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Effect of Respiratory Events on Health-Related Quality of Life in Patients Treated with Long-Term Noninvasive Ventilation

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Abstract
Background: Long-term noninvasive ventilation (NIV) can increase or maintain health-related quality of life (HRQoL) for patients with chronic hypercapnic respiratory failure (CHRF). Evidence from studies systematically assessing how NIV-specific factors influence HRQoL is limited. ***Objectives:*** The objective of this study was to describe HRQoL measured by the Severe Respiratory Insufficiency Questionnaire (SRI) in patients with CHRF treated with long-term NIV and to analyze the associations between HRQoL and hypoxemia, hypercapnia, and respiratory events such as apneas, hypopneas (AHI), and patient ventilator asynchrony (PVA) occurring during long-term NIV. ***Methods:*** We included sixty-seven stable patients with established long-term NIV due to neuromuscular disease or thoracic cage disorders in a prospective cross-sectional study at Oslo University Hospital. Patients answered the SRI and underwent daytime arterial blood gases, nocturnal pulse oximetry, sleep polygraphy, and nocturnal transcutaneous CO_2. ***Results:*** The mean global SRI for 62 patients was 64.8 ± 14.5, with the highest score in SRI Social Relationships (79.5 ± 15.6). There were no differences in HRQoL between the different patient groups. Compliant patients had a significantly higher score in SRI Attendant and Sleep. Residual nocturnal hypoxemia affected both the subscale SRI "Respiratory Complaints" and SRI "Attendant Symptoms and Sleep." Persisting daytime hypercapnia, nocturnal hypoventilation, and high AHI affected the subscale SRI "Anxiety" negatively, while frequent PVA was associated with a lower score in SRI "Physical Function." ***Conclusion:*** In a group of patients with long-term NIV, undesired respiratory events during NIV are associated with lower HRQoL in several of the SRI subscales. We suggest designing interventional studies to confirm the possible relationship between HRQoL and respiratory events during long-term NIV.

Introduction

Long-term mechanical ventilation (LTMV) provided through a mask is an efficient treatment for patients with chronic hypercapnic respiratory failure (CHRF) due to neuromuscular diseases, restrictive thoracic disorders,

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obesity hypoventilation syndrome (OHS), central hypoventilation syndromes, and chronic obstructive pulmonary disease (COPD) [1–3]. The number of patients treated with LTMV is increasing [3, 4], especially due to increased use of long-term noninvasive ventilation (NIV) [5]. In Norway, the prevalence of LTMV increased from 20/100,000 in 2007 [6] to 51/100,000 in 2019, of whom 99% were treated with long-term NIV [7]. Similar figures in Sweden and Finland in 2019 were 33/100,000 inhabitants (97% NIV) [8] and 39.5/100,000 inhabitants (98% NIV) [9], respectively.

The goal of long-term NIV is to reduce mortality and morbidity and to increase or maintain health-related quality of life (HRQoL) [10]. Assessing HRQoL can provide information about the range of problems that affect patients [11] and has also proven to be of value for predicting mortality [12, 13]. For patients with CHRF, curative treatment is rarely available, and the treatment itself can cause burdensome side effects, such as pressure sores or persistent leakage from the mask [14]. In these cases, HRQoL is an important and sometimes the principal outcome [11, 15–17]. When measuring HRQoL, it is important to distinguish between generic and specific instruments [11]. Generic instruments are most useful in general surveys on health and for comparison between patient groups or between patient groups and the general population [11]. A disease-specific instrument is suitable for studies of specific therapeutic interventions [11, 18]. Commonly used instruments in studies of HRQoL in patients with CHRF include the Maugeri Foundation Respiratory Failure Questionnaire, the Sickness Impact Profile, the Short-Form 36, the Chronic Respiratory Questionnaire, and the St. George Respiratory Questionnaire [19]. In recent years, a disease-specific instrument, the Severe Respiratory Insufficiency Questionnaire (SRI), has been developed to better investigate how long-term NIV influences HRQoL [18, 20, 21].

Long-term NIV can improve HRQoL [14, 17, 22–24], but there is a lack of knowledge about which factors influence HRQoL during treatment. Markussen et al. [14] found that both side effects of LTMV treatment and reduced pulmonary function were associated with reduced HRQoL, while satisfaction with the follow-up from health care professionals was associated with better HRQoL. Dyspnea and hospital admission also seem to be associated with lower HRQoL [16]. Increased daytime blood level of bicarbonate can reflect nocturnal hypoventilation [1], and two studies have found an association between decreased physical function measured with the SRI and the level of bicarbonate [25, 26]. A German multicenter randomized controlled study proposed that the use of high ventilator pressure settings, aimed to normalize diurnal $PaCO_2$, could be an explanation for improved HRQoL in patients with COPD treated with long-term NIV [27].

