



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

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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<sub>2</sub> 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.

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

**Abbreviations:** NIV, Non-invasive ventilation; CRF, Chronic hypercapnic respiratory failure; AH, Apnea/hypopnea; PVA, Patient-ventilator asynchrony; AASM, American Academy of Sleep Medicine; SpO<sub>2</sub>, Pulse oximetry; PtcCO<sub>2</sub>, Transcutaneous CO<sub>2</sub>; NMD, Neuromuscular diseases; RTD, Restrictive thoracic disorders; OHS, Obesity hypoventilation syndrome; CHS, Central hypoventilation syndrome; PG, Sleep polygraphy; PVA, 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

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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<sub>2</sub>) and transcutaneous CO<sub>2</sub> (PtcCO<sub>2</sub>) 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<sub>2</sub> 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<sub>2</sub> (Nonin Medical 2500) and PtcCO<sub>2</sub> (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  $\geq 90\%$  for  $\geq 10$  s. Hypopnea were scored if there was a drop in the peak flow signal excursion by  $\geq 30\%$  for  $\geq 10$  s associated with either a  $\geq 3\%$  desaturation or an autonomic activation scored from the pulse waveform [25] (decrease in PWA  $\geq 30\%$ ). 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  $\geq 10$  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

**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 <sup>2</sup> )	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 <sub>1</sub> (% 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 <sub>1</sub> /FVC (%)	63.5 ± 11.9	79.6 ± 12.7	76.8 ± 11.5	74.6 ± 9.2	0.001
PaCO <sub>2</sub> (kPa)	6.2 ± 1.2	6.1 ± 0.7	5.8 ± 0.8	6.3 ± 1.2	0.7
PaO <sub>2</sub> (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.

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<sub>2</sub> and PtcCO<sub>2</sub> 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.

**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%) <sup>a</sup>	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.

<sup>a</sup> Hypopnea 3% desaturation: hypopnea defined on the basis of a drop in SpO<sub>2</sub> ≥ 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 <sup>a</sup>	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.

<sup>a</sup> Hypopnea 3% desaturation: hypopnea defined on the basis of a drop in SpO<sub>2</sub> ≥ 3%.

### 3.4. Overnight SpO<sub>2</sub> and PtcCO<sub>2</sub> and association with respiratory events

SpO<sub>2</sub> was successfully recorded in all patients. Median time spent with SpO<sub>2</sub> < 90% (SpO<sub>2</sub>90) was 3% (IQR: 0-15). Mean SpO<sub>2</sub> was 92.3% (± 3.9). Median oxygen desaturation index (ODI) with a ≥ 3% desaturation was 6.1 (IQR 1.6–11.1). SpO<sub>2</sub>90 was > 10% of TRT in 21 patients (31%). In one patient PtcCO<sub>2</sub> was not available due to technical problems; thus 66 recordings were analysed. Median% of TRT spent with PtcCO<sub>2</sub> above 6.7 kPa and 7.3 kPa was 7.5% (IQR 0-68) and 0% (IQR 0-3) respectively. Mean PtcCO<sub>2</sub> was 6.4 kPa (± 0.9). Twenty-nine and 14 patients spent more than 20% of TRT with a PtcCO<sub>2</sub> 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<sub>2</sub> or PtcCO<sub>2</sub>. ODI

**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 <sup>a</sup> (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.

<sup>a</sup> Desynchronization 3% desaturation on the basis of a drop in SpO<sub>2</sub> ≥ 3%.

and AHI were significantly correlated ( $\rho = 0.56$   $r^2 = 0.31$   $p < 0.001$ ), as were SpO<sub>2</sub>90 and AHI ( $\rho = 0.3$   $r^2 = 0.11$   $p = 0.005$ ), SpO<sub>2</sub>90 and PVA% ( $\rho = 0.25$ ,  $r^2 = 0.06$   $p = 0.04$ ), SpO<sub>2</sub>90 and PVAI ( $\rho = 0.25$   $r^2 = 0.06$   $p = 0.04$ ) and SpO<sub>2</sub>90 and TDI ( $\rho = 0.26$   $r^2 = 0.07$   $p = 0.03$ ).

There was no correlation between time with spent with a PtcCO<sub>2</sub> above 6.7 kPa, above 7.3 kPa or mean PtcCO<sub>2</sub> 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: 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

**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.

**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.

scored only in periods without AH. Double triggering and auto triggering were rare. No correlation was found between respiratory events and overnight PtcCO<sub>2</sub>.

#### 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 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.

#### 4.4. Overnight SpO<sub>2</sub> and PtcCO<sub>2</sub> and association with respiratory events

We found a significant association between AHI and both ODI and SpO<sub>2</sub>90. Conversely, no correlation was found between AHI or asynchrony and nocturnal PtcCO<sub>2</sub> or between leaks and either nocturnal SpO<sub>2</sub> or PtcCO<sub>2</sub>. SpO<sub>2</sub>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<sub>2</sub> 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<sub>2</sub>90. Desynchronizations associated with desaturation were rare and asynchrony explained only 6% of the variance of SpO<sub>2</sub>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<sub>2</sub>, reflects 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<sub>2</sub> [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]. Here 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 substantially to acquisition of data. SA and MQ scored the sleep studies. SA, ET, ALK, MQ, OHS and JJ contributed substantially 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 <http://dx.doi.org/10.1016/j.rmed.2017.10.025>.

#### Transparency document

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