophy
• Other hereditary neuromuscular disorders: polyneuropathy, Charcot Marie Tooth and others
Acquired neuromuscular disorders
• Post-polio Syndrome
• Brain damage: Cerebral palsy, and others
• High spinal cord injuries
• Amyotrophic lateral sclerosis/motor neurone diseases
• Other acquired neuromuscular disorders; Degenerative brain diseases, Mb Parkinson, Multiple sclerosis, Myasthenia Gravis and others
Chest wall disorders
• Kyphoscoliosis: idiopathic, congenital, secondary to neuromuscular disorders, connective tissue disorder and others
• Post tuberculosis sequelae
• Thoracoplasty
• Other skeletal disorders
Ventilatory control abnormalities
• Congenital central alveolar hypoventilation
• Idiopathic central alveolar hypoventilation
• Central hypoventilation related to a medical disorder (brain stem diseases/injuries); stroke, tumour, infection, surgery, Arnold-Chiari malformation
• Central hypoventilation related to chronic use of opioid or other medications/substances
Obesity hypoventilation syndrome
Pulmonary disorders
• COPD, Cystic fibrosis, other lung parenchymal disorders

1.2.1. Sleep and breathing in healthy individuals

Sleep affects breathing even in healthy individuals, resulting in a reduction of ventilation, particularly during rapid eye movement (REM) sleep. Several mechanism are involved: loss of wakefulness drive to breathe[14] and blunted response to hypoxia and hypercapnia,[15 16 17] inhibition of accessory respiratory muscles during REM sleep,[18-20] increased upper airway resistance[21], and supine posture resulting in cephalad movement of diaphragm with reduced functional residual capacity (FRC).[22 23] In REM sleep, skeletal muscle hypotonia, with exception of the diaphragm, impairs the accessory respiratory muscles ability to compensate for the mechanical effects of supine position. In addition, the reduction of central responsiveness to hypoxia and hypercapnia and the increased upper airway resistance is most prominent during REM sleep. Therefore, the effect of sleep on ventilation is a reduction in ventilation which is most pronounced in REM sleep.[24]

There is a decline in metabolic rate in healthy individuals during sleep. However, the reduction in ventilation during sleep is greater than the reduction of CO_2 production.[25] Thus, a mean increase of $PaCO_2$ of 0.5-0.8 kPa and a peak increase of 1.2 kPa can be observed during sleep in healthy individuals.[26]

These normal physiological changes predispose to sleep hypoventilation in patients with reduced capacity of the inspiratory muscles, increased load to the diaphragm, or abnormal respiratory control. Sleep hypoventilation is the hallmark of the disorders leading to chronic hypercapnic ventilatory failure, although other sleep related pathophysiological mechanism may be of importance, as outlined below.

1.2.2. Neuromuscular disorders

In many NMD the respiratory muscles can be affected due to a variety of pathophysiological mechanisms.[8] This may cause hypoventilation, especially if the diaphragm function is affected (Table 3).[7-9] A restrictive pattern will be seen in pulmonary function tests.[27] Hypoventilation will first occur in REM sleep where there is a lack of compensation by the accessory respiratory muscles. Initially this is seen as short episodes of hypopnea and hypoventilation[28 29] and has been known as “the canary of the coal mine”, representing an early warning sign of respiratory muscle involvement.[27] As the underlying disease progresses, more prolonged hypoventilation is seen in REM sleep. Subsequently, continuous hypoventilation occurs, independent of sleep stage, ultimately leading to daytime hypercapnia.[28-30]

The pattern of sleep disordered breathing may be further complicated by other mechanisms. Development of scoliosis or obesity increases the load on weakened respiratory muscles and may contribute to hypoventilation. In addition, upper airway obstruction may occur since upper airway involvement in some NMD predisposes to obstructive events. Upper airway muscle hypotonia may be present in disorders like Duchenne muscular dystrophy,[31-33] acid maltase deffiency[34] and myotonic dystrophy.[35] Pharyngeal neuropathy is seen in Charcot-Marie-Tooth,[36] and bulbar dysfunction often complicates Amyotrophic lateral sclerosis (ALS)[37 38] and post-polio syndrome.[39] Anatomic causes like macroglossia[27] and craniofacial abnormalities are also observed in some syndromes with neuromuscular engagement.[9 40] In some diseases like Duchenne muscular dystrophy and ALS, the reported frequencies of upper airway involvement vary considerably. This could be due to evaluation performed at different stages; i.e. due to a bimodal distribution of events with obstructive events occurring early and central hypopnea /hypoventilation later in the course of the diseases.[27] Also, as discussed later, events may be misclassified.[41] Reduced sensitivity of chemoreceptors involved in the control of ventilation is present in some NMD and may lead to central apnea-hypopnea and contribute to development of hypoventiation.[4] Central events, and in particular Cheyne-Stokes breathing may also be present secondary to heart failure in NMD disorders with cardiac involvement, although this has rarely been reported.[42 43] Finally, the slight hypoxemia occurring as a consequence of sleep hypoventilation may be aggravated by atelectasis or co-exiting lung disease. The impaired ability to cough in many NMD may lead to secretion stagnation in the lower airways, recurrent pulmonary infections and atelectasis.[7 44]

1.2.3. Chest wall disorders

Chest wall disorders include disorders of the sternum, ribs and the spine resulting in chest wall deformity and /or rigidity. This may affect ventilation. Impaired ventilation is mainly due to decreased chest wall compliance and, to a lesser degree, decreased lung compliance resulting from micro atelectasis.[10] A restrictive pattern will be seen in pulmonary function tests. [10 45 46] The decreased compliance of the chest wall increases the load on the respiratory muscles and can lead to hypoventilation and hypercapnic respiratory failure (Table 3).[45 46] This is most commonly seen in kyphoscoliosis, especially if the Cobb angle is > 90°, [45 47 48] sometimes as a result of thoracoplasty,[49] but rarely seen in disorders like pectus excavatum and ankylosing spondylitis.[46 50] Similar to NMD, hypoventilation first occurs during REM sleep, gradually progressing to non-REM sleep and wakefulness, as well.[51 52] Development of

daytime hypercapnia is associated with severe scoliosis appearing at early age and with markedly reduced lung function (Forced vital capacity (FVC) < 50%).[53] For the same degree of daytime hypoxemia as in patients with interstitial lung disease and COPD patients, kyphoscoliotic patients have been found to be more severely ventilatory impaired during sleep, both with respect to hypercapnia and hypoxemia.[54]

The pattern of sleep disordered breathing may further be complicated by other mechanisms: Scoliosis may be secondary to NMD occurring at a young age, resulting in a combination of increased load to weakened respiratory muscles aggravating hypoventilation as outlined above. In addition, lung hypoplasia is seen when scoliosis appears in young children,[53]and lower airway obstruction is reported to be common in scoliosis.[55 56] This may lead to concomitant hypoxemia (out of proportion of the hypoventilation). Also, upper airway obstruction may occur: High apnea-hypopnea index (AHI) in severe kyphoscoliotic patients and upper airway obstruction predominantly in REM sleep, have been reported.[57 52] Finally, mechanical obstruction of the central airway due to bronchial torsion may further complicate ventilation in severe kyphoscoliosis.[58]

1.2.4. Ventilatory control abnormalities

The control of breathing is a complex function and an overview of mechanisms involved can be found in a recent review by Adler et al.[59] If abnormalities of this function reduce the drive to breathe, insufficient ventilation may occur, referred to as central hypoventilation. A rare group of disorders primarily affect the control of breathing. In children with congenital central hypoventilation syndrome,[60] identified by mutation of the PHOX2B gene,[61] abnormal ventilatory sensitivity to CO_2 and hypoxia leads to severe hypoventilation during sleep while normal ventilation during wakefulness is observed. Recently, a case series of this syndrome manifistated in adulthood have been reported.[62] Central hypoventilation may also be caused by brain stem injuries affecting the central control of breathing. [63] (Table 1) The most frequent cause of central hypoventilation is probably related to opioid use in patient with chronic pain, chronic dyspnoea, or in patients treated for opiate addiction. [64-66] Central sleep apnea/hypopnea are also frequently observed in opioid users.[67] In the majority of ventilatory control abnormalities sleep hypoventilation develops first, and is most severe, in REM sleep. In congenial central hypoventilation, however, sleep hypoventilation primarily occurs in Non-REM sleep.[4] In addition, central sleep apnea is frequently observed.[4] Patients with hypoventilation primarily due to NMD, chest wall disorders and obesity develops reduced

ventilatory response to CO_2.[68-70] This secondary ventilatory control abnormality is believed to contribute to the persistence and progression of hypoventilation[59 71] and probably explains the observation of central apnea and hypopnea in many of these patients.[4]

1.2.5. Obesity hypoventilation syndrome

OHS is characterised by obesity (Body mass index (BMI) > 30), daytime hypercapnia and sleep disordered breathing.[4] Hypercapnia is worsened during sleep, and is often worse in REM sleep than NREM sleep.[4] The mechanisms leading to hypoventilation and daytime hypercapnia in obesity is complex, multifactorial and not fully understood. Important mechanisms include alterations in pulmonary function, the presence of sleep related breathing abnormalities, and changes in ventilatory control.[11]

The excess weight places an increased mechanical load on the respiratory system resulting in reduction of lung volumes. OHS patients have lower total lung capacity, expiratory reserve volume (ERV) and FRC compared with non-obese persons and compared with eucapnic obese patients[72] Also, OHS patients seem to have lowered chest wall compliance and lung compliance, and increased peripheral airway resistence.[73-75] Breathing at low volumes can promote small airway closure during exhalation and lead to the development of intrinsic positive end-expiratory pressure, which is further aggravated by supine postion.[76] These alterations in pulmonary function will increase the work of breathing, and may cause hypoventilation. However, other persons with equivalent degree of obesity frequently have normal daytime $PaCO_2$,[77 78] strongly suggesting other mechanisms to be involved.

A spectrum of respiratory disturbances during sleep has been identified in OHS including sleep hypoventilation, obstructive sleep apnea (OSA), and prolonged obstructive hypoventilation due to partial upper airway obstruction.[79] OSA is present in most patients, but 10-15% has sleep hypoventilation without apnea-hypopnea.[79 80] During sleep, short (apnea or hypopnea) and/or longer (sleep hypoventilation) events with abnormal ventilation leads to accumulation of CO_2. An insufficient inter-apnea ventilation to eliminate accumulated CO_2, both by shortened inter-apnea duration and reduced post-event hyperventilation, has been shown in hypercapnic obese patients with OSA.[81 82] This leads to an imbalance between periods of CO_2 loading, and periods with compensatory CO_2 unloading. Consequently, PCO_2 is accumulated during sleep. However, this does not explain why persistent daytime hypercapnia occurs.

Awake patients with OHS can voluntarily hyperventilate, achieving normal or near normal $PaCO_2$.[83] This suggests a predominant role for non-mechanical causes of daytime hypercapnia in OHS; i.e. impairment of ventilatory control. Increase of $PaCO_2$ due to hypoventilation will lead to compensatory increase of bicarbonate to buffer a decrease in pH. Elevated bicarbonate has been shown to blunt ventilatory response to CO_2.[84 85] Therefore, this adaptation mechanism may contribute to the development of a chronic hypercapnic state.[86] Using an experimental model, Norman et al. nicely showed how respiratory-renal interactions may contribute to the development and perpetuation of chronic awake hypercapnia in patients with OHS.[71] Obesity related humoral factors may also affect ventilatory control. The respiratory stimulant hormone Leptin is elevated in OHS, and resistance to Leptin have been suggested as one factor leading to insufficient increase in ventilation in obese patient contributing to the development of hypercapnia.[87 88]

1.2.6. From sleep hypoventilation to daytime hypercapnia

Overall, the development of hypoventilation and hypercapnic respiratory failure may be seen as an imbalance between load on the ventilatory system and its capacity or strength to overcome this load (Figure 2).[89]

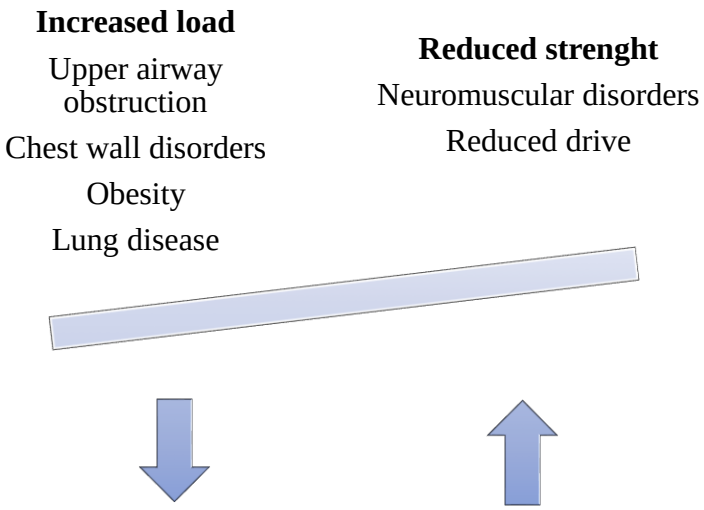

Figure 2. If the load on the ventilatory system > strength to overcome this load, hypoventilation may occur.

Upper airway obstruction, chest wall disorders, obesity and co-exiting pulmonary disorders places increased load to the system. NMD and conditions with reduced drive to breathe, reduces the strength of breathing. Reduced drive can be due to conditions primarily affecting

ventilatory control, but may also develop secondary to any hypoventilation disorder. Sleep itself causes both increased load and reduced strength.

Combinations of these mechanisms may be seen; for example in development of scoliosis in NMD, upper airway involvement in NMD, and with the use of opioids in kyphoscoliotic patients. In addition, OSA is frequent in the general population, and may co-exist with sleep hypoventilation.

Obviously, the time from sleep hypoventilation occurs until severe hypercapnic respiratory failure develops vary greatly depending on the underlying disorder. In addition progression will be influenced by co-exiting pathophysiological mechanisms and co-morbidities, as outlined above.[4]

1.3. Symptoms and signs of hypoventilation

Symptoms and signs of hypoventilation are often non-specific and occur insidiously. They may be attributed to or masked by the underlying disorder and might be overlooked. Symptoms include dyspnea, orthopnea, recurrent air-way infections, fatigue, morning headache, daytime sleepiness, sleep disruption and nocturnal dyspnea.[9] Signs may include rapid shallow breathing, use of accessory respiratory muscles, paradox breathing, especially in supine position, tachypnea and, in severe cases, signs of cor pulmonale.[9]

1.4. Long-term non-invasive ventilation

For the patients with disorders associated with chronic hypercapnic respiratory failure curative treatment is rarely available. Long-term mechanical ventilation (LTMV) is one of the few treatment options which improve outcome and symptoms. There is no international consensus on the definition of LTMV. Still, the term LTMV is commonly used for mechanical ventilation, both non-invasive and invasive, carried out in the patients home, at nursing homes or in other long-term care facilities (i.e.: outside the ICU/hospital), and the treatment is applied on a daily basis for a prolonged period of time. Patients treated primarily for OSA, are not classified as LTMV-patients.[90] The national registry for LTMV in Norway defines LTMV as continuous mechanical ventilation for at least 4 hours per day > 6 weeks outside the hospital setting.[91]

LTMV can be provided by either using NIV or invasive ventilation through a cannula via a tracheostoma. A NIV-system consists of a non-invasive interface (mask), an airflow generator (ventilator) and a circuit connecting the ventilator to the interface. NIV is usually delivered

via an oro-nasal or nose mask. Nasal prongs or mouthpieces are utilized in some patients.[92] The ventilator circuit can be single -or dual-limb and have an active exhalation valve or a passive exhalation port.[92] An active exhalation valve opens during expiration; controlled by the ventilator. A passive exhalation port is simply an opening allowing air to pass out and can either be in the circuit hose itself or in the interface (Figure 3).

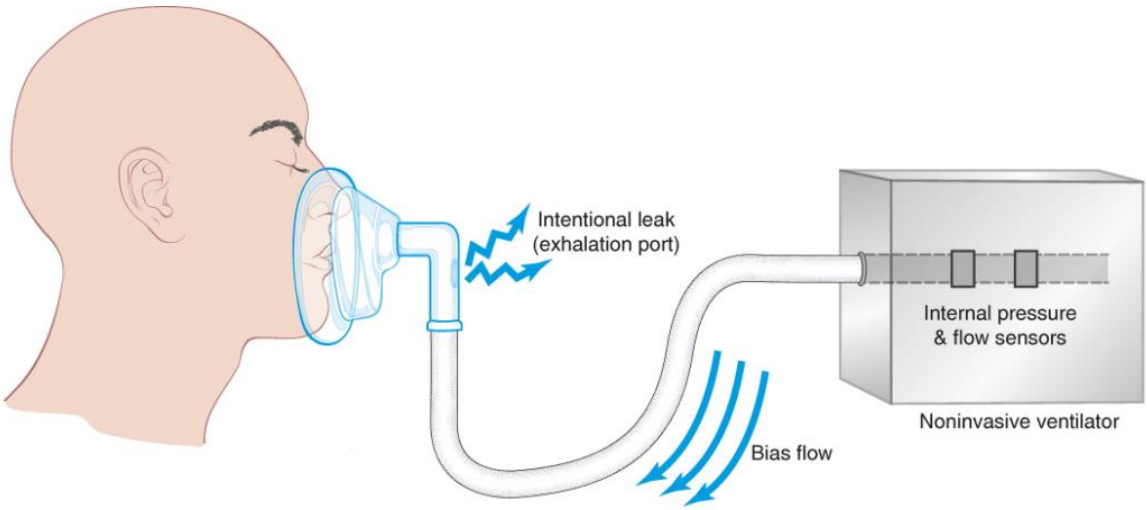

Figure 3. Illustration of a NIV ventilator with a single limb circuit with a passive exhalation port. (Used with permission by Adam Alter: Previously published by Alter et al. in Annals of the American Thoracic Society[93])

Most intensive care ventilators have a dual-limb circuit with separate hoses for inspired and expired gases and an active exhalation valve. Most ventilators specially designed for NIV, have a single-limb circuit either with an active exhalation valve or a passive exhalation port. In settings with an active exhalation valve, a mask with no exhalation port (non-vented mask) is used. In LTMV settings, passive exhalation ports are most commonly placed in the mask (vented mask).

A range of ventilators specifically designed to provide long-term NIV are available, each with a spectrum of ventilator modes, i.e. patterns of patient-ventilator interaction. It is beyond the scope of this thesis to describe these ventilators and modes in detail, but descriptions can be found in reviews by Hess et al [92] and Chatburn et al[94]

NIV is predominantly provided with pressure control; the airflow delivered by the ventilator is pressure controlled (limited). Most commonly used are bi-level positive airway pressure (BPAP) devices.[95] An understanding of unwanted events occurring during NIV requires knowledge about how these devices operates. Therefore, in the following, main characteristics of BPAP are described.

BPAP-ventilators provide sequences of breaths, each consisting of alternation between two levels of pressure; inspiratory positive airway pressure (IPAP) and an expiratory positive airway pressure (EPAP). These pressures, pre-set by the clinician, are created by airflow from the ventilator. The raised pressure during inspiration (IPAP minus EPAP) assists inspiration. A continuous flow (bias flow) from the ventilator ensures EPAP. This bias flow also flushes expired CO_2 from the circuit out through the exhalation port (Figure 3) and is required for flow triggering.[93]

The breath sequence varies in terms of how inspiration is started and stopped. This depends on the criteria allowed to trigger (start) and cycle off (stop) IPAP, as set by the clinician. The initiation of IPAP can be patient or device triggered. In patient triggered IPAP, a flow change in the circuit generated by the patient`s spontaneous inspiratory effort causes the ventilator to change from EPAP to IPAP (flow/spontaneous triggered). A device triggered IPAP will occur if a minimum backup respiratory rate is set and the patient's spontaneous breathing rate falls below this rate (time/device triggered). The cycle of from IPAP to EPAP can be patient or device dependent. Patient dependent cycle off will occur when the inspiratory flow reaches a predefined % of the maximum inspiratory flow (flow/spontaneous cycle). Device dependent cycle off will occur when a preset inspiratory time (time/device cycle) is met (Figure 4-6)

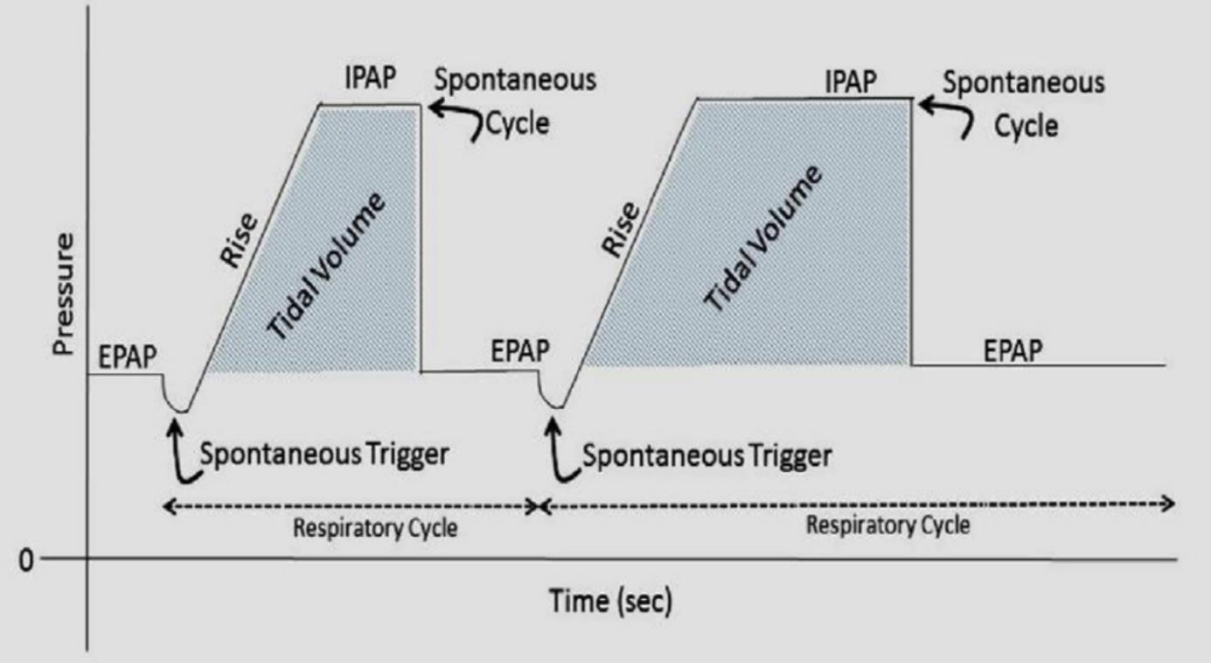

Figure 4. Both breaths: flow/spontaneous trigger and flow/spontaneous cycle. Spontaneous cycle allows for various inspiratory time according to the inspiratory effort of the patients. (Used with permission by Elsevier: Previously published by Selim et al.in Chest[96])

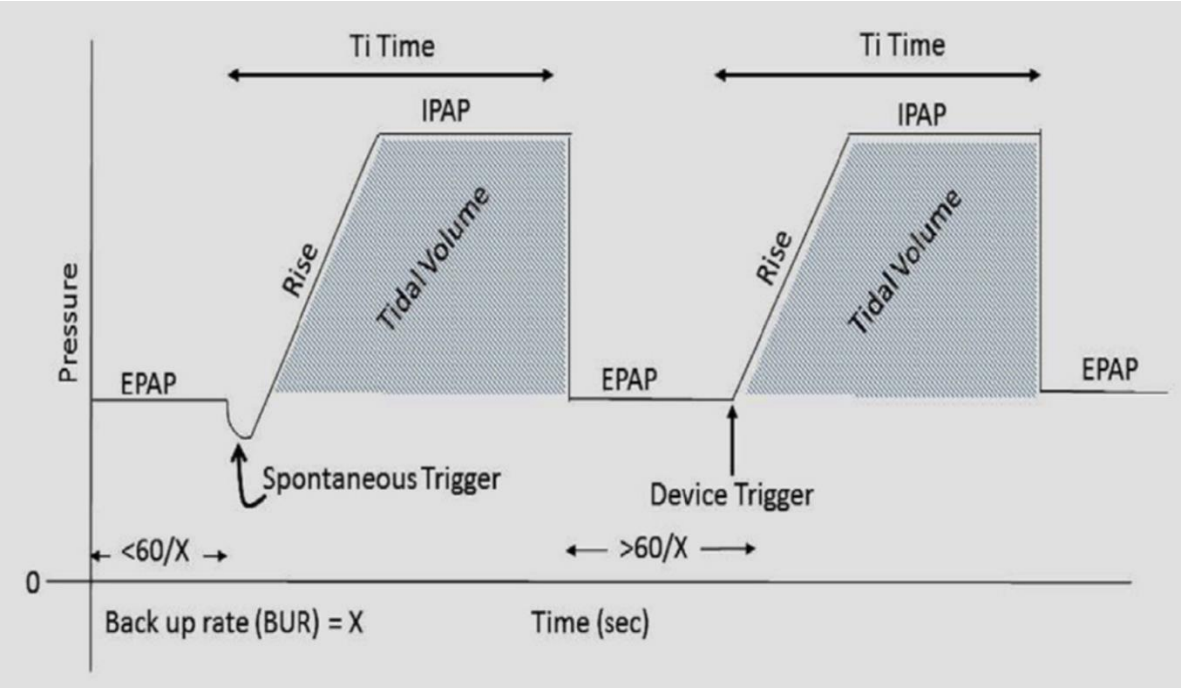

Figure 5. First breath: Flow/spontaneous trigger and device/time cycle. Second breath: device/timed trigger as the patient's breathing rate falls below backup respiratory rate, and device/time cycle. Same inspiratory time (Ti Time) in both breaths, as set by the clinician. By some manufacturer and mode, device/time cycle only apply for device/timed trigger breaths. (Used with permission by Elsevier: Previously published by Selim et al.in Chest[96])

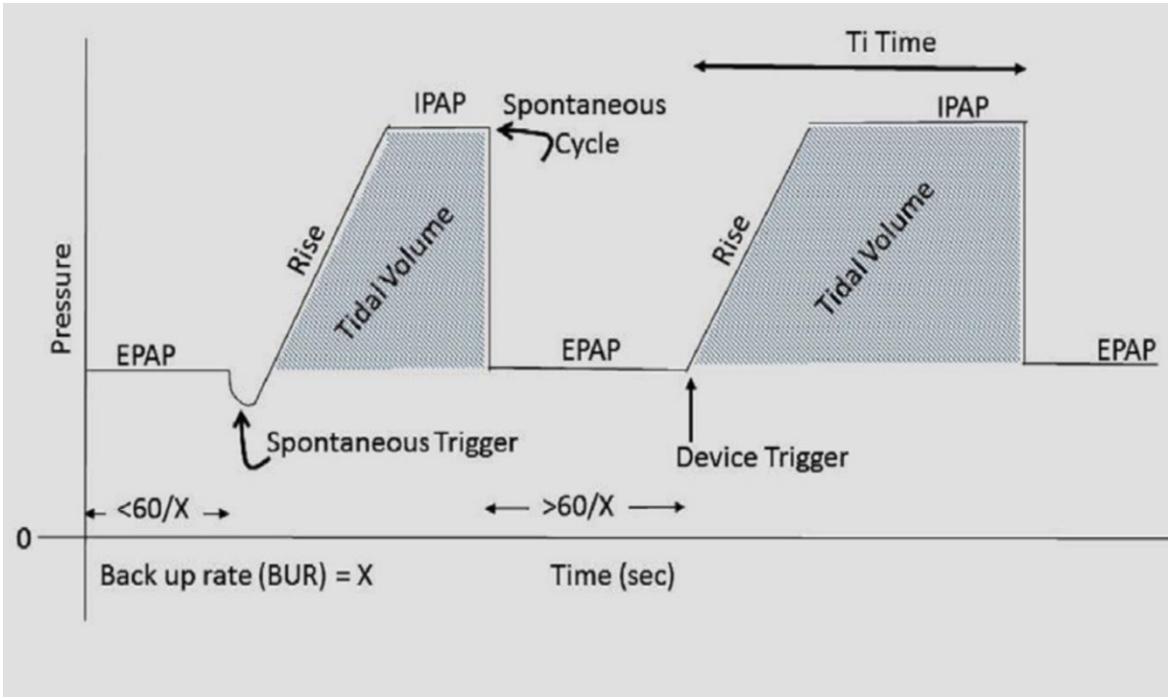

Figure 6. First breath: flow/spontaneous trigger and flow/spontaneous cycle. Second breath: device/timed trigger and device/time cycled. (Used with permission by Elsevier: Previously published by Selim et al.in Chest[96])

In most ventilators the trigger sensitivity (i.e. the amount of flow needed to trigger the device) and the cycle off criterion (i.e. the % of the maximum inspiratory flow), can be set by the clinician. However, some devises have incorporated algorithms for automatic adaptation of trigger and cycle.[96 97] Setting of a timeframe for when flow cycle can occur is also possible in some devices.[96] A minimum inspiratory time can be set to avoid short shallow breathing, and a maximum inspiratory time can be set to avoid prolonged inspiration. Within this timeframe, flow cycling is allowed, if the cycle off criterion is met.[96]

BPAP devices is always pressure controlled, but according to how breaths are triggered and cycled 3 main patterns can be described:[94]

1) Pressure Controlled - Continuous Spontaneous Ventilation (PC-CSV): All breaths are triggered and cycled by the patient. The sensitivity of the flow trigger and flow cycling is set by the clinician. Also referred to as spontaneous mode. (S-mode)
2) Pressure Controlled - Continuous Mandatory Ventilation (PC-CMV): all breaths are triggered and cycled by the device. Breathing rate and inspiratory time is set by the clinician. Also referred to as pressure control mode or timed mode (T-mode)
3) Pressure Controlled - Intermittent Mandatory Ventilation (PC-IMV): Breaths can be triggered by the patient, however if breathing rate is lower than a pre-set backup respiratory rate, a mandatory device triggered breath is given. Cycle of from IPAP may be flow or device cycled both for patient and device triggered breath. However, this varies by manufacturer. Also referred to as Spontaneous-timed-mode (ST-Mode) or, if all breaths are device/time cycled; pressure assist-control mode.

In all modes described above, IPAP and EPAP are set by the clinicians. Recently some BPAP devises have incorporated modes enabling IPAP to vary according to predefined targets; volume-assured pressure support mode (VAPS).[96] Also, some have auto- adjusting EPAP intended to overcome variation in the needed EPAP to stabilize upper airway.[96 98] The ventilator mode used and the setting of the various parameters will influence on the respiratory events which may occur during NIV, as will be explained later.

1.4.1. Epidemiology and trends in LTMV

Epidemiologic data are lacking in most parts of the world. The largest study is the survey based Eurovent analysis showing that the estimated prevalence of LTMV per 100,000 inhabitants in 2001-2002 ranged from 0.1 in Poland to 10 in Sweden, with an average

prevalence of 6.6.[90] Only 13% of the patients received ventilation via tracheotomy. A similar, more recent survey showed a minimum prevalence of LTMV of 9.9 and 12.0 per 100,000 in Australia and New Zealand, respectively, with only 3.1% receiving invasive ventilation and OHS being the largest group.[99] A Canadian survey reported a prevalence of 12.9/100,000, and that more than half of individuals had neuromuscular disease.[100] In Massachusetts, USA the prevalence of LTMV increased from 2.8 to 7.4 per 100,000 inhabitants from 1983 to 2006.[101] In 2006, 48% of these patients were living at home, of whom 76% were using invasive ventilation. Based on Medicare claims in the USA, King reported that 47981 patients were using LTMV, with 6.6% using invasive ventilation.[102] Although patients receiving BPAP due to OSA could not be excluded from these data, the authors concluded that NIV is progressively replacing tracheostomy for treatment at home. In Ontario, Canada an increased incidence of home mechanical ventilation over time has been reported (from 1.8/100,000 in 2000 to 5.0/100,000 in 2012).[103]

In the Eurovent survey the reported prevalence in Norway was 7.8 /100,000.[90] A national registrar for LTMV was established in Sweden in 1996 and in Norway in 2002, reporting annually. Based on data from the registrar, the prevalence in Norway in 2007 was 19.9/100,000.[104] In 2017 the incidence was 7.4/100,000, and the prevalence 46/100.000. In the registered adult population, 36% were treated for OHS, 28% for neuromuscular diseases and 24% for chronic pulmonary diseases. In nearly 80% of the patients with NMD, treatment was initiated electively. Only 2% of the patient who initiated LTMV in 2017 was ventilated invasively, and 96% of the patients in the registrar between 2002 and 2017 had NIV. [105] In Sweden the prevalence in 2017 was 30/100.000, with OHS being the most frequent indication in adults (40%). [106]

Although these epidemiological LTMV-data often are survey based and from different periods of time, some remarkable changes have been observed over the last three decades: 1) there is a large increase in the use of LTMV, 2) the majority of patients are treated non-invasively 3) patients at risk of developing hypoventilation are increasingly being monitored in order to detect hypoventilation and initiate LTMV, 4) there has been a shift from providing LTMV to patients that could not be weaned from acutely initiated invasive ventilation to elective initiation of nocturnal NIV, and 5) there has been a widening of indications including increasing use in OHS and in COPD patients with chronic respiratory failure. All of these international trends are observed in Norway, as well.

1.4.2. Indications for LTMV

Recommendations for the appropriate timing of treatment with LTMV include both strategies for identifying patients at risk and criteria for initiation. Indications are generally based on a combination of symptoms of hypoventilation and physiological criteria. A consensus conference report from 1999 concluded that NIV should be initiated in patients with restrictive thoracic disorders with symptoms and one of the following physiologic criteria: $PaCO_2 \geq 6.0$ kPa or nocturnal oximetry demonstrating SPO2 ≤ 88% for 5 consecutive minutes and, for progressive neuromuscular disease, maximal inspiratory pressures < 60 cm H_2O or FVC < 50% predicted.[6] Other, both international disease specific guidelines and various national guidelines, suggest similar criteria[107-111] The Norwegian national guidelines for LTMV recommends that patients with neuromuscular disease and restrictive thoracic disorders should be followed up with regular evaluation of symptoms of hypoventilation and measurement of lung function.[91] In symptomatic patients and in patients with FVC (VC) < 60% of predicted value, daytime and nocturnal ventilation should be measured. LTMV should be considered in patients with symptoms of hypoventilation and daytime and/or sleep hypoventilation. Special consideration is also recommended in the evaluation of obese patient with symptoms of sleep disordered breathing. OHS, defined as a BMI > 30 and daytime $PaCO_2 > 6.0$ kPa not explained by other causes, is considered to be an indication for LTMV in the Norwegian guidelines.

1.4.3. Effects of LTMV on survival, symptoms and general health

Small portable non-invasive positive pressure ventilators and masks became available in the late 1980s. Soon after, several case series of the effect LTMV on life expectancy and quality of life in chest wall disease and NMD were published.[56 112-114] Recommendations for the use of LTMV were implemented in disease specific[115 116] and general guidelines,[6] although randomised controlled studies demonstrating effect were lacking. NIV has become well established in many of these conditions, and for ethical reasons it is unlikely that randomised controlled studies with survival as an end point will be performed.[117 118] In addition, many of the diseases treated with long-term NIV are very rear, making large studies difficult to perform. Three recent systematic reviews have evaluated the effect of long-term NIV:
1) A Cochrane review evaluating the effect of nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders identified 10 quasi-randomised or randomised controlled trials (RCT) with only 4 studies reporting on survival.[119]

The authors concluded that mechanical ventilation at night may relieve the symptoms of chronic hypoventilation, reduce the risk of unplanned hospitalisation, and prolong survival. However, the quality of the studies was very low.

2) A systematic review including RCT and prospective non-randomised studies concluded that patients with ALS/MND had reduced somnolence and fatigue, as well as prolonged survival with NIV.[118] For OHS, reduction in somnolence and fatigue, dyspnoea and sleep quality was demonstrated. For restrictive thoracic disorders measures of dyspnoea sleep quality, physical function and health, mental and emotional health and social function improved.

3) A recent systematic review included all types of original studies, except for case studies, reporting on patient centred outcome or health resource utilization in patients receiving LTMV. They identified 26 unique studies reporting data on at least one patient-centred outcome other than survival in 4425 LTMV users[120]. The authors concluded that LTMV likely provides quality of life benefit and reduced hospitalizations in patients with chronic respiratory failure CRF secondary to NMD, restrictive thoracic disorders and OHS.

1.4.4. Initiation and titration of NIV

In most patients, NIV aims to reduce mortality and morbidity and improve quality of life. In order to achieve this, NIV settings should be adjusted in order to: 1) reduce sleep fragmentation and improve sleep quality, 2) decrease the work of breathing and provide respiratory muscle rest, 3) normalize or improve gas exchange and 4) relieve or improve symptoms of sleep hypoventilation.[121] As outlined above, the pathophysiological mechanism leading to hypercapnic respiratory failure vary, and in some patients symptomatic improvement and palliation may be the main goal. Thus, titration should be individualized both according to the goal of the treatment and the pathophysiological mechanisms involved. The principals of titration of NIV include 3 main objectives:

1) Ensure effective ventilation. This should be conceptualized in a double-compartment respiratory model[96] (Figure 7):

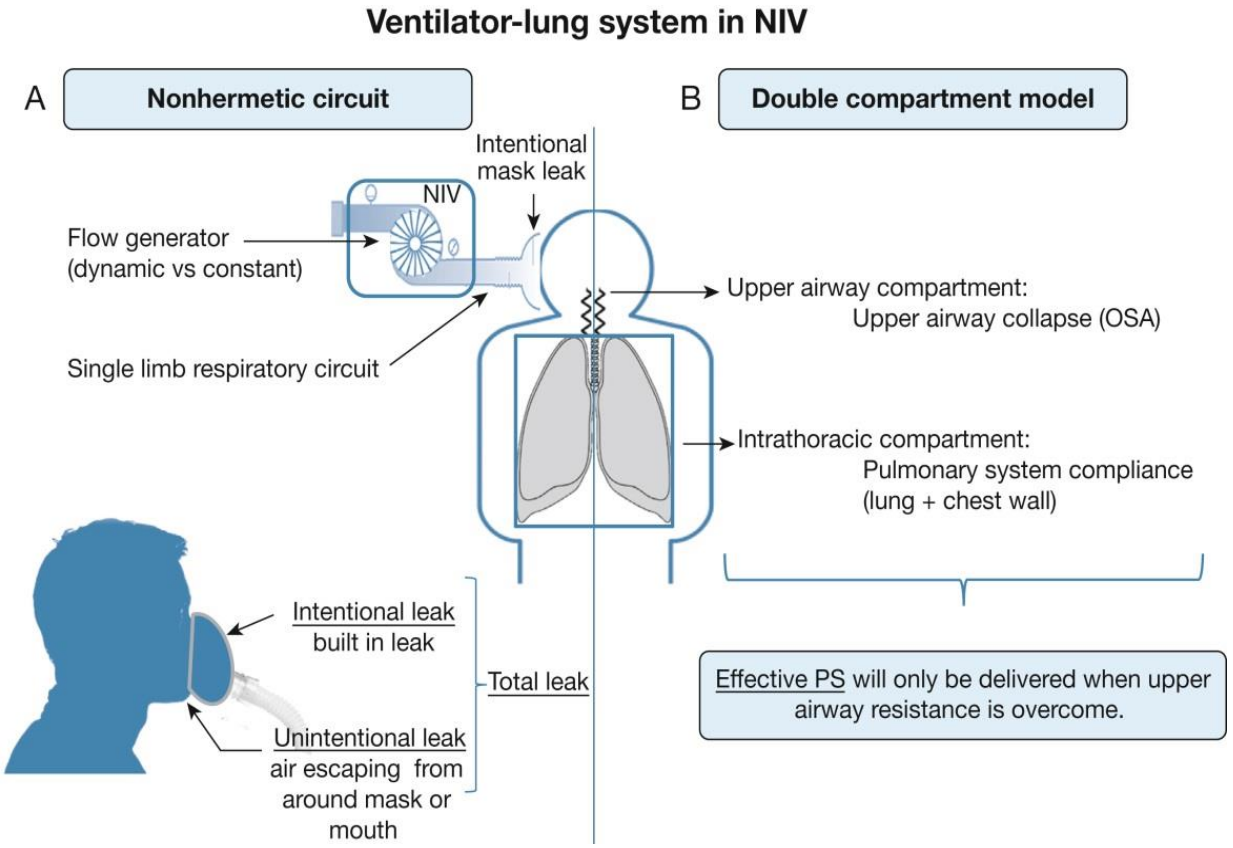

Figure 7. NIV ventilation illustrated as a double-compartment model. See text for details. (Used with permission by Elsevier: Previously published by Selim et al.in Chest[96])

First: Setting of expiratory pressure to ensure CO_2 clearance from the ventilator circuit and to treat any concomitant upper airway obstruction to allow delivery of airflow to the lung.
Second: Setting of inspiratory pressure, inspiratory triggering and cycle and backup respiratory rate in order to treat hypoventilation and central apnea/hypopnea:
2) Individualize settings like rise time, trigger and cycling sensitivity to optimize patient comfort and patient-ventilator synchrony:
3) Select and fit mask to avoid unacceptable leak at the given NIV-settings.
NIV is predominantly applied during sleep. According to AASM, NIV titration with polysomnography (PSG) is the recommended method to determine an effective level of nocturnal ventilatory support in patients with known daytime or sleep hypoventilation.[121] However, this is not possible in many centers, and various approaches are used when initiating long-term NIV, including pragmatic outpatient initiation using clinical judgment or titration using limited tools like arterial blood gases and nocturnal pulse oximetry.[108 121]

1.5. Follow-up of LTMV

There is no international consensus on how LTMV should be followed-up after initiation of therapy. According to the Norwegian National Guidelines for LTMV, patients on long-term NIV should be followed-up 4-6 weeks after initiation of therapy and then 2-4 times a year depending on the underlying disorder.[91] Presumed progression, patient's compliance and other patient related factors are also of importance. Follow-up should consist of a clinical evaluation including evaluation of the overall goals of treatment, evaluation of technical equipment including routines for maintenance and use, and monitoring of ventilation. Monitoring of ventilation should include both evaluation of daytime and nocturnal ventilation. This thesis will focus on monitoring of ventilation with emphasis on nocturnal ventilation.

1.6. Nocturnal monitoring of long-term non-invasive ventilation

Nocturnal monitoring of ventilation aims to detect and, if possible, correct respiratory events during sleep. Sleep related respiratory events such as sleep hypoventilation, obstructive or central apnea/hypopnea may be present during NIV. This may be primarily related to the disease involved. In addition, events may be specifically related to NIV: NIV may induce obstructive or central events and leaks or patient-ventilator asynchrony (PVA) may occur. In the following, respiratory events that may be present during NIV and the main mechanisms involved will be described.

1.7. Respiratory events during NIV

1.7.1. Sleep hypoventilation, obstructive or central events

Disease related sleep hypoventilation, obstructive or central events.

In addition to sleep hypoventilation, obstructive or central apnea/hypopnea may be present in in patients treated with NIV. The events occurring will depend on pathophysiological mechanisms involved and has been described above according to the various disorders causing chronic hypercapnic respiratory failure. It will also vary according to how the specific disorder affects individual patients.

The events may persist after the initiation of NIV or occur over time after the initiation of NIV. Several types of events may persist after the initiation of NIV: 1) if an insufficient EPAP is applied during initiation, upper airway obstruction may persist. 2) Central events may persist if no or insufficient backup respiratory rate is applied, or if the inspiratory pressure is insufficient to compensate for the reduced inspiratory effort during the central events. 3) Hypoventilation may persist if the ventilatory support is insufficient for example during REM-sleep.

There are several reasons for respiratory events to persist after NIV initiation. First, if a pragmatic outpatient approach is used to initiate NIV without the use of diagnostic respiratory polygraphy (RPG) and/or transcutaneous CO_2 ($PtcCO_2$), co-existing upper airway obstruction, the amount of central events and hypoventilation might be missed and not fully corrected for. Second, the use of RPG/PSG and $PtcCO_2$ during the diagnostic work-up prior to initiation of NIV, will detect these events. Still, sleep related events may have been misclassified resulting in incorrect ventilator settings, especially in NMD: Pseudo-central events as obstructive due to reduced but present inspiratory effort, and obstructive events as central if the inspiratory strength is insufficient to move thorax and abdomen against a closed airway.[27] Also, paradoxical thoraco-abdominal movement, usually a sign of upper airway obstruction, may be present if the diaphragm is weakened without upper airway obstruction, or may not be present during obstructive events.[27]

Last, NIV can be titrated utilizing RPG/PSG to ensure correct settings.[121] Still, the chosen NIV settings may represent a compromise between the settings needed, and what is feasible in practice. This may include lowered pressure to avoid leaks and the use of settings according to patients' tolerance and preferences. Thus, allowing the patient to adapt to treatment over time and aiming to optimize settings during later follow-up.

Over time, progression of the disease may lead to de novo sleep related respiratory events. Hypoventilation may occur due to progression of the underlying disease with increased weakening of inspiratory muscles, increased load to the ventilatory system due to weight gain, increased scoliosis, or increase of upper airway resistance.[121] Obstruction of the upper airway may appear due to weight gain or because the upper airways become affected by the underlying disorder, for example the upper airway muscles in NMD. It has also been observed, that severe therapy resistant upper airway obstruction occurs in supine position late in the course of Duchenne muscular dystrophy and ALS (Michel Toussaint, personal communication).