Correction of diurnal hypercapnia, nocturnal hypoventilation [27–29], and improvement of oxygen saturation [2] are considered important in the follow-up of CHRF patients receiving long-term NIV. Reduction of undesired respiratory events, such as obstructive and central apneas, hypopneas, and patient ventilator asynchrony (PVA) [2, 30–32] may also be of importance. Thus, there is an increasing awareness of the necessity of regular nocturnal monitoring and adjustment of the ventilator to reduce the frequency of undesired respiratory events and normalize the patients' blood gases [1, 32, 33].

Few studies [27, 34] have investigated the association between HRQoL and physiological parameters such as daytime hypercapnia, nocturnal hypoventilation, apnea, hypopnea, and PVA in stable patients treated with long-term NIV. The aims of this study were to (1) describe HRQoL measured by the SRI in a population of stable CHRF patients treated with long-term NIV and (2) analyze the associations between HRQoL and persisting hypoxemia and hypercapnia, as well as respiratory events such as apneas, hypopneas, and PVA occurring during long-term NIV treatment.

Materials and Methods

The study protocol was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, No. = 2012/1142 and registered at clinicaltrials.gov (NCT01845233). Written informed consent was obtained from all patients.

Patients

All CHRF patients scheduled for a regular follow-up visit for treatment with long-term NIV at the Department of Pulmonary Medicine at Oslo University Hospital between April 2013 and May 2014 were evaluated for inclusion. Patients treated for neuromuscular diseases, restrictive thoracic disorders, OHS, and central hypoventilation syndrome for a minimum of 3 months were eligible. Exclusion criteria were age under 18 years, inability to cooperate, hospitalization due to an acute exacerbation, and modification of the treatment within the last 3 months.

Study Design

Data collection in this prospective cross-sectional study was performed when patients were hospitalized overnight for their follow-up visit. This study is part of a larger research project "Monitoring long-term nocturnal non-invasive ventilation for chronic hypercapnic respiratory failure: What are the basic tools?" [1].

Measurements

Health-Related Quality of Life

HRQoL was measured with the SRI. The SRI is a self-administered multidimensional tool which has shown very good psychometric properties [18, 20], good construct validity, and acceptable ceiling and floor effects [25, 35]. It has been translated into several languages, including Norwegian [36]. The SRI form consists of 49 items grouped into seven subscales: "Respiratory Complaints," "Physical Functioning," "Attendant Symptoms and Sleep," "Social Relationships," "Anxiety," "Psychological Well-being," and "Social Functioning." The participants rated each item by using a five-point Likert scale from "strongly agree" to "strongly disagree." The total score of the seven subscales is referred to as the Summary Scale (SRI-SS) and varies from 0 to 100, with a higher score indicating better HRQoL [20]. The respondents were asked to relate their answers to the week preceding their elective evaluation.

Respiratory Events

Nocturnal hypoxemia, nocturnal hypoventilation, apneas/hypopneas, and PVA occurring during NIV were measured and evaluated as previously described [31, 33]. In short, nocturnal hypoxemia was evaluated with continuous overnight pulse oximetry (SpO_2) (Nonin Medical 2500, Minn., USA). We evaluated two different values from the pulse oximetry.

1. SpO_2 < 90% in % of total recording time (SpO_2 < 90%)
2. Recurrent SpO_2 oscillations, defined as ≥5 events/hour with a 4% oxygen desaturation from baseline lasting 10–90 s (ODI4%) [31].

Nocturnal hypoventilation was evaluated with continuous transcutaneous CO_2 measurement ($PtcCO_2$) (TCM Tosca, Radiometer, Denmark). We defined nocturnal hypoventilation according to the American Association of Sleep Medicine (AASM).

1. Increase in $PtcCO_2$ to a value >7.3 kPa for ≥10 min and/or an increase in $PtcCO_2$ >1.3 kPa in comparison to an awake value, exceeding 6.7 kPa ≥10 min ($AASM^{1\&2}$)

Daytime hypercapnia was evaluated by arterial blood gas sampling from the radial artery between 12:00 and 2:00 p.m., after the patient had been seated and breathing room air for 30 min. We considered $PaCO_2$ ≥6 kPa as abnormal. The occurrence of apnea, hypopnea, and PVA was documented by nocturnal polygraphy (Embletta Gold, Embla, USA) during NIV. The following signals, as recommended by the SomnoNIV group [37], were used: mask pressure, flow rate in the circuit measured by a pneumotachograph close to the mask, abdominal and thoracic movements with respiratory inductive plethysmography effort belts, body position, and pulse oximetry. The polygraphies were manually scored by two experienced physicians [30].

