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

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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

**Keywords**

Non-invasive ventilation; Chronic hypercapnic respiratory failure; Hypoventilation; Sleep; transcutaneous CO2, diagnostic accuracy

**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 an SpO2 < 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

## 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 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.

## Materials and methods

### 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.

**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.

**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.

**Index tests**

**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_2$90) was ≥ 10% of total recording time (TRT) or if recurrent $SpO_2$ oscillations were present. Recurrent $SpO_2$ oscillations were defined as ≥ 5 events/hour with 3% oxygen desaturation from baseline lasting 10-90 seconds (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 hours/night of use or a pattern suggestive of discomfort (i.e. fragmented use or multiple short periods of ventilator use).

**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/ $HCO_3^-$ ≥ 27 mmol/L[17] and 3/ $SpO_2$90 ≥10% of TRT[14]; for detection of apnea-hypopnea: 1/ ODI3% ≥ 5; 2/ $AHI_{software}$ > 7.2 (based on a receiver operating characteristic (ROC) curve analysis described in the supplement) and for detection of PVA: ODI3% ≥ 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 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 ($AASM_2$).[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.

**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.

**Results**

Ninety-five patients met the inclusion criteria. Twenty-eight patients were not included for reasons detailed in figure 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).

**Index tests**

**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 24hours/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 liters/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).

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: AASM 1 and/or AASM 2 | | $PtcCO_2$ > 6.5 kPa > 10 % of TRT | | $PtcCO_2$ max ≥ 6.5 kPa | | Total number of patients N = 66* |
|---|---|---|---|---|---|---|---|
| | 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*(70%) |
| $SpO_2$90 ≥10% of TRT | | | | | | | |
| Normal | 33 (50%) | 12 (18%) | 26 (39%) | 19 (29%) | 14 (21%) | 31 (47%) | 45*(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*(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. *PtcCO2 data missing in one patient; see text for explanation.

## 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_2$90 ≥ 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).

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* | 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.*Data missing in two patients; see text for explanation

## 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 hours). Results are summarized in Table 2 and table 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.

## Index tests compared with reference tests

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

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* | 93% (68-100) | |
| Specificity* | 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.
*Representing result from 65 patients; se text for explanation.

Scatterplots of comparison of $PtcCO_2$ with $SpO_2$ and $AHI_{polygraphy}$ with ODI3% and $AHI_{software}$ are shown in figure 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. (Table 3S-5S supplement)

**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 to 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 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.

**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.

**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 centers 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.

**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.

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