NIV related upper airway obstruction

The upper airway may be involved in disorders causing hypoventilation or due to co-existence of OSA. In addition, upper airway obstruction may be induced by NIV. This was described in patients under NIV-treatment already in 1991[122], and also in subsequent experimental studies.[123-125] The authors have concluded that this is partly due to hypocapnia secondary to NIV-induced hyperventilation, but other factors like high flow or high tidal volume may contribute. Rabec et al found that this type of NIV-induced "inspiratory block" with simultaneous reduced thoraco-abdominal movement caused significantly mask leaks in 7of 75 patients treated with long-term NIV.[126] Thus, these events can be said to be both obstructive (glottic closure) and central (reduction of drive to breath); still probably of central origin (central induced glottic closure). In line with this, it has been suggested that obstructive events occurring during NIV should be separated into those with and without reduction of ventilatory drive.[127] This has therapeutic consequences, as obstructive events without drive reduction should lead to increase of EPAP, while events with obstruction and reduction of drive should be suspected to be due to hyperventilation and glottic closure, and lead to reduction of ventilatory support.

Recent findings have further complicated the problem of upper airway obstruction. In a case report Vrijsen et al. nicely described how NIV induced upper airway obstruction in an ALS patient.[128] This was caused by back movement of the tongue and was resolved by changing from an oro-nasal mask to nasal mask. Decreased movement of thorax and abdomen was observed during the obstructive events. In OSA, it has been reported that residual obstructive events during CPAP were lower in patients with nasal mask and that higher pressure was needed in patients with oro-nasal masks.[129] Furthermore, upper-airway obstruction not present prior to NIV, was found in of 14% of 212 patient patients during initiation of NIV, all using

an oro-nasal mask.[130] NIV induced upper airway obstruction was significantly higher in patients with NMD compared with non-NMD patients. Also, Sayas et al investigated 212 patients during initiation of long-term NIV.[131] Thirteen patients had persistent upper airway obstructions during NIV despite an EPAP titrated up to 12 cm H_2O. In all patients, increased inspiratory effort was observed during the obstructive events. Videolaryngoscopi during NIV identified the mechanism and site of obstruction in all cases; soft palate collapse in 2; epiglottic backward movement in 5, retroglossal collapse in 2 and paradoxical vocal cord movement in 2. Improvement was demonstrated in 9 patients after changing from oro-nasal to nasal mask. Also, IPAP/EPAP was reduced in 9 patients. An interesting parallel to these observations is the results of Andersen et al showing that mechanical insufflation-exsufflation used to assist cough in ALS patients caused laryngeal adduction during insufflation predominantly at the supraglottic level.[132] The effect also occurred at lower pressure levels, as the disease progressed.[133]

Although these observations are limited in number, they are in line with the clinical impression in many centers that some obstructive events during the course of NIV-treatment are neither resolved by increase of EPAP nor by reduction ventilatory support. These events appear to be NIV related, and not caused by hypocapnia.

NIV related central events

In spontaneous breathing patients central apnea and hypopnea may occur cyclical or intermittent.[4] At least cyclical central events are believed to be due repetitive reduction of $PaCO_2$ below the apnea threshold. A distinct type of these events is Cheyne-Stokes breathing with typical crescendo-decrescendo pattern of flow, frequently seen in patients with heart failure.[4] In contrast, intermitted central apnea observed in spontaneously breathing patients with hypoventilation disorders, also occurs during periods with hypercapnia, probably as an effect of impaired ventilatory control.[4]

Central apnea and hypopnea may also be related to NIV. Reduction of drive, without upper airway obstruction has been observed during NIV.[134] This may be due to NIV-induced hyperventilation resulting in $PaCO_2$ beyond the apnea threshold.[127] Also, events with periodic crescendo-decrescendo events were observed in 8 of 20 patients with OHS during nocturnal NIV.[135] In this study, overnight $PtcCO_2$ was not lower in the group with periodic breathing. It has been suggested that NIV-induced reduction of CO_2 in subject who remains hypercapnic may lead to central apnea and hypopnea.[127] However, this phenomenon is not yet fully understood.

The distinction between central and obstructive events is not clear-cut. Many patients have both central and obstructive events, and there is also an overlap in pathophysiology; a central apnea may be associated with a closed upper airway and obstructive events may occur in periods with reduced ventilatory drive.[4] It is beyond the scope of this thesis to address this further, but the subject has been reviewed by others.[136-138]

The differentiation between obstructive and central events relies on detection of continuous or increased inspiratory effort during events with reduced airflow. In clinical practice using RPG/PSG, inspiratory effort or drive to breathe is detected with thoraco-abdominal belts. A continuous or increased inspiratory effort causes thoraco-abdominal movements reflected in the amplitude of the belt signals. However, this method has limitation and may not detect all inspiratory efforts. Patients with reduced inspiratory strength or increased load to the respiratory system, like NMD, may not be able to move thorax and abdomen sufficiently against a closed airway.[27] Thus, these episodes may be interpreted as obstruction with reduction of respiratory drive. With the use of more sensitive methods for inspiratory effort such as esophageal pressure or diaphragm or parasternal electromyogram, this effort would have been detected.[139]

With these limitations, the central and obstructive events potentially being present during long-term NIV and possible mechanism can be summarized as follows in Table 4:

Table 4. Central and obstructive events occurring during NIV and possible mechanism.

Events:		**Possible mechanism:**
Obstructive events:		
Upper airway obstruction without reduction of ventilatory drive	Disease related	Upper airway involvement of the underlying disorder Co-existing OSA
	NIV related	Obstruction at glottic or supraglottic level: backward movement of tongue or mandible, high pressure or flow, use of oro-nasal mask
Upper airway obstruction with reduction of ventilatory drive (including reduction of thoraco-abdominal movement)	Disease related	Insufficient inspiratory strength to move thorax and abdomen against a closed airway
	NIV related	NIV induced hyperventilation resulting in hypocapnia
Central events	Disease related	Disorder with abnormal ventilatory control or opioid use Secondary to hypoventilation Co-existing central sleep apnea
	NIV related	NIV induced hypocapnia NIV induced reduction of CO_2 without hypocapnia?

1.7.2. Leaks

NIV is a non-hermetic application of ventilatory support usually provided with pressure via a mask. Thus, there is a risk of air leaks. Leaks can be seen as the difference between the volume of air delivered from the ventilator and the air delivered to the patient. Long-term NIV is frequently provided with a BPAP. In this setting, the total leak consists of intentional and unintentional leak. Intentional leak, either through an exhalation port in the mask or in the ventilator hose, enables the washing out of exhaled air from the circuit in order to avoid rebreathing. Unintentional leak represents the variable leak between the mask contour and the face or, if a nasal mask is used, leak through the mouth. This leak may appear if the mask fitting is poor, commonly caused by choosing a mask that is too large.[140] High pressure, fitting the mask headgear too tightly or poor maintenance of mask contour may also cause leaks. Even if leaks are minor during daytime, it may appear or be further aggravated by sleep: mask leak due to mask displacement or mouth leak due to opening of the mouth during sleep. Leaks may also be secondary to obstruction of the upper airway occurring during sleep.[126]

1.7.3. Patient-ventilator asynchrony

There has been an increasing interest in PVA occurring during invasive and non-invasive mechanical ventilation.[141] Still, no consensus exists on the terminology of asynchrony. The phenomenon has been described in terms of *phase asynchrony* and *flow asynchrony.*[142] Phase asynchrony refers to a condition in which a mismatch between neural (the patient) and mechanical (the ventilator) assisted breath occurs. Flow asynchrony refers to a condition where the ventilator flow delivered is inadequate to match the patients ventilatory flow demand.[142] In addition, periods with total uncoupling of patient and ventilator rhythm lasting several minutes have been describe during sleep in patients on long- term NIV.[135] Recently, another type of PVA not fitting with classification outlined above, has been described.[141 143] This event, named reverse triggering, is characterised by an inspiratory effort apparently triggered by the ventilator and occurs in mandatory delivered mechanical breaths around the transition phase from inspiration to expiration.[143]

Patient–ventilator asynchronies have also been classified as 1) major (ineffective triggering, auto-triggering, and double triggering) and 2) minor (premature or anticipated cycling, prolonged or delayed cycling and triggering delay).[144]

During assisted mechanical ventilation there is a complex interaction between patient and ventilator.[145] The mechanisms causing PVA have mostly been studied during acute care, but also so to some extend during LTMV.[141] The ventilator response to patient effort depends on 1) the triggering variable, 2) the variable that controls gas delivery, and 3) the cycling off criterion, as described above.[145] Modern ventilators especially designed for long-term NIV, have a number of variables with options to be set by the clinician. Both incorrect mode and settings of variables, like trigger and cycling criteria, may cause asynchrony.[97 141 146] During NIV for acute respiratory failure, high leaks have been shown to be associated with PVA.[147] Similar effect are likely to occur during LTMV, but few studies have reported on this.[97 141 148 149] The ventilator may also be triggered without a inspiratory effort from the patients: This may be due to leaks, changes of airway pressure, flow due to cardiac oscillation or water in the circuit due to condense.[150-152]

Factors related to the pathophysiology of the patients may also cause asynchrony, although few studies have addressed this topic during long-term NIV. Upper airway resistance may cause obstructive apnea-hypopnea, but also increases the inspiratory load and thereby reduce the patient's ability to trigger the ventilator.[127 153] In a bench study it has also been shown that upper airway obstruction in combination with leaks can cause PVA.[154]

Both weak inspiratory muscles, as in NMD, and reduced ventilatory drive may cause weak inspiratory effort and are believed to cause PVA.[141 153 155]

In COPD patients treated with NIV for acute respiratory failure, ineffective triggering have been associated with high intrinsic positive end- expiratory pressure ($PEEP_{intrinsic}$) and these events have been reduced by counterbalancing intrinsic PEEP by applying external PEEP by the ventilator.[156] Dynamic hyperinflation induced by high ventilatory support may increase $PEEP_{intrinsic}$ resulting in ineffective effort.[157] In stable COPD patients treated with NIV, ineffective effort was reduced after adjusting ventilator setting, including reduction of IPAP in all patients.[158] Carlucci et al. reported that ineffective effort, although frequent, did not differ between patients with obstructive or restrictive disease during initiation of LTMV in stable patients.[159] Also, the occurrence of asynchrony was not correlated to any variable of respiratory mechanics including $PEEP_{intrinsic}$, recorded during spontaneous breathing. The frequency of ineffective efforts was associated with a higher level of pressure support.

In a study on patients with NMD, Fanfulla found a high frequency of ineffective effort during nocturnal NIV.[153] Still, by changing the ventilator settings after thorough invasive measurement of respiratory mechanics, the frequency of ineffective effort was significantly reduced in all patients. Also, this new settings lead to a significant reduction of $PEEP_{intrinsic}$. In

both settings, a continuous spontaneous mode was used. In both studies referred above, the authors suggest that dynamic hyperinflation due to "over- assistance" from the ventilator may cause PVA. This may illustrate that PVA, in addition to be caused by inadequate response of the ventilator to patient effort and patient factors causing reduced ability to trigger the ventilator, may be related to the response of the patient to ventilator assisted breaths.[145] Types of PVA and possible mechanisms are given in Table 5.

Table 5. Types of patient-ventilator asynchrony, main characteristics and possible mechanisms.

Type of asynchrony	Main characteristics	Possible mechanism
Phase asynchrony	Mismatch in time between neural (the patient) and mechanical (the ventilator) assisted breath occurs	
Triggering phase	Triggering of inspiration from the phase of expiration	
Ineffective triggering	Inspiratory effort by the patient not sensed by the ventilator (missed triggering) or occurring late (delayed triggering)	Weak inspiratory effort High intrinsic PEEP/dynamic hyperinflation Upper airway obstruction Mask or circuit leaks Inappropriate trigger sensitivity setting on the ventilator
Auto-triggering	Sequences of rapid ventilator delivered breaths not triggered by the patient and much higher than the set ventilator backup respiratory rate	Cardiogenic oscillation Mask or circuit leaks Inappropriate trigger sensitivity setting on the ventilator Condensate in the ventilator circuit
Double triggering	Two consecutive inspirations delivered from the ventilator separated by a very short expiratory time	High inspiratory demand from the patient Short ventilator inspiratory time (relative to patient inspiratory drive)
Cycling phase	Cycling of from inspiration to expiration	
Premature cycling	Ventilator inspiratory time ends prior to the end of neural inspiratory time	Inappropriate cycle setting on the ventilator.
Delayed cycling	Ventilator inspiratory time exceeds neural inspiratory time.	Mask or circuit leaks Inappropriate cycling settings on the ventilator
Other		
Uncoupling	Sequences with total uncoupling of patient's inspiratory effort and ventilator rhythm.	Demands a mode with mandatory breaths. Mechanisms as with ineffective triggering outlined above
Reverse triggering	Inspiratory effort apparently triggered by the ventilator	Reflex mediated neuro-mechanical coupling
Flow asynchrony (Pressure mode)		
Insufficient	Delivered ventilator flow is insufficient to match the patients ventilatory flow demand	Large amount of leaks not compensated by the ventilator. Inspiratory pressure to low Rise time setting on the ventilator to long i.e. the time to reach peak pressure during inspiration.
Excessive	Excessive ventilator flow compared to patients demand	Inspiratory pressure support to high Rise time to short

1.8. Definition, detection and frequencies of sleep hypoventilation and other respiratory events during NIV

An overview of the recommended definition of events during NIV, methods used for their detection and reported frequencies of these events is described below. Based on published studies the knowledge gap will be outlined. Studies published after the start of the data collection for this thesis will primarily be referred to in the Discussion part.

1.8.1. Definition, detection and frequency of Sleep hypoventilation

Definition of sleep hypoventilation

A variety of definitions of sleep hypoventilation has been used in previous studies, mostly based on expert opinions.[6 160-162] In the 2012 update of the AASM Manual for the Scoring of Sleep and Associated Events, a widely accepted scoring manual in the community of sleep and respiratory medicine, the following diagnostic criteria were given:[163]

> *Score hypoventilation during sleep if either of the below occurs:*
> *a. There is an increase in the arterial PCO_2 (or surrogate) to a value > 7.3 kPa for ≥ 10 minutes.*
> *b. There is ≥ 1.33 kPa increase in arterial PCO_2 (or surrogate) during sleep (in comparison to an awake supine value) to a value exceeding 6.7 kPa for ≥ 10 minutes.*
> *If reporting hypoventilation, the duration of hypoventilation as a percentage of total sleep time should be reported.*

This recommendation was based on data suggesting that healthy individuals rarely have a $PaCO_2$ > 7.3 kPa during sleep, and, for criterion b, that the change in $PaCO_2$ from wakefulness to sleep should reach an absolute sleeping $PaCO_2$ value that clearly represents hypoventilation. The minimum duration of 10 minutes, was based on consensus, admittedly arbitrary and acknowledging that normative data for the amount of total sleep time at different $PaCO_2$ values does not exist in sleeping adults[163]. $PtcCO_2$ is the recommended surrogate for arterial PCO_2 when performing sleep studies during NIV.[163] Several other definitions have been used for sleep hypoventilation. This will be further discussed in the Discussion part.

Detection of hypercapnia and sleep hypoventilation

Arterial puncture with blood gas analysis is the "gold standard" for measuring arterial carbon dioxide tension ($PaCO_2$). Daytime arterial blood gases (ABG) will detect the presence of daytime hypoventilation. However, the sampling requires expertise, can be difficult to perform in patients with severe deformities or obesity, and is rarely available in sleep centers or in the patient's home.[163] In addition, it can be painful and carries a risk for complications.[164] An elevated daytime $PaCO_2$ may be a reflection of nocturnal accumulation

of CO_2. However as outlined above, sleep hypoventilation may be present in spite of normal daytime $PaCO_2$, underlining the importance of nocturnal monitoring in order to detect sleep hypoventilation. Single arterial puncture during sleep might detect sleep hypoventilation, but it does not reflect the variations during sleep due to sleep stages, positioning or leaks during NIV. The puncture may be taken in periods without hypoventilation, and it will also disrupt sleep. [165] Frequent arterial sampling during sleep requires arterial catheterization, which is not available on a routine basis. $PtcCO_2$, on the other hand, allows non-invasive and continuous measurements of CO_2.[166] End tidal CO_2 can also be used for continuous monitoring of $PaCO_2$, but is not suited for monitoring during NIV. [163 165]

Transcutaneous CO_2

Even though transcutaneous measurement of CO_2 was described already in 1960[166] and has been commercially available since 1980, inaccuracy and impracticalities of $PtcCO_2$ measurement have limited its daily use. [167] Recent developments have improved the technique, making it more practical in use.[167] The use of $PtcCO_2$ in monitoring patients with chronic hypoventilation requires a good agreement with $PaCO_2$. For overnight continuous measurements, it also needs to maintain a low instrumental drift over time. Finally, the method must be feasible for overnight studies; i.e. there should be low numbers of erroneous measurement due to displacement of the sensor, interference with the NIV mask or other technical problems. $PtcCO_2$ have shown good agreement with ABG measurement in a wide range of patient groups, including a geriatric population, patients with ALS, patients with severe obesity, and patients with acute dyspnoea and acute respiratory failure.[168-171] Conversely, studies performed in settings like emergency departments, operating theatres and ICUs have shown poorer or conflicting results.[172-175] Thus, the clinical setting and the population studied seem to influence on the usefulness of $PtcCO_2$. Factors like respiratory acidemia, hemodynamic instability, skin vasoconstriction and vasopressor treatment have been associated with poorer agreement.[172 174 176] In addition, the sensor temperature and the site used for sensor placement may influence on the results.[177 178] A limited number of studies have reported on the accuracy and precision of $PtcCO_2$ in patients with CRF, and all these studies have reported low bias.[179-183] However, the reported limits of agreements varied. In addition, three of the studies reported that both bias and limits of agreement increased with higher CO_2 levels,[179-181] in contrast to Storre et al who found that the agreement was unchanged in a sub-group of hypercapnic patients.[183] Most studies reporting on instrumental drift of $PtcCO_2$ have used older devises and included a limited number of patients.[179 181 184 185]

Also, the methods used and the results differ.[182 183 186] This is reflected in the conflicting recommendations regarding the necessity of drift correction of the results during continuous overnight monitoring with PtcCO2.[163 187]

Frequency of sleep hypoventilation during NIV

A limited number of studies have systematically used $PtcCO_2$ to investigate the frequency of sleep hypoventilation during the follow-up of patients under treatment with long-term NIV. In a prospective study on 50 children treated with long-term NIV and without symptoms of sleep hypoventilation, Paiva et al found that 42% had nocturnal hypercapnia detected by $PtcCO_2$.[188] In a retrospective study, Nardi et al. found that in a routine evaluation of 58 patients treated with home mechanical ventilation (29 with NIV), 24 had sleep hypoventilation.[161]

1.8.2. Definition, detection and frequency of apnea-hypopnea and patient-ventilator asynchrony

Definition of respiratory events during NIV

In addition to hypoventilation, events like apnea and hypopnea, leaks and PVA can be present during nocturnal NIV, as outlined above. AASM provides scorings rules for sleep related respiratory events including the scoring of apnea-hypopnea during NIV.[5] In a series of articles, the European SomnoNIV group has published a framework for the detection of such events, specifically during NIV.[127 165 189]

The AASM Manual for the Scoring of Sleep and Associated Events recommend the use of the same criteria for apnea and hypopnea during positive airway pressure therapy (PAP), as for diagnostic studies without treatment.[5] For the scoring of apnea and hypopnea during NIV, the main criteria are as follows:

Scoring of apnea

1. Score a respiratory event as an apnea when BOTH of the following criteria are met:
   a. There was a drop in peak signal excursion by ≥ 90% of pre-event baseline using a PAP device flow.
   b. The duration of the ≥ 90% drop of sensor signal is ≥ 10 seconds.
2. Score an apnea as obstructive if it meets apnea criteria and is associated with continuous or increased inspiratory effort throughout the entire period of absent airflow
3. Score an apnea as central if it meets apnea criteria and is associated with absent inspiratory effort throughout the entire period of absent airflow
4. Score an apnea as mixed if it meets apnea criteria and is associated with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event.

Scoring of hypopnea (Recommended criteria)

1. Score a respiratory event as hypopnea if ALL of the following criteria are met:
   a. The peak signal excursions drop by ≥ 30% of pre-event baseline using a PAP device flow.
   b. The duration of the ≥ 90% drop in signal excursion is ≥ 10 seconds.
   c. There is a is a ≥ 3% oxygen desaturation from pre-event baseline or the event is associated with an arousal

The AASM criteria for hypopnea have been under discussion and have varied over time. The criteria outlined above were introduced in the 2.0 version in 2012, which also provided scoring criteria for an optional sub classification of hypopnea as either central or obstructive.[163] The later will be further addressed in the Method section. In the 2.2 version from 2015, criteria for scoring of apnea and hypopnea with RPG (i.e.: without the scoring of sleep) was included in the manual, recommending the same criteria as for PSG with the exception that hypopnea can only be scored when flow reduction is associated with a 3% desaturation and not with an arousal. The criteria outlined above remains the same in the latest AASM Manual version 2.5, published online April 2018.[5] Although the clinical practices recommendations from AASM emphasis the importance of detecting and correcting for leaks and PVA during titration of NIV,[121] the AASM scoring manual do not mention these events and they do not provide criteria for scoring them.

The publications from the SomnoNiv groups focus specifically on respiratory events during NIV, including leaks. Overall, they defined events as the occurrence of a modification, discontinuity or instability of ventilation which had deleterious consequences on SpO2, $PtcCO_2$ and/or sleep (i.e. arousals or microarousals). In contrast to AASM, they also differentiate between obstructive events with and without reduction in respiratory drive. They provide descriptions, including examples, on how the different events will appear in polygraphy traces. However, they do not provide specific criteria like length of time of the events, the amount of flow reduction and specification for associated consequences of events, like criteria for desaturation. Also, they do not describe the various PVA that can occur during NIV.

Thus, there is no consensus on specific definitions and scoring rules for leaks and PVA occurring during NIV. This issue will be further addressed in the Method section and discussed in the Discussion section of the current thesis.

Detection of events

Respiratory events can be detected by respiratory RPG/PSG[5 127] But, this requires the addition of sensors for device pressure and flow signals. The pressure signal can be obtained by 1) connecting the pressure transducer sensor (which is normally used for flow signals in diagnostic sleep studies) to the mask,[127] or 2) by incorporating the pressure signal from the ventilator into the polygraph.[121] The flow signal can be obtained by 1) using a pneumotachograph inserted into the ventilator circuit[127] (see method section for details) or 2) incorporating the flow signal from the ventilator in the polygraphy.[5] The effect of respiratory

events on ventilation can be measured by pulse oximetry and a $PtcCO_2$ sensor, as outlined above. The effect of the respiratory events on sleep requires the use of PSG, including scoring of sleep stages and arousal/awakenings. Autonomic activation, measured as pulse wave amplitude reduction with photoplethysmography, can be used as a surrogate for arousals in patients treated with NIV.[190]

The effect of the ventilator mode, settings, and type of ventilator circuit on the semiology of the respiratory events adds further complexity to the scoring of RPG/PSG during NIV, as described by Gonzales et al.[127] The use of flow versus pressure limited mode, passive versus active expiratory valve, and ventilator settings like backup respiratory rate, inspiratory time, and cycle and trigger settings will affect how the respiratory events appear on the flow and pressure signal. Thus, scoring of these events requires experience and has been described as probably being the most demanding task in sleep related respiratory problems.[191] Still, at the time of planning of this thesis, no studies had reported on interrater agreement in scoring respiratory events in this setting.

Frequencies of events

A limited number of studies have systematically studied the types and frequency of respiratory events during the follow-up of patients under treatment with long-term NIV, using RPG/PSG. In a study of 16 patients with NMD, Crescimanno et al. found a low frequency of respiratory events, including PVA.[192] Similarly, Atkeson et al reported low AHI in a study on 19 ALS patients.[193] In contrast to the study by Crescimanno et al., Atkeson et al found a high frequency of PVA. This is in line with a study on a heterogeneous group of 48 patients on long-term NIV where a high frequency of ineffective effort were found in all patient groups.[155] In a group of 20 patients with OHS Guo et al found a high AHI in 4 patients and a high frequency of PVA in 11 patients.[135] The limited data addressing this subject is reflected in a recent review in Thorax, underlining the need for further studies to document the prevalence of these events during NIV.[127]

1.9. Detection of sleep hypoventilation and other respiratory events during NIV, using simpler tools

An increasing number of patients are treated with long-term NIV. In addition, monitoring long-term NIV with $PtcCO_2$ and RPG/PSG is expensive, difficult to perform and not readily available. Therefore, there is an interest as to whether more available tools can be useful in detecting nocturnal events in NIV-patients.[165]

1.9.1. Detection of sleep hypoventilation

Daytime arterial blood gas

In clinical practice, daytime ABG may be used to detect sleep hypoventilation in two different ways. Morning ABG can be obtained in order to detect night-to-morning increase in CO_2. However, the patients will often be awake at the time of blood sampling and have resumed daytime ventilatory pattern. ABG may also be obtained later during the day; i.e. independent of the wake-up time. In this setting, the rationale is that improved nocturnal ventilation is reflected in normalization of daytime ventilation. Daytime hypercapnia being present prior to NIV-treatment may be normalized by nocturnal NIV,[112 113] and daytime ABG is implemented in the routine follow-up of NIV at many centers. ABG can be performed later in the day, making it feasible also in an outpatient setting. Still, the amount of sleep hypoventilation needed for daytime $PaCO_2$ to occur is not known. Few studies compared daytime $PaCO_2$ with the nocturnal $PtcCO_2$. In children under long-term NIV, daytime $PaCO_2$ was a poor predictor of sleep hypoventilation[188] In the retrospective study by Nardi et al, 16 of 24 patients with sleep hypoventilation had a normal daytime $PaCO_2$.[161] However, in half of the patients ABG was obtained in the morning, while the rest was obtained in the afternoon. In neither of these studies the AASM criteria for hypoventilation were used.

Nocturnal pulse oximetry

Continuous nocturnal monitoring of SpO_2 with a pulse oximeter is readily available and can be used to detect nocturnal desaturations. Two patterns can be recognised: prolonged desaturation (typically lasting10-30 minutes) and recurrent short desaturations (typically lasting 10-90 seconds). [165] The latter may reflect short respiratory events, as described below, while prolonged desaturations during NIV can be due to ventilation/circulation mismatch in patients with obesity or pulmonary disorders, insufficient pressure support, alveolar

hypoventilation, or prolonged leaks. [165] Thus, pulse oximetry is not specific, and measurement of nocturnal CO_2 is needed to distinguish sleep hypoventilation from other causes of hypoxemia.[165] In addition, the sensitivity of pulse oximetry for detecting hypoventilation will be impaired in patients receiving supplemental oxygen, although this is normally not provided for patient receiving long-term NIV for restrictive disorders.

More important, the results of recent studies have questioned the sensitivity of nocturnal SpO_2 for detecting hypoventilation. In a prospective study monitoring long-term NIV with nocturnal $PtcCO_2$ in 50 children, Paiva et al. found that all of the patients with nocturnal hypercapnia had a normal nocturnal pulse oximetry.[188] Similarly, Nardi et al. found a low sensitivity of pulse oximetry for detecting sleep hypoventilation in 58 LTMV-patients with neuromuscular diseases.[161] However, the number of studies is limited, is either performed on children or retrospectively[161], and the AASM criteria for hypoventilation have not been employed. The need for further knowledge is underlined in a recent review in Thorax, were it was stated that studies are needed to determine the usefulness of oximetry as a screening tool in this setting.[165]

1.9.2. Detection of leaks, apnea-hypopnea and patient-ventilator synchrony

Pulse oximetry

During NIV, leaks and patient- ventilator asynchrony, in addition to obstructive and central events, may cause short desaturations.[165] Thus, recurrent desaturations detected with a pulse oximeter are not specific for the event causing them. Only a limited number of studies have reported on the association between respiratory events and desaturation. In a study of nine patients with OHS, three sleep studies with PSG were performed with three different NIV settings.[190] Apnea and hypopnea were scored if flow reduction was associated with desaturation and/or micro-arousal. Of the 2474 obstructive and central events scored, 91% were associated with a 4% desaturation. Atkeson et al found no correlation between percentage of time with PVA and events with 3% oxygen desaturation/hour, oxygen desaturation index (ODI), and Guo et al found no difference in ODI in patient with and without high frequency of PVA.[135 193] Fanfulla et al found that high frequencies of PVA was associated with poor gas exchange, but did not report on ODI.[155] No studies have reported on the accuracy of ODI for detecting these events during NIV, compared with polygraphy.

Data from ventilator software

Most modern ventilators used for LTMV have incorporated a monitoring unit including flow and pressure sensors, in addition to software providing automatic analyses of the data. These ventilators can store large amounts of data. Both longitudinal and day-by-day data synthesis and detailed data are available. Data include pattern of use and respiratory events like leaks, apnea and hypopneas.[165]

Leaks

Data on leaks can be obtained from the ventilator software. In a closed circuit, this can be measured as the difference between the delivered volume and the expired volume measured by the ventilator. However, LTMV is frequently provided with single limb circuit with an intentional leak. In this setting total leaks is the sum of intentional and unintentional leak (Figure 8). The amount of intentional leak will depend on the given mask and the pressure settings.

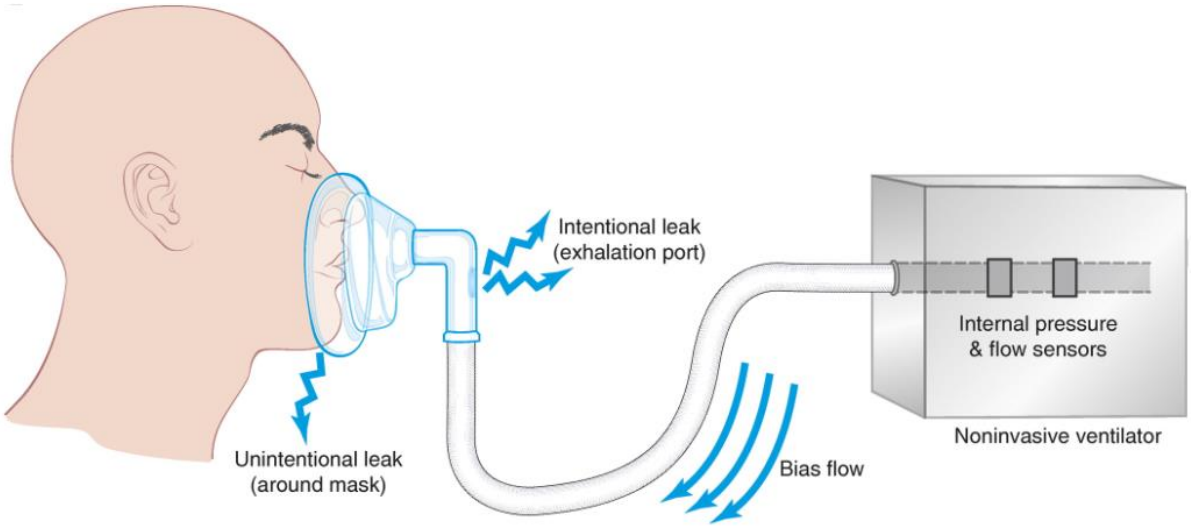

Figure 8. Illustration of intentional leak through a passive exhalation port and unintentional mask leak. A continuous bias flow "washes out" expired air through the exhalation port. (Used with permission by Adam Alter: Previously published by Alter et al. in Annals of the American Thoracic Society.[93])

Given this complexity, several studies have reported on the ventilator software's ability to report leaks. How leaks are reported by the ventilator software differs between the manufacturers; some report total leak and some unintentional leak[194]. In addition, the reported

leaks may represent leaks averaged from the whole respiratory cycle, or only leaks occurring during the expiratory face of the cycle. Bench studies have also shown that reliability of leak assessment by the ventilator software is highly variable from one device to another[194], with excellent result for some devices and average or even poor results for other devices tested.[194-196] Finally, the magnitude of leaks which is of clinical significance is not established, although leaks > 24 l/min have been suggested.[197] In addition, the recommended threshold for large leaks vary amongst manufacturers.[198]

A limited number of studies have reported on the frequency of large leaks detected with ventilator software. In a study including 41 stable patients treated with long-term NIV for a mean time of 4 months, 17% of the patients had large leaks (defined as a value higher than the compensatory capacity of the ventilator) with a mean time of large leaks 31% of the duration of the session.[199]. Rabec et al. studied the amount of leak from 500 traces from one NIV ventilator type (ResMed) in 166 patients treated for acute respiratory failure, elective initiation of long-term NIV, or at follow-up 4-6 month after initiation of long-term NIV.[195] Large leaks (defined as being > 24 l/min > 20% of the overnight period) was found in 32% of the measured occasions. Leak was significantly higher in the patients treated for acute respiratory failure. In the NIV follow-up group, large leaks were found in 25% of the patients. In contrast to this, Pasquina et al. reported that leaks were low in most patients in a study on 150 patients treated with LTMV for a mean period of 4 years.

Apnea-hypopnea

From most ventilators used for long-term NIV, an AHI from the ventilator software ($AHI_{software}$) can be obtained.[165] However, the algorithms and criteria for detecting apnea and hypopnea are not based on the same criteria as ASSM and vary between manufacturers. At the start of the data collection for this thesis, no studies had reported on the agreement between $AHI_{software}$ and AHI from RPG/PGS. Only one study had reported on data from $AHI_{software}$: Pasqiuna et al. reporting data from ResMed software in 105 patients treated with LTMV, found that median AHI in NMD was 6.1 (IQR: 1-11.4) and in OHS 3.4 (IQR: 2.1-7.7).[200]

Compliance

Most ventilators provide data on the pattern of use of NIV, both long-term statistics and night-by-night detailed use.[165] Thus, the average use can easily be obtained and in addition, pattern of use indicating poor adaptation and patient discomfort can be detected.[200]

1.10.The impact of respiratory events during NIV

Leaks, apnea-hypopnea and PVA have been shown to negatively affect sleep quality during NIV. [135 149 153 192] Also, leaks may have a negative effect on gas exchange.[201] However, studies of the impact of PVA, both on sleep quality and gas-exchange, are limited and conflicting.[153 202 203] In a recent randomised controlled trial, NIV titrated with PSG during sleep was associated with less PVA and better adherence to treatment compared with daytime titration of NIV. [204]However, no difference was found in sleep disruption between the two groups. Titration of NIV settings during sleep using PSG and including $PtcCO_2$ have shown to improve sleep quality in ALS patients.[205] In addition, both nocturnal desaturations and obstructive events, even without desaturation, are shown to be associated with poorer prognosis in patients with ALS.[206 207] A relatively low daytime $PaCO_2$ 3-6 months after initiation of NIV and lower annual increase of $PaCO_2$ have been associated with better prognosis in patients with chest wall disorders.[208 209] Recently, in a retrospective study on 55 patients with NMD treated with mechanical ventilation, residual sleep hypoventilation was associated with higher mortality and ICU admission for acute respiratory events.[210] Thus, there is an increasing knowledge and awareness of the necessity of nocturnal monitoring of long-term NIV.

1.11.Monitoring long-term NIV during sleep; current practice

No consensus exists regarding which tests to include in the monitoring of long-term NIV during sleep, and methods used vary from a single ABG to PSG.[165 211] AASM recommendations for best clinical practice state that PSG should be used for NIV titration at initiation of treatment, and that respiratory function of patients on long-term NIV at follow-up should be assessed by measures of oxygenation and ventilation (ABG, end-tidal CO_2, and $PtcCO_2$).[121] This assessment is typically carried out during quiet breathing while awake and at rest. A repeated NIV titration study with PSG should be considered only if respiratory function or sleep quality deteriorates. Others have recommended nocturnal SpO_2 or a combination of daytime ABG sampling and nocturnal SpO_2.[165 211]

Recently, a step-by-step algorithm for monitoring NIV has been proposed by the SomnoNIV group. This algorithm suggests that a combination of clinical evaluation, daytime ABG, nocturnal SpO_2 and a synthesis report from the ventilator software should be used as the first step in a clinical pathway of monitoring long-term NIV (Figure 9).[165]

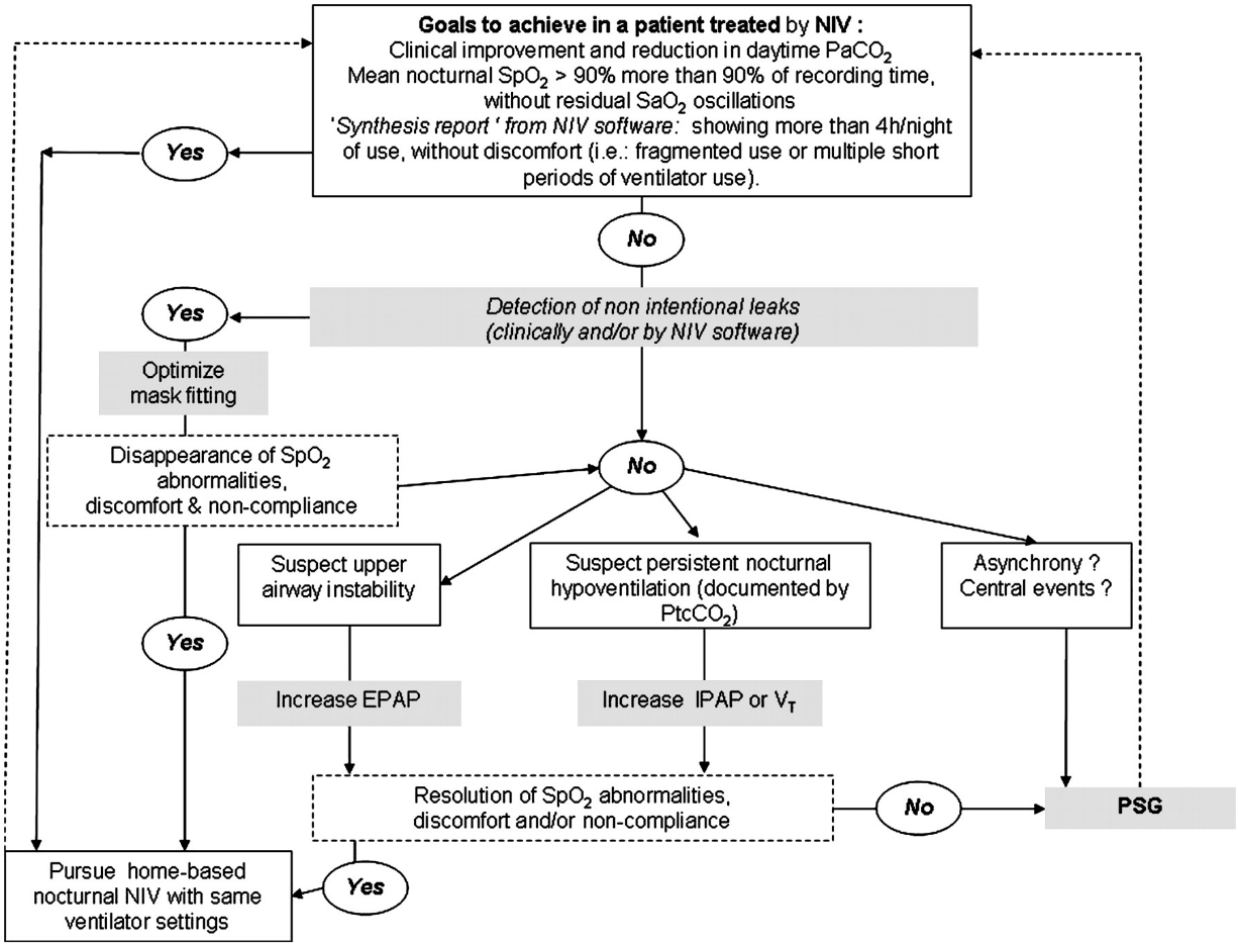

Figure 9. A proposed algorithm for the monitoring of nocturnal NIV. (Used with permission by Elsevier: Previously published by Janssens et al. in Thorax[165])

If normal, home NIV should be pursued. An abnormal test should prompt clinical interventions or further diagnostic testing. Suspected high leaks, either clinically or based on ventilator software data, should lead to modification of NIV interface. Suspected upper airway obstruction based on recurrent short desaturations should lead to modification of EPAP. When daytime hypercapnia or prolonged nocturnal desaturations are present, sleep hypoventilation should be suspected. Hypoventilation should be documented with $PtcCO_2$ if available and lead to increase of inspiratory ventilatory support. Clinically suspected central apnea or PVA should lead to further testing with RPG/PSG.

However, this proposed algorithm is based on consensus, and none of these proposed test regimens has been prospectively evaluated in a population treated with long-term NIV. There is an ongoing debate on how to monitor long-term NIV.[212]

2. Hypothesis and aims

2.1. Hypothesis

On this background, we hypothesized that: Clinical examination, a syntheses report from the ventilator software, nocturnal SpO_2 measurement, and daytime arterial blood gas analysis are sufficient as screening tools to detect sleep related respiratory problems in patients with chronic hypoventilation treated with NIV.

2.2. Aims of this thesis

Paper I

- To determine whether $PtcCO_2$ is a sufficiently accurate and precise tool for monitoring $PaCO_2$ in patients with chronic hypercapnic respiratory failure treated with long-term NIV.
- To evaluate if the overnight instrumental drift of the $PtcCO_2$ sensor is clinically significant.

Paper II

- To assess the interrater agreement in identifying and quantifying apnea-hypopnea and PVA during nighttime NIV.
- To quantify the frequency and describe the types of both apnea-hypopnea and PVA in a large group of stable patients with chronic hypercapnic respiratory failure during nighttime NIV.
- To study the influence of these events on overnight pulse oximetry and $PtcCO_2$

Paper III

- To quantify the frequency of sleep hypoventilation detected with $PtcCO_2$ in a large group of stable patients with chronic hypercapnic respiratory failure during nighttime NIV
- To analyze the ability of a combined test panel to detect sleep hypoventilation and other sleep related respiratory events using RPG and nocturnal $PtcCO_2$ as reference standards.
- To analyze the ability of selected test to detect specific nocturnal respiratory events:
  - Nocturnal SpO_2 and daytime ABG as markers of sleep hypoventilation,
  - ODI and $AHI_{software}$ as markers of apnea-hypopnea and
  - ODI as a marker of PVA, using the same reference standards.

3. Material and methods

3.1. Studia design

This thesis is based on data from a prospective cross-sectional study on patients with chronic hypercapnic respiratory failure treated with NIV.

3.2. Study population and setting

The patients were recruited from the Department of Pulmonary Medicine at Oslo University Hospital (OUS) Ullevål. OUS is responsible for the follow-up of patients treated with LTMV in the major areas of the city of Oslo. In this particular field of medicine, OUS serves all but 3 areas of Oslo, a population of approximately 510 000 in 2013. We have written indications for LTMV in our institution. They are based on the Norwegian national guideline for LTMV and in are line with international guidelines. Usually we initiate long-term NIV during a 3-5 days hospital stay, and NIV settings are titrated with the aid of nocturnal monitoring with pulse oximetry, $PtcCO_2$ and RPG (RPG). After the initiation of treatment, patients are readmitted after 6 weeks for overnight monitoring and if necessary re-titration of the NIV settings. Patients are then offered regular follow-up at our clinic 1-4 times a year depending on the underlying disorder and individual patient's factors.

All patients treated with long-term NIV for chronic hypoventilation due to neuromuscular diseases, restrictive thoracic disorders, OHS and central hypoventilation syndrome for a minimum of 3 months, and who were scheduled for a regular follow-up visit between April 2013 and May 2014, were consecutively evaluated for inclusion. Exclusion criteria were: age under 18 years, inability to co-operate, hospitalization due to an acute exacerbation, or modification of NIV-treatment within the last 3 months.

3.3. Methods

The data collection for this study was performed during a planned follow-up visit. All patients included were admitted to the ward at the Department of Pulmonary Medicine. Measurements of height, weight and pulmonary function were performed. Information on type of mask, ventilator and ventilator settings were obtained, and use of other medical devices like supplementary oxygen, humidifier for the ventilator and cough assist device were retrieved during the time of hospitalization. Other data like diagnosis, length of NIV-treatment,

medication and co-morbidity, were obtained from the medical record of the patient. All nocturnal measurements were performed during NIV-treatment. An overview of the main methods used in the study are given in Table 6 and described below.

Table 6. Overview of the main methods used in the study and their purposes in paper I-III

Methods	**Purposes**		
	Paper I	Paper II	Paper III
Day time ABG	Reference standard for daytime $PaCO_2$		Part of the combined test panel Index test for sleep hypoventilation
Day time $PtcCO_2$	Index test for daytime $PaCO_2$		
Clinical evaluation			Part of the combined test panel
Data from ventilator software			Part of the combined test panel Index test for AHI
Nocturnal SpO_2			Part of the combined test panel Index test for sleep hypoventilation Index test for AHI and PVA
Nocturnal $PtcCO_2$ and ex vivo PCO_2 test	Instrumental drift of $PtcCO_2$		
Nocturnal $PtcCO_2$			Frequencies of sleep hypoventilation Reference standard for sleep hypoventilation
Respiratory polygraphy		Interrater agreement Frequencies and types of AHI and PVA	Reference standard for AHI and PVA

ABG: arterial blood gases; AHI: apnea-hypopnea index; PVA: patient-ventilator asynchrony

3.3.1. Arterial blood gases

Daytime $PaCO_2$ was measured from blood sampling obtained from the radial artery performed between 12:00 and 2:00 PM. The samplings were performed after the patients had been seated and breathing room air for at least 30 minutes and immediately analysed (COBAS B 221, Roche, Germany).