Criteria for apnea and hypopnea were adapted from the scoring rules of the AASM [38] and reported as apnea-hypopnea index (AHI): number of events/hour of total recording time. We used the cutoff value ≥5 for abnormal AHI. Criteria for PVA were adapted from previous studies [30] and reported as PVA index (PVAI): number of events with asynchrony/hour of total recording time and the percentage of total recording time with PVA (PVAT). We used two different definitions for abnormal PVA: PVAI ≥10 and PVAT ≥10%.

Compliance was quantified by using data memorized by the ventilator software downloaded with Rescan 04.01.013 software for ResMed ventilators and with Encore Pro 2 2.1.6.0 software for Philips Respironics ventilators. Summary data including compliance and leak covering the 3 months prior to the regular follow-up visit and the study night were collected. Patients were considered compliant if the 3-month synthesis report showed a mean use of their ventilator ≥4 h/night.

Statistical Analyses

Demographic variables such as age, body mass index (BMI), duration of ventilator use, daytime PaO_2, daytime $PaCO_2$, FEV_1, FVC, and FEV_1/FVC and the SRI scores were inspected for normality. We reported the variables as mean ± standard deviation (SD) if normally distributed, otherwise as median and interquartile range (IQR). The same descriptive analyses were performed with the SRI scales, both in the patient group as a whole, and after dividing the population into different groups based on gender, diagnoses, and BMI (</≥30 kg/m^2). Associations between SRI subscales and respiratory variables such as % of total recording time with nocturnal SpO_2 <90%, and ODI4%, daytime $PaCO_2$, and nocturnal $PtcCO_2$, apneas, hypopneas, PVA, and average use over the prior 3 months were tested for significant associations using the bivariate test Pearson's *r*. Further, we controlled for confounders such as age, gender, and diagnoses.

Between groups comparisons were performed by independent-samples *t* tests. Results were considered significant when *p* was <0.05, 2-tailed. Effect size of mean differences was calculated by using Cohen's *d* [39] and reported as small if the value was between 0.2 and 0.5, moderate if 0.5–0.8, and strong if above 0.8 [11]. Statistical analyses were performed with SPSS (version 25, USA).

Results

Patients

In total, 95 of the evaluated patients met the inclusion criteria and 67 were included (Fig. 1). Of these 67 patients, four did not answer the SRI questionnaire, while one answered only the first page, resulting in complete data from 62 patients (Fig. 1). The largest group was patients with neuromuscular diseases, followed by OHS, restrictive thoracic disorders, and central hypoventilation syndromes. Main characteristics of these patients are presented in Table 1. The majority of patients were ventilated using bi-level spontaneous-timed mode and an oronasal mask (Table 2).

HRQoL Measured with the Severe Respiratory Insufficiency Questionnaire

There were few missing items in the SRI except for item 31, addressing the respondents' marital status, which 21 patients left unanswered. As outlined in Table 3, the mean SRI-SS for 62 patients was 64.8 (SD 14.5). Patients with central hypoventilation syndrome and restrictive thoracic disorders reported the highest (best) HRQoL scores, while patients with OHS reported the lowest HRQoL scores. However, differences between groups did