3.3.2. Data from ventilator software

Data memorized by ventilator software were downloaded with Rescan 04.01.013 software for ResMed ventilators and with Encore Pro 2 2.1.6.0 software for Philips Respironics ventilators. Data covering both the prior 3 months and the study night were downloaded and three months compliance data, data on leaks and AHI covering both the prior three months and the study night were collected. During the study night the ventilators were used between 11.00 PM to 7.00 AM.

3.3.3. Clinical evaluation

A clinical evaluation was performed by the pulmonary physician in charge of the ward the day after the overnight measurements. The physician had access to the clinical information of the patients including daytime $PaCO_2$, nocturnal SpO_2 and data from the ventilator software, but was blinded to the $PtcCO_2$ and polygraphy results. The physician evaluated if the patient had symptoms of sleep disordered breathing (morning headaches, daytime sleepiness, fatigue, sleep disruption, nocturnal dyspnea, and perceived asynchrony with the ventilator). A short questionnaire was used to record whether the physician evaluated clinical status as satisfactory or not.

3.3.4. Nocturnal pulse oximetry

Continuous overnight SpO_2 was measured with Nonin 2500 with a finger sensor (Nonin Medical INC, USA) from 11.00 PM to 7.00 AM and was analysed with NVision 5.02 (Nonin Medical INC, USA) after visual inspection and exclusion of obvious artifacts. Although continuous SpO_2 signal is integrated in the polygraphy, we used this additional measurement allowing overnight SpO_2 to be evaluated separately.

3.3.5. Transcutaneous CO_2

All $PtcCO_2$ measurements were performed with TCM Tosca with the Sensor 92 (Radiometer, Denmark) (Figure 10). The sensor was attached via a single-use ear clip to the patients' earlobe (Figure 10) and probe temperature set at 43 °C, according to the recommendations from the manufacturer. The raised skin temperature leads to an increase in blood and tissue PCO_2 by approximately 4.5% / °C (anaerobic factor). In addition, living epidermal cells produce CO_2, contributing to the level of CO_2 measured with $PtcCO_2$ by a constant amount

(metabolic constant).[167] Both these factors can be automatically adjusted for by the device. We activated the temperature correction, and the metabolic correction was set to 0.5 kPa, according to the recommendations from the manufacturer. The replacement of the membrane of sensor 92 was performed every 14 day according to the routine in our department, based on recommendations from the manufacturer, or if indicated by the automatic detector within the device. We chose TCM Tosca because it has been used for several years in our ward. We presumed that the staff's knowledge of the handling the device would contribute to minimize technical problems and erroneous recordings.

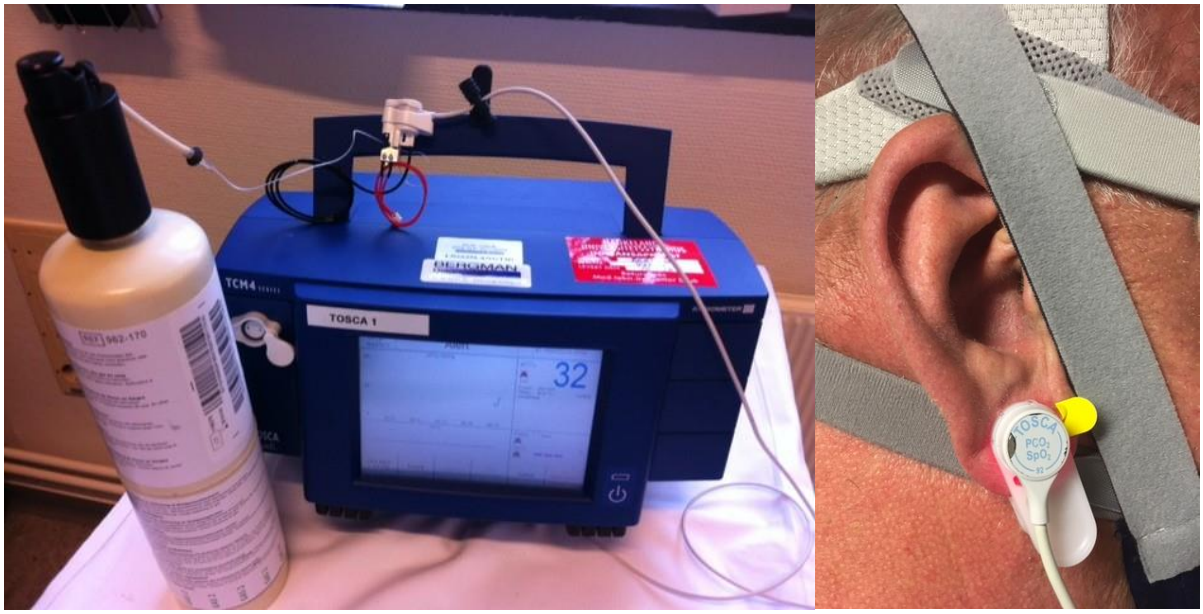

Figure.10. Left: TCM Tosca with sensor 92. The cylinder contains a gas mixture with a known concentration of CO_2 A special test unit connects the sensor 92 to the cylinder for the ex vivo PCO_2 measurement. Right: Sensor 92 connected with a single-use ear clip to the earlobe. (Private photo)

Daytime $PtcCO_2$ measurement of transcutaneous CO_2

Daytime $PtcCO_2$ was performed simultaneously with the ABG sampling. $PtcCO_2$ was monitored continuously for at least 22 min to allow stabilisation of $PtcCO_2$ readings before the measurement was recorded, as recommended by the manufacturer. Daytime $PtcCO_2$ was defined as the $PtcCO_2$ measurement 2 minutes after the ABG sampling. This was done due to the known lag-time of the measured $PtcCO_2$ compared to arterial CO_2.[186 213]

Instrumental drift of transcutaneous CO_2

The overnight instrumental drift of the TCM Tosca capnography was assessed with repeated ex vivo measurements. The sensor of the TCM Tosca was attached to a cylinder containing a gas mixture with a known concentration of CO_2 (Calibration Gas mixture for Blood Gas Analyzers, 11·2% CO_2, balanced N_2, Radiometer, Denmark) (Figure 10). A special test unit provided by the manufacturer of TCM Tosca was used for this attachment (Figure 10). A similar unit was used in a recent study.[183] (Jan H. Storre: personal communication). This procedure was performed at 11:00 PM, after auto-calibration of the sensor, before attaching the sensor to the patient, and repeated at 7:00 AM, before recalibration of the sensor. The instrumental drift was defined as the difference between PCO_2 measured in the morning and the previous evening. We chose a repeated ex vivo measurement for the evaluation of instrumental drift for several reasons: First, we wanted to evaluate the instrumental drift simultaneously as we evaluated sleep hypoventilation with $PtcCO_2$. Second, a repeated ex vivo measurement has recently been used in two other studies.[183 186] Finally, alternative methods previously reported, have measured instrumental drift by repeated comparison between $PtcCO_2$ and ABG. Repeated ABG was either obtained from an indwelling arterial catheter, or from repeated percutaneous arterial or capillary blood gas sampling.[179 182 185 214] We evaluated these methods to be to invasive; potentially painful for the patients, and that they probably would disturb sleep.

Nocturnal transcutaneous CO_2

Nocturnal $PtcCO_2$ was performed with continuous measurement from 11.00 PM to 7.00 AM. The signal from TCM Tosca was integrated in an attended RPG (Embletta Gold, Embla, USA) The nurses on the night shift were instructed to inspect the signals at least every hour and to adjust the sensor in case of poor signal quality, but not to recalibrate the sensor. The data were downloaded and, after visual inspection and exclusion of obvious artifacts, analysed with Visi-Download (Stowood Scientific Instruments LTD, UK).

3.3.6. Respiratory polygraphy

An attended RPG (Embletta Gold, Embla, USA) was performed between 11.00 PM and 7.00 AM. Signals were inspected as described above. This was conducted during NIV-treatment with the patients' usual ventilator settings. We used the following signals for the scoring of respiratory events, as recommended by the SomnoNIV group:[127] 1) mask pressure measured

by connecting a tube to the oxygen port in the mask or, in cases where nasal pillow masks were used, to a connector inserted into the ventilator circuit (Figure 11 and 12), 2) flow in the ventilator circuit measured by inserting a pneumotachograph close to the mask (Figure 11), 3) thoracic and abdominal movements recorded with respiratory inductive plethysmography effort belts, and 4) SpO_2 monitored by pulse oximetry with a finger sensor.

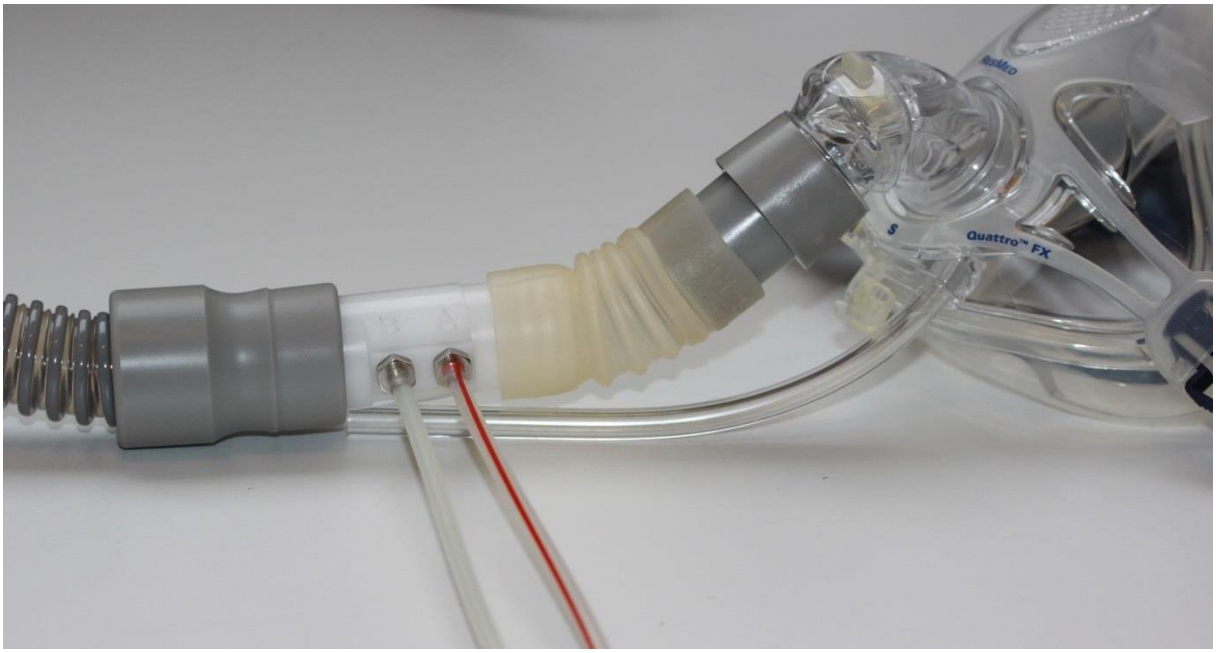

Figure11. A tube connected to the oxygen port in the mask was used for mask pressure measurement. A pneumotachograph inserted in the ventilator circuit close to the mask for flow measurement in the circuit (Private photo).

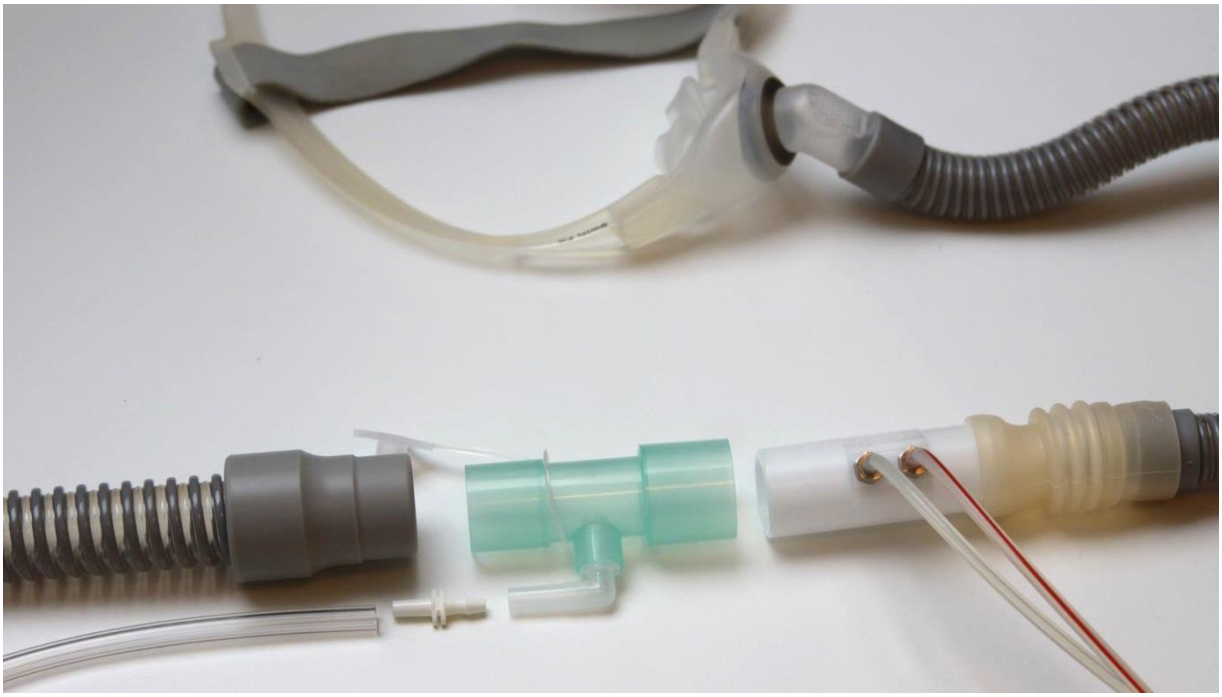

Figure 12. A connector inserted into the ventilator circuit for pressure measurement in circuit during NIV provided with nasal pillow mask (Private photo).

In addition, photoplethysmographic pulse wave amplitude (PWA) was obtained with the pulse oximeter. This signal was used to calculate autonomic activation and used as a surrogate for arousal.

The SomnoNIV group recommends the use of a pneumotachograph inserted in the circuit close to the mask for flow measurement, while AASM recommends the use of the flow signal from the ventilator. We choose to use the pneumotachograph for two reasons. First, this enabled the use of the same sensor in all patients regardless of the type of ventilator in use. Second, the equipment used (Embletta Gold) does not enable the integration of the signals from the ventilator when used in attended studies.

Scoring of apnea and hypopnea

Magnus Qvarfort and Sigurd Aarrestad independently scored all the polygraphies and were blinded to each other's results. We manually scored the entire recordings in epochs of a maximum of 2 minutes by visual inspection of the signals. The scoring criteria for apnea and hypopnea and the sensors used were adapted from ASSM.[163] The sensors and criteria used for scoring of apnea and hypopnea are summarized in Table 7.

Table 7. The sensors and criteria used for scoring of respiratory events:

Apnea-hypopnea	
Signal	**Sensor**
Flow	Pneumotachograph inserted in the circuit close to the mask
Inspiratory effort (Thoraco-abdominal movement)	Respiratory inductive plethysmography belts.
Desaturation	Pulse oximetry
Autonomic activation	Photoplethysmographic pulse wave amplitude
Event	**Criteria**
Apnea	A drop in peak flow signal excursion by ≥ 90% for ≥ 10 seconds.
Sub-classification of apnea:	
• Obstructive apnea	Presence of continuous or increased inspiratory effort throughout the entire period of absent airflow.
• Central apnea	Absent inspiratory effort throughout the entire period of absent airflow.
• Mixed apnea	Absence of inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event.
Hypopnea	A drop in the peak flow signal excursion by ≥ 30% for ≥ 10 seconds associated with either a ≥ 3% desaturation or an autonomic activation scored from the pulse waveform (decrease in PWA ≥ 30%).
Sub-classification of hypopnea:	
• Obstructive hypopnea	Presence of an increased flattening of the inspiratory flow signal and/or an associated thoraco-abdominal paradox during the event but not before the event.
• Central hypopnea:	Absence of both an increased flattening of the inspiratory flow signal and an associated thoraco-abdominal paradox during the event but not before the event.

PWA: pulse wave amplitude

Total recording time, the denominator for computing respiratory event indices, was defined as: [time lapse between lights out and lights on] - [total movement time]. Events were calculated and reported as number/hour of TRT. The indexes calculated and their definitions are given in Table 8:

Table 8. Indexed and definitions calculated for apnea and hypopnea

Index	Definition
Apnea-hypopnea index	Apnea + hypopnea/hour of TRT
Apnea index	Apnea/hour of TRT
Hypopnea index	Hypopnea/hour of TRT
Central hypopnea index	Central hypopnea/hour of TRT
Obstructive hypopnea index	Obstructive hypopnea/hour of TRT
Hypopnea 3% desaturation index	Hypopnea associated with 3% desaturation/hour of TRT
Hypopnea autonomic activation index	Hypopneas with an autonomic activation/hour of TRT

TRT: Total recording time

We included sub-classification of hypopnea in the scoring (optional in the recommendation from AASM). Previous clinical experience and a pilot study performed prior to the conduct of this study have shown that hypopnea is much more frequent than apnea during NIV. We therefore chose to include sub-classification of hypopnea in order to better be able to differentiate between patients with predominantly obstructive and central events.
When scoring, we took into account the descriptions on how the different events will appear in RPG traces, provided by the SomnoNIV group.[127] However, the scoring criteria for apnea and hypopnea were adapted from ASSM.[163] These are widely accepted, used for sleep studies and research worldwide, and include criteria for the scoring of apnea and hypopnea during NIV. In addition, the publications from the SomnoNIV group do not provide detailed criteria for the events, like duration, degree of desaturation and flow reduction, making it difficult to score in a consistent way.

Scoring of Patient- ventilator asynchrony

The sensors used were according to the recommendations from the SomnoNIV group[127] and have been used by others.[135 151 153 215] Neither the AASM nor the SomnoNIV group provide scoring criteria for PVA.[127 163] Therefore, the criteria used for asynchrony were adapted from previous studies[135 151 153] The sensors and criteria used for scoring PVA are summarized in Table 9.

Table 9. The sensors and criteria used for scoring of respiratory events

Patient-ventilator asynchrony	
Ventilator rhythm Derived from flow and pressure curves in the polygraphy traces	
Signal	**Sensor**
Flow	Pneumotachograph inserted in the ventilator circuit close to the mask.
Pressure	Pressure sensor connected to the mask or the ventilator circuit
Patient's inspiratory efforts Derived from thoraco-abdominal and/or the flow and pressure curves in the polygraphy traces	
Signal	**Sensor**
Thoraco-abdominal movement	Respiratory inductive plethysmography belts
Flow	Pneumotachograph inserted in the ventilator circuit close to the mask.
Pressure	Pressure sensor connected to the mask or the ventilator circuit
Event	**Criteria**
Desynchronization	Uncoupling of the patient's inspiratory efforts and onset of the ventilator pressurization for ≥ 10 seconds and at least three consecutive breaths. The end of the event is defined by the occurrence of three consecutive synchronized breaths. Ineffective efforts are included in this category. Periods with at least three consecutive ineffective respiratory efforts with ventilator pressurization on backup respiratory rate are also scored as desynchronization.
Auto-triggering:	Occurrence of at least three rapid pressurizations at a respiratory rate of ≥ 40 breaths/min and clearly above that of the patient's respiratory rate.
Double-triggering:	Two cycles separated by a very short expiratory time, defined as less than one-half of the mean inspiratory time with the first cycle triggered by the patient.

The length of time with PVA events was summarized as the percentage of TRT with patient-ventilatory asynchrony (PVA %). Events were calculated and reported as number/hour of TRT. The indexes calculated and their definitions are given in Table 10:

Table 10. Indexed and definitions calculated for patient-ventilator asynchrony events

Index	Definition
Patient-ventilator asynchrony index	All patient-ventilator asynchrony events/ hour of TRT
Total desynchronization index	All desynchronization events/hour of TRT
Desynchronization index	Desynchronization events without 3% desaturation or autonomic activation /hour of TRT
Desynchronization 3% desaturation index	Desynchronization events with 3% desaturation/hour of TRT
Desynchronization autonomic activation index	Desynchronization events with autonomic activation/hour of TRT
Double-triggering index	Double-triggering events/hour of TRT
Auto-triggering index	Auto-triggering events/hour of TRT

TRT: total recording time

Additional sensors for inspiratory effort such as esophageal pressure or diaphragm electromyogram were not included. We considered these methods to be to troublesome for the patient during a regular follow-up. Due to the lack of additional sensors for inspiratory effort, we did not include cycling asynchrony in the scoring of asynchrony.

We used the following hierarchical strategy for scoring:
1) Respiratory events were not scored during periods with high unintentional leaks. Periods with high unintentional leaks in the polygraphy was defined as a fall in the pressure signal and, in pressure-controlled ventilators, a simultaneous increase in flow signal.[127] When a non-vented mask was used, an amputation of the expiratory flow curve was also interpreted as high unintentional leaks.
2) PVA was not scored in sequences where apnea or hypopnea was present.
3) PVA was not scored in sequences where signals from both the thoracic and the abdominal belts were poor or in sequences where both pressure and flow signals were lost.

Although leaks were evaluated as outlined above, the quantification of leak was analysed from the data from the ventilator software. Prior to the study, a pilot study was performed and the scoring criteria and scoring strategy were evaluated, including discussions with international experts in the field in difficult cases.

3.4. Criteria for abnormal tests

A dichotomization of variables was used for the calculation of the frequencies of sleep hypoventilation, high AHI and PVA and for the evaluation of the index test compared with the reference standards. The following criteria were used:

3.4.1. Index tests

The combined test panel

The combined test panel was adapted from the algorithm suggested by the SomnoNIV group. It was defined as a combination clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2 and assessment of compliance (from ventilator software). The combined test panel was classified as abnormal if any of the following criteria for abnormal tests were met:

1) Clinical evaluation: The clinical status was evaluated as non-satisfactory by the physician.
2) Daytime $PaCO_2$: $PaCO_2$ > 6.0 kPa, based on conventional criteria for abnormal daytime $PaCO_2$.
3) Nocturnal SpO_2:
    a. Percentage of time spent with SpO_2 < 90% (SpO_290) ≥ 10% of total recording time.
    b. Recurrent SpO_2 oscillations: ≥ 5 events/hour with ≥ 3% oxygen desaturation from baseline lasting 10-90 seconds (ODI3%). This criterion was based on current clinical practice in our department.
4) Compliance: The 3-month synthesis report showed less than 4 hours/night of use or a pattern suggestive of discomfort (i.e. fragmented use or multiple short periods of ventilator use).

The criteria outlined above were also discussed with members of the SomnoNIV group.

Selected tests for detecting specific nocturnal respiratory events

1) Markers of sleep hypoventilation:
    a. Nocturnal SpO_2: SpO_290 ≥ 10% of total recording time.
    b. Daytime ABG Daytime $PaCO_2$: 1) $PaCO_2$ > 6.0 kPa and 2) HCO_3^- ≥ 27 mmol/L
2) Markers of high AHI:
    a. Nocturnal SpO_2: ODI3%.
    b. $AHI_{software}$: The data obtained in the study was used to determine the cut-off values. This is further explained in the Statistical section of this thesis.
3) Marker of PVA: ODI3%.

3.4.2. Reference standards

Transcutaneous CO_2

Nocturnal $PtcCO_2$ values were used to score sleep hypoventilation according to the following pre-specified cut-off values:

1) $Hypoventilation_{AASM}$: An increase in $PtcCO_2$ to a value > 7.3 kPa for ≥ 10 minutes ($AASM_1$) and/or an increase in $PtcCO_2$ ≥ 1.3 kPa in comparison to an awake value exceeding 6.7 kPa ≥ 10 minutes ($AASM_2$).
2) $Hypoventilation_{TRT}$: $PtcCO_2$ > 6.5 kPa ≥ 10% of TRT.
3) $Hypoventilation_{MAX}$: Peak $PtcCO_2$ > 6.5 kPa.

The AASM criteria for hypoventilation used in the first cut-off value above was published in 2012 and based on a consensus, as outlined in the background section.[163] During the planning of this study, we anticipated a debate on the definition of sleep hypoventilation and included several cut-off values for the analyses of sleep hypoventilation, including criteria 1-3 above. This issue is still under debate. In the final analysis and reporting of the data we chose to use the AASM criteria, and in addition criteria 2 and 3 above, as they have been shown to be of prognostic significance in patients with nocturnal hypercapnia.[162 210 216]

Respiratory polygraphy

Apnea-hypopnea

The AHI index derived from polygraphy is a continuous variable, and the clinically relevant threshold of high AHI during NIV is not established. We acknowledged this in the planning of this study and described the frequency of patients having abnormal AHI according to several pre-defined cut-off values (AHI > 5, AHI > 10 and AHI > 15) in Paper II. In Paper III abnormal AHI was defined as an AHI > 10 when we used polygraphy as a reference standard. This was based on two recent studies using this value[217 218]

Patient-ventilator asynchrony

Previous studies have stated that asynchrony in more than 10% of breaths is clinically relevant.[147 151 219] In our study, we did not count the numbers of asynchronous breaths, but the percentage of time with asynchrony of the total recording time. We anticipated that the included patients would have a relatively stable and low respiratory frequency, and therefore considered 10% of total recording time spent with asynchrony as equivalent to 10% of breaths with asynchrony. This threshold was used as the main threshold for high PVA.

4. Summary of results

Ninety-five patients were eligible for inclusion, 6 died before their scheduled follow-up and 4 did not appear for follow-up. Of the 85 patients that met for their follow-up, 18 were excluded; seven did not want to participate, five did not speak English or Norwegian, four had a recent acute hospitalization due to respiratory problems, and two had have a recent change of NIV-treatment.

4.1. Paper I

Validity of transcutaneous PCO_2 in monitoring chronic hypoventilation treated with non-invasive ventilation

The aims of this study were:

1) To evaluate whether $PtcCO_2$ is a sufficiently accurate and a precise tool for monitoring $PaCO_2$ during routine follow-up visits in a large group of patients with CRF treated with long-term NIV, and
2) To evaluate if overnight drift of the $PtcCO_2$ sensor is clinically significant in this setting.

Paired samples of $PaCO_2$ measured with ABG and simultaneous $PtcCO_2$ was successfully obtained from all 67 patients. Bias, the mean of differences between $PaCO_2$ and $PtcCO_2$, was 0.23 kPa (SD 0.28 kPa). Limits of agreement were: − 0.32-0.79 kPa. $PaCO_2$ values ranged from 3.97 kPa to 9.0 kPa and 36 (53%) of the patients were hypercapnic ($PaCO_2$ > 6.0 kPa). In this subgroup of patients, bias was 0.3 kPa, and limits of agreement were: −0.28-0.84 kPa. Instrumental drift of $PtcCO_2$ was measured in all patients. One patient disconnected the sensor prior to the morning measurement and an obvious technical error occurred in one measurement. Thus, 65 measurements were evaluated. The mean drift of $PtcCO_2$ defined as the difference between morning and evening $PtcCO_2$ readings of 11.2% CO_2 gas sample, was 0.14 ± 0.54 kPa/8 h (p = 0.04; 95% CI: 0.01–0.27).

In conclusion: $PtcCO_2$ accurately reflects $PaCO_2$ over a large range of PCO_2 values in patients with chronic hypoventilation, and the instrumental drift of the $PtcCO_2$ measurement was low during an 8-hour measurement. Thus, in clinical practice $PtcCO_2$ is a valid tool to measure PCO_2 during sleep in the follow-up of patients treated with long-term NIV. It can also be used as a replacement of ABG for daytime measurements of $PaCO_2$ in patients in which arterial puncture is difficult to perform, or in settings like the patients' home or in sleep centers. Furthermore, $PtcCO_2$ can be used to evaluate the prevalence of sleep hypoventilation in patients treated with nocturnal NIV. This is of importance for future research looking at

significance of sleep hypoventilation during NIV on patient outcome. Last, and of importance for this study, $PtcCO_2$ can serve as a reference test in the evaluation of other diagnostic test for sleep hypoventilation (Paper III).

4.2. Paper II

Sleep Related Respiratory Events during Non-Invasive Ventilation of Patients with Chronic Hypoventilation

The aims of this study were:

1) To quantify the frequency and describe the types of both AH and PVA in a large group of stable patients with CRF during night-time NIV.
2) To analyse the influence of these events on ventilation, and
3) To assess interrater agreement in identifying and quantifying AH and PVA.

Twenty-three (34%) patients had an AHI > 5/hour and 16 (24%) above 10/hr. Obstructive hypopnea was by far the most frequent event. Fourteen patients (21%) spent more than 10% of the total recording time in asynchrony, and 25 patients (37%) had a PVAI > 5%. The interrater agreement rate (kappa) for classifying AH according to a cut-off value of AHI > 10 was 0.96 ($p<0.001$), was classified as an almost perfect agreement. For the interrater agreement of scoring asynchrony the Intraclass correlation coefficient (ICC) was classified as strong and there was a substantial agreement in classifying the degree of asynchrony according to different cut-off values. Unintentional leaks were low in the majority of patients. No correlation was found between respiratory events and nocturnal hypercapnia.

In conclusion: We found a high frequency of respiratory events in patients treated with long-term NIV, underlining the importance of implementing a strategy for the detection of these events during the follow-up of these patients. The scoring of respiratory events during NIV is complex and time consuming. Still, we found that these events can be scored with a very high interrater agreement. Thus, in clinical practice polygraphy can reliably be used to evaluate the types and frequencies of these events. This is also of importance for future research looking at significance of respiratory events during NIV on patient outcome. In addition, and of importance for this study, the high interrater reliability in the scoring of these events strengthens the use of polygraphy as a reference test in the evaluation of other diagnostic tests for apnea-hypopnea and PVA (Paper III).

4.3. Paper III

Diagnostic accuracy of simple tools in monitoring patients with chronic hypoventilation treated with non-invasive ventilation; a prospective cross-sectional study

The aims of this study were:

1) To analyse the ability of a combined test panel to detect sleep hypoventilation and other sleep related respiratory events using RPG and nocturnal $PtcCO_2$ as reference standard.
2) To analyse the contribution of specific components of the test panel to detect specific nocturnal respiratory events using the same reference standards.

The following index tests for detection of sleep hypoventilation and respiratory events were performed:

1) A combined test panel defined as a combination of clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2 and assessment of compliance (from ventilator software).
2) Daytime $PaCO_2$, HCO_3^- and nocturnal pulse oximetry as separate index tests for sleep hypoventilation.
3) Nocturnal pulse oximetry and $AHI_{software}$ as separate index tests for apnea and hypopnea and
4) Nocturnal pulse oximetry as a separate index test for PVA.

Nocturnal $PtcCO_2$ was used as a reference standard for sleep hypoventilation and RPG as a reference standard for detection of apnea-hypopnea and PVA.

Very few patients had symptoms of sleep related breathing disorders in spite of the presence of nocturnal respiratory events in a significant proportion of patients. Sleep hypoventilation was confirmed in 23–50 of the patients according to the 3 definitions used for sleep hypoventilation. Sensitivity of the combined test panel for sleep hypoventilation was 87% (95% confidence interval 66–97), 84% (66–95), and 80% (66–90) and specificity was 40% (25-56), 43% (26-61) and 63% (35-85) according to the 3 definitions used for sleep hypoventilation. Sensitivity of nocturnal SpO_2 for sleep hypoventilation was 48% (27–69), 39% (22–58) and 38% (24–53), and of daytime $PaCO_2$ 74 (52–90), 74% (55–88) and 68% (53–80). Sensitivity and specificity of ODI3% for AHI ≥ 10 was 94% (70-100) and 59% (44-72), respectively. Sensitivity and specificity of $AHI_{software}$ for AHIpolygraphy ≥ 10 was 93%

(68–100) and 92% (81–98), respectively. All tests used had a poor sensitivity and specificity for detecting PVA.

In conclusion: We found a high frequency of sleep hypoventilation in patients under treatment with LTMV. However, a combined test panel, nocturnal SpO_2 and daytime $PaCO_2$ all had insufficient accuracy for detecting and ruling out sleep hypoventilation. This underlines the importance of implementing $PtcCO_2$ in the regular follow-up of these patients. ODI3% had a high sensitivity but low specificity for AHI, thus a high ODI3% can be used to select patients in need of polygraphy to detect the cause of frequent desaturations. Polygraphy during NIV is not available in many centers following-up patients with LTMV. In this situation, given the high sensitivity and specificity of $AHI_{software}$ for AHI $\geq$ 10, $AHI_{software}$ can be used to guide change in ventilator settings; i.e. increase EPAP in order to treat upper airway obstruction. This can limit the use of polygraphy to patients unresponsive to treatment modification. In centers with easy access to polygraphy, $AHI_{software}$ can be used to select patients in need of a titration study with polygraphy during NIV.

5. Discussion

In this thesis we have demonstrated that it is important and possible to systematically evaluate the presence of undesired nocturnal events during NIV in patient with chronic hypercapnic respiratory failure. In the regular follow-up of these patients the presence of sleep hypoventilation and respiratory events like apnea-hypopnea and PVA should be evaluated. $PtcCO_2$ is an accurate and precise tool for monitoring $PaCO_2$ without instrumental drift in this population, thus it can be used to detect sleep hypoventilation. Furthermore, RPG during NIV can be scored with a high inter-rater agreement when clearly defined scoring rules are applied. It can be used to detect apnea and hypopnea, including sub classification of hypopnea and PVA. We found that sleep hypoventilation, hypopnea and PVA were frequent, even though very few patients had symptoms indicating this. A suggested combined test panel proved to have insufficient accuracy in detecting these events. Also, we have confirmed the findings of other that daytime ABG and nocturnal SpO_2 are insufficient tests to detect sleep hypoventilation. Obstructive hypopnea was the most frequent event, and could be accurately detected by the $AHI_{software}$. Therefore, $PtcCO_2$ and evaluation of $AHI_{software}$ should be implemented in the routine follow-up of these patients.

A central aim of this thesis is to evaluate tests for detection of respiratory events and sleep hypoventilation in patients with chronic hypoventilation treated with long- term NIV. Central theoretical aspects of test evaluations are outlined below, followed by methodological considerations for this study, summary of its strength and limitations, and finally, statistical and ethical considerations. Then the main findings and clinical implications of the study will be discussed and future studies will be suggested.

5.1. Theoretical aspects

A medical test refers to any method used for collecting information about the health status of a patient, including laboratory tests, imaging procedures, elements from medical history and physical examination, or a combination of these.[220] Medical tests can be used for the diagnosis of a specific disease, but also to predict prognosis, to screen, to detect treatment selection markers, or to monitor a disease and the effect of treatment.[220 221] The evaluation of the performance of a test involves many aspects and perspectives. Horvath et al have distinguish between five key component of this evaluation: 1) analytical performance, 2) clinical performance, 3) clinical effectiveness and 4) cost-effectiveness of a test and 5) broader impact like legal, ethical and organisational consequences of testing.[221] The clinical

performance of a test refers to the ability of a test to detect patients with a specific clinical condition or in a physiological state, also referred to as the target condition.[220] This can be evaluated in a diagnostic accuracy study.[221] In such studies the performance of a test (i.e. index test) is compared with a clinical reference standard.[222]

A diagnostic accuracy study should also include evaluation of the added benefit of a test. In order to do this, the purpose and role of a test in the clinical pathway has to be defined.[221] The clinical pathway refers to the typical or standardized care for a specific clinical problem, in a specific population.[223]

The purpose of a test describes the intended clinical use of the test and how it will be used to improve clinical management in practice. This could be in a diagnostic setting, or in relation to screening, staging, or monitoring disease progression and treatment.[221]

The role of a test describes the intended position of a test in an existing clinical pathway. This could be as a replacement, triage or add-on test.[224]

The intended role of a replacement test is to replace an existing test, because it is more accurate, easier to perform, cheaper, less invasive or less risky or troublesome for the patient. A triage test is intended to be used before other tests are ordered in an existing clinical pathway. Although a triage test can be less accurate then an existing test, it can limit the need for more costly or invasive tests. Add-on test is intended to be used after other tests in an existing clinical pathway. It can be more accurate, but more costly, invasive or less attractive by other reasons. Add-on tests are intended to be used only on a subset of patient with a specific result in other tests.[224]

Defining the purpose and the role of a test under evaluation is important for several reasons. First, it will influence on the type of study to be used. The clinical performance of a test with a diagnostic purpose can be evaluated in a diagnostic accuracy study, typically a cross-sectional study.[221] Evaluation of the clinical effectiveness will often need another design, for example a randomised test-treatment study. [222] Second, it will point out which population to study and the specific clinical context the test should be evaluated in.[221] Third, it will guide how we apply the index test and reference standard within the chosen population, which has been nicely described by Bossuyt et al.[224] Fourth, it will guide how we evaluate the result of the performance of an index test. For example, whether we emphasise the ability of a test to rule out or rule in a target condition, as captured in the mnemonic SNOUT and SPIN outlined below:

SNOUT: high SeNsitivity, test Negative, rules OUT and
SPIN: high SPecificity, test Positive, rules IN[225]
Last, the purpose and the role of a test should be included in the reporting of the study, as pointed out in the guidelines for reporting diagnostic accuracy studies.[220] This is important for correct implementation of the results in clinical practice and for correct inclusion of studies in the making of meta-analyses in the field of diagnostic accuracy.[226]

Studies of diagnostic accuracy are often either case-control or cross-sectional. [227] In a case control study, also referred to as "two gate design", the numbers of cases and controls are set by the investigator, and the participants with the disease (cases) are selected from a different population than the participants without the disease (controls).[228] This will allow for a testing of sensitivity and specificity of a test for a target condition when applied in both groups. However these studies have been shown to overestimate accuracy and are generally not representative of a test's accuracy in clinical practice.[229] In a cross-sectional study, all participants suspected to have the target condition undergo the index test. The presence or not of the target condition is verified in all participants with the reference standard.[222]

A key issue of a study of diagnostic accuracy is to evaluate a question arising from clinical practice; i.e. can a test help to diagnose a patient's condition? The ability to answer this question depends both on the internal and the external validity of the study.[230] Internal validity is a function of both bias and imprecision.[231] Bias can be defined as a systematic deviation from the true values as a consequence of a defect of the design or conduct of a study. In a study of diagnostic accuracy bias will lead to estimates of the performance of a test that differ systematically from its true accuracy. This error will not be corrected by repetition, while imprecision is due to a random error that can be "balanced out" by repetition.[231]

Variation, on the other hand, refers to differences in the true (unbiased) accuracy of a test across studies.[229] Variations of the performance of a test across studies may be due to differences in the conditions of the study (differences in test protocol, setting, study populations or in how the target condition is defined).[226 231 232] These conditions may vary from those which the test is intended to be used. If so, *the applicability* of the results in the clinical context and the research question it intends to answer may be reduced.[229 231] The applicability; i.e. the external validity is determined both by the internal validity and the sources of variation.

5.2. Methodological considerations

We aimed to evaluate tests intended to be used in patients treated with LTMV. The purpose of these tests is to detect undesired respiratory events during the routine follow-up of these patients. The potential role for daytime $PtcCO_2$ is to serve as a replacement test for ABG, thus avoiding invasive test for $PaCO_2$. The potential role of the other index tests are to serve as triage tests, and guide the need for treatment adjustment or further testing with $PtcCO_2$ and RPG. $PtcCO_2$ and RPG are associated with higher costs, lack of availability and require expertise. In the following I will discuss the methodology used for these test evaluations, with emphasis on internal and external validity, and the strength and limitation will be summarised. As outlined previously, we also had other aims for this study, including description of the frequencies and types of respiratory events occurring during LTMV. Methodological considerations regarding these aims will also be included, when relevant.

5.2.1. Internal validity

The evaluation of internal validity will focus primarily on potential biases. Bias can be related to patient selection, index tests, reference standards, as well as flow and timing.[226]

Patient selection

The patients included in a study should be representative of the patients who, according to the research questions, will be submitted to the test in clinical practise.[233] This will depend on the methods used for sampling of patients and if the patient group recruited by this method yield a representative sample. The latter will be discussed in the section on variation below. Both the study design and the method used to enrol patients may lead to bias,[229] also referred to as *selection bias*.[227]

Study design. We used a cross-sectional design aiming to include all patients having chronic hypoventilation treated with NIV and who were scheduled for a regular-follow-up. Cross-sectional design reflects reality better and is associated with higher overall accuracy than case-control studies.[229 234] In addition, case-control will not allow measurement of prevalence because this is set by the ratio of cases to controls. We also aimed to study the frequencies of sleep hypoventilation and other respiratory events. By using a cross-sectional design, we were able to describe the frequencies of these target conditions in the group of patients studied.

Patient enrolment. If eligible patients are enrolled retrospectively and not consecutively or randomly, a selection bias may occur. In addition, it may occur as a consequence of the

inclusion and exclusion criteria used, including exclusion of patients difficult to classify with the reference standard. Our study was performed prospectively, and we evaluated consecutively for inclusion all patients planned for a regular follow-up of LTMV. In addition, we had few exclusion criteria and did not exclude patients who potentially could be difficult to diagnose; i.e. patient with severe deformities due to their underlying muscular or skeleton disorder, severe obesity, or co-morbidity like COPD.

Index Test

Test review bias (information bias) may occur if the interpretation of the index test is influenced by knowledge of the results of the reference standard.[229] This is particularly important when a subjective evaluation of the index test is involved. The physician evaluating the patient's symptoms as part of the combined index test in paper III, was blinded to the results of the $PtcCO_2$ and polygraphy tests. The other index tests used in this study were objective measurements like ABG and SpO_2, unlikely to be biased by the researchers knowing the results of the reference standard.

Threshold selection: For all of the index tests, pre-specified cut-off values were used, except for $AHI_{software}$. As outlined in the Statistical section this cut-off value was obtained from the data collected in this study. This "data-driven" threshold selection may have led to a biased estimation of the sensitivity and specificity off $AHI_{software}$ for AHI > 10/hour.

Reference standard

Bias due to inappropriate or imperfect reference standard. It is recognised that very few tests in medicine are perfect; i.e. have a sensitivity and specificity of 100% under all circumstances. Therefore, the term "reference standard" is preferred to the term "gold standard".[227] A reference standard can misclassify the target condition which may bias the diagnostic accuracy of the index test. In addition, a reference standard can be difficult to perform, and if this occurs in a substantial and non-random sample of the participants, it may bias the diagnostic accuracy of the index test.

We used polygraphy as the reference standard for AHI. As outlined in the background section, performing polygraphy and scoring of respiratory events with polygraphy during NIV is complex. We used an attended polygraphy and were able to perform this complex procedure in all patients. The occurrence of respiratory events may vary during the night. Therefore, the entire night was scored. The median study time was 462 minutes (IQR: 451-478) and median ventilator backup respiratory rate 12 breaths/minute (IQR: 10-15), thus more

than 370 000 respiratory cycles were scored both for apnea-hypopnea and PVA. Furthermore, we used a pre-specified scoring protocol, tested prior to the study, as outlined in the Method section. Two pulmonologists scored all of the studies; both had long experience in scoring polygraphy during NIV and were blinded to each other's results. In paper II we demonstrated a high interrater reliability in the scoring of respiratory events. Thus, this reference standard was applied in all patients without large error of classification.

We used $PtcCO_2$ as reference standard for sleep hypoventilation. The $PtcCO_2$ signal was integrated in the attended polygraphy, and we were able to perform this procedure successfully in all but one patient. We used pre-specified criteria for the scoring of sleep hypoventilation, as outlined in the Method section. The accuracy and the instrumental drift of $PtcCO_2$ has been a subject of debate. In paper I we demonstrated a good accuracy of $PtcCO_2$ in measuring PCO_2 and a low instrumental drift. Consequently, $PtcCO_2$ can serve as a reference standard for sleep hypoventilation in our setting. Thus, this reference standard was applied in all but one patient without large error of classification.

Diagnostic review bias may occur if the interpretation of the reference standard is influenced by knowledge of the results of the index test.[229] This is particularly important when a subjective evaluation of the reference standard is involved. The two pulmonary physicians scoring the polygraphy were blinded to the results of the index tests, and the diagnosis of sleep hypoventilation was based on objective measurement with $PtcCO_2$.

Incorporation bias may occur if the result of the index test is used for establishing the target condition.[229] We used ODI associated with a ≥ 3% oxygen desaturation as an index test for AHI. Desaturation of 3% is also incorporated in the definition of hypopnea which in turn is included in calculating AHI. However, desaturation used as an index test was defined as an oxygen desaturation ≥ 3% from baseline lasting 10–90 s, while a hypopnea was defined as a flow reduction with an associated desaturation of ≥ 3% without any criterion for the length of desaturation. Thus, ODI3% is measured differently from desaturation used for hypopnea scoring, and ODI3% is not directly incorporated in establishing the final AHI.

Flow and Timing

Biases may be related to how the tests are applied and completed in the included patients.

Disease progression bias may occur when there is a time lag between the index test and the reference test and the disease progress during this time lag. *Treatment paradox bias* may

occur when treatment is started based on the results of the index test, and the reference standard is performed after treatment has started.[229] The index tests and reference standards were applied simultaneously; i.e. the nocturnal measurements were performed during the same night, and the comparison between daytime ABG and daytime $PtcCO_2$ was obtained simultaneously (except from the 2 minutes delay as explained in the Method section). In one patient, the 3-months compliance data from the ventilator software could not be obtained, and the results from the previous 3-month period was used. According to the patient, the pattern of use was the same in these two periods.

In the comparison of daytime $PtcCO_2$ with $PaCO_2$ from ABG, all patients were tested with both methods. Similar, in the comparison of the index tests for nocturnal events with polygraphy and nocturnal $PtcCO_2$, all patients were tested with both the index tests and reference standards. This paired study design strengthens the ability of our study to evaluate daytime $PtcCO_2$ as a potential replacement test for daytime $PaCO_2$ measurement and the other index tests as potential triage tests for nocturnal events.

Also, we performed the same reference standard in all patients included, avoiding *partial verification bias* (i.e.: bias occurring when the target condition is verified with the reference standard only in a selected sample of patients) and *differential verification bias* (i.e.: bias occurring when the target condition is verified with a different reference standard in a selected sample of patients. [229]

One patient removed the $PtcCO_2$ sensor prior to the morning measurement for instrumental drift of the sensor. Otherwise, none of the patients withdraw from the study. In one patient, the nocturnal $PtcCO_2$ signal was uninterpretable for obvious technical reasons. In two patients, abdominal and thoracic belt signals from the polygraphy were poor for > 2 hours, but polygraphy yielded satisfactory signals for at least 5 hours in all participants. In two patients, $AHI_{software}$ were not available. The missing data were handled by exclusion of the paired data for the relevant statistical analysis. Due to the low number of missing data, this did not influence on the results.

Sample size

The target population for this study is of limited size; even so 67 patients were included. As outlined in the Background section, this represents a larger sample size than most other studies with similar research questions. There is limited evidence of the effect of sample size on diagnostic accuracy studies.[229] One meta-analysis comparing accuracy across studies found

higher accuracy in studies with < 30 participants,[235] while another found no association.[236] However, the internal validity is a function of both bias and imprecision. The precision of the accuracy of the index tests in paper III is expressed by the 95% confidence interval of the sensitivity and specificity. The relatively wide confidence intervals reported limit the internal validity of this study. This imprecision could be due to sample size; a larger sample size may have improved these values. The precision of the accuracy of $PtcCO_2$ compared with $PaCO_2$ in paper I is expressed with the limits of agreement in the Bland-Altman blot. The low limits of agreement reported strengthen the internal validity of these results.

5.2.2. External validity

The external validity: i.e. the ability to generalise the results, depends both on the sources of bias and of variations. This evaluation will focus on potential sources of variation that may limit the applicability of our results. Variations may be related to patient selection, index test and reference standard.[226]

Patient selection

The diagnostic test under evaluation may perform differently in different populations, and therefore cause variation in the results of a diagnostic accuracy study.[233] This may be due to demographic features or variations in the spectrum of the target conditions in the studied population.

The population tested may vary in demographic features. We included patients with chronic hypoventilation due to a large number of disorders. However, as outlined in the background section they have in common a theoretical risk of having the target conditions high AHI, PVA and/or sleep hypoventilation during NIV and therefore represent the intended population for this study. The main demographic features were reported in our study and are in line with those reported by others in terms of gender, age, subgroups, BMI, co-morbidities and pulmonary function.(Table 1S, Paper III).[200 237 238]

This study evaluated target conditions occurring during NIV, and the tested population may vary from others in how NIV-treatment is applied. Therefore, we reported details of the NIV settings and associated treatment (Table 1S, Paper III). Some of the key features were as follows: 1) Patients with obesity hypoventilation had a significantly higher EPAP, a patient group known to frequently have co-existing OSA. 2) All patients had mandatory backup respiratory rate. 3) All patients used state of the art ventilators either from ResMed or Philips Respironics, devises used worldwide. 4) A wide range of interfaces were used: Thirty-one, 23

and 13 patients used an oro-nasal-, nasal-mask, or nasal prongs, respectively. 5) Thirty-three patients used a humidifier attached to the NIV device. 5) Only one patient used supplementary oxygen. Overall, these characteristics are in line with those reported by others. [200 237 238]

The spectrum of the target condition may differ from other populations in severity and prevalence. This is sometimes referred to as *spectrum bias*. But this is a result of a true variation and not a result of a bias in the measured accuracy within the study, also referred to as a spectrum effect.[239] The spectrum of the target condition will be influenced by several factors including the study setting, referral patterns and prior testing.[229] We included patients enrolled in our LTMV program and scheduled for a regular follow-up. The indications and titration of LTMV in our institution is based on Norwegian guidelines and are in line with international guidelines.

All patients included had undergone prior testing both during initiation of NIV and during successive follow-up. This could- and probably did- lead to an accumulation of remaining "difficult to diagnose" respiratory events within each of the included patients. In Norway, and at least in many European countries, patients with NIV are followed-up on a regular basis including at least some kind of evaluation of nocturnal ventilation. Thus, the situation for our patients resembles the "real world" situation for this group of patients.

At the time of the conduct of this study all patients with LTMV in all but three areas of Oslo were followed up by our institution and more than 70% of the population scheduled for a regular follow-up during a one-year period were included.

In summary, the patients included in our study are likely to be representative for a population of patients treated with Long-term NIV scheduled for a regular follow-up.

If, on the other hand, patients are referred for a specific clinical problem, for example symptoms or poor compliance, the severity and prevalence of the target disorder may differ from our population. In this situation, the tests evaluated may perform differently. Thus, our results may not be applicable to these settings.

We did not include COPD patients. COPD patients differ substantially from other patient groups treated with LTMV. They have respiratory failure primarily due to severe ventilation/perfusion mismatch, while the patients included in our study have respiratory failure primarily due to hypoventilation. In addition, most COPD are treated with long-term oxygen (LTOT) therapy in addition to LTMV, while most patients treated with LTMV for

hypoventilation do not require LTOT. Thus, our results may not applicable for COPD patients treated with LTMV.

Index tests

Variation in the use of the index test can limit the applicability of the result. This can be due to variation in the interpretation of the test caused by inter- or intra-observer variability or by clinical information available to the interpreter. In addition, differences in test technology and the execution of the test may cause variations.

One of the index tests was defined as a combination of clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2 and assessment of compliance (from ventilator software). The clinical evaluation was performed by a pulmonary physician experienced in evaluating patients with LTMV. During the time of the study, this involved several physicians according to the ordinary working plan of the department. This evaluation is subjective with the risk of observer variation. We did not evaluate inter-observer or intra-observer reliability and acknowledge that others may have evaluated the patients differently. This may limit the external validity of the results of this test. However, this evaluation was only one of several items of this test, as outlined above. All the other items are objective measurements, making it less likely that the overall score would differ substantially if evaluated by others.

The physician performing the clinical evaluation had access to all clinical information of the patients including daytime $PaCO_2$, nocturnal SpO_2 and data from ventilator software, but blinded to the $PtcCO_2$ and polygraphy results. The availability of this clinical information may have influenced on the clinical evaluation performed by the physician. However, only three patients were evaluated as having unsatisfactory symptom control in spite of the fact that a substantial number of patients had abnormal values of the data from daytime $PaCO_2$, nocturnal SpO_2 or data from ventilator software. Thus, it is reasonable to conclude that the availability of clinical information did not have a major impact on the clinical evaluation. In addition, this way of conducting clinical evaluation represents the “real world” in how physicians evaluate patients during follow-up of LTMV.

AHI from ventilator software

$AHI_{software}$ was used as an index test for high AHI. These data are obtained from an incorporated monitoring unit in the ventilator and are downloaded to ventilator specific software providing automatic analyses of the data. Thus, the performance of this index test

depends on the algorithm calculating $AHI_{software}$. This technology may vary between ventilators and may change over time. We analyzed data from six different devises from ResMed and 2 from Philips Respironics. A separate analysis limited to data from ResMed devises, was also performed (Supplementary data, paper III). The software used for downloading data and the criteria for the algorithm calculating AHI were the same for all ResMed devises and all Philips Respironics devises, respectively (Table 11).

Table 11 Software used for downloading and criteria for AHI calculation for the various ventilators used

Ventilator	No	Software	Criteria for AHI calculation*	
			Apnea	Hypopnea
ResMed:				
VPAP III ST-A	7	Rescan 04.01.013	> 75% airflow reduction	> 50% airflow reduction
S8 VPAP IV ST	20		> 10 seconds	> 10 seconds
S9 VPAP ST	15			
S9 VPAP ST-A	5			
Stellar 150	8			
Elisée 150	2			
Philips Respironics:				
BIPAP AVAPS	9	EncorePro 2	> 80% airflow reduction	> 40% airflow reduction
BIPAP SYNCHRONY	1	2.1.6.0	> 10 seconds	> 10 seconds

No: numbers of patients. * Data provided by the manufacturers.

The performance of $AHI_{software}$, as an index test, is limited to the devises tested or using the same technology, in particular ResMed devises, and should be confirmed for other devises by other studies. The devises tested in our study are used worldwide, and the results should therefore be applicable for many ventilator users.
The executions of the index tests used were described in detail in the relevant papers, allowing for interpretation of variation in results compared with other studies.

Reference standard

Variation in the use of the reference standard can also limit the applicability of the result. This can be due to how the reference standard is applied and how the target condition is defined.

Polygraphy for the detection of apnea-hypopnea and patient-ventilator asynchrony

We used a state of the art polygraphy system adapted to be used during NIV, as outlined in the Method section. The method was applied in a standardised way based on the recommendations from the manufacturer. In addition, we used the widely accepted scoring rules of AASM for the scoring of AHI. PSG is an alternative reference standard. AHI from

PSG is calculated by the use of total sleep time as the denominator while the denominator in polygraphy studies is the total recording time. In addition, with PSG hypopnea can be scored if a flow reduction is associated with either a desaturation or an arousal, while polygraphy cannot identify the latter. Thus, the use of polygraphy instead of PSG in the scoring of respiratory events may have led to an underestimation of AHI, and especially hypopnea. To compensate for this we used autonomic activation as a surrogate for EEG arousals in the identification of hypopnea. Also, polygraphy instead of PSG reflects routine practice in many centres due to the limited access to PSG.

The scoring rules for PVA were adapted from previous literature. However as outlined in the background section, there is no consensus on how to define and score asynchrony. In addition, other methods like esophageal pressure or diaphragm or parasternal electromyogram may be more sensitive in detecting asynchrony. Thus, the amount of asynchrony may have been underestimated. We used polygraphy both to describe the frequencies and types of respiratory events (Paper II) and as reference test for the evaluation of the index tests (Paper III). Variations in these results may occur when other definitions and sensors are used for the detection of AHI and PVA.

Transcutaneous CO_2 for the detection of sleep hypoventilation

We used a state of art $PtcCO_2$ devise in a standardised way, as recommended by the manufacturer. We used the AASM criteria for sleep hypoventilation. However, these are based on consensus, and are still not widely applied. Other definitions of sleep hypoventilation have been shown to be of clinical importance, as well. We acknowledged these shortcomings and included three different definitions of sleep hypoventilation. All three definitions were used both for the estimation of the frequency of sleep hypoventilation and when $PtcCO_2$ was used as reference test for the evaluation of the index tests. Still, variation in both frequency and accuracy may occur if sleep hypoventilation is defined differently.

The study included only one of the commercially available $PtcCO_2$ devises, only one probe position (i.e. earlobe), and one temperature setting (43° C). Thus, the finding of a low instrumental drift demonstrated in paper I is limited to this device. In addition, the use of other devises and other probe positions and temperature settings may have given other results for the accuracy of $PtcCO_2$ for detecting PCO_2 and for establishing the prevalence of sleep hypoventilation. However, a recent meta-analysis of the accuracy of $PtcCO_2$ have shown that the use of TCM Tosca, the use of earlobe position and temperature > 42 °C were associated

with better accuracy for PCO_2 compared to other devices, probe positions and lower temperature settings. Therefore, it is not likely that other settings would have given more "true" values.

Our team has a long experience with the use of $PtcCO_2$ for nocturnal measurements, including appropriate handling of the device and knowledge about necessary maintenance procedures. In addition, the conductance of the $PtcCO_2$ measurement was probably optimised during the study period due to the knowledge of the ongoing study. In the "real world", the procedure may have been less thoroughly performed, influencing the results. Thus, our results may be generalised only to a clinical setting with optimal handling of the $PtcCO_2$ device.

5.3. Summary of strength and limitations

A major strength of this study is the systematic exploration of respiratory events during NIV and, in addition, the systematic evaluation of methods used to detect these events. We believe that the methodological thoroughness in the conduct of the study limited the potential biases and strengthened its internal validity. Equally important, the studied patient sample was representative for the intended population of the research questions. This was due to the study design, the patient enrolment strategy used, and the demographic features and disease spectrum of the actual study population. This is the first study to evaluate apnea-hypopnea, PVA and sleep hypoventilation in a representative adult population with chronic hypercapnic respiratory failure during NIV. Also, this study is the first to evaluate a proposed algorithm for the follow-up of these patients. We evaluated the use of both $PtcCO_2$ and RPG, thus strengthening the findings of both the frequencies of the events described and their use as reference standards in the evaluation of other methods. Our study provides new knowledge which can be of importance for a rare, but severely affected group of patients. Our findings may be generalised to other clinical settings and should be taken into account when designing strategies for the monitoring of NIV- patients with chronic hypercapnic respiratory failure.

Still, our study has some limitations. The results of the accuracy analysis performed for the index test for respiratory events in paper III showed relatively wide confidence intervals. Thus, the results should be interpreted with caution and should be tested by others in even larger patient samples.

The frequencies of the respiratory events, including sleep hypoventilation, will depend on how they are defined and the sensors used, as outlined above. This will in turn influence on

the evaluation of the accuracy of the index test. We used widely accepted criteria for AHI, and also included three different definitions for sleep hypoventilation. In addition, the sensors and the criteria used were described in detail, making variation from similar studies possible to interpret. Even so, our results are limited to the specific criteria and the sensors used in this study.

The threshold selected for $AHI_{software}$ was calculated based on data from the study and not pre-defined, as outlined above. Therefore, this threshold may be biased and should be tested independently by others. Also, the threshold of $AHI_{software}$ depends on the algorithm for the specific device, and our results are limited to the devices used and should probably be tested specifically for other devices.

Non-invasive measurement of CO_2 can be a useful method in a large range of clinical settings. However, $PtcCO_2$ may perform differently in different setting, as outlined in the Background section, and our results may not be applicable for other settings than the specific population studied. Similarly, the good performance of the $PtcCO_2$ demonstrated in our study may be limited to the specific device, probe position and temperature setting tested.

We did not include COPD patients treated with LTMV. Thus, our results may not be applicable for this specific group of patients. Finally, it must be underlined that the patients were tested during a regular follow-up and not due to referral for a specific problem. Our results may not be applicable for patients treated with LTMV and referred for evaluation due to a specific problem like daytime sleepiness, nocturnal dyspnoea, poor compliance, perceived PVA etc.

5.4. Statistical considerations

An overview of the statistical methods used in the papers this thesis is based upon, are given in Table 12. This is followed by a discussion regarding some of the methods used.

Table 12. Statistical method used in paper I-III

Method	Paper I	Paper II	Paper III
Correlation			
Pearson's coefficient of correlation	$PaCO_2$ from ABG and $PtcCO_2$		
Spearman's rank order		Respiratory events and gas exchange	
Agreement			
Bland and Altman	$PaCO_2$ from ABG and $PtcCO_2$		
Cross-tabulation for sensitivity and specificity			Index test and reference standard
Intra class correlation coefficient		Interrater agreement in scoring respiratory events	
Kappa measurement of agreement		Interrater agreement in scoring respiratory events	
Comparison			
Paired sample t-test	Instrumental drift of $PtcCO_2$		
One-way ANOVA		Patients characteristic	Patients characteristic
Kruskal-Wallis		Ventilator settings between all patient group	Ventilator settings between all patient group
Mann-Whitney U test		Ventilator settings between two patient groups	Ventilator settings between two patient groups

ABG: arterial blood gasses; $PtcCO_2$: transcutaneous CO_2; ANOVA: analysis of variance

Descriptive data where presented as mean and standard deviation for normally distributed data and as median and interquartile range for non-normally distributed data. P-values below 0.05 were considered significant. In paper I and II, IBM SPSS version 23 and MedCalc version 14.10.2 were used for statistical analysis, and IBM SPSS version 24 and MedCalc version 15.4 were used in paper III.

Correlation and agreement between $PaCO_2$ measured with ABG and transcutaneous CO_2. Pearson's coefficient of correlation was used to measure correlation between $PaCO_2$ measured with ABG and $PtcCO_2$. Correlation measures to what degree two variables are related. With the use of ABG and $PtcCO_2$ to measure $PaCO_2$, a correlation would be expected since both methods are designed to measure the same. Also, if $PaCO_2$ varies considerable in the sample analysed, a high correlation can be found if the variance is reflected in both tests applied. Thus, a high correlation does not necessarily mean that $PtcCO_2$ and $PaCO_2$ from ABG are in

agreement. Pearson's coefficient of correlation reflects linear relationship between the two variables, not the differences.[240]

Therefore we also used the Bland and Altman plot analysis.[241] This method is widely used to compare the agreement between two different clinical methods measuring the same. It calculates the mean differences between the two methods, random fluctuations around this mean and an agreement interval within 95% of the differences fall. The later tells us the interval, in which the difference between two methods is likely to be for most subjects. Whether the limits of agreements are acceptable or not has to be defined, according to the clinical purpose of the test. For $PtcCO_2$ we defined this a priori to be 1 kPa based on previous studies and clinical practice. Graphically, the difference of the two paired measurements is plotted against the mean of the two measurements. The difference is often calculated and plotted in the measured unit (i.e. kPa in our study). But the differences can also be expressed as percentages of the values on the Y-axis (i.e. proportionally to the magnitude of measurements). This will graphically show if the differences vary according to the magnitude of kPa. Previous studies have shown an increased difference between $PtcCO_2$ and $PaCO_2$ from ABG for higher $PaCO_2$ levels. Still, we choose to report the differences in unit (kPa) and not as percentage. This will allow for comparison with others, as most studies have reported in this way. Instead, we reported a sub-analysis of the differences in patients with $PaCO_2$ > 6.0 kPa.

The differences between $PaCO_2$ from ABG and $PtcCO_2$ are plotted against the mean of the results of the two methods. This reflects that none of the two methods necessarily represent the "true" value of $PaCO_2$. It has been stated that if one of the two methods represent the reference standard or a more "true" value (as one would assume $PaCO_2$ from ABG is in our study), the differences could better be plotted against this value on the x-axis. However, this is not recommended in most cases, as it will always appear to show a relation between difference and magnitude when there is none.[242]

Instrumental drift of overnight transcutaneous CO_2 measurement

Instrumental drift was calculated as the mean difference between morning and evening measurement of a gas mixture with a known concentration of CO_2, using paired sample t-test. There was a statistically significant instrumental drift, but the mean difference was low. We reported the number of patients with clinically significant drift as very low based on the same clinical evaluation as for the difference of $PaCO_2$ and $PtcCO_2$ (1 kPa/8 hours). This was based on clinical practice, but there is currently no published consensus on the acceptable level of

instrumental drift in this setting. Therefore, we also displayed graphically in a box-and-whisker plot the range of differences to allow the reader to get an impression of the magnitude and direction of the instrumental drift for each of the patients.

Interrater agreement in scoring respiratory events

Scoring of respiratory events during NIV is performed by visual inspection of the polygraphy traces. Although this is based on pre-defined criteria, the scoring is subjective and there could be individual variations in the interpretation of the traces. The scorings were used for calculating of the prevalence of high AHI and PVA in II and as reference standards in paper III. Therefor it was of interest to evaluate the agreement between the two scorers who independently evaluated each patient. Agreement and reliability is often used interchangeably in reports on reproducibility between raters, as it is used by us.[243 244] Still, a distinction between agreement and reliability have been underlinded.[244 245] Reliability can be defined as the ability of a rater or a measurement to differentiate between subjects or objects, while agreement is the degree to which scores or ratings are identical.[243] It has been stated that the Bland-Altman method is the only realistic way of dealing with inter-rater agreement.[246] However, the intraclass correlation is considered a better approach.[246] We used ICC for quantifying the extent of agreement among the two scores of polygraphy for the continuous variables (i.e. AHI, OHI, PVAI and more). This was based on a 2-way mixed model. The levels of agreement using the ICC for continuous variables were classified as follows: 0.00-0.25 = little, 0.26-0.49 = low, 0.50-0.69 = moderate, 0.70-0.89 = strong, 0.90-1.00 = very strong.[247 248] We also evaluated the agreement in dichotomisation patients in categories having either high or low index for the various respiratory events. The categories were based on pre-specified cut-off values described in the Method section. This could have been reported as percent of agreement (number of agreement scores / total scores). However, this approach will not take into account agreement occurring by chance. We therefore used kappa (Cohen's unweighted kappa) which provides a chance corrected index of interrater agreement/reliability. For the kappa measurement of agreement for categorical variables, results were classified as follows: < 0 = no agreement, 0-0.20 = slight agreement, 0.21-0.40 = fair agreement, 0.41-0.60 = moderate agreement, 0.61-0.80 = substantial agreement, 0.81-1.0 = almost perfect agreement.[249]

Diagnostic accuracy of the index tests for detecting sleep hypoventilation and respiratory events

All the index tests used, except for the combined test panel, are measured in continuous variables. Also, all the reference standards are measured in continues variables. Still, from a clinical point of view a dichotomisation of all these variables are relevant. The specific cut-of values and the rationale for these values are given in the Method section. This also allowed for the calculation of sensitivity and specificity. The cross tabulations of the results of the index test against the results of the reference standard were reported, in addition to the calculated sensitivity and specificity. Including the cross tabulation is recommended by the STARD 2015 guidelines for reporting diagnostic accuracy studies. [220] This allows performing of alternative analysis not reported by us, like positive and negative predictive values and additional analysis such as including data in meta-analysis.

All the cut-off values used for the index test were pre-specified, except for the cut-off values of $AHI_{software}$ for detection of high AHI. The various $AHI_{software}$ cut-off values for detecting $AHI_{polygraphy} > 10$ was obtained by use of receiver operating characteristics (ROC) curves. Youden's index J was calculated to determine the cut-off values with the maximum sensitivity and specificity. Due to variation by change, the point chosen on the ROC plot may be above the true value. This "data-driven" threshold selection may have caused an overestimation of the sensitivity and specificity of $AHI_{software}$ for apnea-hyponea.[250] We presented the scatterplot of $AHI_{polygraphy}$ compared with AHI from RPG, from each patient. (Paper III, supplement). Thus, allowing the reader to evaluate these data.

Sample size

The main aim of this study was to evaluate the diagnostic accuracy of a combined test panel for detecting sleep related respiratory events. This test has not previously been evaluated in a population treated with long-term NIV. As we used a cross-sectional study design and not case-control, the group with the disease (cases) vs. the participants without the disease (controls) could not be planned.[227] At the time of planning this study, the prevalence of respiratory events in a population representative for those being tested in our study, was not known. Neither did the pilot testing of the methods we performed prior to this study allow for any reasonable calculation of the prevalence due to large variation in the small sample size. Indeed, an additional aim of this study was to describe the prevalence of respiratory events in this population. Thus, our study had an explorative approach. After consultation with a

statistician we concluded that a formal sample size calculation would be very arbitrary. From knowledge of the number of patients enrolled in our LTMV program, we estimated that approximately 100 patients could be eligible for inclusion. Taken into account patient refusing to participate, not appearing for follow-up, being excluded according to the exclusion criteria or missing data, we evaluated the possible sample size to be reasonable according to the research questions and in comparison with other similar studies on this relatively rare group of patients. Still, care was to be taken to report data showing the statistical uncertainty (i.e. precision) given the relatively low sample size.

5.5. Ethical considerations

This study, reported in paper I-III, was conducted according to the ethical principles of the Declaration of Helsinki. The study was approved by the Regional Committee for Medical and Health Research Ethics (registration number: 2012/1142) and was registered in ClinicalTrials.gov 11th of March 2013 (registration number: CT01845233). The Norwegian National Advisory Unit on Long-term Mechanical Ventilation, Haukeland University Hospital and the Norwegian Neuro Muscular Diseases Foundation (Foreningen for muskel syke) funded the study. The funders had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the papers for publication. Paper III was reported according to Standards for Reporting Diagnostic Accuracy (STARD).[220] All participants provided a written informed consent prior to entering the study.

The patients eligible for this study had chronic respiratory failure and were treated with long-term NIV. Also, they were enrolled in our LTMV program and were regularly followed up at our institution. This raised some particular ethical issues:

Principal of beneficence

The scientific knowledge potentially gained from the study, should outweigh the potential risks and burdens for the participants.[251] We evaluated the risk of harm, including painful investigation, to be minor in this study. The study was conducted during a regular follow-up of LTMV. Most of the data collected, were data routinely obtained during a follow-up visit, including ABG. Still, according to our LTMV program at the time of the study, RPG and $PtcCO_2$ was not routinely performed in all patients and not all patients were admitted to hospital for their routine follow-up. Although these measurements do not cause any pain or

other risk of harm to the patients, the study could represent an inconvenience for the participants. For patients with chronic diseases, and especially patients with NMD, severe obesity or deformities, as in this study, spending a night in the hospital could represent an inconvenience. Also, in the case of technical failure of the equipment, patients would be asked to repeat the measurement the following night. Even so, this study was particularly addressed for this population, and could not have been performed in other study populations.
To minimize the burden on the participants several precautions were taken:
First, two sleep labs in single-bed rooms within the ward were dedicated to the conduct of the study, in which one was especially equipped for patients with movement disabilities. Second, care was taking both prior to the study and during the study to minimise the numbers of erroneous measurements. Last, all the ABG samplings were conducted by a physician with expertise in this potentially painful procedure.
Our study aimed to increase the knowledge specifically about long-term NIV, knowledge that could improve the efficacy of the treatment for the group of patients studied, but also for the participants.

Consent

All the eligible patients received verbal and written information about the study. Care was taken to inform about potential benefits and risks and burdens. It was emphasized that RPG and $PtcCO_2$ could be performed even if they declined to participate. All eligible patients were chronical ill, and had regularly follow-up visits at our institution. This dependent relationship warranted particular cautiousness when seeking informed consent.[251] All eligible patients received written information and a request to participate, posted together with the admission letter for the planned follow-up visit, prior to their attendance at the hospital. Thus, allowing them time to consider.

Access to study data

The physician in charge of the patient was given access to RPG and $PtcCO_2$ measurements after the data collection for this study, but prior to the patients discharge from the hospital. This ensured the evaluation of these data in the context of each patient and allowed for treatment adjustment according to the results of these measurements.

6. Discussion of the main findings

6.1. Accuracy of transcutaneous CO_2

We found that $PtcCO_2$ accurately reflected $PaCO_2$ in a wide range of $PaCO_2$ values. The bias (mean of difference between $PaCO_2$ and $PtcCO_2$) and limits of agreement were low. Our results are in agreement with other studies on patients with chronic respiratory failure.[180 183 252] Still, wider limits of agreement have been found in studies on similar group of patients, and lower accuracy and wider limits of agreement have been found in patients with high $PaCO_2$ levels.[179-182] These differences could be due to low numbers of included patients, differences in temperature setting of the sensor, site of sensor placement or use of older devices.

A recent systematic review and meta-analysis estimated pooled mean bias and population limits of agreement (LoA) between $PtcCO_2$ and $PaCO_2$.[253] Data from 73 studies published between 2000 and 2016 were analysed and included 7021 paired measurements taken from 2817 participants. For the analysis, an outer confidence bounds for 95% LoA of 1kPa between $PtcCO_2$ and $PaCO_2$ was deemed as clinically acceptable. The mean bias between $PaCO_2$ and $PtcCO_2$ was only 0.01 kPa, but the 95% LoA was -2 kPa − 2 kPa. The meta-analysis included a large variety of settings and patients groups, different types of devises, sensor placement, and senor temperature. Results within the clinical acceptable range were found for sub analysis of studies limited to the use of the Tosca device (44 studies), but not for the SenTec device (30 studies). Also, substantial differences were found according to the sensor placement and temperature setting. In the 44 studies placing the sensor on the earlobe, the LoA were within the clinically acceptable range, while when the sensor was placed on the chest or forearm, LoA were outside the clinically acceptable range. Furthermore, in a sub-analysis of studies where the temperature of the sensor was set to 42°C, LoA were wide (−3.3 to 3.5 kPa), while in studies using temperature > 42°C, the LoA were within the clinically acceptable range (-0.9 – 0.9 kPa). Sub-analysis according to the clinical setting and patient group showed that the LoA were within the clinically acceptable range for studies on adults in ICU, children undergoing surgery or in ICU, and adults undergoing lung function testing. The LoA for studies including patients with chronic respiratory failure were -1.1 – 1.1 kPa. The studies which were included in this latter sub-analysis used different devises, temperature and sensor placement, and the clinical setting also varied (Table 13).

Table 13. Studies included in the sub-analysis comparing $PaCO_2$ and $PtcCO_2$ in patients with chronic respiratory failure

Author Year	No	Clinical setting	Sensor temperature	Probe placement	Device	Bias kPa	95% C.I.
Aarrestad 2016	67	Chronic hypercapnic respiratory failure	43	Earlobe	Tosca	0,23	-0.32-0.79
Cavalier 2005[180]	48	Chronic hypercapnic respiratory failure	44	Chest	TCM3	0,10	-0.70-0.89
Hazenberg 2011[182]	15	Chronic hypercapnic respiratory failure	42	Earlobe	Tosca	-0,40	-1.27-0.47
Herrejon 2006[254]	30	Various respiratory diseases	42	Earlobe	SenTec	0,02	-0.62-0.66
Janssens 2005[168]	40	Acute or chronic respiratory failure	43	Chest	TCM3	-0,01	-1.13-1.11
Janssens 2001[179]	28	Geriatric patients	43	Chest	TCM3	0,37	-0.64-1.39
Parker 2007[255]	48	Various respiratory diseases	42	Earlobe	Tosca	-0,04	-1.35-1.27
Török 2008[256]	19	Patients assessed for long-term oxygen therapy	42	Earlobe	SenTec	-0,11	-1.02-0.79
Tonelli 2015[257]	29	Chronic pulmonary hypertension	45	Forearm	PeriFlux	-0,41	-2.00-1.17

N: numbers of included patients; C.I: confidence interval. The studies used in the meta-analysis are confirmed by A.Conway, first author of: Accuracy and precision of transcutaneous carbon dioxide monitoring: a systematic review and meta-analysis. Thorax 2019; 74(2):157.

In our study bias was low and limits of agreement acceptable. We believe the use of the Tosca device, sensor temperature of 43°C, and use of the earlobe for sensor placement contributed to the good performance of the $PtcCO_2$ found in our study.

6.2. Instrumental drift of transcutaneous CO_2

We found a low instrumental drift. Drift was defined as the difference between evening and morning measurements of CO_2 concentration in a gas with a known CO_2 content. This method has been used in two other studies, as well. In a study of 10 patients, a significant instrumental drift was found using the SenTec device.[186] In a more recent study on 3 different devises (SenTec DM, Tosca 500 and TCM4 Tina), a low instrumental drift was found in 24 patients.[183] Other studies have used change of difference between $PaCO_2$ measured with ABG and $PtcCO_2$ over time as an expression of instrumental drift. One small study on six patients reported a significant linearly increase in this difference over time. Four other studies, all with low number of patients included, found low levels of drift, in line with our results.[179 181 182 214] Therefore our results confirms that for the device tested, a systematic in vivo calibration prior to, or after overnight measurement, is not necessary.

6.3. Prevalence of sleep hypoventilation

In our study, prevalence of sleep hypoventilation varied according to the definition used: 35% according to the AASM criteria, 47% had $PtcCO_2$ > 6.5 kPa > 10% of total recording time, and 76% had a maximum $PtcCO_2 \geq 6.5$ kPa. In the 31 patients with $PtcCO_2$ > 6.5 kPa > 10%, median % time spent with $PaCO_2$ > 6.5 kPa was 69% (IQR 44−92) of total recording time. In the retrospective study by Nardi et al. on 58 patients treated with home mechanical ventilation, 41% had maximum $PtcCO_2 \geq 6.5$ kPa.[161] In a recent retrospective study on 55 NMD patients treated with LTMV, Ogna et al. reported the following prevalence of sleep hypoventilation:13% according to ASSM, 27% had $PtcCO_2$ > 6.5 kPa > 10% and 42% had a maximum $PtcCO_2 \geq 6.5$ kPa.[210] Paiva et al found that 42% of children spent > 10% of the recording time > 6.7 kPa in spite of long-term NIV.[188] All these studies confirm that a substantial amount of patients treated with long-term NIV have sleep hypoventilation when monitored by $PtcCO_2$.

As outlined above, the prevalence of sleep hypoventilation in our study depends on the definition used, in line with the study by Ogna et al.[210] A similar finding was reported in a recent retrospective study on 232 spontaneously breathing patients with NMD.[258] This study compared the prevalence of sleep hypoventilation according to the AASM criteria, with other definitions proposed in recent literature. A marked difference in the prevalence of hypoventilation according to the different definitions used was revealed. Of note in our study is the substantial lower prevalence found by using the AASM criteria for hypoventilation compared to the other definitions used. A similar result was found in the two retrospective studies referred above.[210 258] Thus, our results confirms the findings of these retrospective studies: The frequency of sleep hypoventilation varies according to the definition used, and was lowest when using the AASM definitions. This result may be of importance, as values for sleep hypoventilation other than those used by the AASM have been shown to be of prognostic importance: In NMD, peak nocturnal $PtcCO_2$ > 6.5 predicts the development of daytime hypercapnia and the need for treatment with LTMV.[162 216] Also, $PtcCO_2$ > 6.5 kPa > 10% of the night in patients with NMD treated with LTMV have been shown to be associated with increased mortality and acute ICU admission due to respiratory failure.[210]

6.4. Interrater agreement in polygraphy scoring during NIV

Our study is the first to report on interrater agreement in scoring both apnea-hypopnea and asynchrony in patients treated with long-term NIV. We found a very strong interrater

agreement rate in the scoring of apnea-hypopnea: ICC was 0.97 (95% C.I. 0.94-0.98). In addition, the agreement rate (kappa) for classifying patients according to a cut-off AHI > 10 was almost perfect (0.96). The interrater agreement rate in the scoring of the percentage of total recording time with PVA was strong: ICC was 0.85 (0.75-0.91) and the total desynchronization index time was 0.87 (0.79-0.92). Since the start of the data collection for this thesis, two other studies have reported on the interscorer correlation of scoring respiratory events during NIV. Alvarez et al scored apnea-hypopnea with polygraphy in 26 patients with OHS stable on NIV-treatment for a mean time of 18 ± 8 months.[259] Events were defined as a flow reduction associated with 3% desaturation of SpO_2, adapted from SomnoNiv. Events were summarised as event index (EI). They found an interrater agreement of 0.84 (Cohens kappa coefficient) for classifying patients according to a cut-off EI > 10/hr. Ramsay et al. evaluated asynchrony during the initiation of long-term NIV.[260] They evaluated the inter-rater reliability of scoring asynchrony in a one hour section of recorded data in 10 of 27 included patients. Intra-class correlation coefficient between two scorers was 0.84 (0.79-0.99). Even though the scoring criteria used and the sensors for detecting events differ in these studies, respiratory events during NIV can be scored with good interrater agreement using pre-defined criteria for the events.

6.5. Prevalence of respiratory events

Unintentional leaks were low in the majority of patients, while high AHI and PVA were frequently observed.

6.5.1. Leaks

Leaks were low according to ventilator software and rarely observed in the polygraphy traces. Previous works have found high amounts of leaks in a substantial proportion of patients.[195 199] The patients in both these studies had been treated with long-term NIV for a relatively short time. Similar to our results, Fernandez et al and Pasquina et al reported low unintentional leaks obtained from the ventilator software in patients treated with NIV for 18±8 months and 4.1±2.6 years, respectively.[200 259] This indicates that problems with leaks may be reduced over time: The patients may use the mask more correctly over time or have the mask adjusted during follow-up after initiation of NIV. Also, improvement in mask technology may have reduced problems with leaks compared to masks used in older studies.

6.5.2. Apnea-hypopnea

We found that 34% and 24% of the patients had an AHI > 5/hr and >10/hr, respectively. Of the patients with AHI > 10/hr, median AHI was 19 (IQR 16-25) and median obstructive hypopnea index was 17/hr (IQR 14-21). Thirty-one percent of patients with OHS had an AHI > 10/hr. This is in line with two other studies reporting AHI during long-term NIV in OHS.[135] [259] Also, 22% of patients with NMD in our study had a high AHI. This is in contrast to Crescimanno et al. who found a low frequency of AHI in 16 patients with NMD.[192] This study did not use a flow sensor in the ventilator circuit[127] or a flow signal from the ventilator.[121] Neither were the recommended AASM criteria for the scoring of apnea-hypopnea used.[163] Similarly, Atkeson et al reported low AHI in 19 ALS patients, without using a recommended flow sensor and without including hypopnea in the scoring.[193] Thus, AHI may have been underestimated in these studies. In 35 patients with ALS, Vrijsen et al found an AHI of 2.9 (IQR: 0.0–9.8)/h sleep and 3.5 (IQR: 0.4–7.7)/hours of sleep in the bulbar and in the non-bulbar group of patients, respectively. However, this was after meticulous NIV titration using PSG for three consecutive nights during initiation of NIV only one month prior to the evaluation. The number of patients with AHI > 10/hour was not reported in this study.
Apnea was rarely seen in our study. Other studies have not systematically reported on frequencies of apnea vs. hypopnea during regular follow-up of NIV-treatment. Contal et al scored AHI in OHS patients during NIV on three consecutive nights with three different ventilator settings: 1) No, 2) low and 3) high backup respiratory rate.[261] In the setting with no backup respiratory rate, apnea was by far the most frequent event both for obstructive and central events. All the patients included in our study had an intermittent or continuous mandatory backup respiratory rate. When the ventilator is not triggered by the patient during an apnea, it will provide a mandatory breath according to the backup respiratory rate. Even with a closed airway, the inspiratory pressure delivered by the mandatory ventilator breath will probably cause a peak flow signal too high for the apnea criteria to be met. This may explain the low frequency of apnea found in our study. In addition, it shows the limitation of the AASM apnea criteria during NIV and underlines the importance of scoring hypopnea during NIV.
Most of the hypopnea found in our study were obstructive. In the study by Contal et al central events were infrequent in the setting with low and high backup respiratory rate, but significantly higher when no backup respiratory rate was applied.[261] The low frequency of central events in our study indicates that the backup respiratory rate and inspiratory pressure

provided were sufficient to avoid central apnea and hypopnea, as long as the there was no upper airway obstruction. As we did not differentiate between obstructive events with and without reduction of ventilatory drive, obstructive events of central origin related to NIV induced hypoventilation could not be estimated.

After the planning of this study, several studies have reported an association between the use of oro-nasal mask and upper airway obstruction. We therefor evaluated this aspect, as well, and found a significantly higher obstructive hypopnea index in patients using oro-nasal vs. nasal mask. Our study was not designed to study any causal relationship. Still, the observed association underlines the need to evaluate the mask used in the occurrence of obstructive events during NIV. In summary, high AHI was frequent and obstructive hypopnea was the most frequent event. Apnea and central hypopnea were rarely observed during long-term NIV with a mandatory backup respiratory rate.

6.5.3. Patient-ventilator asynchrony

Twenty-one percent of patients spent > 10% of the recording time in asynchrony, and 37% had > 5 PVA events/hr. In line with our study, a high frequency of PVA have been described during long-term NIV in patients with ALS,[193] OHS[135], and in a heterogeneous group of patients.[155] In contrast, Cresimanno found a very low frequency of PVA in a group of NMD patients.[192] More recently Ramsay et al and Vrijsen et al described a high level of asynchrony during initiation of NIV[202] and one month after initiation of NIV, respectivly.[203] Details of the studies reporting on PVA during long-term NIV are given in Table 14.

Table 14. Studies reporting on patient-ventilator asynchrony during long-term NIV in patients with chronic hypercapnic respiratory failure

Author (Year) Patient group	No	Asynchrony events reported and main characteristic of definition				Sensors	Main results
		Ineffective effort, Uncoupling of the patient's inspiratory efforts and onset of the ventilator pressurization	Double triggering	Auto triggering	Cycling		
Aarrestad (2017) Heterogeneous group of patients	67	Uncoupling of the patient's inspiratory efforts and onset of the ventilator pressurization for ≥ 10 seconds and at least 3 consecutive breaths. Including ineffective efforts.	Two cycles separated by a very short expiratory time. (< ½ mean inspiratory time)	At least three rapid pressurizations at a respiratory rate of ≥ 40 breaths/min and clearly above that of the patient's respiratory rate	Not reported	Thoraco-abdominal belts Pressure at mask Pneumotachograph in ventilator circuit	21% of patients had PVA > 10% of TRT 37% had a PVA index > 5/hour
Vrijsen (2016)[203] ALS	35	Uncoupling of the patient's effort and the ventilator response. A sequence of three ineffective efforts was scored as one PVA No minimum duration	A ventilator breath, triggered or non-triggered by the patient, quickly followed by a second ventilator breath	At least three rapid successions of ventilator breaths with a frequency higher than the patient's spontaneous effort	Cycling of the ventilator to the expiratory phase when the patient is still performing inspiratory effort	Thoraco-abdominal belts Pressure at mask Pneumotachograph in ventilator circuit	Non-bulbar patients: PVA index: 31 (15-49) % of TST: 3.5 (1.4–5.1) Bulbar patients PVA index: 32 (17-55) % of TST: 3.0 (1.7–5.8)
Ramsay (2015)[260] Heterogeneous group of patients	28	Patient exhibits inspiratory effort demanding a breath without a corresponding breath being delivered by the ventilator. No minimum duration	Two breathing cycles of the ventilator delivered separated by a short expiratory time (up to 1 second)	Auto-triggering represents an inappropriate ventilator delivered breath that is not triggered by the patient.	Premature, delayed and auto cycling scored. (see reference for definitions)	Parasternal electromyography Thoraco-abdominal belts.	PVA in 28±19% of breaths PVA > 10% of breaths in 79% of patients (range 11–63% of breaths
Crescimanno (2012)[192] Neuro-muscular disorders	18	Uncoupling of the patient's inspiratory efforts and onset of the ventilator pressurization No minimum duration	To cycles separated by a very short expiratory time	At least three rapid pressurizations clearly above that of the patient's respiratory rate	Late cycling scored	Thoraco-abdominal belts Pressure at mask	Asynchrony index 4.32 (IQR 1.75-6.25)
Atkeson (2011)[193] ALS	19	Central apnea, non-triggered patient effort, out-of-phase patient effort/ventilator, ineffective triggering Lasting one breath or more	Double effort with double-triggered ventilator assist	Not reported	Not reported	Thoraco-abdominal belts Pressure at mask	Total asynchrony index 69 ± 45.5 Total asynchrony 17 ± 19% recording time
Guo (2007)[135] OHS	20	Uncoupling of the patient's respiratory efforts and onset of ventilator pressure support for at least 10 s and three consecutive breaths	Not reported	At least three rapid successions of pressurizations at a respiratory rate > 40 breaths/min, clearly above patient's respiratory rate	Not reported	Thoraco-abdominal belts Pressure at mask	PVA found in 11 patients Average sleep time with PVA: 32 ± 23% of TST (range: 6 to 73%).
Fanfulla (2007)[155]	48	Presence of patient respiratory movement without concomitant breath from ventilator No minimum duration	Not reported	Not reported	Not reported	Thoraco-abdominal belts Pressure at mask	Ineffective effort 48% ± 40 /hour 4.1% of breaths 8 patients > 100 events /hour

No: number of patients; PVA: patient-ventilator asynchrony; TRT: total recording time; TST: total sleep time; IQR: interquartile range.

Ineffective effort (including uncoupling of the patient's inspiratory efforts and onset of the ventilator pressurization) was the most frequent reason for PVA in all studies reporting high level of asynchrony. We found a low frequency of double triggering and auto triggering, but we did not score cycling asynchrony. When reported, frequencies of double triggering, auto triggering and cycling asynchrony were low in all studies in Table 14. Still, there is a large variation in the level of asynchrony between studies. The number of patients with a high level of asynchrony varies considerably between studies, from 16% in the study by Fanfulla et al to 79% in the study by Ramsay et al. Several reasons have been suggested to explain this difference: 1) the type of disorder studied; 2) use of different ventilators with different triggering and cycling algorithms; 3) the titration procedure used for NIV settings; and 4) differences in definitions of scoring PVA.[203] As shown in Table 14 the definition for PVA varied markedly, especially in the scoring of events involving ineffective triggering. Similar to our study, Guo et al limited the scoring to events lasting > 10 seconds and lasting a minimum of three consecutive breaths, while others scored asynchrony breath by breath, without a criterion for a minimum duration.