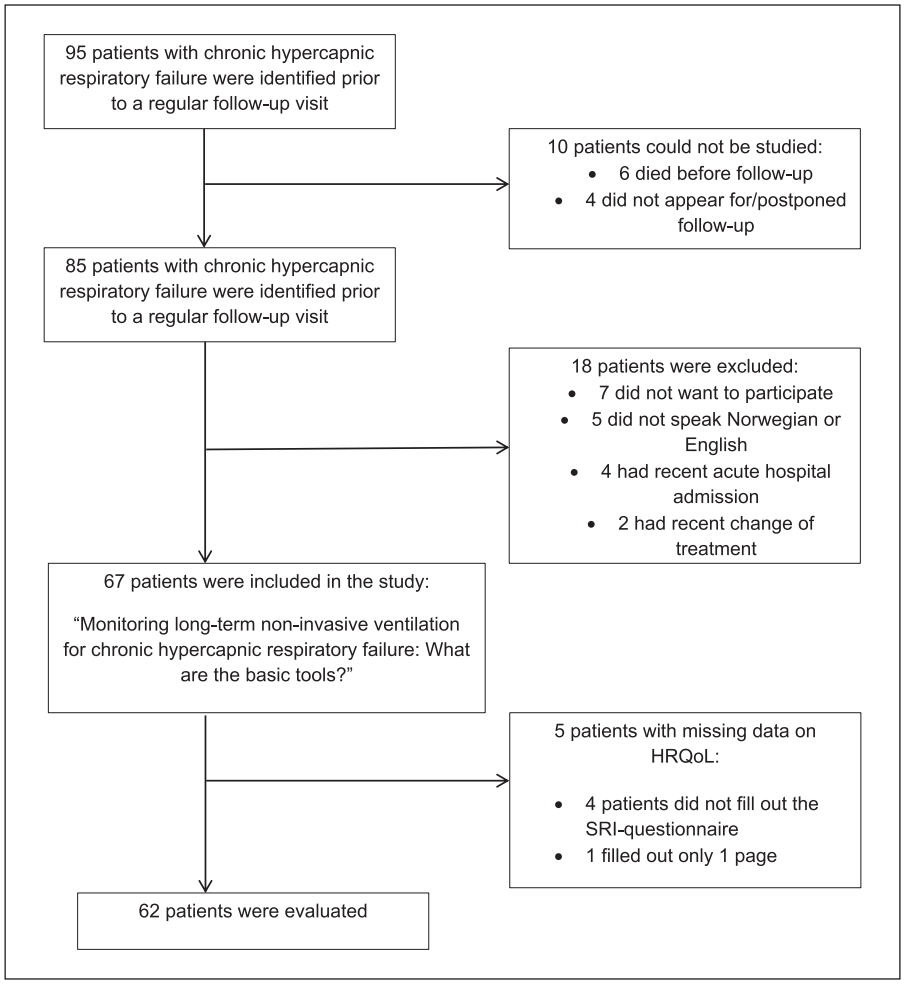

Fig. 1. Flowchart showing the number of identified patients and reasons for not participating.

not reach statistical significance. The mean SRI-SS was in the upper half of the scale in all patient groups. Except for SRI "Physical Function," all of the SRI subscales were in the upper half of the scale, with the highest scores being in the SRI subscale "Social Relationships." Neither age nor duration of NIV treatment was significantly associated with any of the SRI subscales. There were no significant differences in SRI subscales related to gender or BMI <30/>30 kg/m^2 (Table 3).

Compliance

Compliance data were analyzed for all patients. The median use of the ventilator was 8 h per day (8–9.3), and 85% were considered compliant (mean use >4 h/day) over a period of 3 months. When comparing patients with acceptable compliance (>4 h, $n = 53$) with noncompliant patients (<4 h, $n = 9$), we found a significant difference in the mean SRI subscale "Attendant and Sleep Symptoms" (67.8 [SD 17.2] vs. 52.8 [SD 22.9], $p = 0.02$) indicating a higher symptom burden in the noncompliant group. The effect size (Cohen's *d*) was 0.7, which is considered moderate.

Respiratory Events and Association with HRQoL

Nocturnal Hypoxemia

Nocturnal SpO_2 was successfully recorded in all patients, and median nocturnal SpO_2 was 93% (IQR: 91–95). One patient had supplementary oxygen [30]. No significant associations between mean nocturnal SpO_2 and any of the SRI subscales were observed. However, we found a significant negative association between time spent below 90% (SpO_2 <90%) and the SRI subscale "Respiratory Complaints," suggesting that nocturnal hypoxemia is associated with a higher degree of respiratory symptoms ($r = -0.34$, $p = 0.01$). A similar negative association was observed between ODI4% and the SRI sub-

Table 1. Main characteristics of the study population

Patients	All patients (n = 67)	OHS (n = 16)	RTD (n = 10)	NMD (n = 36)	CHS (n = 5)
Male/female	35/32	8/8	3/7	20/16	4/1
Comorbidities: COPD/heart failure/renal failure/chronic opioid use	12/7/1/6	9/5/1/2	0	3/2/0/3	0/0/0/1
FEV_1, % predicted	47.0±24.5	58.3±22.3	48.3±32.3	37.1±17.8	78.6±16.7
FVC, % predicted	51.4±26.4	71.3±22.2	50.6±31.3	38.2±17.9	84.6±10.5
FEV_1/FVC, %	75.0±13.6	63.5±11.9	76.8±11.5	79.6±12.7	74.6±9.2
Age, years	57.7±19.2	65±12	45.±25	59±19.2	49±14
BMI, kg/m^2	28.1±7.7	36.7±5.2	26.5±8.1	24.8±5.7	28.0±5.8
LTMV duration, month, median (IQR)	54 (14–94)	35 (7–58)	80 (34–94)	57 (13–118)	60 (24–111)
Daytime PaO_2, kPa	9.4 (1.5)	8.4 (1.5)	9.5 (1.0)	9.6 (1.5)	9.9 (1.7)
Daytime $PaCO_2$, kPa	6.1±0.9	6.2±1.2	6.1±0.7	5.8±0.8	6.3±1.2

Values presented as mean±SD, unless specified otherwise. OHS, obesity hypoventilation syndrome; RTD, restrictive thoracic disorders; NMD, neuromuscular diseases; CHS, central hypoventilation syndrome; n, number of patients; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; BMI, body mass index; LTMV, long-term mechanical ventilation; IQR, interquartile range; PaO2, partial pressure of oxygen in arterial blood; PaCO2, partial pressure of carbon dioxide in arterial blood; kPa, kilo pascal.