Several other reasons can also explain the differences between studies. The sensors used to detect asynchrony varied. Ramsay et al used a surface parasternal electromyography, a method shown to be more sensitive in detecting inspiratory effort.[260] In the studies relying on changes in thoraco-abdominal movement and flow/pressure curves to detect inspiratory effort, asynchrony may have been underestimated (Table 14). Still, a recent study reported that detection of ineffective effort from flow and pressure curves was accurate compared with reference standard esophageal pressure.[262] In this study, flow was measured using a pneumotachograph situated between the mask and the ventilatory circuit, and the mask pressure was measured using a differential pressure transducer. Methods similar to those we used.

In addition, several studies only used thoraco-abdominal movement to detect inspiratory effort. RPG tracings, including flow signal from a pneumotachograph, has been reported to allow for detection of triggering or cycling asynchrony that is much more difficult to detect on PSG tracings in which a pneumotachograph is not included.[215] However, data comparing scoring of PVA with and without the use of a pneumotachograph is limited. Finally, both upper airway obstruction and leaks may cause asynchrony.[127] We limited scoring of asynchrony to periods without high leaks and apnea-hypopnea. In the other studies, scoring of asynchrony included periods with apnea-hypopnea or leaks,[192 203] apnea-hypopnea or leaks were not reported,[135 155 260] and one study included central apnea as asynchrony.[193] In

summary, there are large differences in the criteria for PVA and methods used to detect PVA. Even so, most studies, including ours, found high level of PVA in a substantial proportion of patients treated with LTMV.

The SomnoNIV group have recently published a framework for the detection and classification of PVA with polygraphy during NIV. [263] For the detection of PVA, they recommend the use of pressure at the mask and flow from a pneumotachograph combined with abdominal and thoracic belts. Furthermore, they state that PVA should be limited to periods without leaks and upper airway obstruction: i.e. PVA should be evaluated after the correction of leaks and obstructive events. Also, definition of and examples are provided for the various PVA events.[263]

6.6. Patient-ventilator asynchrony and gas exchange

No correlation was found between asynchrony and nocturnal desaturation or sleep hypoventilation. Also, an association between asynchrony and desaturation were rarely seen in the polygraphy traces. This is in concordance with most other studies.[135 203 260] In contrast, Fanfulla et al found that high prevalence of ineffective effort was correlated with nocturnal desaturation.[155] In this study, 12 of 48 patients had a ventilator setting with spontaneous mode (S-mode) i.e. no backup respiratory rate. S-mode has been associated with desaturation compared to the use of a backup respiratory rate in two cross-over studies.[261 264] However, in both studies desaturation was reported to be related to occurrence of obstructive and central events and not asynchrony, which is in agreement with the findings in our study, in which obstructive hypopnea frequently was associated with desaturation. In the study by Fanfulla et al, apnea-hypopnea was not scored, and ineffective effort is known to occur during upper airway obstruction. Thus, desaturation may have been related to obstructive events both in patients with s-mode and with a backup respiratory rate.

No correlation was found between asynchrony and sleep hypoventilation. A result in line with the other studies reporting on this aspect,[135 203 260] while sleep hypoventilation was not reported in the study by Fanfulla et al.[155]

6.7. Detection of sleep hypoventilation and other respiratory events during NIV, using simpler tools

To the best of my knowledge, this is the only study to evaluate a proposed test panel serving as the first step in evaluation the efficacy of nocturnal ventilation during long-term NIV. The test panel is a combination of clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2, and assessment of compliance (from ventilator software). We found that very few patients were evaluated to have symptoms of sleep related breathing disorders, although sleep hypoventilation, high AHI and PVA was present in a significant proportion of patients. The test panel was abnormal in 70% of the patients.

6.7.1. Detection of sleep hypoventilation

The accuracy of the combined test panel for detecting sleep hypoventilation was poor. Although sensitivity was moderate (80-87% depending on the definition for hypoventilation) the specificity was low. Of the 46 patients with abnormal test panel results, 40 patients had prolonged nocturnal desaturations and/or elevated daytime $PaCO_2$. In this situation, sleep hypoventilation should be suspected according to the algorithm proposed by the SomnoNiv group, as outlined in the background section. This should preferably be confirmed by $PtcCO_2$. Therefore, in order to confirm sleep hypoventilation, $PtcCO_2$ would be needed in a large number of patients. The combination of prolonged nocturnal desaturations and/or elevated daytime $PaCO_2$ had a low specificity for NH. Thus, relying on these tests to diagnose sleep hypoventilation, without confirmation with $PtcCO_2$, may incorrectly lead to increased ventilatory support in a substantial proportion of the patients. In addition, in 5-15% of patients with a normal test panel, sleep hypoventilation was in fact present which, if relying solely on the test panel, would not have been detected without measurement of $PtcCO_2$.

We found that abnormal nocturnal SpO_2 had a low sensitivity for sleep hypoventilation. This confirms the results of two other retrospective studies on NMD patients treated with LTMV[161 210] and one prospective study on children during nocturnal NIV[188]: the ability of nocturnal SpO_2 to rule out sleep hypoventilation is poor. A similar result has recently been reported in two studies evaluating sleep hypoventilation in spontaneously breathing patients with NMD or thoracic cage disorders.[258 265] In addition, daytime hypercapnia had a low sensitivity for sleep hypoventilation in our study. Again, this finding is in concordance both with studies on patients during long-term NIV[161 188] and several studies on spontaneously breathing patients

with NMD or thoracic cage disorders.[216 258 265 266] Neither abnormal daytime HCO_3^- nor a combination of the criteria "abnormal daytime $PaCO_2$" and/or "abnormal nocturnal SpO_2" had an increased sensitivity for sleep hypovntilation. In summary, none of the index test evaluated could accurately detect sleep hypoventilation.

6.7.2. Detection of apnea-hypopnea

The combined test panel had a high sensitivity of 91% for AHI > 10. Of the 46 patients with an abnormal test panel, 36 patients had a high ODI3%. In a situation with recurrent short desaturations, persisting after correction of leaks, upper airway obstruction could be suspected, according to the proposed algorithm by SomnoNiv. This should lead to an increase in EPAP. Leaks were low in our study, and indeed, ODI3% had a high sensitivity for detecting high AHI. This reflects that most hypopneas were associated with desaturations, which is in concordance with the results of Adler et al.[190] However, specificity of ODI3% for detecting a high AHI was low. This indicates that frequent short desaturations also could be caused by other mechanisms than apnea-hypopnea. Thus, relying solely on ODI3% to diagnose upper airway obstruction would wrongly lead to an increase of EPAP in a substantial proportion of the patients.

$AHI_{software}$, on the other hand, had both high sensitivity and specificity for AHI. These results are similar to the results of Georges et al comparing $AHI_{software}$ and manually scored AHI during three different ventilator settings in 10 patients with OHS.[218] They reported a sensitivity of 91% and a specificity of 100% of the ventilator software for detecting AHI > 10 scored with PSG. Also, in a study on 26 OHS-patients during NIV, a mean difference of 3.3 (limits of agreement -2.0 – 8.6) between the AHI manually scored with RPG and $AHI_{software}$ was reported.[259] Due to recent technological advances in the built-in monitoring systems in NIV devices, several other parameters from ventilator software can be used for monitoring long-term NIV. This includes the possibility to connect additional sensors to the device and remote monitoring and remote adjustment of ventilator settings. Further details on this is beyond the scope of this thesis, but can be found in a recent review. [267] The review states that further studies evaluating automated analyses of AHI by NIV devises are needed.

Obstructive hypopnea was by far the most frequent event in our study. An increase of EPAP has been shown to correct obstructive events during NIV in most cases,[131] even in patient with NIV-induced obstructive events in patients using an oro-nasal mask.[130] Therefore, in the presence of a high $AHI_{software}$, obstructive events could be suspected and an increase of EPAP

seems a reasonable option, especially in settings with limited access to RPG/PSG during NIV. However, treatment response should be evaluated. This evaluation should ensure that the new EPAP setting is adequate or, if not, can detect obstructive events caused by mechanism not responding to an increase in EPAP, as outlined in the background section. In setting with access to RPG during NIV, high $AHI_{software}$ can be used to select patients for this procedure.

6.7.3. Detection of patient-ventilator asynchrony

Neither the combined test panels nor ODI3% could accurate detect PVA. The rationale for detecting PVA during sleep is far from clear, at least in asymptomatic patients with good compliance. As outlined above, PVA may have limited impact on gas-exchange. PVA is claimed to have an impact on sleep quality,[135 153] but more recent studies have challenged this assumption.[203] A recent review concluded that it is unclear whether PVA causes sleep fragmentation.[202] Also, studies on prognostic impact of PVA in asymptomatic patients are lacking.

7. Conclusion and clinical implications

$PtcCO_2$ accurately reflects $PaCO_2$ in patients with chronic hypercapnic respiratory failure, and overnight instrumental drift of the $PtcCO_2$ sensor is low in most patients.
RPG reliably identifies and quantifies apnea-hypopnea and PVA during night-time NIV according to pre-specified scoring rules.

Implications:

- $PtcCO_2$ can be used to measure $PaCO_2$ in these patients, especially when ABG is difficult to perform. This can be in settings like sleep clinics, in the patient's home, or in patients in whom ABG is difficult to obtain.
- $PtcCO_2$ can be used to monitor $PaCO_2$ continuously during sleep in patients treated with long-term NIV.
- RPG can be used to detect prevalence and relevance of apnea-hypopnea and PVA during NIV.

Sleep hypoventilation is frequent in patients with chronic hypercapnic respiratory failure treated with long-term NIV. The frequency of sleep hypoventilation varies according to the definition used, and is lowest when using the AASM definitions.
A proposed combined test panel consisting of a combination of clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2 and assessment of compliance (from ventilator software) is not accurate in detecting sleep hypoventilation. In addition, overnight SpO_2 and daytime ABG cannot accurately detect sleep hypoventilation.

Implications:

- Overnight efficacy of NIV should be systematically monitored in order to detect sleep hypoventilation.
- Nocturnal $PtcCO_2$ should be implemented in the routine follow-up of in these patients.
- When $PtcCO_2$ is performed during sleep, reporting of CO_2 levels should not be limited to the AASM criteria for sleep hypoventilation. Recently published Norwegian guideline for objective measurements during sleep recommend the reporting of the following: Presence of hypoventilation according to AASM, $PtcCO_2$ in supine position prior to sleep, maximal $PtcCO_2$,% of recording time with $PtcCO_2$ > 7.3 kPa, > 6.7 kPa and > 6.5 kPa.[268]

Both high AHI and PVA are frequent during long-term NIV-treatment. PVA is not associated with poor gas-exchange. A proposed combined test consisting of combination of clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2 and assessment of compliance (from ventilator software) is not accurate in detecting these events. Also, overnight SpO_2 cannot accurately detect high AHI or PVA. $AHI_{software}$ in the device studied can detect high AHI, and obstructive hypopnea is by far the most frequent event.

Implications:

- Overnight efficacy of NIV should be systematically monitored in order to detect high AHI.
- The rationale for detecting PVA in asymptomatic patients remains unclear.
- In the presence of a high $AHI_{software}$, obstructive hypopnea should be suspected and a trial with increased EPAP could be implemented. RPG can be limited to non-responders to this treatment adjustment.
- RPG is needed if detection of PVA is warranted

In conclusion, the main hypothesis of this thesis, namely that clinical examination, a syntheses report from the ventilator software, nocturnal SpO_2 measurement, and daytime arterial blood gas analysis are sufficient as screening tools to detect sleep related respiratory problems in patients with chronic hypoventilation treated with NIV, was falsified.

In line with this, Janssens et al have recently published a modification of the SomnoNIV algorithm for monitoring nocturnal efficacy of long-term NIV.[269] The use of $PtcCO_2$ as a routine tool, the use of ventilator software for detecting abnormal AHI, and the need to perform RPG/PSG when PVA is suspected are underlined in this algorithm (Figure 13).

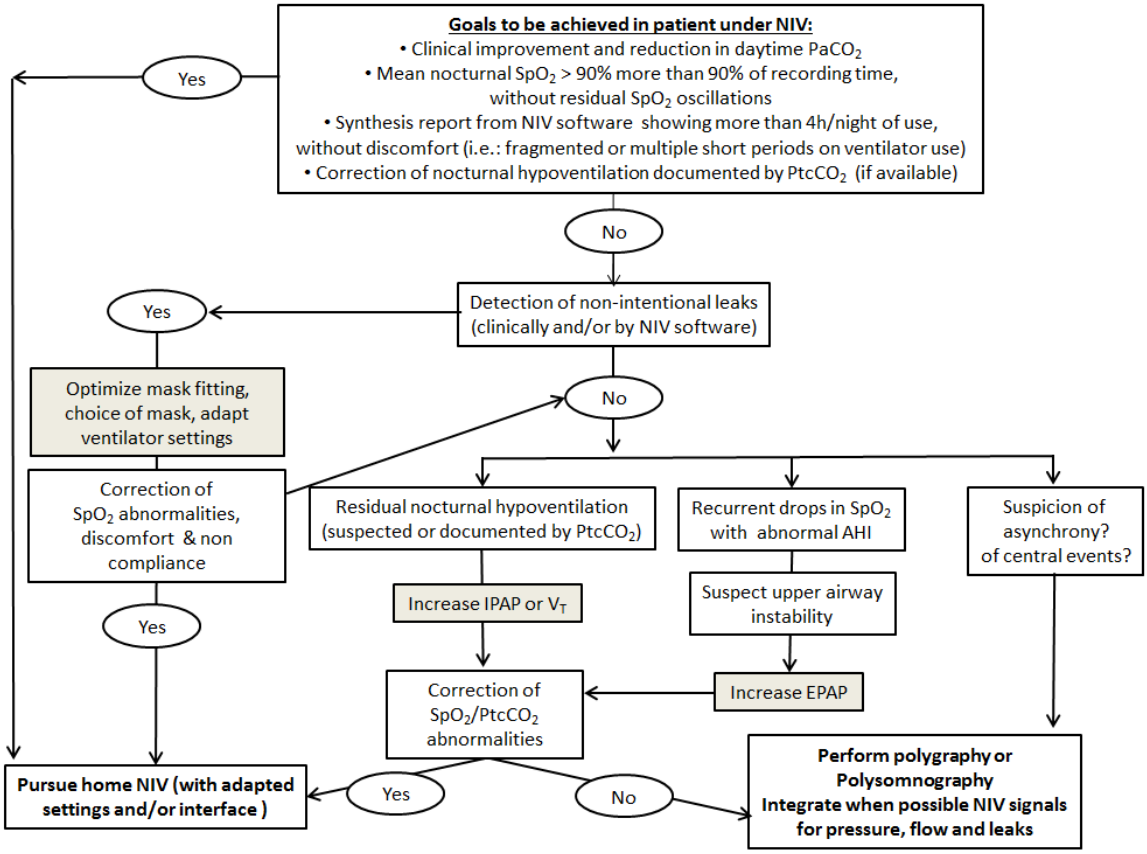

Figure 13. A proposed algorithm for the monitoring of nocturnal NIV. (Used with permission by Taylor and Francis Group: Previously published by Janssens et al. in Non-Invasive Ventilation and Weaning, 2nd Edition, eddied by Mark Elliott, Stefano Nana and Bernd Schönhofer[269]

8. Proposals for future studies

- To study the clinically relevant threshold for sleep hypoventilation measured with $PtcCO_2$
- To study the effect of correcting sleep hypoventilation on outcome like adherence to therapy, symptoms, health related quality of life, survival and morbidity.
- To study the feasibility of implementing $PtcCO_2$ in home monitoring of patients on long-term NIV.
- To validate the interrater agreement of scoring respiratory events during NIV, preferably by comparing scoring performed in different centres.
- To study the impact of PVA on adherence to therapy, symptoms, health related quality of life, survival and morbidity.
- To validate the cut-off levels found in our data for detecting high AHI with ventilator software.
- To study the accuracy of ventilator software for detecting high AHI in other devices than those used in this study.
- To explore the usefulness of machine learning in automatic data analysis of the large amount of data collected by NIV devices.

9. References

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10. Appendix

Papers I-III

Errata

I

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Validity of transcutaneous PCO_2 in monitoring chronic hypoventilation treated with non-invasive ventilation

Sigurd Aarrestad [a, b, *], Elin Tollefsen [c, d], Anne Louise Kleiven [a], Magnus Qvarfort [a], Jean-Paul Janssens [e, 1], Ole Henning Skjønsberg [a, f, 1]

[a] Department of Pulmonary Medicine, Oslo University Hospital, Ullevål, Oslo, Norway
[b] Norwegian National Advisory Unit on Long Term Mechanical Ventilation, Haukeland University Hospital, Norway
[c] Department of Thoracic Medicine, St. Olavs Hospital, Trondheim, Norway
[d] Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway
[e] Division of Pulmonary Diseases, Geneva University Hospitals, Switzerland
[f] University of Oslo, Oslo, Norway

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ABSTRACT

Background: Non-invasive ventilation (NIV) is an efficient treatment for patients with chronic hypercapnic respiratory failure (CRF), but requires regular monitoring to detect both diurnal and nocturnal residual hypercapnia.
The present study was designed to determine 1) whether transcutaneous PCO_2 ($PtcCO_2$) is a valid tool for monitoring $PaCO_2$ in this group of patients, and 2) if overnight instrumental drift of the $PtcCO_2$ sensor is clinically significant.
Methods: Sixty-seven patients with CRF on long term NIV were included. Arterial blood gases (ABG) were sampled from the radial artery during $PtcCO_2$ measurement. $PtcCO_2$ was recorded 2 min after ABG sampling. Instrumental drift was tested by measuring a gas of known CO_2 concentration after autocalibration of the sensor in the evening, and on the following morning.
Findings: $PaCO_2$ values ranged from 3·97 kPa to 9.0 kPa. Thirty-six (53%) patients were hypercapnic. Correlation between $PaCO_2$ and $PtcCO_2$ was highly significant ($r^2 = 0.9$, $p < 0.0001$), Bias (d) and SD of bias (s) were 0.23 kPa and 0.28 kPa respectively, with a minor underestimation of $PaCO_2$. Limits of agreement ($d \pm 2s$) were; −0.32; 0.79 kPa. None of the paired values of $PaCO_2/PtcCO_2$ had a difference exceeding 1 kPa. The mean drift of $PtcCO_2$ was 0.14 ± 0.54 kPa/8 h ($p = 0.04$; 95% CI: 0.01–0.27).
Interpretation: With the device tested, in stable patients under NIV-treatment for CRF, $PtcCO_2$ accurately reflects $PaCO_2$. $PtcCO_2$ can be used to monitor CO_2 overnight during NIV without any clinically significant drift.
Trial registration N°: NCT01845233.

1. Introduction

Non-invasive ventilation (NIV) is an efficient treatment for patients with chronic hypercapnic respiratory failure (CRF) due to neuromuscular diseases, (NMD), restrictive thoracic disorders (RTD), obesity hypoventilation syndrome (OHS), and central hypoventilation syndromes (CHS). Regular assessment of the efficacy of ventilation is recommended, usually including a daytime sampling of arterial blood gases (ABG) and nocturnal pulse oximetry [1,2].

The importance of correcting daytime arterial CO_2 ($PaCO_2$) in patients treated with long term nocturnal NIV has recently been stressed [3–6]. ABG analysis is the gold standard for measuring $PaCO_2$. However, ABG sampling requires expertise, can be painful and difficult to perform in patients with severe deformities or morbid obesity, and carries a risk of complications [7]. Furthermore ABG analysis is rarely available in sleep centres [8] or in patients' homes.

Abbreviations: ABG, Arterial blood gas; CRF, Chronic hypercapnic respiratory failure; NIV, Non-invasive ventilation; NMD, Neuro muscular diseases; OHS, Obesity hypoventilation syndrome; PaCO2, Arterial CO2; PtcCO2, Transcutaneous PCO2; RTD, Restrictive thoracic disorders; CHS, Central hypoventilation syndrome.

* Corresponding author. Oslo University Hospital, Ullevål, Postboks 4956 Nydalen, 0424 Oslo, Norway.
E-mail address: UXSIRR@ous-hf.no (S. Aarrestad).

[1] The authors have contributed equally to the conduction of the study.

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ABG analysis, although necessary, yields limited information. For instance, daytime ABG are poor predictors of nocturnal hypoventilation [9,10]. Sampling of ABG during sleep may detect nocturnal hypoventilation, but will not reflect variations of $PaCO_2$ related to sleep stages, position or mask leaks. Nocturnal pulse oximetry, although useful and easy to perform, may underestimate nocturnal hypoventilation [8,9,11], and it cannot discriminate nocturnal hypoventilation from other causes of hypoxaemia [2].

Transcutaneous monitoring of carbon dioxide ($PtcCO_2$) allows non-invasive and continuous measurements of $PaCO_2$. Although the accuracy of $PtcCO_2$ has been a subject of debate, $PtcCO_2$ monitors have become easier to use in clinical practice [12] and have shown acceptable agreement with $PaCO_2$ in a geriatric population [13], in patients with acute dyspnoea [14], patients with ALS [15], patients with severe obesity [16] and during cardiopulmonary exercise testing [17]. Conversely, studies conducted at emergency departments [18,19], during surgery [20,21] and in ICUs [20] report conflicting or poorer results, indicating that validity of $PtcCO_2$ may depend on the population studied and the clinical setting in which it is used. The small number of studies conducted in patients with CRF treated with NIV have either used older $PtcCO_2$ devices [22,23] or included a limited number of patients [24–26].

Although continuous $PtcCO_2$ measurement for 5–8 h is well tolerated, without causing cutaneous lesions, one concern is the overnight drift of the $PtcCO_2$ signal. Most studies addressing this issue include a limited number of patients, and both the methods used to measure the instrumental drift and the results differ considerably [22,23,25–30]. The uncertainty regarding $PtcCO_2$ drift is reflected in the conflicting recommendations regarding drift correction after nocturnal $PtcCO_2$ recordings [8,31,32]. This cumbersome procedure implies *in vivo* calibration with arterial or capillary blood gas sampling, adding discomfort for the patient and limiting its use in sleep centres and in patients' homes.

The present study was designed to determine 1) whether $PtcCO_2$ is a sufficiently accurate and precise tool for monitoring PaCO2 during routine follow-up visits in a large group of patients with CRF treated with long term NIV, and 2) if, in this setting, overnight drift of the $PtcCO_2$ sensor is clinically significant.

2. Materials and methods

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics, NO = 2012/1142. Written informed consent was obtained from all participants.

2.1. Patients

Patients with CRF due to NMD, RTD, OHS or CHS on long term NIV for a minimum of 3 months and scheduled for a regular follow-up visit were included. Exclusion criteria were: age below 18 years, inability to co-operate, hospitalization due to an acute exacerbation or change of NIV-treatment <3 months before inclusion.

2.2. Measurements

Daytime ABG sampling from the radial artery was performed after the patients had been seated and were breathing room air for at least 30 min and then immediately analysed (COBAS B 221, Roche, Germany). Daytime and overnight $PtcCO_2$ was measured with a TCM Tosca® with the Sensor 92 (Radiometer, Denmark) attached via a single-use ear clip to the patients' earlobe and probe temperature set at 43 °C [33]. Auto-calibration, membrane replacement, temperature and metabolic correction were performed according to manufacturer's recommendations. Overnight $PtcCO_2$ signal was integrated to an online sleep recording system (Embletta Gold, Embla, Broomfield, USA). The $PtcCO_2$ sensor measures changes in pH produced by CO_2 diffusing through the skin to a buffer solution in the electrode. In order to measure the instrumental drift of the TCM Tosca capnograph, repeated ex vivo measurements of a calibration gas with a known CO_2 concentration were performed. The sensor was attached to a test unit containing the calibration gas and the PCO_2 was recorded. (Calibration Gas mixture for Blood Gas Analyzers, 11·2% CO_2, balanced N_2, Radiometer, Denmark).

2.3. Study design

Patients were hospitalized for their regular NIV follow-up. Prior to daytime ABG sampling, performed between 12:00 and 2:00 PM, $PtcCO_2$ was monitored continuously for at least 22 min to allow stabilisation of $PtcCO_2$ readings, as recommended by the manufacturer. Daytime $PtcCO_2$ was defined as the $PtcCO_2$ value recorded 2 min after ABG sampling [28,34]. The same sensor membrane was used during the night-time measurements. During overnight $PtcCO_2$ recordings, the signal quality was checked at least hourly. The instrumental drift was assessed by a repeated ex vivo calibration test. PCO_2 was measured using a gas mixture with a known CO_2 concentration. This procedure was performed at 11:00 PM after auto-calibration of the sensor, before attaching the sensor to the patient, and repeated at 7:00 AM before recalibration of the sensor.

2.4. Statistics

Correlation between $PtcCO_2$ and $PaCO_2$ was assessed by calculating Pearson's coefficient of correlation. Comparison between $PtcCO_2$ and $PaCO_2$ was performed according to Bland and Altman: mean difference between $PtcCO_2$ and $PaCO_2$ (d: bias), standard deviation of d (s: precision) and limits of agreement (LA = d ± 2s) were reported. A maximum bias of 1 kPa was considered as acceptable based on previous studies [20,25–27]. Paired sample t-tests were used to determine if the instrumental drift was significantly different from zero. P-values below 0.05 were considered significant. SPSS Software for Windows and MedCalc version 14.10.2 were used for statistical analysis.

2.5. Role of the funding source

The study was funded by the Norwegian National Advisory Unit on Long Term Mechanical Ventilation, Haukeland University Hospital and the Norwegian Neuro Muscular Diseases Foundation. The funders had no involvement in study design, in collection, analysis and interpretation of data, in writing of the report, or in the decision to submit the paper for publication.

3. Results

All patients with long term NIV scheduled for a regular follow-up visit at the Department of Pulmonary Medicine of Oslo University Hospital Ullevål between April 2013 and May 2014 were evaluated: 95 patients met the inclusion criteria. Twenty-eight patients were not included (Fig. 1). The remaining 67 patients were treated with NIV for OHS (n = 16), NMD (n = 36), CHS (n = 5) or RTD (n = 10). Main characteristics of patients are given in Table 1.

3.1. Comparison between transcutaneous and arterial PCO_2

Paired samples of ABG and $PtcCO_2$ were analysed in all 67 patients. $PaCO_2$ values ranged from 3.97 kPa to 9.0 kPa. Correlation between $PaCO_2$ and $PtcCO_2$ was highly significant ($r = 0.95$ $p < 0.0001$). Ninety percent of the variability of $PtcCO_2$ was

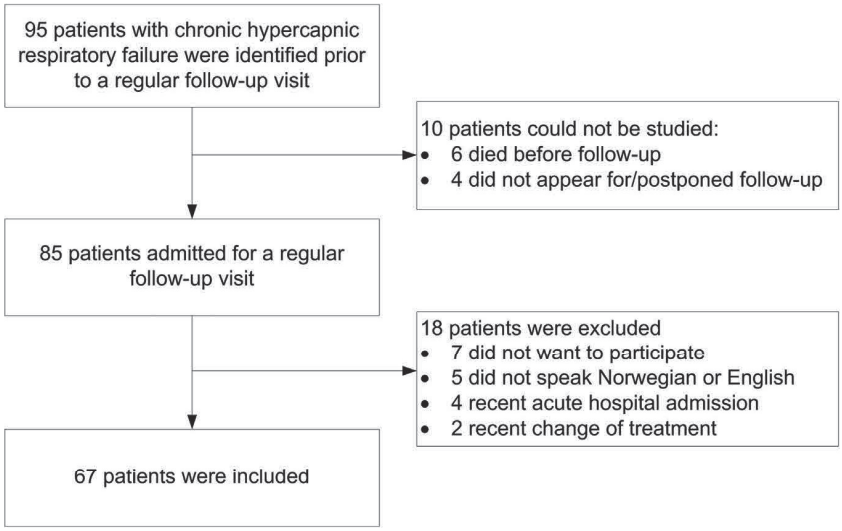

Fig. 1. Flow chart showing numbers of identified patients and reasons for not participating.

explained by changes in $PaCO_2$ ($r^2 = 0.9$, $p < 0.0001$). Bias (d) and SD of bias (s) were 0.23 kPa and 0.28 kPa, respectively, with $PtcCO_2$ on average slightly underestimating $PaCO_2$. Limits of agreement ($d \pm 2s$) were; −0.32; 0.79 kPa (Fig. 2). None of the paired values of $PaCO_2$/$PtcCO_2$ differed by more than 1 kPa.

Mean $PaCO_2$ was 6·1 kPa (SD 0.9). Thirty-six (53%) of the patients were hypercapnic ($PaCO_2 > 6.0$ kPa), while none of the patients had a respiratory acidemia (pH < 7.3) and only 2 had a pH < 7.34. Agreement between $PaCO_2$ and $PtcCO_2$ in the sub-group of patients with a $PaCO_2 > 6.0$ kPa did not differ from that of the entire group; bias was 0.3 kPa, and limits of agreement were: −0.28; 0.84 kPa.

3.2. Instrumental drift of $PtcCO_2$

One patient disconnected the sensor prior to the morning measurement, and one recording showed an obvious technical error (morning $PtcCO_2$: 15 kPa). Thus, 65 paired measurements were analysed.

In six patients there was an intermittent loss of $PtcCO_2$ signal during the night: in two patients the sensor fell off and had to be reconnected (one needed a new ear clip), and in four patients there was probably a temporary displacement of the sensor, which corrected itself without interference from the staff. None of these incidents required recalibration of sensor or change of membrane.

The mean drift of $PtcCO_2$ (difference between morning and evening $PtcCO_2$ readings of 11.2% CO_2 gas sample) was 0.14 ± 0.54 kPa/8 h ($p = 0.04$; 95% CI: 0.01–0.27) (Fig. 3). Of the 3 measurements showing a difference >1 kPa/8 h, 2 had a temporary loss of $PtcCO_2$ signal.

Table 1
Main characteristics of study population (N = 67).

Age, years	57.7 ± 19.2
Male/female, n	35/32
Duration of NIV, months (range)	54.4 (3–324)
BMI, kg/m^2	28.1 ± 7.7
$PaCO_2$, kPa[a]	6.1 ± 0.9
PaO_2, kpa[a]	9·4 ± 1.5
pH	7.38 ± 0.04
FEV_1, % of predicted value	47 ± 24
FVC, % of predicted value	51 ± 26

Values presented as Mean ± SD, unless specified otherwise.
[a] Values reported were sampled in patients seated and breathing room air for at least 30 min.

4. Discussion

To our knowledge, this is the first study to compare arterial with transcutaneous values of PCO_2 and to measure overnight instrumental drift of $PtcCO_2$ in a large group of patients treated with NIV for CRF. Our results show that daytime $PaCO_2$ values were strongly correlated with $PtcCO_2$, over a wide range of $PaCO_2$ values, with a low bias and clinically acceptable limits of agreement. Importantly, none of the paired values of $PaCO_2 - PtcCO_2$ had a difference exceeding 1 kPa. Our data also show that $PtcCO_2$ can be used for overnight monitoring of NIV, most often without any clinically significant drift: overnight drift exceeded 1 kPa in 3 cases only. Finally, few problems related to the measurements occurred: one recording showed an obvious technical error, and 2 patients required reconnection of the sensor, without recalibration.

Bias (the mean of differences between $PaCO_2$ and $PtcCO_2$) was

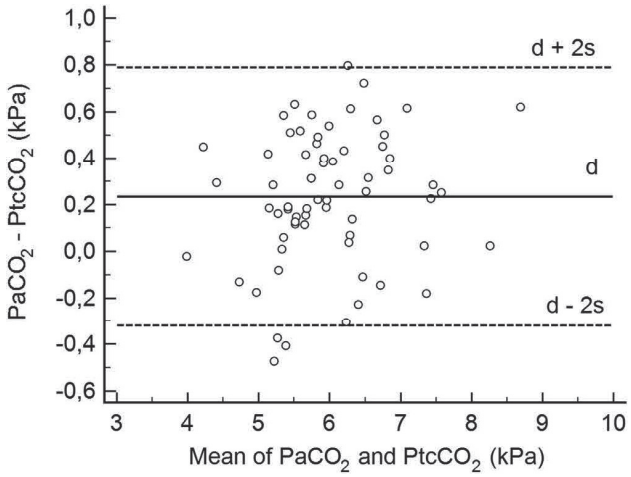

Fig. 2. Bias and limits of agreement of $PtcCO_2$ compared with $PaCO_2$ (n = 65).

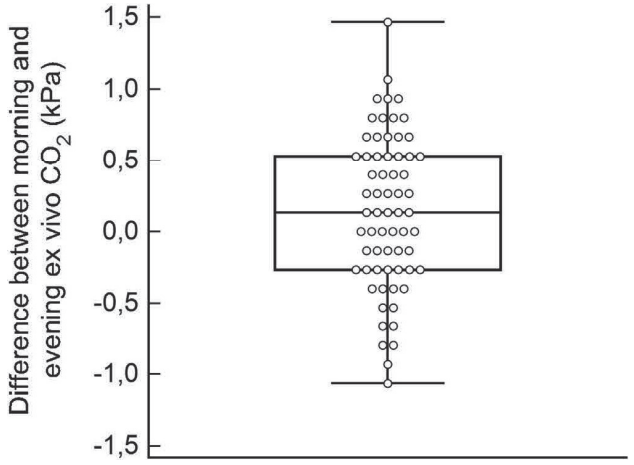

Fig. 3. Box-and-whisker plot of the difference between each paired measurement of ex vivo CO_2 testing. (n = 65). The central box represents median and 25 to 75 percentile values; 0.13 kPa and −0.27–0.53 kPa. The horizontal line extends from the minimum to the maximum value.

low (0.26 kPa), and Δ($PaCO_2$-$PtcCO_2$) never exceeded the previously defined clinically acceptable range of ±1 kPa [26,27]. Limits of agreement were also within values reported as acceptable: ±1.33 kPa [18], ±1.0 kPa [26] and ±0.67 kPa [14]. This is comparable with studies performed on other patient groups [13,15–17,35]. Patients included in the current study were in a stable clinical condition, without severe respiratory acidemia, hemodynamic instability, hypothermia, profound skin vasoconstriction or vasopressor treatment, factors which have all been associated with higher bias values and/or wider limits of agreement [18,20,36]. Indeed, in a study of 53 critically ill ICU patients, Bendjelid et al. compared more than 400 paired measurements of $PaCO_2$ and $PtcCO_2$ [27]: 19% of all paired measurements were defined as discordant, i.e. with a Δ($PtcCO_2$-$PaCO_2$) exceeding 1 kPa. The temperature of the sensor has also been shown to influence the accuracy of $PtcCO_2$ measurements. Nishiyama et al. suggested that sensor temperature should be at least 43 °C [33] as in the current study. Higher probe temperatures may indeed increase local hyperaemia in the capillary bed and thus have a positive impact on bias and limits of agreement of $PtcCO_2$; conversely, the poorer results found in previous studies may have been influenced by the use of lower sensor temperatures [20,27,36]. However, several studies using a probe T° of 42 °C showed similar results to ours [15–17,25], suggesting that other factors such as technical improvements in devices may also play an important role. Since our study did not compare different temperature settings and different sensors, we cannot quantify the importance of these factors.

Previous studies of $PtcCO_2$ in patients with chronic hypoventilation most often included a limited number of patients, few non-COPD patients, and were conducted with older devices or during NIV. The only study of stable patients with chronic hypoventilation breathing spontaneously included 12 patients (6 non-COPD), and showed both a low bias and low limits of agreement [24]. However, accuracy decreased and limits of agreement increased with higher CO_2-values (>7.3 kPa), a finding also described in other studies [22,23]. In our data, accuracy and limits of agreements were unaffected by increasing levels of $PaCO_2$. This discrepancy could be due to the low number of patients included or the devices assessed in the studies mentioned above [22–24]. Another study compared overnight $PtcCO_2$ with repeated ABG from an indwelling catheter in 15 patients: bias was low, but with wide limits of agreement [26], probably caused by "outliers" amongst a low number of measurements. Our results are in agreement with an overnight study of 24 patients with CRF (9 non-COPD patients) by Storre et al., reporting a good agreement between capillary ABG and $PtcCO_2$ during NIV. In two of the three devices tested (Sentec DM and Tosca 500), discrepancies exceeding the clinically acceptable threshold of 1 kPa were rare (1–2% of the recordings). Bias was low and limits of agreement were unchanged in the sub-group of measurements with a $PaCO_2$ > 6.7 kPa [25]. A compilation of studies reporting on $PtcCO_2$ performance is summarized in Table 2 [37–53] (For details see Supplementary data).

ABG remain the gold standard for detecting daytime hypercapnia. However, our data suggest that PtcCO2 can be a valid substitute in hemodynamically stable patients, and prove to be particularly useful in settings were ABG sampling is difficult to perform, such as sleep clinics or home monitoring of long term mechanical ventilation. A critical requirement for obtaining reliable $PtcCO_2$ measurements is appropriate handling and knowledge of the equipment and procedure. Our team has long term experience with use of the $PtcCO_2$ device, probably contributing to the low number of technical problems encountered.

The second aim of the investigation was to study the instrumental drift of the $PtcCO_2$ sensor during overnight NIV-treatment. Mean drift was 0.02 kPa/hrs. Only one of the paired measurements showed an overnight drift exceeding 1.33 kPa, while three exceeded 1 kPa [27]. Thus, our study confirms that the vast majority of overnight $PtcCO_2$ recordings were performed without any clinically significant drift.

Instrumental drift during $PtcCO_2$ measurements has been evaluated using various methods (Table 2). In an 8 h sleep study of 6 stable ICU patients, change in bias over time was used as a measurement of drift [30]. $PaCO_2$-$PtcCO_2$ difference increased linearly from 0.22 kPa to 0.72 kPa, suggesting an instrumental drift. Using the same methodology on a limited number of patients, 4 studies found lower levels of drift [16,22,23,26]. Another study performed on 29 healthy individuals found no significant drift during continuous 4 h $PtcCO_2$ recordings [45].

Two studies evaluated instrumental drift with a method similar to ours. Storre et al. calculated the total drift as the difference between 2 in vitro calibration measurements performed at the beginning of $PtcCO_2$ monitoring and after 4 h in 10 patients [28], showing a significant drift of 0.17 kPa/h. Conversely, in an 8 h-overnight study of 24 patients using three different devices (SenTec DM, Tosca 500 and TCM4 TINA), a low drift of $PtcCO_2$ was observed [25]. The results of this study, using modern devices, are in concordance with ours. Recent developments of $PtcCO_2$ devices may have contributed to improved results when compared to studies using older devices. Although newer devices still measure CO_2 by determining changes in pH of an electrolyte solution in the sensor separated from the skin by a permeable membrane, developments have been made both in the algorithm of the devices and the sensor [12]. For instance, modern algorithms allow automatic correction for the anaerobic factor and for the metabolic constant, and sensors are smaller and better protected. Overall, results of the current and other recent studies show good agreement between $PtcCO_2$ and $PaCO_2$ in patients with chronic hypoventilation, questioning the need for an initial *in vivo* calibration (i.e.: by ABG). In addition, the low instrumental drift diminishes the need for an *in vivo* or an ex vivo calibration at the end of an overnight monitoring. Thus, overnight monitoring of $PtcCO_2$ can be performed reliably in settings where ABG are not readily available, with a low percentage of erroneous readings.

A few problems related to the overnight measurements of PtcCO2 were observed. In one patient, an obvious technical error occurred. We did not observe any conflict between the interface banding (mask) and the PtcCO2 sensor connected to the earlobe.

Table 2
Compilation of clinical data from 2005 to 2014 reporting on sensor temperature, bias, limits of agreement and drift of transcutaneous CO_2.[e]

Author	Year	No. of patients	Capnograph	Temperature of sensor °C	Patient group/clinical setting	Bias kPa[a,b]	Limits of agreement kPa[a,b]	Drift methods/hr	Drift/hrs kPa[c]
Chronic respiratory failure treated with long term mechanical ventilation									
Aarrestad	2015	67	TCM Tosca	43	Breathing spontaneously/ NIV	0·2	−0.3–0.8	Ex vivo/8 h	0·02
Storre [25]	2011	24	TCM4 Tina	42	NIV/sleep study	−0·2	−2.1–1.7	Ex vivo/8 h	−0·05
		24	SenTec	42	NIV/sleep study	0·1	−0.6–0.9	Ex vivo/8 h	0·01
		24	Tosca 500	42	NIV/sleep study	0·1	−0.9–1.1	Ex vivo/8 h	−0·07
Hazenberg [26]	2011	15	Tosca	42	NIV/ICU	−0·4	−1.3–0.5	Change in bias/8 h	n.s
Cuvelier [24]	2005	12	TCM3 Tina	44	Breathing spontaneously	0·1	−0.7–0.9	n.a.	
Acute medical illness/emergency department									
Delemere [14]	2012	48	Tosca 500	42	Acute dyspnea/ED	0·1	−0.5–0.7	n.a.	
Gancel [48]	2011	21	Tosca 500	42	ARF/ED	0	−0.8–0.8	n.a.	
Kelly [18]	2011	46	TCM4	n.a	ARF/NIV/ED	0·8	−1.3–3.0	n.a.	
Nicolini [35]	2011	80	Tosca	n.a	ARF/NIV/IRCU	0·1	−0.5–0.7	n.a.	
Perrin [19]	2011	24	Tosca 500	n.a	ARF/ED	0	−0.5–0.5	n.a.	
MCVicar [49]	2009	49	Tosca 500	42	Acutely ill/ED	0	−0.9–0.9	n.a.	
Storre [28]	2007	10	SenTec	42	ARF on CRF/NIV/Ward	0·6	−0.5–1.8	Ex vivo/4 h	0·17
Cox [51]	2005	22	Tosca	42	ARF/NIV/IRCU	0·1	−0.6–0.9	n.a	
Surgery/intra and postoperative care									
Liu [21]	2014	21	TCM4	44	Laparoscopic/bariatric	0·1	−0.2–0.5	n.a.	
Nishiyama [37]	2011	10	Sentec	42	Abdominal	0·2	−1.0–1.5	n.a.	
		10	TCM4	43		0·2	−0.6–0.9	n.a.	
De Oliveira [38]	2010	40	Tosca 500	42	Hysteroscopy	−0·2	−1.3–0.8	n.a.	
Xue [39]	2010	16	SenTec	n.a	Prolonged laparoscopic	−0·1	−1.0–0.7	n.a.	
Chakravathy [40]	2010	32	TCM4	43	Cardiac	−0·2	−1.2–0.9	n.a.	
Hirabayashi [41]	2009	15	TCM3	44	Abdominal/ventilated	0	−0.7–0.6	n.a.	
		24	TCM3	44	Abdominal/postoperative	−0·1	−1.2–1.0	n.a.	
Fanelli [53]	2008	13	SenTec	n.a	Major surgery/ postoperative	0·5	−0.7–1.8	n.a	
Bolliger [20]	2007	122	SenTec	42	Cardiac/thoracic	−0·6	−2.6–1.5	n.a	
		122	Tosca 500	42		−0·3	−1.7–1.1		
Bendjelid [27]	2005	55	Tosca	42	Major surgery/critical ill	−0·2	−1.8–1.4	n.a	
Stein [50]	2006	30	Tosca 500	42	Vascular/abdominal/ thoracic	−0·7	−1.7–0.2	n.a.	
Nishiyama [47]	2006	5	TCM4	43	Abdominal	0·1[d]	−1.2–1.3	n.a.	
Intensive care unit									
Berlowitz [30]	2011	6	TCM3 Tina	43	Stable	−0·2	−0.7–0.2	Change in bias/8 h	−0·06
Hinkelbein [42]	2008	34	TCM4	41–42	Critically ill/transport	0·1	−1.9–2.1	n.a.	
Johnson [43]	2008	38	Sentec	42	Stable/ventilated/LTAC	0·1	−1.0–1.1	n.a.	
Bolliger [20]	2007	50	SenTec	42	Critical ill/surgery	−0·4	−1.9–1.2	n.a	
		50	Tosca	42	Critical ill/surgery	−0·4	−1.5–1.0		
Rodriguez [36]	2006	50	SenTec	42	Critically ill	0	−1.3–1.2	n.a	
Senn [44]	2005	18	Tosca	42	Critically ill	−0·4	−1.3–0.5	n.a.	
Other patients groups/settings									
Rafiq [15]	2012	40	Tosca 500	42	ALS	−0·1	−0.7–0.6	n.a.	
Randerath [45]	2010	29	Tosca 500	42	Healthy subjects/Ward	−0·8	−2.4–0.8	Change in bias/4 h	0·02
Fuke [52]	2009	9	Tosca	42	Healthy/experimental	0·2	−0.5–1.0	n.a.	
Maniscalco [16]	2008	35	Tosca	42	Obese patients/Ward	−0·2	−0.5–0.1	n.a.	
Stege [17]	2009	21	Tosca 500	42	Respiratory diseases/CPET	0	−0.8–0.7	n.a.	
Parker [46]	2007	48	Tosca	42	Respiratory diseases/ Ward	0	−1.4–1.3	n.a.	
Janssens [13]	2005	40	TCM3 Tina	43	Geriatric patients	0	−1.1–1.1	n.a.	

n.a. = Not available from original publication; ED = Emergency department; ARF = Acute respiratory failure; NIV = Non-invasiv ventilation; CPET = Cardiopulmonary exercise test; IRCU = Intermediate respiratory care unit; LTAC = Long term acute care facility; CRF = Chronic respiratory failure; n.s = No significant drift.

[a] Bias = $PaCO_2$-$PtcCO_2$.

[b] In studies including drift measurements, baseline and drift uncorrected values are displayed if available.

[c] Studies with drift measurement ≥4 h.

[d] Data from chest placement.