Table 2. Ventilator settings and interface by all patients and ventilator settings by disease group

Ventilator settings	All patients	OHS	RTD	NMD	CHS
IPAP,* cmH_2O	16 (14–19)	20 (14–24)	16 (15–18)	16 (12–18)	12 (11–16)
EPAP, cmH_2O	5 (4–6)	8 (6–10)	5 (4–7)	4 (4–6)	4 (2–6)
Backup respiratory rate, breaths/min	12 (10–15)	12 (10–13)	13.5 (12–15)	12 (10–15)	15 (10–16)
Ventilator mode; bi-level ST/PS-VT/VCV/PCV, n	57/8/1/1				
Interface; oronasal/nasal/nasal prongs, n	31/23/13				

Values presented as median and IQR, unless specified otherwise. OHS, obesity hypoventilation syndrome; RTD, restrictive thoracic disorders; NMD, neuromuscular diseases; 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; n, number of patients. * In PC mode, peak inspiratory pressure is reported; in PS-VT/VCV, mean overnight inspiratory pressure is provided.

scale "Attendant Symptoms and Sleep" (p = −0.34, p = 0.01), implying that an increased ODI4% is associated with a worse "Attendant Symptoms and Sleep" score. In the group with abnormal ODI4% versus those with a normal ODI4% (Table 4), significantly lower "Attendant Symptoms and Sleep" scores were observed in the group with abnormal ODI4%. The effect size (Cohen's d) was moderate (d = , and 0.7).

Hypercapnia and Hypoventilation

Daytime $PaCO_2$ was available for all patients. Nocturnal $PtcCO_2$ was performed in all patients, but the device malfunctioned in 1 patient.

The score of the SRI subscale "Anxiety" was significantly lower (i.e., worse) in patients with daytime hypercapnia compared to normocapnic patients. This was also the case for patients with nocturnal hypoventilation (Table 4). Thus, there seems to be an association between both daytime hypercapnia and nocturnal hypoventilation and increased perceived anxiety. The effect size was moderate (Cohen's d = 0.7 and 0.6, respectively) in the significant associations between CO_2 and anxiety.

Apnea and Hypopnea

Polygraphy was available for all patients. We found no significant associations between AHI and the SRI scales. However, patients with an abnormal AHI reported more

Table 3. Severe Respiratory Insufficiency Questionnaire scores in patient groups divided into gender, body mass index, and diagnoses

SRI scales	All patients (*n* = 62)	Male (*n* = 35)	Female (*n* = 32)	OHS (*n* = 16)	RTD (*n* = 10)	NMD (*n* = 32)	CHS (*n* = 4)	BMI <30 (*n* = 39)	BMI >30 (*n* = 23)
SRI-SS	64.8 (14.5)	63.2 (13.0)	66.6 (15.9)	62.8 (13.5)	68.6 (18.7)	63.2 (13.7)	76.6 (8.3)	65.2 (14.9)	64.3 (14.1)
Respiratory Complaints	63.0 (17.6)	62.0 (16.2)	64.0 (19.3)	63.4 (15.2)	72.9 (16.2)	57.9 (18.4)	76.6 (7.5)	62.5 (18.5)	63.8 (16.4)
Physical Function	46.4 (23.7)	42.1 (22.7)	51.0 (24.2)	37.0 (22.5)	55.4 (28.0)	46.4 (22.6)	61.5 (15.0)	48.6 (24.8)	42.6 (21.7)
Attendant Symptoms and Sleep	65.6 (19.0)	66.2 (17.9)	64.9 (20.4)	67.2 (18.6)	66.4 (17.0)	63.5 (20.8)	73.2 (11.1)	67.0 (17.4)	63.0 (21.4)
Social Relationships	79.6 (15.6)	79.5 (15.3)	79.8 (16.1)	80.6 (15.2)	78.3 (18.7)	78.6 (15.2)	87.5 (14.4)	77.4 (16.4)	83.4 (13.5)
Anxiety	64.9 (24.7)	62.5 (25.3)	67.5 (24.2)	63.4 (25.3)	72.5 (22.6)	60.9 (25.9)	80.0 (11.5)	65.8 (24.0)	63.5 (26.4)
Psychological Well-Being	68.1 (17.7)	67.0 (16.5)	69.3 (19.1)	67.1 (20.3)	65.6 (24.8)	68.5 (14.7)	75.7 (12.5)	67.9 (16.9)	68.4 (19.5)
Social Function	66.3 (19.8)	63.0 (18.8)	69.8 (20.7)	60.2 (16.0)	69.1 (24.8)	66.6 (19.9)	81.6 (16.6)	66.9 (21.0)	65.2 (18.8)

Values presented as mean (SD), unless specified otherwise. SRI, Severe Respiratory Insufficiency Questionnaire; n: number of patients; NMD, neuromuscular diseases; RTD, restrictive thoracic disorders; CHS, central hypoventilation syndrome; OHS, obesity hypoventilation syndrome; BMI, body mass index; SS, summary scale.