[e] Based on a systematic Pub Med search for literature published between 2005 and March 2015.

However displacement of the interface banding due to patient movement may have contributed to the intermittent loss of signal seen in 6 patients. If this problem occurs, an alternative location for the sensor could be a solution, preferably the upper chest [47]. An overnight drift of more than 1 kPa was observed in 3 patients. In 2 of these patients an intermittent loss of $PtcCO_2$ signal was observed. Recalibration of the sensor after these incidents would probably have improved the results in these cases. Visual inspection of the overnight graphic display in addition to absolute values of $PtcCO_2$ could help the clinician in detecting these occasional events and in interpreting the results. Figs. 4–5 show examples of graphic displays of overnight $PtcCO_2$.

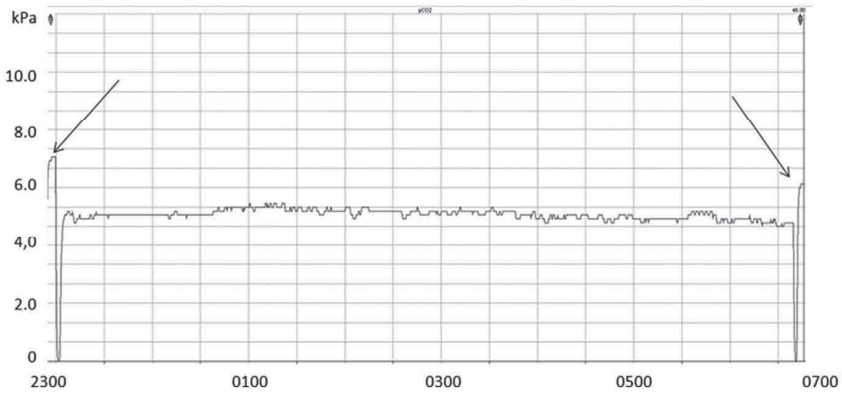

Fig. 4. 8 h overnight normal $PtcCO_2$ tracing. Arrows show ex vivo measurements.

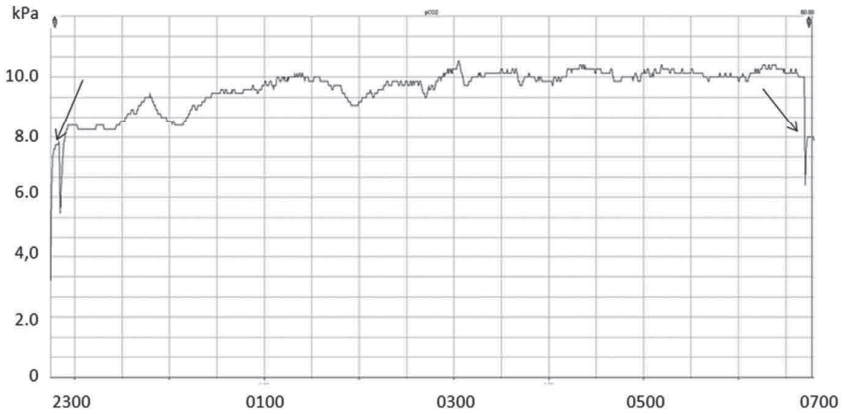

Fig. 5. 8 h overnight $PtcCO_2$ tracing; severe hypercapnia with an increase overnight. Arrows show ex vivo measurements.

There are some limitations to our study. We only evaluated one of the commercially available $PtcCO_2$ devices and only one probe position i.e. the earlobe. Thus, the relevance of our findings is theoretically limited to this equipment and probe position. However, our results are similar to those presented by Storre et al. [25] using the Tosca 500 with a chest probe instead of an earlobe probe. The Tosca 500 uses an identical sensor, algorithm, and CO_2 detection method as the TCM Tosca. These authors also obtained similar results using the SenTec device [25]. The wider limits of agreement found using the TCM4 Tina may be due to the lower sensor temperature used [25]. Finally, Cuvelier et al. using the TCM3 Tina with the sensor temperature set to 44 °C, reported similar bias and limits of agreement as in our study [24].

5. Conclusions

In a large group of patients with a variety of diseases causing chronic hypercapnic respiratory failure, we found that the accuracy of transcutaneous measurement of CO_2 tension was acceptable for estimating $PaCO_2$ over a wide range of CO_2 levels. In addition, the overnight instrumental drift of the $PtcCO_2$ sensor was minor, questioning the necessity of systematic *in vivo* or ex vivo calibration.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.01.017.

Author contributions

S.A. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.A, A.L.K. and M.Q. contributed substantial to acquisition of data. S.A, E.T, A.L.K, M.Q, J.J. and O.H.S. contributed substantial to the study concept and design, data interpretation, critical revision of the manuscript for important intellectual content, and final approval of the manuscript.

Declaration of interests

S.A, E.T, A.L.K, M.Q, J.J. and O.H.S. have no potential conflicts of interest with any companies/organizations whose products or services may be discussed in this article.

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Other contributions

This study was performed at Oslo University Hospital Ullevål, Department of Pulmonary Medicine.

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Supplementary data

Literature search for data presented in table 2.

A Pub Med search for papers studying the relationship between arterial ($PaCO_2$) and transcutaneous values of PCO_2 ($PtcCO_2$), including at least results on bias and limits of agreement was performed with the following search items:

>transcutaneous carbon dioxide monitor OR transcutaneous carbon dioxide,

>monitors OR transcutaneous carbon dioxide monitoring OR transcutaneous

> CO_2 monitor OR transcutaneous CO_2 monitors OR transcutaneous CO_2

>monitoring OR (Tosca AND (transcutaneous OR carbon OR CO_2)) OR ("Blood

>Gas Monitoring, Transcutaneous"[Mesh] AND ("Carbon Dioxide"[Mesh] OR

>Tosca OR transcutaneous carbon dioxide OR transcutaneous CO_2))

The search was performed on March 4, 2015 covering studies on adults, human and published between 2005 and March 2015. Eight hundred and seventy-seven articles were identified. All titles were evaluated and 76 abstracts and 51 articles were read. Thirty-four articles were included in the compilation in table 2.

II

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Sleep related respiratory events during non-invasive ventilation of patients with chronic hypoventilation

Sigurd Aarrestad[a,b,c,*], Magnus Qvarfort[a], Anne Louise Kleiven[a], Elin Tollefsen[d,e], Ole Henning Skjønsberg[a,c,1], Jean-Paul Janssens[f,1]

[a] Department of Pulmonary Medicine, Oslo University Hospital, Ullevål, Norway
[b] Norwegian National Advisory Unit on Long Term Mechanical Ventilation, Haukeland University Hospital, Norway
[c] University of Oslo, Oslo, Norway
[d] Department of Thoracic Medicine, St. Olavs Hospital, Trondheim, Norway
[e] Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway, St. Olavs Hospital, Postboks 3250 Sluppen, 7006 Trondheim, Norway
[f] Division of Pulmonary Diseases, Geneva University Hospitals, Switzerland, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland

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ABSTRACT

Background: Non-invasive ventilation (NIV) is increasingly used in the treatment of patients with chronic hypercapnic respiratory failure (CRF). Residual sleep related respiratory events under NIV such as obstructive or central apnea/hypopnea (AH), or patient-ventilator asynchrony (PVA), may compromise treatment efficacy and/or comfort.

Aims of study: 1/to quantify the frequency and describe the types of both AH and PVA in a large group of stable patients with CRF during night-time NIV; 2/to analyze the influence of these events on overnight pulse oximetry and transcutaneous CO_2 and 3/to assess interrater agreement in identifying and quantifying AH and PVA.

Methods: We quantified AH and PVA by performing sleep polygraphy in 67 patients during elective follow-up visits. Traces were scored by two trained physicians.

Results: Residual AH were frequent: 34% of the patients had an AH Index > 5/hour, with obstructive hypopnea being the most frequent event. In addition, 21% of the patients had PVA > 10% of total recording time. No correlation was found between respiratory events and overnight hypercapnia. The intraclass correlation coefficients for scoring AHI and time with PVA were 0.97 (0.94–0.98) and 0.85 (0.75–0.91) respectively.

Conclusions: Residual respiratory events are common in patients treated with long term NIV for chronic hypercapnic respiratory failure and can be scored with a very high interobserver agreement. However, these events were not associated with persistent nocturnal hypercapnia; thus, their clinical relevance has yet to be clarified.

ClinicalTrials.gov registration N°: NCT01845233.

1. Introduction

Non-invasive ventilation (NIV) is increasingly used in the treatment of patients with chronic hypercapnic respiratory failure (CRF) [1]. Sleep related respiratory events, such as obstructive or central apnea/hypopnea (AH), or patient-ventilator asynchrony (PVA) under NIV in chronic care settings have been reported [2–6]. Upper airway obstruction during sleep is common in obesity hypoventilation and in many neuromuscular diseases [7–10], and may persist under NIV due to inappropriate ventilator settings. NIV *per se* may also trigger undesired

Abbreviations: NIV, Non-invasive ventilation; CRF, Chronic hypercapnic respiratory failure; AH, Apnea/hypopnea; PVA, Patient-ventilator asynchrony; AASM, American Academy of Sleep Medicine; SpO_2, Pulse oximetry; $PtcCO_2$, Transcutaneous CO_2; NMD, Neuromuscular diseases; RTD, Restrictive thoracic disorders; OHS, Obesity hypoventilation syndrome; CHS, Central hypoventilation syndrome; PG, Sleep polygraphy; PWA, Photoplethysmographic pulse wave amplitude; A, Apnea; H, Hypopnea; OH, Obstructive hypopnea; CH, Central hypopnea; TRT, Total recording time; AHI, Apnea Hypopnea Index; HI, Hypopnea index; CHI, Central hypopnea Index; OHI, Obstructive hypopnea index; TDI, Total desynchronization index; PVAI, Patient-ventilator asynchrony index; PVA%, Percentage of total recording time with patient-ventilatory asynchrony; ICC, intraclass correlation coefficients IQR; IE, Inspiratory effort

* Corresponding author. Oslo University Hospital Ullevål, Postboks 4956 Nydalen, 0424 Oslo, Norway.
E-mail addresses: UXSIRR@ous-hf.no (S. Aarrestad), UXQVMA@ous-hf.no (M. Qvarfort), ANKLEI@ous-hf.no (A.L. Kleiven), elin.tollefsen@ntnu.no (E. Tollefsen), o.h.skjonsberg@medisin.uio.no (O.H. Skjønsberg), Jean-Paul.Janssens@hcuge.ch (J.-P. Janssens).
[1] The authors have contributed equally to the conduction of the study.

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respiratory events [11,12], such as recurrent decreases in ventilatory drive leading to central apnea-hypopnea with or without glottic closure [13,14].

PVA is a mismatch between the patient's respiratory neural pattern (respiratory rate, initiation and termination of inspiration) and pressurization delivered by the ventilator. Ineffective efforts, double triggering or auto triggering are examples of events described both in the ICU and during long-term mechanical ventilation [2,5,13,15–17]. These events may be due to leaks, upper airway instability, intrinsic positive end-expiratory pressure, devices *per se*, or inappropriate ventilator settings [17–19].

NIV aims to improve quality of life and to reduce morbidity and mortality; however, residual respiratory events under NIV may negatively affect survival, sleep quality, gas exchange, tolerance and adherence to treatment and patients' symptoms [2,10,13,15,20]. Thus, in the follow-up of NIV patients, it seems appropriate to detect these events in order to optimize ventilator settings.

Few studies, all with a limited number of patients, have quantified residual obstructive and central events in patients undergoing long term NIV. Both types and frequencies of events vary considerably [2–4,10,21], and only one study [2] used scoring criteria adapted from the American Academy of Sleep Medicine (AASM) [22]. Several studies have shown that PVA frequently occurs during NIV in acute care [11,16–18]. Studies of PVA in CRF patients during sleep, however, are limited and report conflicting results [2,3,5,6].

Scoring of sleep related respiratory events in patients using NIV is time consuming, requires expertise, and has been described as the most demanding task in the analysis of sleep related respiratory problems [23]. Yet, interrater agreement in scoring these events is poorly documented [5,24].

Aims of this investigation were therefore: 1/to quantify the frequency and describe the types of both AH and PVA in a large group of stable patients with CRF during night-time NIV; 2/to analyze the influence of these events on overnight pulse oximetry (SpO_2) and transcutaneous CO_2 ($PtcCO_2$) and 3/to assess interrater agreement in identifying and quantifying AH and PVA.

2. Materials and methods

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics, NO = 2012/1142. Written informed consent was obtained from all participants.

2.1. Patients

We included patients with CRF due to neuromuscular diseases (NMD), restrictive thoracic disorders (RTD), obesity hypoventilation syndrome (OHS) and central hypoventilation syndrome (CHS) who had been treated with long term NIV for a minimum of 3 months and were scheduled for a regular follow-up visit. Exclusion criteria were: age under 18 years, inability to co-operate, hospitalization due to an acute exacerbation or modification of NIV treatment within the last 3 months.

2.2. Ventilator setting

The majority of the patients started NIV in an elective setting. Patients had been admitted for diagnostic evaluation and NIV titration normally for 3-5 days. A mandatory back-up rate was always used and titration of inspiratory support and expiratory positive airway pressure were set with the aid of nocturnal monitoring with pulse oximeter, transcutaneous CO_2 and respiratory polygraphy. A further description of the ventilator titration algorithm is available in the Norwegian national guidelines for long term mechanical ventilation [38]. The included patients used the following mechanical ventilators: ResMed devices: VPAP III ST-A (n = 7), S8 VPAP IV ST (n = 20), S9 VPAP ST (n = 15), S9 VPAP ST-A (n = 5), Stellar 150 (n = 8) and Elisée 150 (n = 2). Philips Respironics devices: BIPAP AVAPS (n = 9) and BIPAP SYNCHRONY (n = 1).

2.3. Measurements

Patients were hospitalized overnight for their regular NIV follow-up visit. Data memorized by ventilator software, covering both the prior 3 months and the study night, were downloaded with Rescan 04.01.013 or Encore Pro 2 2.1.6.0. An attended sleep polygraphy (PG) (Embletta Gold, Embla, USA) during NIV was performed using the following signals as recommended by the SomnoNIV group [14]: mask pressure, flow rate in the circuit measured by a pneumotachograph close to the mask, thoracic and abdominal movements with respiratory inductive plethysmography effort belts, body position, pulse oximetry, and photoplethysmographic pulse wave amplitude (PWA) [25]. Nocturnal blood gases were monitored by SpO_2 (Nonin Medical 2500) and $PtcCO_2$ (TCM Tosca, Radiometer), as previously described [26], and the results were analysed with Nvision 6.4.0.10 and Visi-Download 1.0.

2.4. Definition of respiratory events

We scored respiratory events by visual inspection of the polygraphy traces. Total recording time (TRT), the denominator for computing respiratory event indices, was defined as: [time lapse between lights out and lights on] - [total movement time]. Respiratory events were not scored during periods with high unintentional leaks. Asynchronies were not scored if an apnea or hypopnea was present, if signals from both the thoracic and the abdominal belts were poor, or in case of loss of both pressure and flow signals.

2.4.1. Leaks

Polygraphy signals were interpreted as periods with high unintentional leaks when there was a fall in pressure signal and, in pressure-controlled ventilators, a simultaneous increase in flow signal [14]. When a non-vented mask was used, an amputation of the expiratory flow curve was also interpreted as high unintentional leaks. In addition, reports of estimated unintentional leaks from ventilator software were collected.

2.4.2. Apnea and hypopnea

Criteria for apnea (A) and hypopnea (H) were adapted from the scoring rules of the American Academy of Sleep Medicine [22]. Apnea were scored if there was a drop in peak flow signal excursion by ≥ 90% for ≥10 s, and classified into obstructive, central or mixed apnea according to the AASM scoring rules. Hypopnea were scored if there was a drop in the peak flow signal excursion by ≥ 30% for ≥10 s associated with either a ≥3% desaturation or an autonomic activation scored from the pulse waveform [25] (decrease in PWA ≥ 30%). We sub-classified events fulfilling the criteria's for hypopnea as obstructive (OH) or central (CH). OH were scored in the presence of an increased flattening of the inspiratory flow signal and/or an associated thoraco-abdominal paradox during the event but not before the event. CH were scored in the absence of both an increased flattening of the inspiratory flow signal and an associated thoraco-abdominal paradox during the event but not before the event. (See Figs. S1–S4 in supplement 1). Events were reported as number/hour of TRT, yielding indices for AH-(AHI), H-(HI), CH-(CHI) and OH-(OHI). The number of hypopneas associated with either a 3% desaturation or an autonomic activation was also calculated.

2.4.3. Patient-ventilator asynchrony

Criteria for asynchrony were adapted from previous studies [2,13,16].

Three categories of asynchrony were scored: desynchronization, auto-triggering and double triggering. Desynchronization was scored if there was an uncoupling of the patient's inspiratory efforts and onset of

the ventilator pressurization for ≥10 s and at least three consecutive breaths [2]. The end of the event was defined by the occurrence of three consecutive synchronized breaths. The ventilator rhythm was derived from the flow and pressure curves. The patient's respiratory efforts were derived from thoraco-abdominal tracings [2,13] and/or changes in the flow and pressure curves [13,16]. Ineffective efforts are included in this category. Periods with at least three consecutive ineffective respiratory efforts with ventilator pressurization on back-up rate were also scored as desynchronization. (See Figs. S5 and S6 in supplement 1).

Auto-triggering was defined as the occurrence of at least three rapid pressurizations at a respiratory rate of ≥40 breaths/min and clearly above that of the patient's respiratory rate [2]. (Fig. S7 supplement 1).

Double-triggering was defined as two cycles separated by a very short expiratory time, defined as less than one-half of the mean inspiratory time with the first cycle triggered by the patient [16]. (Fig. S8 supplement 1).

The number of desynchronization events per hour of TRT associated with a 3% desaturation, an autonomic activation or neither of these 2 criteria was calculated. Events were summarized as total desynchronization index (TDI). TDI, auto-triggering and double-triggering events were combined into a patient-ventilator asynchrony index (PVAI): length of time with these events was summarized as the percentage of TRT with patient-ventilatory asynchrony (PVA%).

2.5. Scoring of sleep polygraphy and interrater agreement

The entire PG was manually scored in epochs of a maximum of 2 min for respiratory events according to the definitions provided above. Two pulmonary physicians experienced in scoring sleep studies during NIV independently scored each PG and were blinded to each other's results.

2.6. Statistics

Data are presented as mean ± standard deviation if normally distributed or as median (IQR) otherwise. Differences in patient characteristics were analysed using one-way ANOVA. For analysis of ventilator settings and respiratory events we used Kruskal-Wallis tests when analysing all patient groups and Mann-Whitney U test for comparing two patient groups. Association between respiratory events, overnight SpO_2 and $PtcCO_2$ was assessed using Spearman's rank sum test (rho). Interrater agreement was expressed using either intraclass correlation coefficients (ICC) for continuous variables or kappa measure of agreement for categorical variables. Stratification of level of agreement is provided in the additional file 1. P-values below 0.05 were considered significant. IBM SPSS version 23 was used for statistical analysis.

3. Results

All patients treated with long term NIV and scheduled for a regular follow-up visit at the Department of Pulmonary Medicine of Oslo University Hospital between April 2013 and May 2014 were evaluated. Ninety-five patients met inclusion criteria: 28 patients were not included (see flow chart, Fig. S9 supplement 2). The remaining 67 patients were under NIV for OHS (n = 16), NMD (n = 36), CHS syndrome (n = 5) or RTD (n = 10). Main characteristics of patients are summarized in Table 1 and NIV settings in Table S1 supplement 2.

3.1. Leaks

Periods with high unintentional leaks were rarely observed on the polygraphy traces. Downloaded data from the ventilator were not available in 2 patients using an Elisée ventilator (ResMed, USA); thus data from 65 patients were evaluated. Median of unintentional leaks during the study night for data provided by ResScan software for ResMed ventilators (n = 55) was 2.4 L/min (IQR: 0.0–6.0); median of 95th percentile values was 16.8 L/min (IQR: 4.8–34.2). For data obtained from Encore Pro software for Philips Respironics ventilators (n = 10) median of mean unintentional leaks was 2.4 L/min (IQR: 0–15.2) and median of total leaks was 42.5 L/min (IQR: 25.3–47.0). No correlation was found between leaks and AHI, PVA% or PVAI.

3.2. Apnea and hypopnea

In 2 patients, abdominal and thoracic belt signals were poor for > 2 h but polygraphy yielded satisfactory signals for at least 5 h in all participants. Mean TRT was 453 ± 40 min. AHI ranged from 0 to 31.1/hour. Median AI was 0 (IQR: 0-0), and OH was the most frequent event (Table 2).

AHI was significantly higher in OHS ($p < 0.01$), NMD ($p = 0.02$) and CHS ($p = 0.03$) compared with RTD. OHI was significantly higher in OHS ($p = 0.01$), NMD ($p = 0.02$) and CHS ($p = 0.04$) compared with RTD (Table 2). No significant differences were found in AHI or OHI between OHS, NMD and CHS.

Twenty-three (34%) patients had an AHI > 5/hour and 16 (24%) above 10/hr (Table 3).

In 87% of patients with an AHI > 5, more than 90% of the events were obstructive.

Patients using oro-nasal masks had a significantly higher OHI than patients using nasal masks or prongs (median OHI 8.2 (IQR: 1.3–18.8) vs 1.2 (IQR: 0.2–2.9), $p < 0.001$). Of the 16 patients with an AHI > 10, 14 used an oro-nasal mask.

3.3. Patient-ventilator asynchrony

PVA% ranged from 0 to 45% with a median value of 2% (IQR: 0-7). PVAI ranged from 0 to 25.4 with a median of 2.1 (IQR: 0.4–7.3) (Table 4). No significant differences were found between patient groups. Fourteen patients (21%) had a PVA% > 10, and 25 patients (37%) had a PVAI > 5% (Tables 5 and 6).

Median index and number of patients with an index > 5 were very low for both auto-and double triggering.

3.4. Overnight SpO_2 and $PtcCO_2$ and association with respiratory events

SpO_2 was successfully recorded in all patients. Median time spent with SpO_2 < 90% ($SpO_2$90) was 3% (IQR: 0-15). Mean SpO_2 was 92.3% (± 3.9). Median oxygen desaturation index (ODI) with a ≥3% desaturation was 6.1 (IQR 1.6–11.1). $SpO_2$90 was > 10% of TRT in 21 patients (31%). In one patient $PtcCO_2$ was not available due to technical problems; thus 66 recordings were analysed. Median% of TRT spent with $PtcCO_2$ above 6.7 kPa and 7.3 kPa was 7.5% (IQR 0-68) and 0% (IQR 0-3) respectively. Mean $PtcCO_2$ was 6.4 kPa (± 0.9). Twenty-nine and 14 patients spent more than 20% of TRT with a $PtcCO_2$ above 6.7 kPa and above 7.3 kPa, respectively. Twenty-three (34%) had episodes of nocturnal hypoventilation according to AASM criteria [22].

No correlation was found between leaks and SpO_2 or $PtcCO_2$. ODI and AHI were significantly correlated (rho = 0.56 r^2 = 0.31 $p < 0.001$), as were $SpO_2$90 and AHI (rho = 0.3 r^2 = 0.11 $p = 0.005$), $SpO_2$90 and PVA% (rho = 0.25, r^2 = 0.06 $p = 0.04$), $SpO_2$90 and PVAI (rho = 0.25 r^2 = 0.06 $p = 0.04$) and $SpO_2$90 and TDI (rho = 0.26 r^2 = 0.07 $p = 0.03$).

There was no correlation between time with spent with a $PtcCO_2$ above 6.7 kPa, above 7.3 kPa or mean $PtcCO_2$ and either AHI, PVA%, PVAI or TDI.

3.5. Interrater agreement

The interrater agreement rates (95% confidence interval) in the scoring of AHI, HI,OHI, CHI, Hypopnea 3% desaturation index and Hypopnea autonomic activation index between the two scorers were:

Table 1
Main characteristics of study population.

	OHS	NMD	RTD	CHS	p
Age (years)	65 ± 12	59 ± 19	45 ± 25	49 ± 14	0.04
BMI (kg/m^2)	36.7 ± 5.2	24.8 ± 5.7	26.5 ± 8.1	28.0 ± 5.8	< 0.001
Male/female	8/8	20/16	3/7	4/1	
NIV duration, month, median(IQR)	35 (7-58)	57 (13-118)	80 (34-94)	60 (24-111)	0.18
FEV_1(% predicted)	58.3 ± 22.3	37.1 ± 17.8	48.3 ± 32.3	78.6 ± 16.7	< 0.001
FVC (% predicted)	71.3 ± 22.2	38.2 ± 17.9	50.6 ± 31.3	84.6 ± 10.5	< 0.001
FEV_1/FVC (%)	63.5 ± 11.9	79.6 ± 12.7	76.8 ± 11.5	74.6 ± 9.2	0.001
$PaCO_2$ (kPa)	6.2 ± 1.2	6.1 ± 0.7	5.8 ± 0.8	6.3 ± 1.2	0.7
PaO_2 (kPa)	8.4 ± 1.5	9.6 ± 1.5	9.5 ± 1.0	9.9 ± 1.7	0,049
pH	7.38 ± 0.04	7.39 ± 0.03	7.39 ± 0.03	7.39 ± 0.04	0.85

Values presented as mean ± SD, unless specified otherwise.
OHS: obesity hypoventilation syndrome; NMD: neuromuscular diseases; RTD: restrictive thoracic disorders; CHS: central hypoventilation syndrome.

Table 2
Frequencies of apnea and hypopnea for each disease group.

Event; reported as n/hr	OHS (n = 16)	NMD (n = 36)	RTD (n = 10)	CHS (n = 5)
Apnea-hypopnea index (AHI)	4.5 (2.5-13.5)	2.7 (1.1-9.1)	0.8 (0.1-1.8)	3.8 (2.0-26.3)
Hypopnea index (HI)	4.3 (2.5-13.5)	2.7 (1.1-9.0)	0.7 (0.1-1.8)	3.8 (1.8-26.3)
Obstructive hypopnea index (OHI)	3.2 (1.2-12.9)	2.2 (0.9-8.8)	0.3 (0-1.7)	3.7 (1.4-13.9)
Hypopnea 3% desaturation index (HI3%)[a]	3.1 (2.2-12.2)	1.5 (0.5-6.9)	0.5 (0-1.7)	3.3 (0.3-20.5)
Hypopnea autonomic activation index (HAAI)	0.8 (0.3-1.2)	1.1 (0.3-2.8)	0.2 (0-0.4)	3.0 (0.3-5.8)

Values presented as median and IQR. OHS: obesity hypoventilation syndrome; NMD: neuromuscular diseases; RTD: restrictive thoracic disorders; CHS: central hypoventilation syndrome.
[a] Hypopnea 3% desaturation: hypopnea defined on the basis of a drop in SpO2 ≥ 3%.

Table 3
Stratification of severity of apnea and hypopnea indices for each disease group.

Events; reported as n/hr	OHS (n = 16)	NMD (n = 36)	RTD (n = 10)	CHS (n = 5)
AHI > 5	6	14	1	2
AHI > 10	5	8	1	2
AHI > 15	3	7	1	2
Obstructive hypopnea > 5	5	13	1	2
Obstructive hypopnea > 10	5	8	1	1
Obstructive hypopnea > 15	3	7	1	1
Hypopnea 3% desaturation index > 5[a]	6	10	1	2
Hypopnea 3% desaturation index > 10	4	4	1	2
Hypopnea 3% desaturation index > 15	3	2	1	1

Values presented as number of patients.
AHI: apnea-hypopnea index (N/hr); OHS: obesity hypoventilation syndrome; NMD: neuromuscular diseases; RTD: restrictive thoracic disorders; CHS: central hypoventilation syndrome.
[a] Hypopnea 3% desaturation: hypopnea defined on the basis of a drop in SpO2 ≥ 3%.

0.97 (0.94–0.98), 0.97 (0.95–0.98), 0.95 (0.92–0.97), 0.89 (0.81–0.94), 0.97 (0.96–0.98) and 0.90 (0.83–0.94) respectively and were classified as very strong for all events except for central hypopnea, where agreement was classified as strong.

The agreement (kappa) rates for classifying AH according to cut offs for AHI > 10, HI > 10, OHI > 10 and Hypopnea 3% desaturation index > 10 were 0.96 ($p < 0.001$), 1.0 ($p < 0.001$), 0.96 ($p < 0.001$) and 0.95 ($p < 0.001$) respectively and were classified as an almost perfect agreement for all events.

The interrater agreement in the scoring of PVA%, PVAI and TDI was classified as strong, whereas there was moderate and little agreement for scoring auto- and double triggering, respectively (Table 4). There was a substantial agreement in classifying asynchrony according to different cut offs (Table 5).

4. Discussion

To our knowledge, this is the first study to report the frequency and types of both apnea-hypopnea (scored according to AASM scoring rules) and PVA in a large group of CRF patients treated with NIV. We found that residual AH were frequent: 34% of patients had an AHI > 5/hr. OH was the most frequent event. Furthermore, 21% of patients had PVA > 10% of TRT, taking into account the fact that these events were scored only in periods without AH. Double triggering and auto triggering were rare. No correlation was found between respiratory events and overnight $PtcCO_2$.

4.1. Leaks

Unintentional leaks were low in the majority of patients. Studies reporting on the amount of leaks during long term NIV for CRF are limited and results are conflicting [4,27,28]. Leaks have been associated both with nocturnal desaturation and with asynchrony [4,27]. However, considering the low level of leaks and the lack of correlation between leaks and respiratory events, leaks were not a significant generator of respiratory events in this study.

4.2. Apnea and hypopnea

Thirty-one percent of OHS patients had an AHI > 10/hr. This is in accordance with previous studies [2,24]. We also found a high residual AHI in patients with neuromuscular diseases, which is in contrast to both Crescimanno et al. and Atkeson et al. [3,4] However Crescimanno et al. did not use the AASM scoring rules [22] and Atkeson et al. did not score hypopnea. In addition, neither of these studies used a flow sensor close to the mask, as recommended by the SomnoNIV group [14], or scored flow reduction from a flow signal derived from the ventilator, as recommended by the AASM [22]. Thus, differences in scoring criteria and equipment for detecting flow reduction might explain these discrepancies. OH was by far the most frequent event both in OHS and NMD. Obstructive events are most probably due to unstable upper

Table 4
Frequencies of types of asynchrony and interrater correlation for scorer A and B for all patients.

Event	A and B combined	Scorer A	Scorer B	ICC (95% CI) Average
% of total recording time with PVA	2 (0-7)	2 (0-8)	1 (0-5)	0.85 (0.75-0.91)
PVA index (N/hr)	2.1 (0.4-7.3)	2.4 (0.6-10.1)	1.4 (0.1-7.5)	0.71 (0.53 - 0.82)
Total desynchronization index (N/hr)	1.4 (0.2- 5.8)	1.0 (0.1 -7.1)	0.8 (0.1-4.8)	0.87 (0.79–0.92)
Desynchronization index (N/hr)	0.7 (0.1-4.7)	0.6(0.1-5.0)	0.3 (0.0-3.0)	0.85 (0.75 - 0.91)
Desynchronization 3% desaturation index[a] (N/hr)	0.1 (0-0.7)	0.1 (0-0.7)	0.0 (0.0-0.4)	0.74 (0.56 - 0.85)
Desynchronization autonomic activation index (N/hr)	0.1 (0-0.5)	0 (0-0.4)	0.0 (0.0-0.5)	0.69 (0.50 - 0.81)
Double-triggering index (N/hr)	0.2 (0-0.5)	0.1 (0-0.8)	0.0 (0.0-0.2)	0.15 (-0.35 - 0.47)
Auto-triggering index (N/hr)	0 (0-0)	0 (0-0)	0.0 (0.0-0.0)	0.63 (0.39 - 0.77)

Values presented as median and IQR. PVA: patient ventilator asynchrony.
[a] Desynchronization 3% desaturation on the basis of a drop in SpO2 ≥ 3%.

airways leading to oropharyngeal collapse. This is common in OHS and is reflected by the higher average EPAP used in this group. Upper airway muscle involvement during disease progression in patients with NMD could lead to similar events. OH may also be caused by glottis closure due to NIV-induced hyperventilation [12]. Recently, obstruction at glottic or subglottic level due to high pressure or flow [29,30] and obstruction at tongue base aggravated by oro-nasal masks [29,31,32] have been suggested as other NIV-related causes of obstructive events. Indeed, we found a higher OHI in patients using oro-nasal vs. nasal masks, suggesting that choice of interface may play a critical role in the control of OH.

In the present study, apneas were rare. All patients used a ventilator setting with intermittent (n = 65) or continuous mandatory (n = 2) ventilation [33]. Ninety-seven% of our patients used a vented mask, and the pneumotachograph measuring flow was placed between the mask and the ventilator. Thus, during an episode of upper airway obstruction, the ventilator will provide a mandatory breath and flow will most likely not be reduced sufficiently to meet the criteria for an apnea. This underlines the importance of also scoring hypopneas in this setting.

4.3. Patient-ventilator asynchrony

PVA varied markedly between patients: 21% had a PVA% > 10% of TRT and 37% had a PVAI > 5/hour. Previous studies suggest that asynchrony implicating more than 10% of breaths is clinically relevant [16,17,34]. The available studies of asynchrony during sleep in stable patients with CRF on NIV show conflicting results [2–4,6,15]. Furthermore, there is presently no consensus as to how to score and report PVA in this setting, thus scoring options are arbitrary. In a recent study, Ramsey et al. found severe PVA in 79% of patients [5]. Our scoring strategy differed from that of Ramsey et al. on several aspects. First, we only scored episodes lasting > 10 s as asynchrony. Secondly, our study, performed in routine conditions, did not include additional indicators of inspiratory effort such as esophageal pressure or diaphragm electromyogram, while Ramsey et al. used a surface parasternal electromyogram to detect neural respiratory drive. Thus, an inspiratory effort (IE) not resulting in a visible change in either thoracic or abdominal belts or in the flow or pressure signals, would not have been detected in our study, and IE may have been underestimated. For the same reason we were not able to score cycling asynchrony. However, the latter was found to be infrequent in the study by Ramsey et al. Thirdly, we limited scoring of PVA to periods without apnea or hypopnea, in accordance with a report on children under NIV [21]. IE or bouts of double- or auto-triggering may occur during OH. Our scoring approach would have identified these events as primarily resulting from upper airway closure, thus decreasing PVA%. Finally, leaks which may be an important generator of asynchrony were low in our study; they were not reported by Ramsey et al.

Table 6
Number of subjects with asynchrony for each disease group according to 3 different criteria.

Events	OHS (n = 16)	NMD (n = 36)	RTD (n = 10)	CHS (n = 5)
Time with PVA > 10% of TRT	2	10	2	0
PVA Index > 5	6	16	3	0
Total desynchronization index > 5	4	12	3	0

Values presented as numbers of patients.

4.4. Overnight SpO_2 and $PtcCO_2$ and association with respiratory events

We found a significant association between AHI and both ODI and $SpO_2$90. Conversely, no correlation was found between AHI or asynchrony and nocturnal $PtcCO_2$ or between leaks and either nocturnal SpO_2 or $PtcCO_2$. $SpO_2$90 integrates both short recurrent desaturations and prolonged desaturation during NIV. Short recurrent desaturations could be caused by AH, leaks or asynchrony, while prolonged desaturations reflect ventilation/perfusion mismatch or persistent alveolar hypoventilation [6,35]. A drop of SpO_2 of ≥3% is a criterion for scoring hypopnea explaining the correlation between AHI and desaturation; however AHI only explained 11% of the variance in $SpO_2$90. Desynchronizations associated with desaturation were rare and asynchrony explained only 6% of the variance of $SpO_2$90. Thus, in the present study, AH and PVA do not seem to be major contributors to oxygen desaturation during overnight treatment with NIV. Other factors, such as ventilation/perfusion mismatch and hypoventilation are probably of greater importance.

Nocturnal hypercapnia, assessed by transcutaneous CO_2, reflects

Table 5
Stratification of severity and interrater agreement in severity stratification of various asynchrony indices.

Event	A and B combined	Scorer A	Scorer B	Agreement(kappa)	p
Time with PVA > 10% of TRT	14	15	12	0.77	< 0.001
PVA Index > 5	25	25	20	0.63	< 0.001
Total desynchronization index > 5	19	19	16	0.73	< 0.001
Auto-triggering index > 5	1	0	1		
Double-triggering index > 5	4	5	1	0.32	< 0.001

Values presented as number of patients. TRT: total recording time; PVA: patient ventilator asynchrony.

persisting alveolar hypoventilation during NIV, taking into account the limitations of this technique [26]. It may result from insufficient ventilatory support, prolonged leaks or prolonged asynchrony [35,36], although the latter has yet to be shown. In addition, a high AHI may lead to accumulation of CO_2 [37]. However, we found no correlation between AHI and nocturnal hypercapnia in our study population. This is probably because AHI in our patients was relatively low, allowing for sufficient interapnea ventilation. Nor did we find any correlation between PVA and hypercapnia. This is in line with a recent study, using similar levels of pressure support and mandatory back up rate, showing that PVA had no demonstrable effect on overnight gas exchange [5].

4.5. Interrater agreement

This is the first study to report on interrater agreement in scoring of both apnea-hypopnea and asynchrony in patients using NIV for CRF. Our results show that scoring AH and classifying AH according to different cut-offs could be done with a high level of interobserver agreement. We also found an excellent interrater agreement in scoring PVA%, PVAI and TDI. This is in line with the study by Ramsay et al. who reported a high intraclass correlation in scoring PVA in a sub study of 10 patients [5]. These findings are of importance for the validity of sleep studies during NIV and for future research looking at significance of residual respiratory events during NIV on patient outcome.

4.6. Limitations

There are several limitations to our study. First, hypopnea may have been underestimated. The AASM suggests scoring hypopnea if a 30% flow reduction is associated with either a desaturation or an EEG arousal using polysomnography. Polygraphy without EEG underestimates hypopnea. We therefore used PWA as a surrogate for EEG arousal to enhance identification of hypopnea [25]. H are presented separately according to whether or not PWA was used as a criterion. As reported in Table 2, H scored using PWA as criterion contributed marginally to the total HI. Polysomnography remains the gold standard for monitoring NIV according to the AASM, but its availability is low in many European countries and thus its systematic use is unrealistic. Secondly, PVA was only scored in the absence of apnea or hypopnea. Although this may have decreased PVAI and PVA%, it leads to a clinically coherent reporting of respiratory events because the first intervention to correct PVA in the presence of leaks, apnea, or hypopnea, would be to correct these events. Nevertheless, future standardisation of PVA scoring and reporting is desirable to help assessing clinical relevance of these events and for comparing studies. Finally, limitations in detection of PVA and IE (absence of additional indicators of inspiratory effort) have been discussed above.

5. Conclusion

In our study population of patients treated with long term NIV for chronic hypercapnic respiratory failure, residual AH were common. OH associated with desaturation were the most frequent events. PVA was also frequent, even if these events were scored only in periods without AH. These results may have implications as to how these patients should be monitored during follow-up. No correlation was found however between respiratory events and persistent nocturnal hypercapnia. Thus, the impact of these events on efficacy of NIV, adherence to therapy, sleep quality, symptoms and quality of life requires further documentation. Although the scoring of respiratory events during NIV is time-consuming, polygraphy can be scored with a very high interobserver agreement.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, NO = 2012/1142. Written informed consent was obtained from all participants.

Conflict of interest statement

SA has received fees for lecturing from Philips-Respironics and ResMed, outside of the presented work. All other authors have no competing interests to declare.

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Authors' contributions

SA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SA, ALK and MQ contributed substantial to acquisition of data. SA and MQ scored the sleep studies. SA, ET, ALK, MQ, OHS and JJ contributed substantial to the study concept and design, data interpretation, critical revision of the manuscript for important intellectual content, and final approval of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmed.2017.10.025.

Transparency document

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Obstructive hypopnea

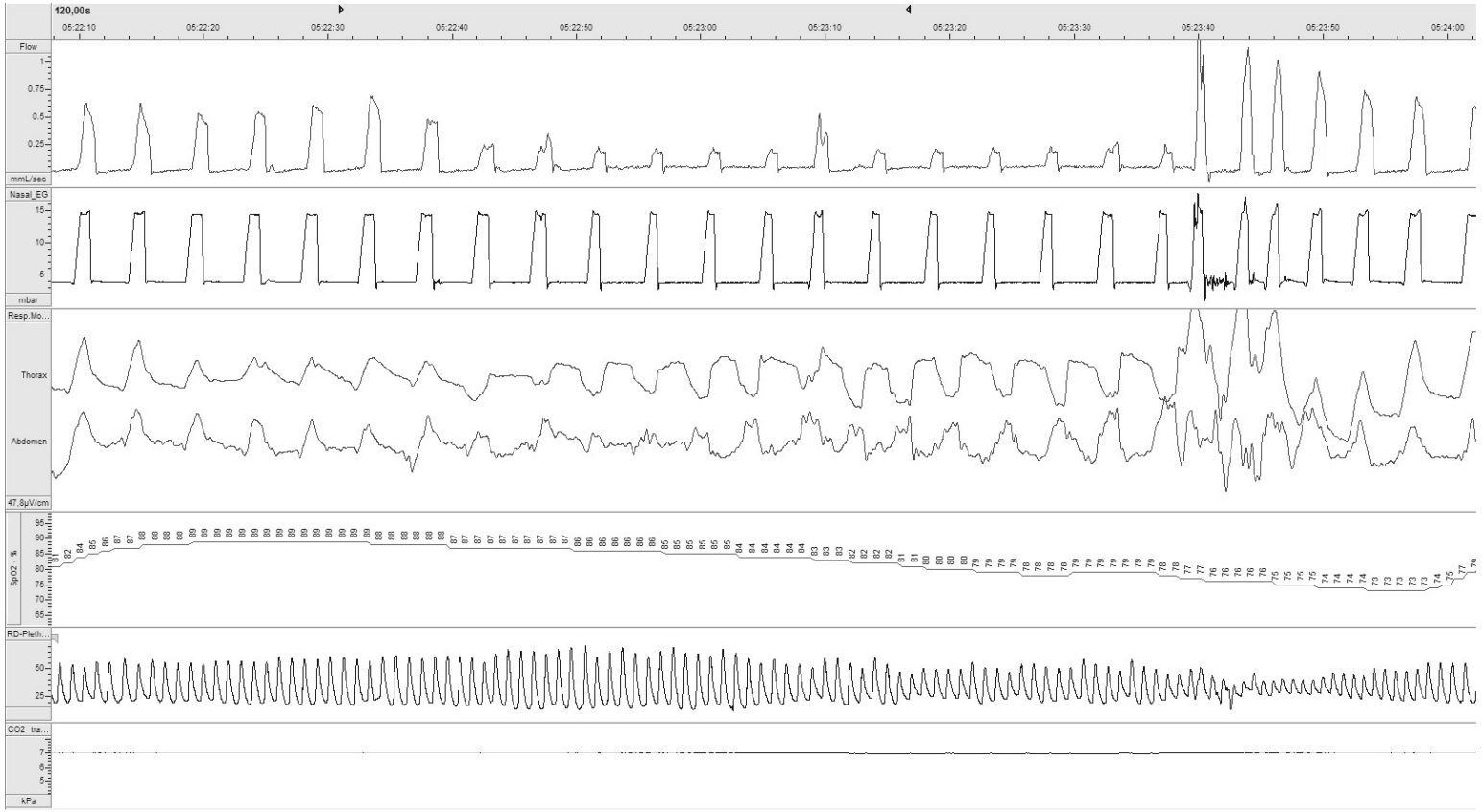


Figure S1. Respiratory polygraphy, 2 minutes epoch. Traces from top to bottom: flow; pressure; thoracic belt; abdominal belt; SpO_2; pulse wave amplitude; $PtcCO_2$. Ventilator settings: Bi-level-PAP; ST-mode; IPAP 15 cmH_2O; EPAP 4 cmH_2O; back-up respiratory rate 13/min; Minimal inspiratory time (TI_{MIN}): 1.0 second; Maximal inspiratory time (TI_{MAX}): 1.3 second. Flow reduction associated with desaturation; event ends with resumption of flow, disappearance of thoraco-abdominal paradox and decrease in pulse wave amplitude (autonomic activation); scored as hypopnea. Because of flattening of the inspiratory flow signal and thoraco-abdominal paradox, this event was classified as obstructive hypopnea.

Central hypopnea

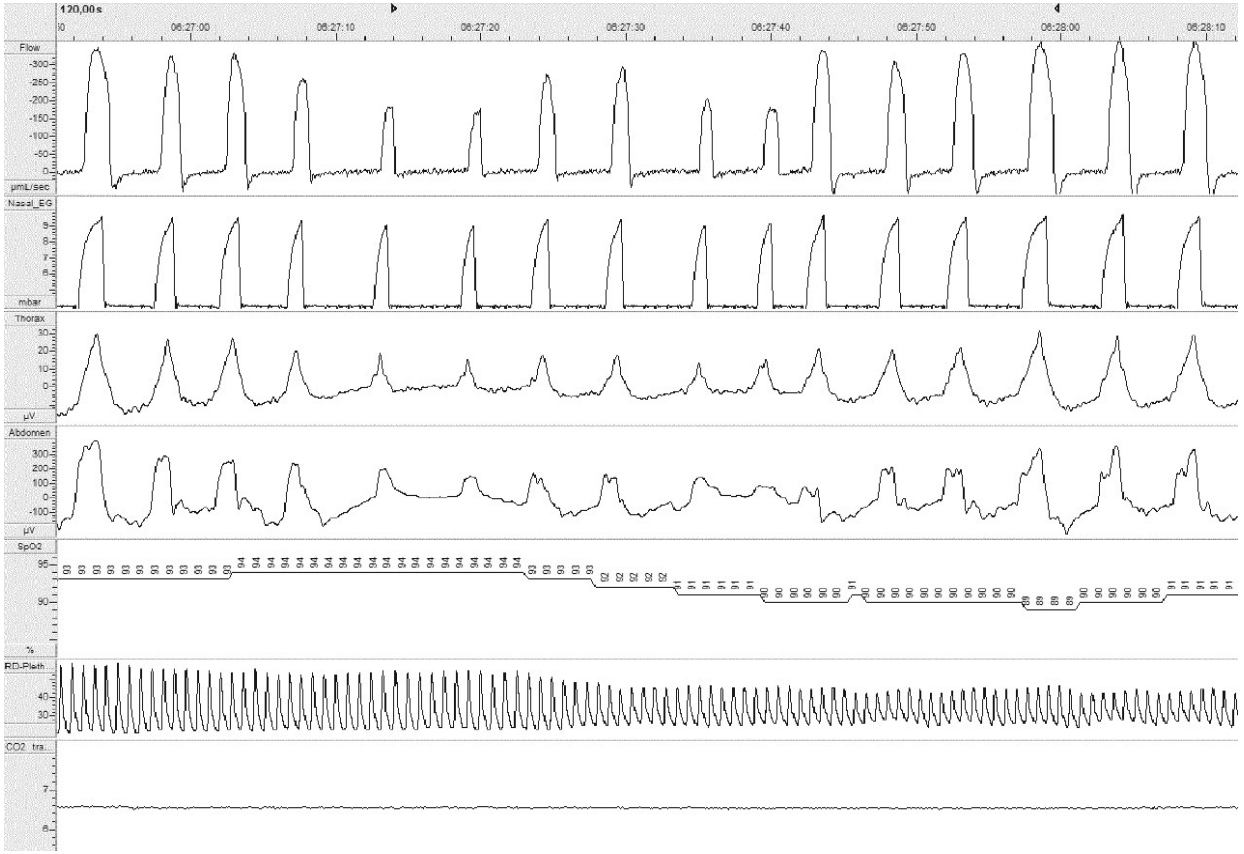


Figure S2. Respiratory polygraphy, 1 minute epoch. Traces from top to bottom: flow; pressure; thoracic belt; abdominal belt; SpO_2; pulse wave amplitude; $PtcCO_2$. Ventilator settings: Bi-level-PAP; ST-mode; IPAP 10 cmH_2O; EPAP 4 cmH_2O; back-up respiratory rate 10/min; Minimal inspiratory time (TI_{MIN}): 0.9 second. Flow reduction associated with desaturation; event ends with decrease in pulse wave amplitude; scored as hypopnea. No flattening of the inspiratory flow signal or thoraco-abdominal paradox; thus, classified as central hypopnea.

Obstructive hypopnea

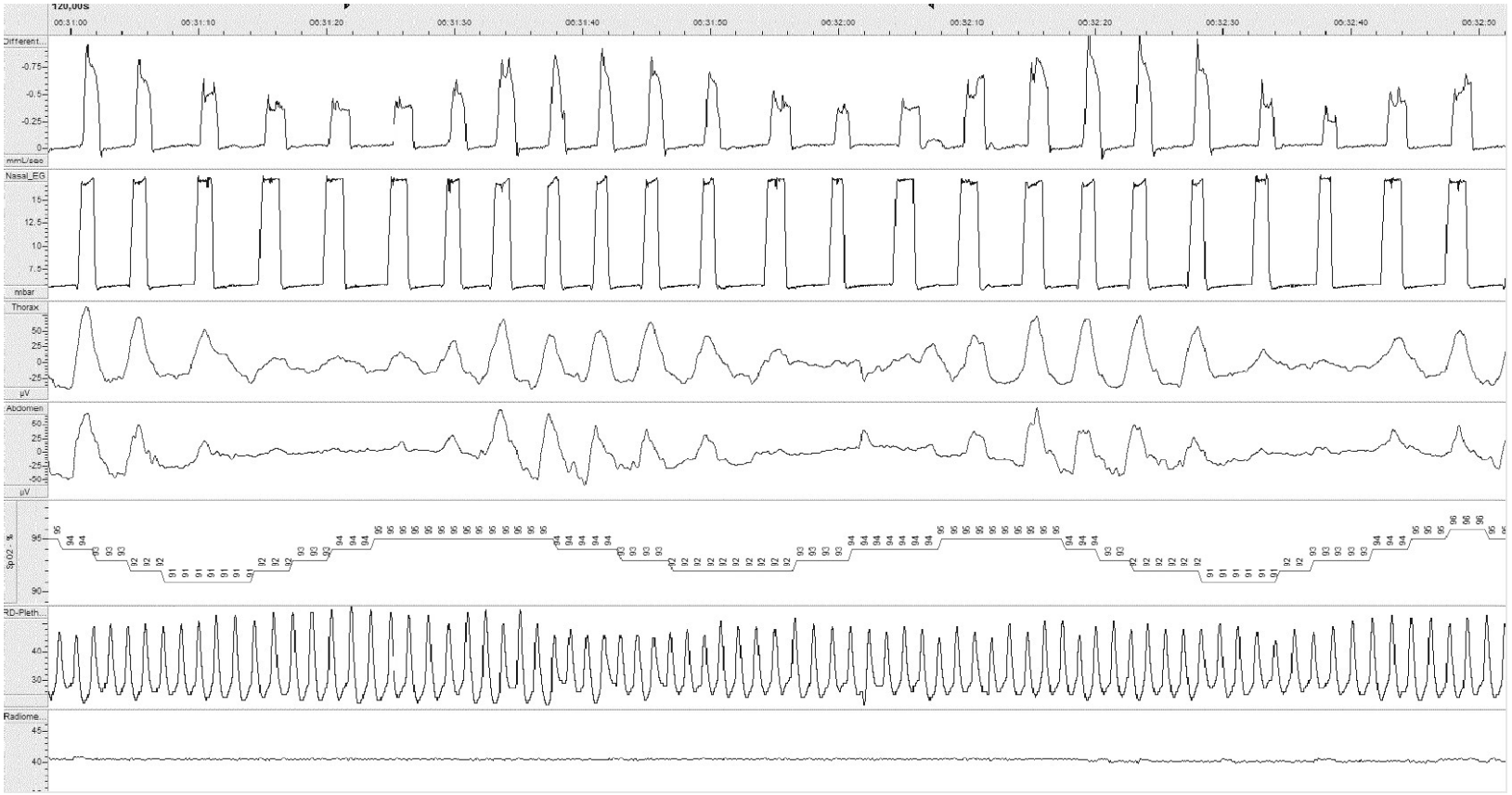


Figure S3. Respiratory polygraphy, 2 minutes epoch. Traces from top to bottom: flow; pressure; thoracic belt; abdominal belt; SpO_2; pulse wave amplitude; $PtcCO_2$. Ventilator settings: Bi-level-PAP; ST-mode; IPAP 18 cmH_2O; EPAP 6 cmH_2O; back-up respiratory rate 12/min; Minimal inspiratory time (TI_{MIN}): 1.1 second; Maximal inspiratory time (TI_{MAX}): 1.6 second. Two events with flow reduction and desaturation, scored as hypopnea. Flattening of the inspiratory flow signal in both events. No thoraco-abdominal paradox in the first event, phase opposition during second event. Both events were classified as obstructive hypopnea.

Obstructive hypopnea

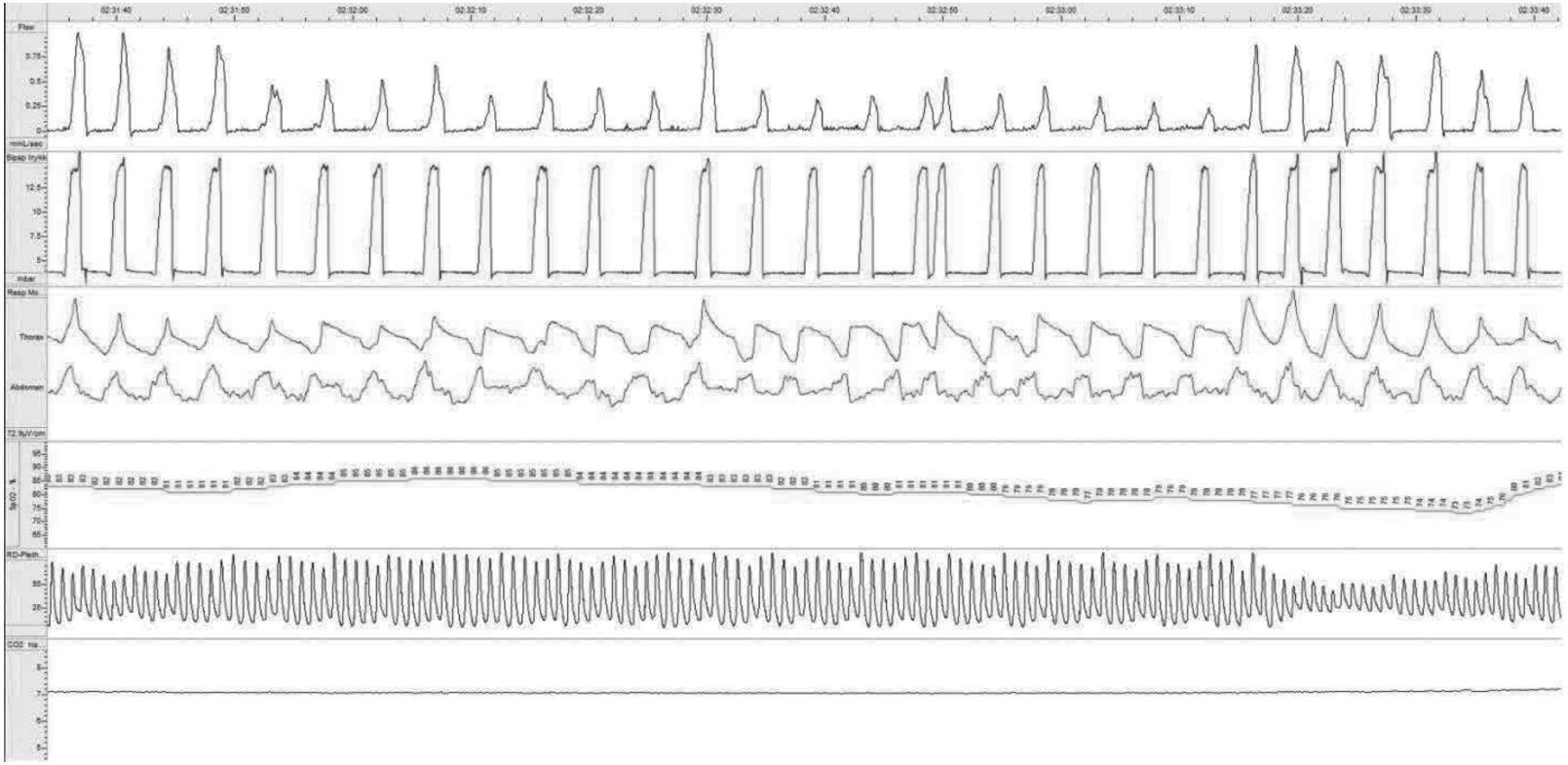


Figure S4. Respiratory polygraphy, 2 minutes epoch. Traces from top to bottom: flow; pressure; thoracic belt; abdominal belt; SpO_2; pulse wave amplitude; $PtcCO_2$. Ventilator settings: Bi-level-PAP; ST-mode; IPAP 15 cmH_2O; EPAP 4 cmH_2O; back-up respiratory rate 13/min; Minimal inspiratory time (TI_{MIN}): 1.0 second; Maximal inspiratory time (TI_{MAX}): 1.3 second. Flow reduction with desaturation; event ends with decrease in pulse wave amplitude (autonomic activation) and resumption of normal flow; event is scored as hypopnea. No flattening of the inspiratory flow signal, but thoraco-abdominal paradox during the event, absent pre-event; thus, event classified as obstructive hypopnea.

Desynchronization (unrewarded efforts)

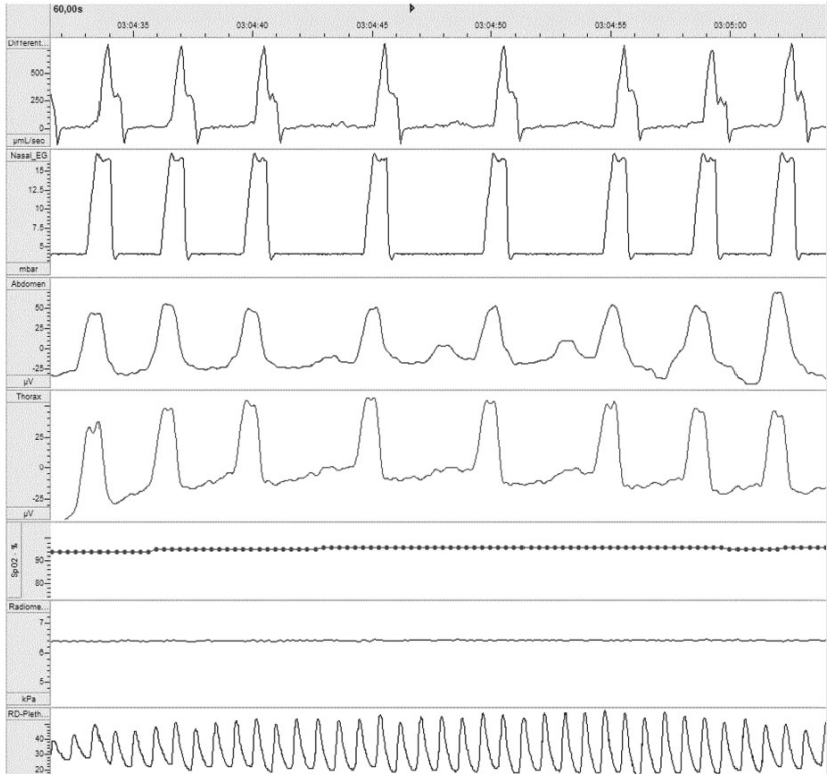


Figure S5. Respiratory polygraphy, 30 sec. epoch. Traces from top to bottom: flow; pressure; abdominal belt; thoracic belt; SpO_2; pulse wave amplitude; $PtcCO_2$. Ventilator settings: Bi-level-PAP; ST-mode; IPAP 17 cmH_2O; EPAP 4 cmH_2O; back-up respiratory rate 12/min; Minimal inspiratory time (TI_{MIN}): 1.0 second; Maximal inspiratory time (TI_{MAX}): 2.0 seconds. No flow reduction. Three consecutive ineffective inspiratory efforts clearly visible on abdominal tracing with small positive deflexions on flow tracing. Ventilator on back-up rate; scored as desynchronization (unrewarded efforts).

Desynchronization (unrewarded efforts).

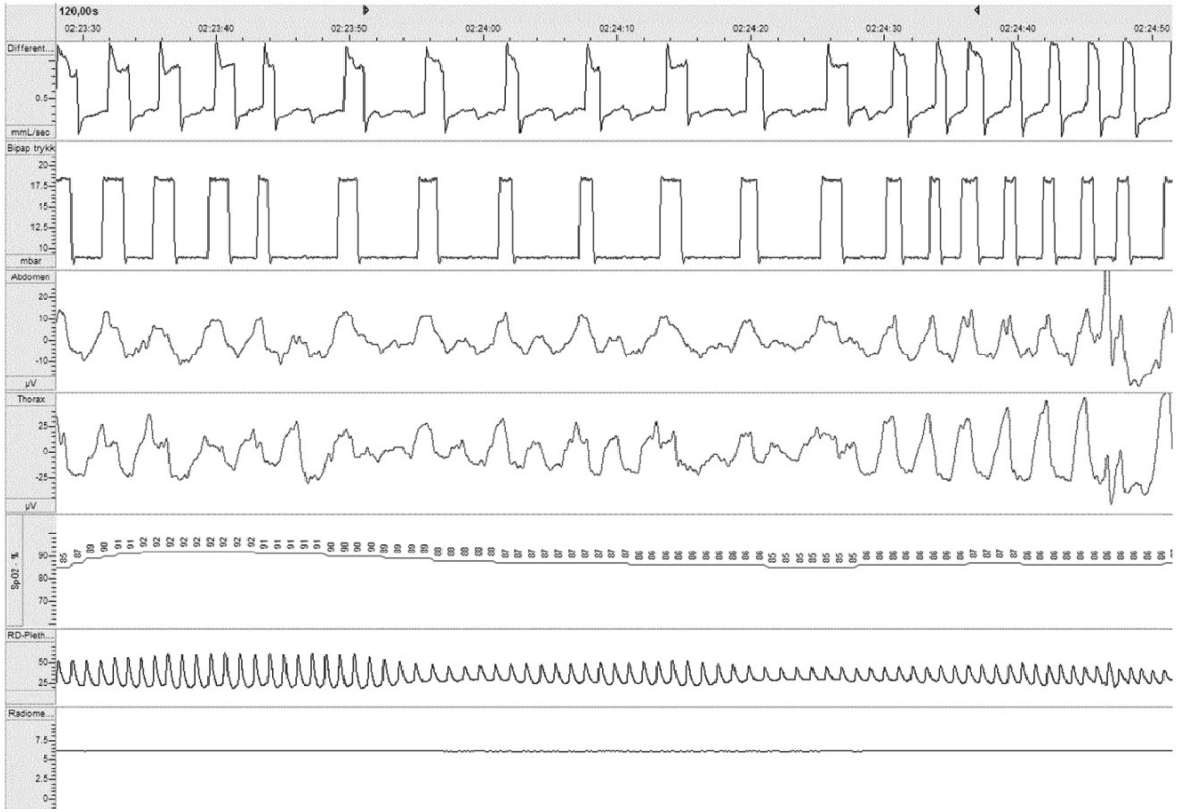


Figure S6. Respiratory polygraphy, 80 sec. epoch. Traces from top to bottom: flow; pressure; abdominal belt; thoracic belt; abdominal belt; SpO_2; pulse wave amplitude; $PtcCO_2$. Ventilator settings: Bi-level-PAP; ST-mode; IPAP 19 cmH_2O; EPAP 9 cmH_2O; back-up respiratory rate 10/min; Minimal inspiratory time (TI_{MIN}): 0.8 second; Maximal inspiratory time (TI_{MAX}): 1.6 seconds. Change in shape of flow tracing compared to end of page; probable due to leaks. No drop in pressure; no major leaks. No flow reduction. Recurrent ineffective inspiratory efforts with small positive deflexions on flow tracing. Ventilator switches to back-up rate. Scored as desynchronization (unrewarded efforts). Associated with desaturation and decrease in pulse wave amplitude (autonomic activation).

Auto triggering

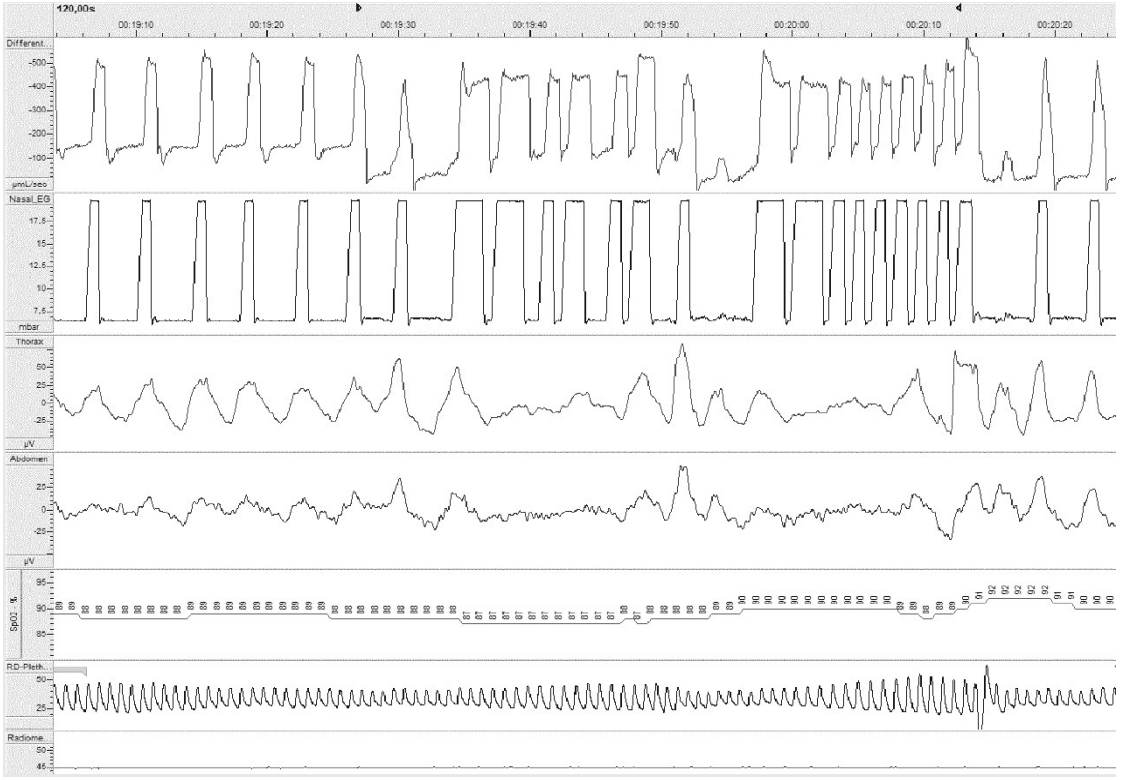


Figure S7. Respiratory polygraphy, 80 sec. epoch. Traces from top to bottom: flow; pressure; thoracic belt; abdominal belt; SpO_2; pulse wave amplitude; $PtcCO_2$. Ventilator settings: Bi-level-PAP; ST-mode; IPAP 21 cmH_2O; EPAP 7 cmH_2O; back-up respiratory rate 10/min; Minimal inspiratory time (TI_{MIN}): 1.0 second; Maximal inspiratory time (TI_{MAX}): 2.4 seconds. Change in shape of flow tracing (width) with minimal flow reduction. Occurrence of > three rapid pressurizations at a respiratory rate (RR) of ≥ 40 breaths/min; RR of ventilator clearly above that of the patient. Scored as auto triggering.

Double-triggering

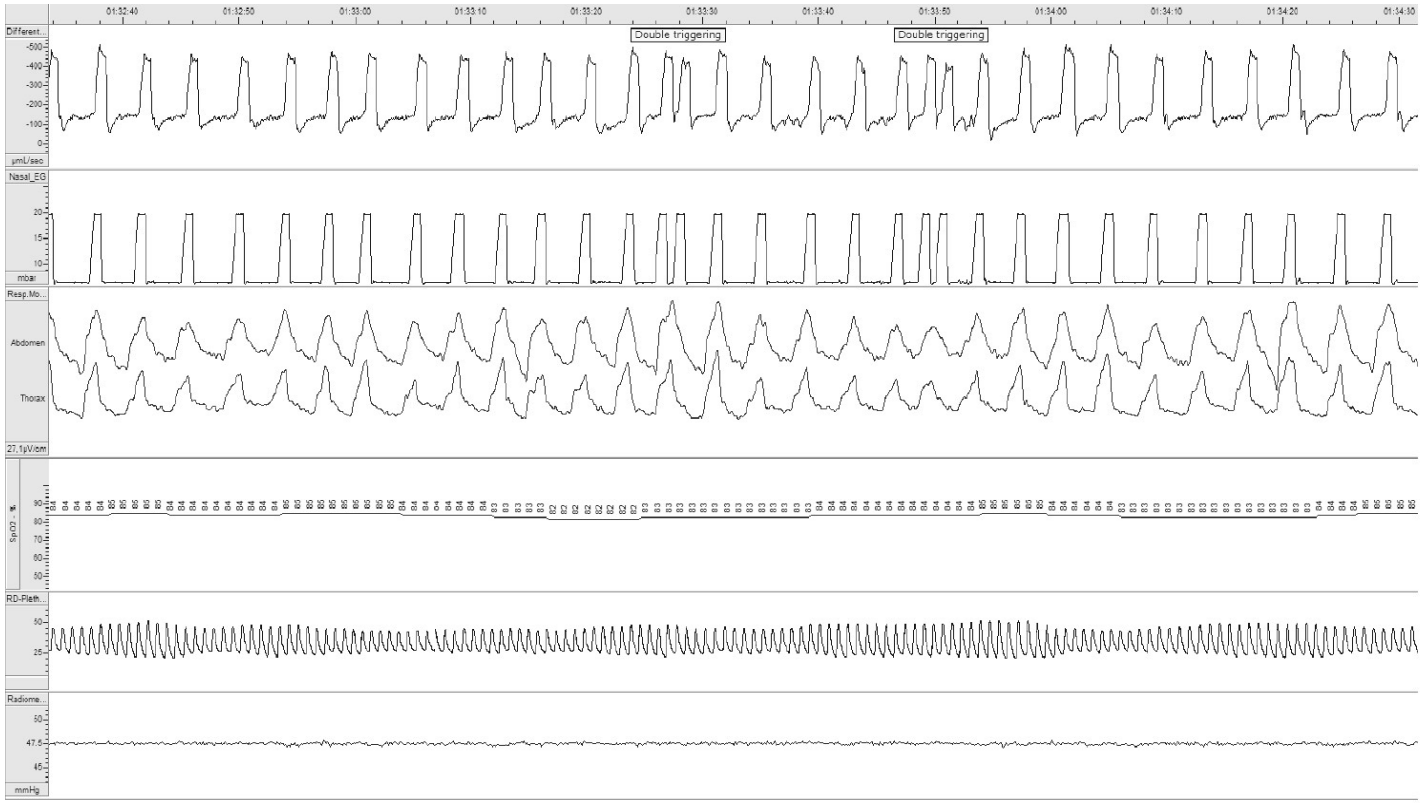


Figure S8. Respiratory polygraphy, 120 sec. epoch. Traces from top to bottom: flow; pressure; abdominal belt; thoracic belt; SpO_2; pulse wave amplitude; $PtcCO_2$. Ventilator settings: Bi-level-PAP; ST-mode; IPAP 21 cmH_2O; EPAP 7 cmH_2O; back-up respiratory rate 10/min; Minimal inspiratory time (TI_{MIN}): 1.0 second; Maximal inspiratory time (TI_{MAX}): 2.4 seconds. No flow reduction. Occurrence of two events with two respiratory cycles separated by a very short expiratory time, defined as less than one-half of the mean inspiratory time with the first cycle triggered by the patient; scored as double-triggering.

Supplementary data 2.

Contents:

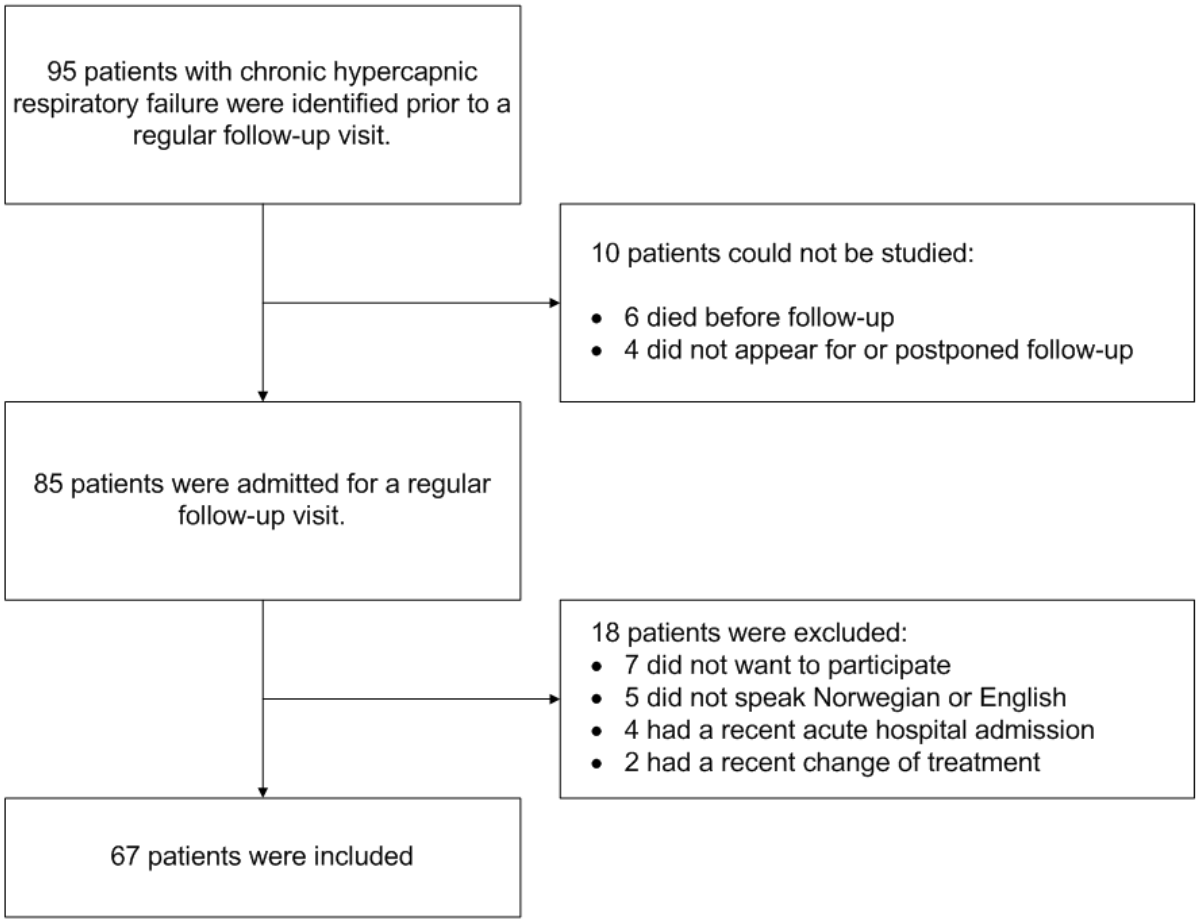
1 Methods

1.1 Statistics

The levels of agreement using the ICC for continuous variables were classified as follows: 0.00-0.25 = little, 0.26-0.49 = low, 0.50-0.69 = moderate, 0.70-0.89 = strong, 0.90-1.00 = very strong.[1 2] For the kappa measurement of agreement for categorical variables, results were classified as follows: < 0 = no agreement, 0-0.20 = slight agreement, 0.21-0.40 = fair agreement, 0.41-0.60 = moderate agreement, 0.61-0.80 = substantial agreement, 0.81-1.0 = almost perfect agreement.[3]

2. Results

2.1 Figure S9: Flow chart of patient inclusion.



2.2 Ventilator settings and equipment by all patient and ventilator settings by disease group

Table S1 Ventilator settings and equipment by all patient and ventilator settings by disease group

Ventilator Settings	All patients	OHS	NMD	RTD	CHS	p
Ipap* (cm H_2O)	16 (14-19)	20 (14-24)	16 (12-18)	16 (15-18)	12 (11-16)	0.03
Epap (cm H_2O)	5 (4-6)	8 (6-10)	4 (4-6)	5 (4-7)	4 (2-6)	<0.001
Back-up respiratory rate (breaths/minute)	12 (10-15)	12 (10-13)	12 (10-15)	13.5 (12-15)	15 (10-16)	0.5
Ventilator mode; Bi-level ST/ PS-VT/VCV/PCV, n	57/8/1/1					
ResMed ventilator / Philips Respironics ventilator, n	57/10					
Supplementary oxygen/humidifier/ cough assist, n	1/33/8					
Interface; oro-nasal /nasal/nasal prongs, n	31/23/13					

Values presented as median and IQR, unless specified otherwise. *In PC mode peak inspiratory pressure was used for calculation and in PS-VT / VCV mean overnight inspiratory pressure was used for calculation.
OHS: obesity hypoventilation syndrome; NMD: neuromuscular diseases; RTD: restrictive thoracic disorders; CHS: central hypoventilation syndrome; I(E)PAP: Inspiratory (expiratory) positive airway pressure; ST; spontaneous-timed; PS-VT pressure support- volume targeted; VCV/PCV volume/pressure controlled ventilation.

3 Long term mechanical ventilation (LTMV) at Oslo University Hospital Ullevål

Indications for LTMV, treatment titration and monitoring of NIV are based on Norwegian national guidelines for LTMV[4], which are in agreement with international recommendations on NIV.

4 References

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III

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Diagnostic accuracy of simple tools in monitoring patients with chronic hypoventilation treated with non-invasive ventilation; a prospective cross-sectional study

Sigurd Aarrestad[a,b,c,*], Magnus Qvarfort[a], Anne Louise Kleiven[a], Elin Tollefsen[d,e], Ole Henning Skjønsberg[a,b,1], Jean-Paul Janssens[f,1]

[a] Department of Pulmonary Medicine, Oslo University Hospital, Ullevål, Oslo, Norway
[b] University of Oslo, Oslo, Norway
[c] Norwegian National Advisory Unit on Long Term Mechanical Ventilation, Haukeland University Hospital, Norway
[d] Department of Thoracic Medicine, St. Olavs Hospital, Trondheim, Norway
[e] Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway
[f] Division of Pulmonary Diseases, Geneva University Hospitals, Switzerland

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ABSTRACT

Objectives: To evaluate the sensitivity and specificity of a screening test panel for nocturnal hypoventilation (NH) and other sleep related respiratory events during monitoring of patients with chronic hypercapnic respiratory failure (CRF) treated with NIV.

Methods: We performed a prospective study at Oslo University Hospital. Eligible for inclusion were consecutive adults with CRF due to neuromuscular diseases or chest wall disorders treated with NIV scheduled for a follow-up visit. All patients underwent the screening test panel (clinical evaluation, daytime arterial blood gas (ABG), nocturnal pulse oximetry (SpO_2) and data from ventilator software) and the reference tests; sleep polygraphy and nocturnal transcutaneous CO_2.

Results: Of 67 patients included, NH was confirmed in 23–50 according to the 3 definitions used for NH, apnea-hypopnea index ($AHI_{polygraphy}$) ≥ 10 was confirmed in 16 and patient-ventilator asynchrony (PVA) ≥ 10% of total recording time in 14. Sensitivity of the combined screening test panel for NH was 87% (95% confidence interval 66–97), 84% (66–95) and 80% (66–90), for abnormal $AHI_{polygraphy}$ 91% (59–100) and for PVA 71% (42–92). Sensitivity for NH of SpO_2 was 48% (27–69), 39% (22–58) and 38% (24–53) and of daytime ABG 74% (52–90), 74% (55–88) and 68% (53–80). Sensitivity and specificity of $AHI_{software}$ for $AHI_{polygraphy}$ ≥ 10 was 93% (68–100) and 92% (81–98) respectively.

Discussion: In patients treated with long term NIV, screening test panel, nocturnal SpO_2 and daytime ABG all failed to accurately detect NH, underlining the importance of nocturnal monitoring of CO_2. $AHI_{software}$ accurately identified obstructive events and can be used to modify NIV settings.

Trial registration: N° NCT01845233.

1. Introduction

Non-invasive ventilation (NIV) is used for long-term treatment of patients with chronic hypercapnic respiratory failure (CRF). The majority of patients receive NIV treatment overnight. Over time, progression of the underlying disease causing CRF [1] or occurrence of other sleep-related events such as upper airway obstruction, may reduce the effectiveness of nocturnal NIV. In addition, NIV-related events

Abbreviations: NIV, Non-invasive ventilation; CRF, Chronic hypercapnic respiratory failure ABG; arterial blood gas, AASM; American Academy of Sleep Medicine, SpO_2; Pulse oximetry NH, Nocturnal hypoventilation; PG, Sleep polygraphy; $PtcCO_2$, Transcutaneous CO_2; ODI, Oxygen desaturation index (ODI); AHI, Apnea/hypopnea Index; PVA, Patient-ventilator asynchrony; NMD, Neuromuscular diseases; OHS, Obesity hypoventilation syndrome; SpO290, percentage of time spent with SpO_2 < 90%; TRT, Total recording time; HI, Hypopnea index; CHI, Central hypopnea Index; OHI, Obstructive hypopnea index; PVA%, Percentage of total recording time with patient-ventilator asynchrony; A, Apnea; H, Hypopnea; OH, Obstructive hypopnea

* Corresponding author. Oslo University Hospital Ullevål, Postboks 4956 Nydalen, 0424, Oslo, Norway.
E-mail address: UXSIRR@ous-hf.no (S. Aarrestad).

[1] The authors have contributed equally to the conduction of the study.

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such as patient-ventilator asynchrony, mask leaks and NIV-induced upper airway obstruction may occur [2,3]. NIV-induced hyperventilation, obstruction at glottic or subglottic level due to high pressure or flow and obstruction at tongue base aggravated by oro-nasal masks have been suggested as NIV-related mechanisms of obstructive events [3–7]. These respiratory events are frequent during NIV [8,9] and may be of prognostic importance [10–12]. Thus, there is an increasing awareness of the necessity of regular nocturnal monitoring of long-term NIV. However, no consensus exists regarding which tests should be included in these follow-up visits and methods used vary from a single daytime arterial blood gas (ABG) measurement to polysomnography (PSG) [13]. American Academy of Sleep Medicine (AASM) recommendations for best clinical practice state that patients on long-term NIV at follow-up should be assessed by measures of oxygenation and ventilation (ABG, end-tidal CO_2, transcutaneous CO_2), carried out during quiet breathing while awake and at rest. A repeated NIV titration study with PSG should be considered only if respiratory function or sleep quality deteriorates [1]. Others have recommended nocturnal pulse oximetry (SpO_2) or a combination of daytime ABG sampling and nocturnal SpO_2 [14,15]. Recently, a step by step algorithm for monitoring NIV has been proposed by the SomnoNIV group [14]. This algorithm suggests that a combination of clinical evaluation, daytime ABG, nocturnal SpO_2 and a synthesis report from NIV software should be used as the first step in a clinical pathway for monitoring long-term NIV. If normal, home NIV should be pursued without modifications, while an abnormal test should prompt clinical intervention, such as modification of NIV interface, settings, or further diagnostic testing. However, none of these proposed follow-up regimens has been prospectively evaluated in a population treated with long term NIV.

We hypothesised that a screening test panel consisting of clinical evaluation, daytime ABG, nocturnal SpO_2, and a synthesis report from NIV software is sufficient for detecting nocturnal hypoventilation (NH) and other sleep related respiratory events during regular follow-up visits of CRF patients treated with long term NIV. The aim of this study was to analyse the ability of a combination of all of the components of the screening test panel to detect nocturnal hypoventilation and other sleep related respiratory events using sleep polygraphy (PG) and nocturnal transcutaneous CO_2 ($PtcCO_2$) as reference tests. In addition, we aimed to analyse the contribution of specific components of the test panel to detect specific nocturnal respiratory events, i.e.: nocturnal SpO_2 and daytime ABG as markers of NH, oxygen desaturation index (ODI) and apnea-hypopnea index (AHI) from NIV software ($AHI_{software}$) as markers of apnea-hypopnea, and ODI as a marker of patient-ventilator asynchrony (PVA), using the same reference tests.

2. Materials and methods

2.1. Patients

Patients eligible for inclusion were consecutive adults with CRF due to neuromuscular diseases (NMD) or chest wall disorders treated with long term NIV scheduled for a regular follow-up visit between April 2013 and May 2014 at the Department of Pulmonary Medicine of Oslo University Hospital. One month prior to their appointment they received a written invitation to participate in the study. Study inclusion criteria were CRF due to NMD, restrictive thoracic disorders, obesity hypoventilation syndrome (OHS) or central hypoventilation syndrome and NIV treatment for a minimum of 3 months. Exclusion criteria were: age below 18 years, inability to co-operate, hospitalization due to an acute exacerbation or change of NIV treatment < 3 months before inclusion.

2.2. Study design

We performed a prospective cross-sectional diagnostic accuracy study. The accuracy of a screening test panel and selected components of the test panel for detecting sleep-related respiratory events during long term NIV was tested, using $PtcCO_2$ and PG as reference tests. Data collection was planned and consecutively performed when participants were hospitalized overnight for their regular NIV follow-up visit. Index tests and reference tests were performed simultaneously in all participants; nocturnal measurements were performed during NIV.

2.3. Measurements

A pulmonary physician experienced in long term NIV evaluated if the patient had symptoms of sleep disordered breathing (morning headaches, daytime sleepiness, fatigue, sleep disruption, nocturnal dyspnea, perceived asynchrony with ventilator). A short questionnaire was used to record whether the physician evaluated clinical status as satisfactory or not. The physician was blinded to the results of $PtcCO_2$ and polygraphy.

Daytime ABG sampling was performed between 12:00 and 2:00 PM while patients were awake and breathing room air, as previously described [9]. Nocturnal SpO_2 (Nonin 2500) was analysed with NVision 5.02 after visual inspection and exclusion of obvious artifacts. Data memorized by ventilator software were downloaded with Rescan 04.01.013 or Encore Pro 2 2.1.6.0. Summary data of 3 months compliance, leaks covering both the prior 3 months and the study night and automated $AHI_{software}$ from the study night were collected.

2.4. Index tests

2.4.1. Screening test panel

The screening test panel was a combination of clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2 and assessment of compliance (from ventilator software). The accuracy of this test panel for detection of hypoventilation, apnea-hypopnea and patient-ventilator asynchrony was evaluated.

The screening test panel was classified as abnormal if any of the following pre-specified criteria were met [14]: clinical status evaluated as non-satisfactory by the physician, abnormal daytime $PaCO_2$ or nocturnal SpO_2, or poor compliance, as defined below. Daytime $PaCO_2 > 6.0$ kPa was considered abnormal. SpO_2 was considered abnormal if the percentage of time spent with $SpO_2 < 90\%$ (SpO_290) was $\geq$ 10% of total recording time (TRT) or if recurrent SpO_2 oscillations were present. Recurrent SpO_2 oscillations were defined as $\geq$ 5 events/hour with 3% oxygen desaturation from baseline lasting 10–90 s (ODI3%). (Oscillation criterion was based on current clinical practice in our department). Compliance was reported as poor if the 3 month synthesis report showed less than 4 h/night of use or a pattern suggestive of discomfort (i.e. fragmented use or multiple short periods of ventilator use).

2.4.2. Selected tests for detecting specific nocturnal respiratory events

The accuracy of selected variables to detect NH, apnea-hypopnea, and PVA was evaluated. Tests were scored as abnormal according to the following pre-specified cut-off values: for detection of NH: 1/daytime $PaCO_2 > 6.0$ kPa [16]; $2/HCO_3^- \geq 27$ mmol/L [17] and 3/$SpO_290 \geq 10\%$ of TRT [14]; for detection of apnea-hypopnea: 1/ODI3% $\geq$ 5 and $2/AHI_{software} > 7.2$ (based on a receiver operating characteristic (ROC) curve analysis described in the supplement) and for detection of PVA: ODI3% $\geq$ 5.

2.5. Reference tests

$PtcCO_2$ (TCM Tosca with Sensor 92, Radiometer, Denmark) was performed and analysed with Visi-Download after visual inspection and exclusion of obvious artifacts as previously described [18]. $PtcCO_2$ was scored as abnormal using the following pre-specified cut off values for hypercapnia:

1. Hypoventilation$_{AASM}$: an increase in $PtcCO_2$ to a value > 7.3 kPa for ≥ 10 min ($AASM_1$) and/or an increase in $PtcCO_2$ ≥ 1.3 kPa in comparison to an awake value exceeding 6.7 kPa ≥ 10 min ($AASM_2$) [19].
2. Hypoventilation$_{TRT}$: $PtcCO_2$ > 6.5 kPa ≥ 10% of TRT [11].
3. Hypoventilation$_{MAX}$: Peak $PtcCO_2$ > 6.5 kPa [20].

Respiratory polygraphy (Embletta Gold, Embla, Broomfield, USA) was performed and scored independently by two pulmonologists, blinded to the results of the index tests, as previously described [9]. In brief: we scored apnea (A) and hypopnea (H) based on criteria adapted from AASM [19]. Hypopneas were sub-classified as either obstructive (OH) or central (CH). A pre-specified threshold of 10 events/hour was used for abnormal $AHI_{polygraphy}$ [21,22]. Criteria for asynchrony were adapted from previous studies [23–25]. The duration of these events was reported as the percentage of TRT with patient-ventilator asynchrony (PVA%). A pre-specified threshold of 10% was used for defining abnormal PVA% [23,26,27].

Polygraphy signals were also evaluated for leaks. Respiratory events were not scored during periods with high unintentional leaks. Asynchronies were not scored if an apnea or hypopnea was present.

2.6. Statistics

Data are presented as mean ± standard deviation if normally distributed, and otherwise as median (IQR). Differences in patient characteristics were analysed using one-way ANOVA. For analysis of ventilator settings we used Kruskal-Wallis tests when analysing all patient groups and Mann-Whitney *U* test for comparing two patient groups. P-values below 0.05 were considered significant. Missing data from 2 $AHI_{software}$ and 1 $PtcCO_2$ were handled by exclusion of the paired data for the relevant analysis. Cross-tabulations were used to calculate sensitivity and specificity with 95% confidence intervals. SPSS 24 and MedCalc 15.4 were used for statistical analysis.