Table 4. Comparison of Severe Respiratory Insufficiency Questionnaire scales and patient scores based on the respiratory endpoints; nocturnal hypoxemia, daytime $PaCO_2$, and nocturnal $PtcCO_2$

SRI scales	Respiratory endpoints					
	ODI 4%		daytime $PaCO_2$		nocturnal $PtcCO_2$	
	<5	>5	<6 kPa	≥6 kPa	hypoventilation AASM[(1&2)]	
	normal	abnormal	normal	abnormal	normal	abnormal
Patients, *n*	*n* = 45	n = 17	*n* = 29	*n* = 33	n = 38[a]	n = 23[a]
SRI-SS	65.3 (15.3)	63.5 (12.3)	67.5 (13.6)	62.5 (15.0)	66.0 (14.2)	63.3 (15.2)
Respiratory Complaints	64.5 (16.1)	58.8 (21.2)	66.4 (17.1)	59.9 (17.8)	62.7 (18.4)	62.4 (16.3)
Physical Function	45.4 (25.3)	49.0 (19.3)	50.9 (25.0)	42.4 (22.0)	47.6 (22.3)	45.3 (26.4)
Attendant Symptom and Sleep	**68.8 (18.1)**	**56.1 (18.2)***	68.3 (17.2)	62.8 (20.1)	66.5 (19.4)	64.4 (18.1)
Social Relationships	78.5 (17.0)	82.6 (10.8)	79.0 (14.4)	80.2 (16.7)	79.8 (15.5)	79.5 (16.2)
Anxiety	67.2 (24.2)	58.8 (25.8)	**73.1 (19.8)**	**57.7 (26.6)***	**70.5 (21.8)**	**56.3 (27.5)***
Psychological Well-Being	68.0 (19.3)	68.4 (13.2)	68.0 (19.5)	68.3 (16.3)	69.1 (17.6)	66.5 (18.6)
Social Function	64.6 (20.8)	70.8 (16.7)	67.1 (65.6)	65.6 (22.1)	65.3 (18.7)	68.5 (22.2)

Values presented as mean (SD). SRI, Severe Respiratory Insufficiency Questionnaire; ODI, oxygen desaturation index; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PtcCO2: partial pressure of carbon dioxide measured transcutaneously; kPa: kilo pascal; AASM: American Association of Sleep Medicine; SD: standard deviation; SRI-SS: SRI Summary Scale * Significant differences $p < 0.05$, 2-tailed. [a]Total of 61 patients analyzed due to a technical error in $PtcCO_2$ measurement in 1 patient.

anxiety than those with a normal AHI (Table 5). The effect size (Cohen's $d = 0.6$) was moderate.

Patient Ventilator Asynchrony

Neither PVAT nor PVAI were significantly associated with SRI scales. However, we found lower scores for "Physical function" in patients with higher levels of PVA (both PVAT >10% and PVAI >10) (Table 5), suggesting a possible association between asynchrony and reduced physical capacity. The effect size (Cohen's $d = 0.5$ and 0.6, respectively) was moderate in both findings.

Leaks

We rarely observed periods with high unintentional leaks on the polygraphy traces. In patients with both ResMed ventilators and Philips ventilators, the median leakage was 2.4 L/min (IQR 0–6.0 and 0–15.2, respectively).

Table 5. Comparison of Severe Respiratory Insufficiency Questionnaire scales and patient scores based on the respiratory endpoints; AHI, PVAI

SRI scales	Respiratory endpoints					
	AHI		PVAT		PVAI	
	<5 normal	>5 abnormal	<10% normal	>10% abnormal	<10 normal	≥10 abnormal
Patients, *n*	*n* = 40	n = 22	*n* = 50	n = 12	*n* = 51	*n* = 11
SRI-SS	66.1 (14.4)	62.1 (14.3)	64.7 (15.4)	65.6 (10.3)	65.2 (14.8)	63.2 (13.0)
Respiratory Complaints	63.5 (17.9)	61.9 (17.4)	63.1 (18.0)	62.2 (16.8)	64.0 (17.4)	58.0 (18.1)
Physical Function	49.0 (23.8)	41.7 (23.3)	**48.3 (25.6)**	**38.5 (10.5)***	**48.4 (25.1)**	**37.1 (12.1)***
Attendant Symptom and Sleep	65.5 (18.7)	65.3 (19.5)	64.2 (18.9)	70.5 (18.6)	64.6 (17.6)	69.2 (24.6)
Social Relationships	79.9 (16.7)	79.2 (13.6)	78.6 (16.4)	83.7 (11.3)	78.7 (16.4)	83.7 (10.3)
Anxiety	**70.3 (21.1)**	**55.2 (28.2)***	64.6 (24.9)	66.3 (25.1)	66.2 (23.2)	59.1 (31.5)
Psychological Well-Being	68.1 (20.1)	68.2 (12.8)	68.0 (18.4)	68.4 (15.3)	67.7 (18.2)	70.1 (16.1)
Social Function	68.0 (18.4)	63.2 (22.3)	65.6 (21.6)	69.4 (9.9)	66.6 (20.6)	65.0 (16.5)

Values presented as mean (SD) or number of patients. SRI, Severe Respiratory Insufficiency Questionnaire; AHI, apnea-hypopnea index, PVAT, patient ventilator asynchrony total recording time; PVAI, patient ventilator asynchrony index; SD, standard deviation; SRI-SS, Summary Scale. * Significant differences $p < 0.05$.

Discussion

In a group of stable patients treated with long-term NIV for restrictive pulmonary disorders, we assessed HRQoL using the Severe Respiratory Insufficiency Questionnaire (SRI) and studied the association between HRQoL and respiratory events such as hypoxemia, daytime hypercapnia, or nocturnal hypoventilation, apneas and hypopneas, PVA, and reduced compliance. Our main findings were that both the SRI-SS and the SRI subscales scores were in the upper half of the scale (i.e., better values) in all patient groups except for the SRI "Physical Function" subscale. Globally, SRI-SS scores were not significantly related to the physiological variables explored. However, we found negative associations between nocturnal hypoxemia and the subscales "Respiratory Complaints" and "Attendant Symptoms and Sleep." We also found negative associations between daytime hypercapnia, nocturnal hypoventilation, and AHI, and the subscale "Anxiety," as well as between PVA and the "Physical Function" subscale. The negative associations imply that a higher number or increased severity of respiratory events were associated with reduced HRQoL.

The SRI-SS of 64.8 (SD 14.5) in our patient population, who had been treated with LTMV for a median duration of 54 months, is in line with previous studies. In a study of stable patients treated with LTMV for 6 years, Markussen et al. [14] found that the SRI-SS was 64.8 (SD 16.8). The highest subscale score of 79.1 (SD 19.5) was in the SRI "Social Relationships" domain, as in our patient population. Windisch [17] has shown that 1 month of LTMV treatment increased the SRI-SS score to a similar value. The increase was preserved after 12 months of treatment. Similar findings were reported by Valko et al. [40] after 6 months of treatment.

A review by MacIntyre et al. [23] concluded that HRQoL in patients with LTMV was generally described as good. Furthermore, the higher scores were more consistent in mental subscales, such as "Social Relationships" compared to subscales exploring symptoms and function, such as "Respiratory Complaints," suggesting that the mental and social health overall is preserved in spite of a severe physical illness. In studies with a majority of COPD patients included, the SRI-SS scores tend to be lower, indicating that COPD patients might experience reduced HRQoL compared to patients with restrictive respiratory disturbances [13, 16, 35]. COPD patients were not included in the current study because the Norwegian national guidelines at that time did not recommend LTMV in COPD patients; hence, the number of patients with COPD treated with long-term NIV at our center was low [10]. However, nine of the patients with OHS had COPD as a comorbidity (Table 1), and this could have contributed to the low HRQoL score in patients with OHS (Table 2).

In the current study, we found significant associations between commonly used measurements for evaluating the efficacy of long-term NIV (nocturnal hypoxemia, daytime hypercapnia, nocturnal hypoventilation, AHI, assessment of PVA) and specific subscales of the SRI. First, diurnal hypercapnia and nocturnal hypoventilation were associated with increased anxiety (SRI-specific subscale), suggesting a negative impact on HRQoL (Table 4).

It was interesting and important to identify that the SRI subscale "Anxiety" was negatively associated with increasing values of nocturnal $PtcCO_2$ also in patients with a normal daytime $PaCO_2$. Thus, in a clinical setting where the evaluation of persisting hypoventilation is solely based on daytime measurements, a possible reason for increased anxiety and reduced HRQoL might be overlooked. Anxiety is rarely listed as a primary symptom of hypoventilation. Symptoms claimed to be related to hypoventilation include dyspnea, fatigue, morning headache, daytime sleepiness, sleep disruption, and nocturnal dyspnea [1]. One could argue that symptoms such as dyspnea can cause anxiety and, according to Feller-Kopman et al. [41], anxiety is a clinical feature of slowly developing hypercapnia. Several studies have shown an improvement in the SRI subscale "Anxiety" after LTMV treatment [26, 40, 42]. Our study suggests that patients treated successfully with long-term NIV who have less daytime hypercapnia, sleep hypoventilation, and apnea-hypopnea may experience less anxiety. We suggest investigating this further in future studies.