3. Results

Ninety-five patients met the inclusion criteria. Twenty-eight patients were not included for reasons detailed in Fig. 2S (Supplement). The remaining 67 patients were treated with NIV for OHS (n = 16), alveolar hypoventilation due to NMD (n = 36), central hypoventilation syndrome (n = 5) or hypoventilation due to restrictive thoracic disorders (n = 10). Main characteristics of patients are given in Table 1S (Supplement).

3.1. Index tests

3.1.1. Screening test panel

Clinical evaluation, ABG and nocturnal SpO_2 were successfully performed in all patients. A 3-month synthesis report and detailed data from the study night were downloaded from the ventilator in 65 patients. Two patients had missing data due to data storage problems with the device. One was ventilator dependent 24/7 and 3-month compliance was set at 24 h/day. For the second patient, the 3-month compliance data from the previous follow-up was used. Thus, compliance data for 67 patients were analysed. Median unintentional leak was > 24 L/minute in 1 patient. The screening test panel was abnormal in 47 (70%) patients: symptomatic: 3; daytime $PaCO_2$ level: 36; abnormal SpO_2: 37; unsatisfactory compliance: 10 (Table 1 and Supplementary Table 2S).

3.1.2. Selected tests for detecting specific nocturnal respiratory events

For the detection of NH: 36 patients (53%) had a daytime $PaCO_2$ > 6.0 kPa; 39 patients (58%) had a HCO_3^- ≥ 27 mmol/L and 21 patients (31%) had a SpO_290 ≥ 10% of TRT. For the detection of apnea-hypopnea: 36 patients (34%) had an ODI3% ≥ 5. $AHI_{software}$ was > 7.2 in 18 patients (27%). For the detection of PVA: 36 patients (34%) had an ODI3% ≥ 5 (Table 2).

3.2. Reference tests

$PtcCO_2$ was performed in all patients. An obvious technical error occurred in one patient. Respiratory polygraphy was performed in all patients. (All recordings lasted > 5 h). Results are summarized in Tables 2 and 2S (supplement). In the 31 patients with hypoventilation according to Hypoventilation$_{TRT}$, median % of TRT spent with $PtcCO_2$ above 6.5 kPa was 69% (IQR 44–92). In the 16 patients with AHI > 10, median AHI was 19 (IQR: 16–25), median OH index was 18 (IQR 14–21) and in 15 of 16 patients > 95% of the events were obstructive [9]. In the 14 patients with PVA% > 10, median PVA% was 17 (IQR: 14–26).

Periods with high unintentional leaks were rarely observed on the polygraphy traces.

3.3. Index tests compared with reference tests

Tables 3 and 4 present the sensitivity and specificity of the index tests for sleep related respiratory events.

Scatterplots of comparison of $PtcCO_2$ with SpO_2 and $AHI_{polygraphy}$ with ODI3% and $AHI_{software}$ are shown in Figs. 3S–5S (supplement). All 3 patients evaluated as symptomatic spent > 40% of TRT with a $PtcCO_2$ above 6.5 kPa and 1 had an AHI > 10. Of the 10 patients with abnormal compliance, 9 had sleep-disordered breathing.

Abnormal daytime HCO_3^- or a combination of criteria "abnormal daytime $PaCO_2$" and/or "abnormal nocturnal SpO_2" did not have an increased sensitivity for NH (Tables 3S–5S supplement).

4. Discussion

In a group of stable patients under long term NIV for CRF, we studied the accuracy of a panel of simple tests (clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2 and compliance) for detecting undesired nocturnal respiratory events during a regular follow-up visit. The intended use of these tests is to monitor nocturnal NIV efficacy and limit the need for $PtcCO_2$ and PSG/PG, methods that are associated with higher costs, lack of availability and which require expertise. Our main findings were that: 1/very few patients had clinical symptoms of sleep related breathing disorders in spite of the presence of undesired nocturnal respiratory events in a significant proportion of patients; 2/neither a screening test panel, nocturnal SpO_2 nor daytime $PaCO_2$ had a sufficient accuracy for detecting NH; 3/$AHI_{software}$ accurately detected apneas or hypopneas and can guide ventilator settings with the devices used in the present study, limiting the need for sleep PG to patients unresponsive to treatment or with suspected PVA; 4/all tests used had a poor sensitivity and specificity for detecting PVA.

This is the first study to prospectively evaluate the usefulness of the test panel proposed by the SomnoNIV group as first step in a clinical pathway for monitoring long term NIV. Seventy percent of the patients had abnormal results for one or more of the tests. Only 3 patients however were symptomatic. Thus relying on medical history alone is insufficient when monitoring patients on long-term NIV. According to the definition used, the screening test panel had a moderate sensitivity (80–87%) for NH (with a low specificity); for detecting a residual AHI > 10/hour, sensitivity was acceptable (91%); it was low however for PVA (71%). Thus the strategy proposed is reasonably effective for detecting a residual AHI > 10/hour, but not for excluding NH – whatever the definition used – or PVA.

Noteworthy is the wide variability in prevalence of NH in this group of patients, depending on the definition used for NH. In the present study we used 3 previously published definitions of NH. There is currently no consensus regarding what level of nocturnal hypercapnia is clinically relevant, although expert-devised scoring rules for sleep

Table 1
Cross-tabulation of $PtcCO_2$ and screening test panel, $SpO_2$90 and daytime $PaCO_2$ for the detection of hypoventilation.

Test applied:	$PtcCO_2$ criteria for hypoventilation:						Total number of patients N = 66[a]
	AASM 1 and/or AASM 2		$PtcCO_2$ > 6.5 kPa > 10% of TRT		$PtcCO_2$ max ≥ 6.5 kPa		
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
Screening test panel							
Normal	17 (26%)	3 (5%)	15 (22%)	5 (8%)	10 (15%)	10 (15%)	20 (30%)
Abnormal	26 (39%)	20 (30%)	20 (30%)	26 (39%)	6 (9%)	40 (60%)	46[a](70%)
$SpO_2$90 ≥ 10% of TRT							
Normal	33 (50%)	12 (18%)	26 (39%)	19 (29%)	14 (21%)	31 (47%)	45[a](68%)
Abnormal	10 (15%)	11 (17%)	9 (14%)	12 (18%)	2 (3%)	19 (29%)	21 (32%)
Daytime PCO_2 > 6.0 kPa							
Normal	25 (38%)	6 (9%)	23 (35%)	8 (12%)	14 (21%)	17 (26%)	31 (47%)
Abnormal	18 (27%)	17 (26%)	12 (18%)	23 (35%)	2 (3%)	33 (50%)	35[a](53%)
Total numbers of patients	43 (65%)	23 (35%)	35 (53%)	31(47%)	16 (24%)	50 (76%)	

Numbers given as number of patients (% of total numbers of patients), $PtcCO_2$: transcutaneous CO_2; $SpO_2$90: nocturnal SpO_2 < 90%; AASM: American Academy of Sleep Medicine. (See text for definition of hypoventilation criteria); TRT: total recording time.
[a] PtcCO2 data missing in one patient; see text for explanation.

Table 2
Cross-tabulation of $AHI_{polygraphy}$ and PVA and screening test panel, ODI and $AHI_{software}$ for the detection of PVA or elevated AHI.

Test applied:	$AHI_{polygraphy}$ ≥ 10		PVA% > 10% of TRT		Total number of patients N = 67
	Normal	Abnormal	Normal	Abnormal	
Screening test panel					
Normal	19 (28%)	1(1%)	16 (24%)	4 (6%)	20 (30%)
Abnormal	32 (48%)	15 (22%)	37 (55%)	10 (15%)	47 (70%)
ODI3% ≥ 5					
Normal	30 (45%)	1 (1%)	24 (36%)	7 (10%)	31 (46%)
Abnormal	21 (31%)	15 (22%)	29 (43%)	7 (10%)	36 (54%)
$AHI_{software}$ > 7.2					
Normal	46 (69%)	1 (1%)			47 (70%)
Abnormal	4 (6%)	14 (21%)			18 (27%)
Data missing[a]	1 (1%)	1 (1%)			2 (3%)
Total numbers of patients	51 (76%)	16 (24%)	53 (79%)	14 (21%)	

Numbers given as number of patients (% of total numbers of patients), AHI: apnea-hypopnea index; PVA; patient-ventilator asynchrony; ODI: Oxygen desaturation index; TRT: total recording time.
[a] Data missing in two patients; see text for explanation.

Table 3
Sensitivity and specificity of screening test panel, SpO_2 and daytime ABG for nocturnal hypoventilation.

Test applied:	$PtcCO_2$ criteria for hypoventilation:		
	AASM 1 and/or 2	$PtcCO_2$ > 6.5 kPa > 10% of TRT	Peak $PtcCO_2$ > 6.5 kPa
Screening test panel			
Sensitivity	87%(66–97)	84% (66–95)	80% (66–90)
Specificity	40% (25–56)	43% (26–61)	63% (35–85)
$SpO_2$90 ≥ 10% of TRT			
Sensitivity	48% (27–69)	39% (22–58)	38% (24–53)
Specificity	77% (61–88)	74% (57–88)	88% (62–98)
Daytime $PaCO_2$ > 6.0 kPa			
Sensitivity	74% (52–90)	74% (55–88)	68% (53–80)
Specificity	58% (42–73)	66% (48–81)	94% (70–100)

Numbers given as % (95% confidence interval). $PtcCO_2$: transcutaneous CO_2; AASM.
American Academy of Sleep Medicine. (See text for definition of hypoventilation criteria).
TRT: total recording time; $SpO_2$90: nocturnal SpO_2 < 90%.

Table 4
Sensitivity and specificity of screening test panel, ODI3% and $AHI_{software}$ for detecting $AHI_{polygraphy}$ and PVA%.

Test applied:	AHI polygraphy > 10	PVA% > 10% of TRT
Screening test panel		
Sensitivity	91% (59–100)	71% (42–92)
Specificity	37% (24–52)	30% (18–44)
ODI3% ≥ 5		
Sensitivity	94% (70–100)	50% (23–77)
Specificity	59% (44–72)	45% (32–60)
$AHI_{software}$ > 7.2		
Sensitivity[a]	93% (68–100)	
Specificity[a]	92% (81–98)	

Numbers given as % (95% confidence interval). ODI: Oxygen desaturation index.
AHI: apnea-hypopnea index; PVA: patient-ventilator asynchrony; TRT: total recording time.
[a] Representing result from 65 patients; se text for explanation.

hypoventilation exist [19]. Peak nocturnal $PtcCO_2$ > 6.5 kPa has been shown to predict the need for long term home mechanical ventilation (LTMV) and daytime ventilatory failure [20] in neuromuscular patients [28] while [$PtcCO_2$ > 6.5 kPa > 10% of TRT] is associated with increased mortality and respiratory events requiring ICU admission in mechanically ventilated neuromuscular patients [11]. The optimal criterion may differ according to the purpose of nocturnal $PtcCO_2$ monitoring: to decide when initiation of LTMV is appropriate or to monitor efficacy of LTMV after treatment has been established. Further studies are necessary to determine the most relevant threshold(s) for $PtcCO_2$.

Our study also aimed to evaluate the performance of specific tests as triage tests for specific nocturnal events. $SpO_2$90 < 10% of TRT and daytime $PaCO_2$ > 6.0 kPa were assessed as markers of NH, ODI3% and $AHI_{software}$ as markers of apnea-hypopnea index above 10 and ODI3% as marker of PVA% > 10% of TRT. More than 50% of the patients with NH had a normal nocturnal $SpO_2$90. Thus, our results confirm the findings of two retrospective studies and one prospective study on children using NIV showing that nocturnal SpO_2 has a poor sensitivity for detecting NH [11,29,30]. In agreement with Nardi et al. the present study also showed that a normal daytime $PaCO_2$ cannot rule out NH, which was present in 9–26% of patients depending on the definition used [29].

Both ODI3% and $AHI_{software}$ performed well in ruling out AHI ≥ 10, while $AHI_{software}$ also performed well in ruling in AHI ≥ 10, the latter

result confirming results of two studies performed in OHS patients on NIV [21,22].

The sensitivity of ODI 3% for detecting PVA% > 10% of TRT was poor, reflecting the fact that PVA events were rarely associated with desaturations [9]. Furthermore, the poor specificity of ODI 3% for PVA reflects the fact that desaturations are frequently caused by other events than PVA.

4.1. Study limitations

Our study has some limitations. $PtcCO_2$ was used as reference test for the detection of NH. Technical problems, accuracy compared with ABG and instrumental drift have been claimed to limit the value of this test. ABG remains the gold standard for detecting hypercapnia, but ABG sampling is not feasible for monitoring CO_2 during sleep without invasive procedures (arterial line, or repeated punctures with arousals). $PtcCO_2$ has been proposed as an acceptable surrogate for monitoring $PaCO_2$ during sleep [14,19]. Indeed, Storre et al. and Hazenberg et al. have shown that PtcCO2 accurately reflects $PaCO_2$ during nocturnal NIV, and in a recent study in the same setting, our group showed that $PtcCO_2$ performed accurately for measuring $PaCO_2$ with a minor instrumental drift in the majority of patients when used by an experienced team [18,31,32].

The use of a type III polygraphy instead of PSG (i.e. without EEG) in the scoring of respiratory events may have led to an underestimation of hypopnea. We used autonomic microarousals (drop of 30% in pulse wave amplitude) as a surrogate for EEG arousals to enhance identification of hypopnea [9] Still, the accuracy of ODI3% and $AHI_{software}$ for detecting AHI could have been overestimated. In many countries, the routine use of PSG for monitoring of NIV is just not possible because of poor availability of sleep laboratories, in spite of the AASM recommendations. Therefore, use of a type III polygraphy instead of PSG reflects routine practice in many centres, with the above-mentioned limitations.

Similarly, when scoring PVA we did not include additional indicators of inspiratory effort such as oesophageal pressure or diaphragm/accessory muscle electromyogram [33,34] because these tests are seldom used in clinical practice.

We did not score asynchrony during episodes of apnea-hypopnea or leaks. Leaks were a minor problem in this cohort: level of leaks detected from ventilator software, and (rarely) on PG, were very low and thus could not substantially influence our results. Not scoring PVA during apnea-hypopnea reflects a clinical pragmatic approach in this situation: apnea-hypopnea may generate PVA, and correcting apnea-hypopnea is the first step to be undertaken. Currently there is no consensus in how to score PVA and scoring was therefore based on previous publications on long term NIV.

Another limitation is the small sample size due to the rareness of the diseases studied, resulting in relatively wide confidence interval of the accuracy analysis performed. Thus, the results should be interpreted with caution.

Finally, a data-driven cut-off value for $AHI_{software}$ was used to enhance the diagnostic accuracy of $AHI_{software}$. Thus these results may be influenced by our cohort and by the devices used, and require further validation with other home ventilators.

4.2. Clinical implications

Persistent NH may have a negative impact on prognosis in NIV-treated patients with CRF [10–12]. Thus, it seems relevant to screen for NH during follow up visits of these patients. However, neither nocturnal SpO_2 nor daytime ABG, nor the combination of tests evaluated in this study is sensitive enough to rule out NH and, when abnormal, these widely used tests are not specific enough to diagnose persistent NH, underlining the importance of nocturnal monitoring of CO_2.

Twenty-four percent of the patients studied had an AHI ≥10, OH being by far the most frequent event. OH are most frequently caused by unstable upper airways leading to oropharyngeal collapse although other mechanisms may be involved [9]. Increase of EPAP has been shown to correct AHI in most cases [4]. Given the high sensitivity and specificity of $AHI_{software}$ for AHI ≥ 10 it seems reasonable to increase EPAP in order to treat upper airway obstruction diagnosed with $AHI_{software}$ especially in clinics without easy access to PSG/PG. Thus, limiting the need for PSG/PG or even invasive studies such as endoscopy [4] to non-responders to treatment modification. In centres were PSG/PG during NIV treatment is readily available the results of $AHI_{software}$ could be used to select patients in need of NIV titration studies utilizing PSG/PG. Our data also suggest that in patients with low levels of mask leaks and ODI3% ≥ 5, PSG/PG is needed to establish the cause of desaturations due to the low specificity of ODI3% for AHI > 10.

The prognostic impact of PVA in patients treated with LTMV remains unclear [35], while results as to its impact on sleep [24,25] and gas-exchange [9,24,33,36] are conflicting. Thus, it is not known to what extend PVA should be systematically sought for and corrected in LTMV. PVA can be a source of discomfort and compromise efficacy of NIV in certain settings [34]. In patients with unexplained poor gas exchange, symptoms of sleep disordered breathing or poor compliance, PVA is a possible explanation. Given the poor accuracy of the tests for detecting PVA in this study, these selected patients would need PG/PSG with markers of inspiratory effort for diagnosis.

The follow up strategies for long-term NIV include, but are not limited to, monitoring of nocturnal ventilation. In addition, models for care of chronic sick patients living at home are evolving [37], as are the development of tele-monitoring for home ventilatory assistance [38]. $PtcCO_2$ can be performed at the patient's home [39] and ventilator software data are increasingly remotely available [38,40]. Our study underlines the importance of nocturnal monitoring using $PtcCO_2$ and the usefulness of ventilator software data and may have implications on the development of future strategies for long-term NIV monitoring.

5. Conclusion

Our data demonstrate the importance of systematically evaluating the efficacy of nocturnal NIV in patients with CRF. Neither a screening test panel consisting of clinical evaluation, daytime $PaCO_2$, nocturnal SpO_2 and compliance, nor nocturnal SpO_2 or daytime ABG accurately detected NH. Thus, implementing $PtcCO_2$ in the routine follow-up of these patients seems appropriate. AHI obtained from a synthesis report from NIV software accurately identified obstructive events. However, further studies are needed to confirm the optimal cut-off value for $AHI_{software}$, probably for each specific ventilator in use. Further studies are also warranted for how to best select patients to be evaluated for PVA.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, NO = 2012/1142. Written informed consent was obtained from all participants.

Competing interests

SA has received fees for lecturing from Philips-Respironics and ResMed, outside of the presented work. All other authors have no competing interests to declare.

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Authors' contributions

SA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SA, ALK and MQ contributed substantial to acquisition of data. SA, ET, ALK, MQ, OHS and JJ contributed substantial to the study concept and design, data interpretation, critical revision of the manuscript for important intellectual content, and final approval of the manuscript.

Appendix A. Supplementary data

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Supplement

Contents

1. Receiver operating characteristics curve and cut-off calculation for $AHI_{software}$

1.1 Statistics

The receiver operating characteristics (ROC) curve was obtained for the various $AHI_{software}$ cut-off values for detecting $AHI_{polygraphy} > 10$. To determine the cut-off value with the maximum sensitivity and specificity, Youden's index J was calculated. We calculated the area under the receiver operating characteristics curve (AUC) to evaluate the accuracy of $AHI_{software}$ in detecting $AHI_{polygraphy} > 10$. A ROC curve was also obtained limited to the 55 patients with ResMed devices.

1.2 Results

Figure 1S shows the receiver operating characteristics (ROC) curve for various cut-off values for $AHI_{software}$. Youden index J was 0.8533 with the associated $AHI_{software}$ cut-off criterion >7.2. Sensitivity and specificity of for $AHI_{software} > 7.2$ for $AHI_{polygraphy} >10$ are reported in table 3 (main text). Area under the ROC curve (AUC) was 0.97 (95% Confidence interval (CI) 0.89 – 1.0). For the patients with ResMed devises AUC was 0.96 (95% CI 0.87 - 1.0, p <0.0001, sensitivity 93 % (CI 66 – 100) and specificity 90% (CI 77 – 97) for $AHI_{polygraphy} >10$ using a cut-off value of $AHI_{software} >7.2$.

2. Figures

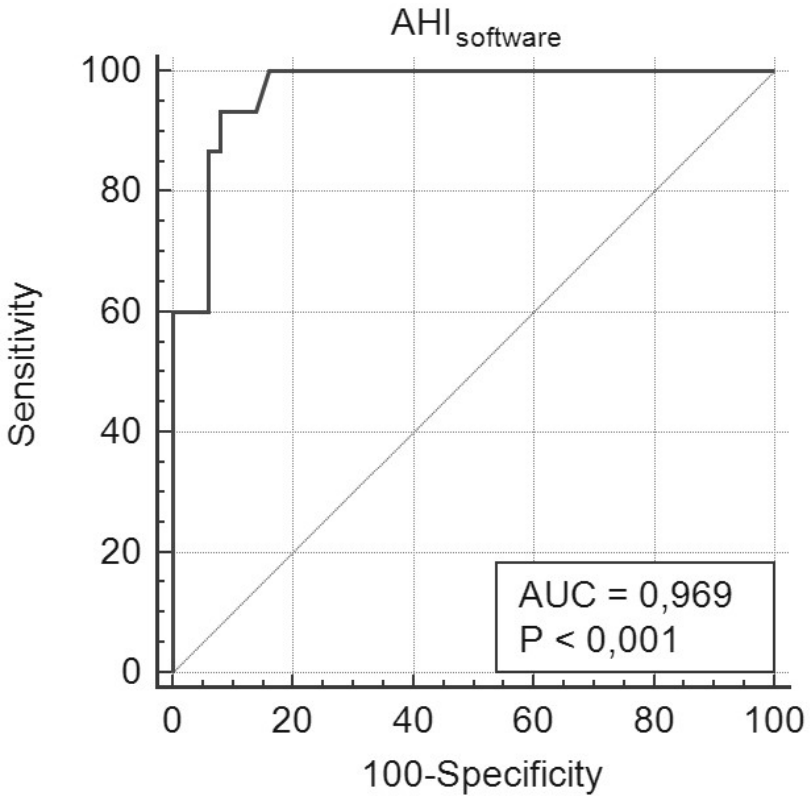

Figure 1S Receiver operating characteristics (ROC) curve for various cut-off values for $AHI_{software}$

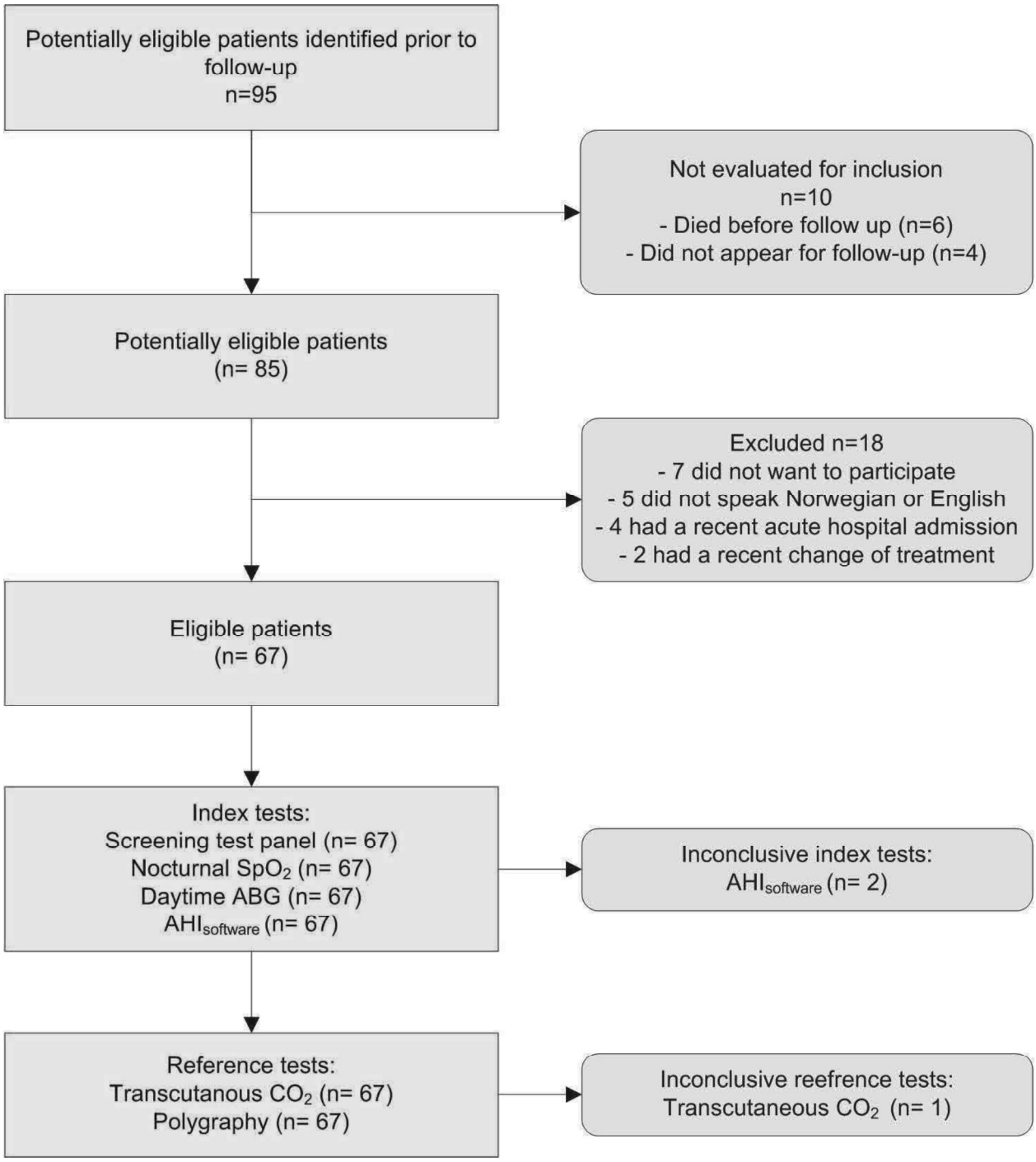

Figure 2S. Flow chart of patient inclusion

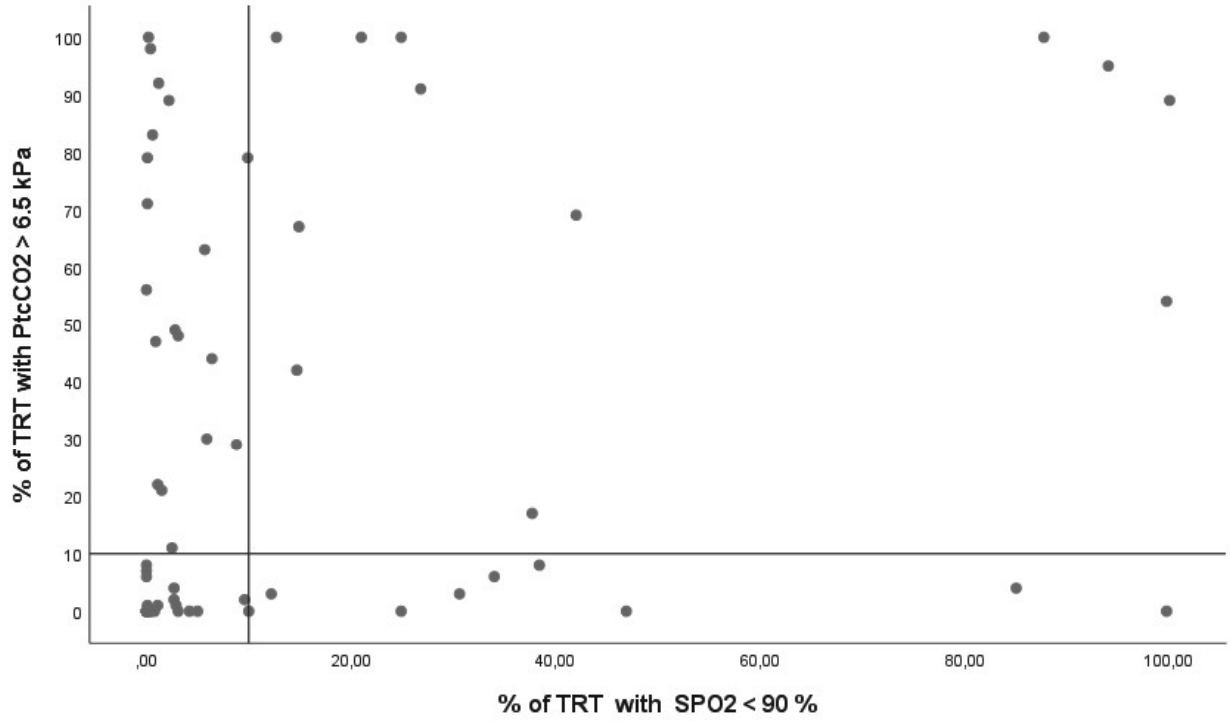

Figure 3S. Scatterplot of transcutaneous CO_2 ($PtcCO_2$) compared with nocturnal SpO_2. Each point corresponds to % of total recording time (TRT) with $PtcCO_2$ > 6.5 kPa and % of TRT with SpO_2 < 90% (matched data from each patient). Horizontal and vertical lines correspond to cut-off values described in main text.

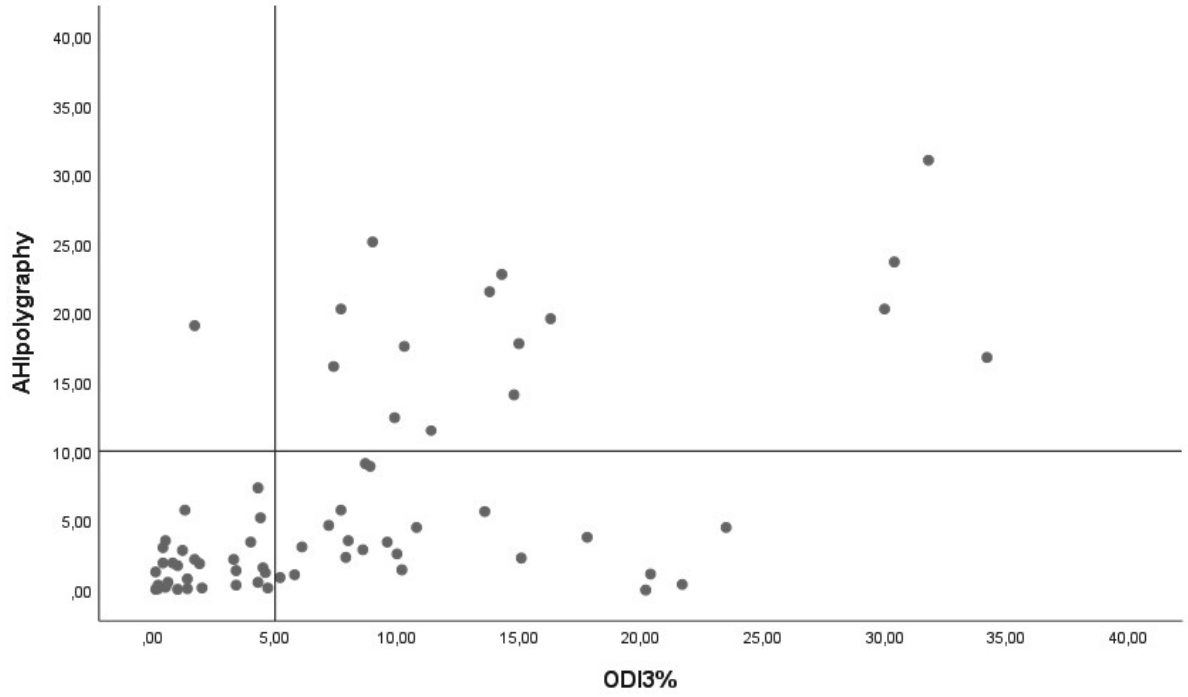

Figure 4S. Scatterplot of $AHI_{polygraphy}$ compared with oxygen desaturation index of 3% (ODI3%). Each point corresponds to $AHI_{polygraphy}$ and ODI3% (matched data from each patient). Horizontal and vertical lines correspond to cut-off values described in main text.

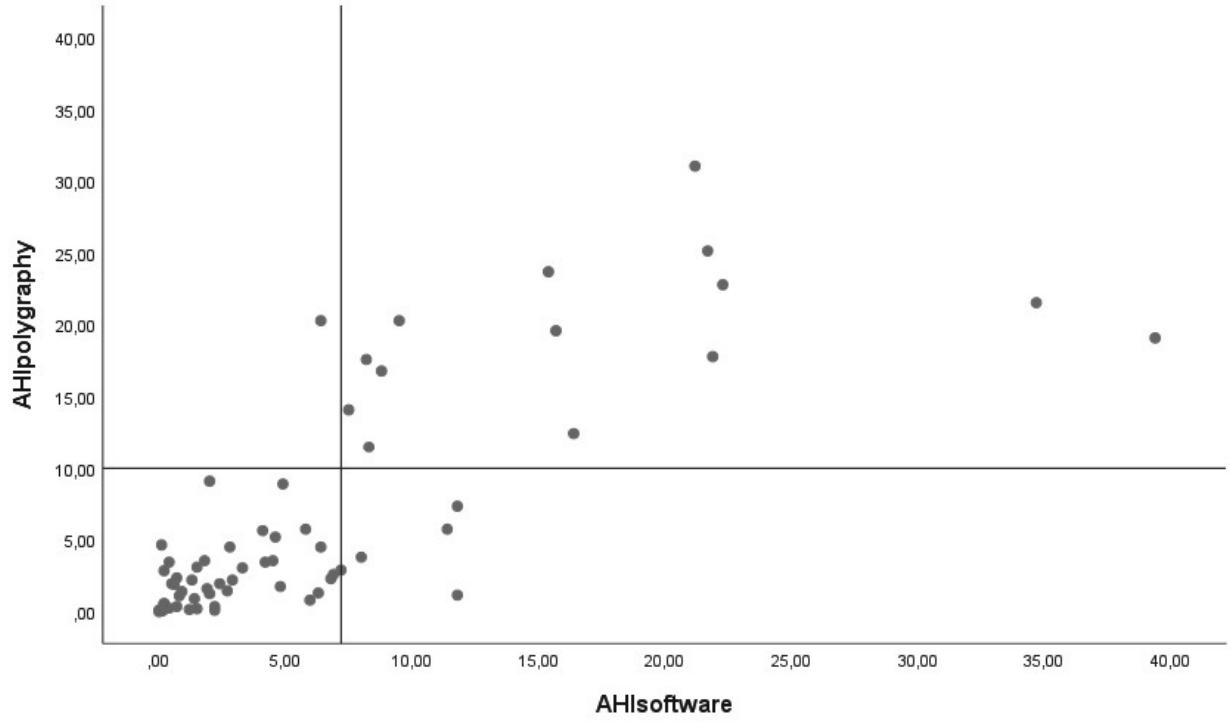

Figure 5S. Scatterplot of $AHI_{polygraphy}$ compared with $AHI_{software}$. Each point corresponds to $AHI_{polygraphy}$ and $AHI_{software}$ (matched data from each patient). Horizontal and vertical lines correspond to cut-off values described in main text.

3. Tables

Table 1S. Main characteristics of study population

	All patients	**Thoracic cage disorder**		**Neuromuscular disorder**		
		OHS	RTD	NMD	CHS	p
	(n = 67)	(n =16)	(n = 10)	(n =36)	(n = 5)	
Age (years)	57.7 ± 19.2	65±12	45±25	59±19	49±14	0.04
BMI (kg/m^2)	28.1 ± 7.7	36.7±5.2	26.5±8.1	24.8±5.7	28.0±5.8	<0.001
Male/female	35/32	8/8	3/7	20/16	4/1	
NIV duration, month, median(IQR)	54 (14–94)	35 (7-58)	80 (34-94)	57 (13-118)	60 (24-111)	0.18
FEV_1(% predicted)	47.0 ± 24.5	58.3±22.3	48.3±32.3	37.1±17.8	78.6±16.7	<0.001
FVC (% predicted)	51.4 ± 26.4	71.3±22.2	50.6±31.3	38.2±17.9	84.6±10.5	<0.001
FEV_1/FVC (%)	75.0 ± 13.6	63.5±11.9	76.8±11.5	79.6±12.7	74.6±9.2	0.001
Comorbidities: COPD/ heart failure/ renal failure/chronic opioid use, n	12/7/1/6	9/5/1/2	0	3/2/0/3	0/0/0/1	
Ventilator Settings:						
IPAP* (cm H2O)	16 (14-19)	20 (14-24)	16 (15-18)	16 (12-18)	12 (11-16)	0.03
EPAP (cm H2O)	5 (4-6)	8 (6-10)	5 (4-7)	4 (4-6)	4 (2-6)	<0.001
Back-up respiratory rate (breaths/minute)	12 (10-15)	12 (10-13)	13.5 (12-15)	12 (10-15)	15 (10-16)	0.5
Ventilator mode;						
Bi-level ST/ PS-VT/VCV/PCV, n	57/8/1/1					
ResMed ventilator / Philips Respironics ventilator, n	57/10					
Supplementary oxygen/humidifier/ cough assist, n	1/33/8					
Interface; oro-nasal /nasal/nasal prongs, n	31/23/13					

Values presented as mean ± SD, unless specified otherwise.

OHS: obesity hypoventilation syndrome; NMD: neuromuscular diseases; RTD: restrictive thoracic disorders; CHS: central hypoventilation syndrome. *In PC mode peak inspiratory pressure was used for calculation and in PS-VT / VCV mean overnight inspiratory pressure was used for calculation.

OHS: obesity hypoventilation syndrome; NMD: neuromuscular diseases; RTD: restrictive thoracic disorders; CHS: central hypoventilation syndrome; I(E)PAP: Inspiratory (expiratory) positive airway pressure; ST; spontaneous-timed; PS-VT pressure support- volume targeted; VCV/PCV volume/pressure controlled ventilation.

Table 2S. Results from daytime ABG, nocturnal SpO_2, ventilator software, transcutaneous CO_2 and polygraphy (n = 67)

Daytime ABG	
$PaCO_2$ (kPa)	6.1 ± 0.9
PaO_2 (kPa)	9.4 ± 1.5
pH	7.38 ± 0.04
HCO_3^- (mmol/L)	26.9 ± 3.4
Nocturnal SpO_2	
Mean SpO_2, %	92.3 ±3.9
$SpO_2$90 % of TRT, median(IQR)	3 (0-15)
ODI3%, median (IQR)	6.1 (1.6–11.1)
Ventilator software	
3 months compliance, hours/day	7.8 ± 4.1
Unintentional leaks:	
Study night: ResMed ventilators (n = 55), (L/min) median (IQR)[a]	2.4 (0.0–6.0)
3 month data: ResMed ventilators (n = 55), (L/min) median (IQR)[a]	4.8 (0.0 -10.2)
Study night: Philips Respironics ventilators (n = 10), (L/min) median (IQR)	2.4 (0.0–15.2)
3 months data: Philips Respironics ventilators (n = 10)[b]	
AHI:	
Study night: AHI ResMed ventilators (n = 55), median (IQR)[a]	3.3 (1.2-8.3)
Study night: AHI Philips Respironics ventilators (n = 10), median (IQR)	3.5 (0.6-6.5)
Transcutaneous CO_2	
$PtcCO_2$(kPa) [c]	6.4 ± 0.9
% of TRT spent with a $PtcCO_2$ above 6.7 kPa, median (IQR)[c]	8 (0-68)
Polygraphy	
TRT, minutes, median (IQR)	462 (451-478)
AHI, median (IQR)	2.9 (1.1-9.1)
PVA % of TRT, median (IQR)	2 (0-7)

Values presented as mean ± SD, unless specified otherwise. ABG: arterial blood gases; $SpO_2$90: percentage of time spent with mean SpO_2 < 90%: TRT: total recording time; ODI: oxygen desaturation index; $PtcCO_2$: Transcutaneous CO_2; AHI: apnea-hypopnea index; PVA; patient-ventilator asynchrony. [a]Data missing in 2 patients; [b]Encore Pro do not provide unintentional leak for 3 months data; [c]Data missing in 1 patients.

Table 3S. Cross-tabulation of $PtcCO_2$ and $SpO_2$90 and daytime $PaCO_2$ combined and HCO_3^- for the detection of hypoventilation

Test performed:	$PtcCO_2$ criteria for hypoventilation:						Total number of patients N = 66*
	AASM 1 and /or AASM 2		PtcCO2 > 6.5 kPa ≥ 10 % of TRT		$PtcCO_2$ max > 6.5 kPa		
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
Daytime $PaCO_2$ > 6.0 kPa or $SpO_2$90 ≥ 10% of TRT							
Normal	22 (33%)	4 (6%)	19 (29%)	7 (11%)	13 (20%)	13 (20%)	26 (39%)
Abnormal	21 (32%)	19 (29%)	16 (24%)	24 (36%)	3 (5%)	37 (56%)	40* (61%)
Daytime HCO_3^- ≥ 27 mmol/L							
Normal	24 (36%)	6 (9%)	22 (33%)	8 (12%)	10 (15%)	20 (30%)	30 (45%)
Abnormal	19 (29%)	17 (26%)	13 (20%)	23 (35%)	6 (9%)	30 (45%)	36* (55%)
Total numbers of patients	43 (65%)	23 (35%)	35 (53%)	31(47%)	16 (24%)	50 (76%)	

Numbers given as number of patients (% of total numbers of patients), $PtcCO_2$: transcutaneous CO_2; AASM: American academy of sleep medicine. (See text for definition of hypoventilation criteria); $SpO_2$90: mean nocturnal SpO_2 < 90%; TRT: total recording time. *$PtcCO_2$ data missing in one patient; see text for explanation.

Table 4S. Cross-tabulation of $PtcCO_2$ and HCO_3^- in patient with normal and abnormal daytime $PaCO_2$ for the detection of hypoventilation

Test performed:	$PtcCO_2$ criteria for hypoventilation:						Total number of patients N = 66*
	AASM 1 and /or AASM 2		PtcCO2 > 6.5 kPa ≥ 10 % of TRT		$PtcCO_2$ max > 6.5 kPa		
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
Daytime $PaCO_2$ > 6.0 kPa							N = 35
HCO_3^- ≥ 27 mmol/L							
Normal	5 (14%)	1 (3%)	4 (11%)	2 (6%)	0 (0%)	6 (17%)	6 (17%)
Abnormal	13 (37%)	16 (46%)	8 (23%)	21 (60%)	1 (3%)	28 (80%)	29* (83%)
Total numbers of patients	18 (51%)	17 (49%)	12 (34%)	23 (66%)	1 (3%)	34 (97%)	
Daytime $PaCO_2$ ≤ 6.0 kPa							N = 31
HCO_3^- ≥ 27 mmol/L							
Normal	19 (61%)	5 (16%)	18 (58%)	6 (19%)	10 (32%)	14 (45%)	24 (77%)
Abnormal	6 (19%)	1 (3%)	5 (16%)	2 (6%)	5 (16%)	2 (6%)	7 (23%)
Total numbers of patients	25 (81%)	6 (19%)	23 (74%)	8 (26%)	15 (48%)	16 (52%)	

Numbers given as number of patients (% of total numbers of patients with daytime PaCO2 > 6.0 kPa (N=35) and daytime PaCO2 ≤ 6.0 kPa (N= 31), $PtcCO_2$: transcutaneous CO_2; AASM: American academy of sleep medicine. (See text for definition of hypoventilation criteria; TRT: total recording time. *$PtcCO_2$ data missing in one patient; see text for explanation.

Table 5S

Sensitivity and specificity of SpO_2 and daytime $PaCO_2$ combined and HCO_3^- for nocturnal hypoventilation

Test applied:	$PtcCO_2$ criteria for hypoventilation:		
	AASM 1 and/or 2	$PtcCO_2$ > 6.5 kPa ≥ 10 % of TRT	Peak $PtcCO_2$ > 6.5 kPa
$SpO_2$90 ≥ 10% of TRT or Daytime $PaCO_2$ ≥ 6.0 kPa			
Sensitivity	83% (61-95)	77% (59-90)	74% (60-85)
Specificity	51% (35-67)	54% (37-71)	81% (54-96)
HCO_3^- ≥ 27 mmol/L			
Sensitivity	74% (52-90)	74% (55-88)	60% (45-74)
Specificity	56% (40-71)	63% (45-79)	63% (35-85)

Numbers given as % (95 % confidence interval). $PtcCO_2$: transcutaneous CO_2; AASM: American academy of sleep medicine. (See text for definition of hypoventilation criteria); TRT: total recording time; $SpO_2$90: mean nocturnal SpO_2 < 90%

Errata

Navn kandidat:

Sigurd Aarrestad

Avhandlingstittel:

Monitoring long-term nocturnal non-invasive ventilation for chronic hypercapnic respiratory failure: What are the basic tools?

Forkortelser for type rettelser:

Cor – korrektur

Side	Linje	Orginaltekst	Type rettelse	Korrigert tekst
22	1	hypoventilasjon	Cor	hypoventilation
33	10	NIV releated	Cor	NIV related
33	26	Recent finding have	Cor	Recent findings have
36	8	leak represent the	Cor	leak represents the
41	35	excursion drop	Cor	excursions drop
44	13	wake up	Cor	wake-up
62	19	clinical	Cor	clinically
63	19	In the subgroup of patients	Cor	In this subgroup of patients,
63	27	8 hour	Cor	8-hour
64	29	test	Cor	tests
72	3	Two pulmonologist	Cor	Two pulmonologists
73	7	3 month	Cor	3-month
75	1	Thirty three	Cor	Thirty-three
75	3	Over all	Cor	Overall
75	21	One year	Cor	One-year
76	10	pulmonary physicians	Cor	pulmonary physician
79	9	clinical settings	Cor	clinical setting
79	22	of others methods	Cor	of other methods
82	30	a statistical significant	Cor	a statistically significant
82	31	clinical significant	Cor	clinically significant
85	2	patient	Cor	patients
94	15	criteria	Cor	criterion
102	2	the clinical relevant	Cor	the clinically relevant