Patients with PVA seemed to be less content with their "physical function." "Physical function" refers to the patient's limitations in physical activities, such as climbing stairs, doing domestic work, or dressing [20]. The pathophysiology of the link between PVA and decreased physical function may vary according to the underlying disorder. In studies reporting a high level of PVA, ineffective efforts were the most frequently observed type of asynchrony [30]. Atkeson et al. [43] also reported a high frequency of this respiratory event in patients with ALS. In a recent review by Baxter et al. [44] regarding ALS patients, regular monitoring was found to be of key importance for optimization of long-term NIV, and the authors particularly recommended examining PVA. Also, the review warned against overreliance on symptom reports, favoring adequate respiratory tests. Neuromuscular patients often have limitations in their physical capacities due to their muscle weakness, including respiratory muscles like the diaphragm [45]. Weak inspiratory muscles may cause ineffective inspiratory efforts [1]. At least two hypotheses can be considered for the observed association: nocturnal PVA may have a negative impact on physical function through reduced quality of sleep and increased work of breathing, or conversely, severely impaired physical function may favor unrewarded inspiratory efforts in spite of treatment with long-term NIV. More thorough evaluation of breathing patterns during sleep is needed to explore these aspects further.

There are few studies on long-term NIV and HRQoL that have found an association between physiological measurements and patient-reported HRQoL. The general lack of association between physiological measurements and HRQoL is often explained by the inadequacy of a physiological value, such as $PaCO_2$ or SpO_2, to reflect the perception and subjective state of the patient [24, 35, 46].

We did not find any significant associations between the physiological measurements performed and the SRI-SS. This could question the clinical relevance of the physiological end-points studied as to their impact on HRQoL. The SRI was specifically developed to cover areas that are relevant for patients with long-term NIV [20]. Compared to the SRI total sum score, the SRI subscales reflect in which specific area the patients have reduced HRQoL. Although we cannot establish a causality, our findings may indicate that selected nocturnal respiratory events affect specific area of HRQoL, best detected with SRI subscales.

Even though several studies have shown an improvement in HRQoL measured with SRI after initiation of long-term NIV, the minimal clinically important difference of the SRI to our knowledge has not yet been defined [14]. Further insight has been provided by Raveling [47] in COPD patients using a combination of clinical and patient-reported anchors, but to our knowledge, there are no studies which have tried to determine the minimal clinically important difference in a patient group with restrictive disorders. Thus, we used Cohen's effect size as a surrogate marker of meaningfulness of differences between groups; this is considered as an acceptable distribution-based evaluation of relevance [39]. The effect size on HRQoL was considered moderate for all the physiological variables studied.

Strengths and Limitations

High quality, prospectively collected respiratory measurements strengthen the current study. In addition, few questions in the SRI were left unanswered, leaving few missing items in our data. Our study, however, has some limitations. First of all, the study population is limited and heterogeneous, which may affect our results. Some of the diseases causing CHRF are rare, and previous studies

often provide similar sample sizes. Second, we did not include patients with COPD. Thus, we cannot provide data regarding this large patient group. On the other hand, the lack of COPD patients decreases the heterogeneity of our population, possibly giving more consistent data regarding patients with restrictive respiratory diseases. Finally, the study design cannot confirm or exclude causality between HRQoL and respiratory endpoints. Future studies should include several centers and be designed to prospectively include interventions targeting respiratory endpoints, such as apneas, hypopneas, and PVA in order to measure the impact of these interventions on HRQoL.

Conclusion

In conclusion, our study shows that patients with long-term NIV have a preserved HRQoL, as assessed by a disease-specific HRQoL scale. Although undesired respiratory events under NIV did not affect the global HRQoL scores, we found relevant negative associations between several of the SRI subscales and events such as hypoxemia, desaturations, daytime and/or nocturnal hypercapnia, AHI, and PVA. These associations suggest that prospective interventional studies should be designed to confirm the possible relation between HRQoL and respiratory events during long-term treatment with NIV.

Statement of Ethics

The study protocol was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, No. = 2012/1142 and registered at clinicaltrials.gov (NCT01845233). Written informed consent was obtained from all patients.

Conflict of Interest Statement

Anne Louise Kleiven has received the ResMed grant from the Norwegian Society of Pulmonary Medicine. Sigurd Aarrestad has received fees for lecturing from Philips Respironics and ResMed outside of the presented work. All the other authors have no competing interests to declare.

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Author Contributions

Anne Louise Kleiven has 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. Anne Louise Kleiven and Sigurd Aarrestad contributed substantially to acquisition of data. Anne Louise Kleiven, Sigurd Aarrestad, Heidi Øksnes Markussen, Ole Henning Skjønsberg, and Jean-Paul Janssens 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.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (ALK anklei@ous-hf.no) upon reasonable request. Further inquiries can be directed to the corresponding author.

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