Impact of Intelligent Volume-Assured Pressure Support on Sleep Quality in Stable Hypercapnic Chronic Obstructive Pulmonary Disease Patients: A Randomized, Crossover Study

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Key Words

Chronic obstructive pulmonary disease · Sleep · Noninvasive positive-pressure ventilation · Intelligent volume-assured pressure support

Abstract

Background: Noninvasive positive-pressure ventilation (NPPV) using intelligent volume-assured pressure support (iVAPS) combines volume- and pressure-preset NPPV and therefore uses a variation of inspiratory positive airway pressures. **Objectives:** The effect of iVAPS on sleep quality in stable hypercapnic patients with chronic obstructive pulmonary disease (COPD) has not been determined. **Methods:** In this randomized, open-label, two-treatment, two-period, crossover study, patients were randomized to receive high-intensity (HI)-NPPV and then iVAPS or iVAPS and then HI-NPPV. Patients were studied in hospital for 2 consecutive nights, employing full polysomnography (PSG), transcutaneous partial pressure of CO₂ (PtcCO₂) monitoring, blood gas analysis and a visual analog scale (VAS)-based sleep questionnaire. After discharge, patients used HI-NPPV and iVAPS at home, each for 6 weeks. They had to answer a VAS question concerning sleep every morning, and were telephoned weekly and asked additional questions. At the end of each treatment period, they were visited at home for the determi-

nation of blood gases and treatment adherence, and to change the NPPV mode. **Results:** Fourteen patients were enrolled. In-hospital PSG measurements showed no difference in sleep quality between iVAPS and HI-NPPV. At home, patients reported more restful sleep during iVAPS than HI-NPPV ($p = 0.04$). Blood gases during spontaneous breathing at home did not differ with iVAPS and HI-NPPV, and there was a greater decrease in PtcCO₂ during iVAPS than during HI-NPPV ($p = 0.003$). **Conclusion:** Although sleep quality in hospital was not different between iVAPS and HI-NPPV, COPD patients with chronic hypercapnic respiratory failure reported a trend towards more restful sleep at home with iVAPS. In addition, nocturnal hypercapnia was effectively treated with iVAPS.

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Introduction

Noninvasive positive-pressure ventilation (NPPV) can be administered using either volume- or pressure-preset settings. Although it has been shown that both these modes improve blood gases, sleep quality and health-related quality of life to a similar extent [1–3], the pressure-preset NPPV approach is usually used for home mechanical ventilation [4, 5]. New modes of NPPV that combine

volume- and pressure-presets, so-called hybrid modes, have been developed to combine the advantages and overcome the disadvantages of the two approaches [6]. The majority of studies investigating the use of hybrid modes have been performed on patients with obesity hypoventilation syndrome [7, 8]. The most recent studies show no differences between NPPV using target volume or a fixed level of inspiratory positive airway pressure (IPAP) [9]. However, patients who receive predominately controlled ventilation (i.e. those in whom >50% of breaths occur without triggering the ventilator) have a better outcome than those with predominately assisted ventilation [6, 9]. This is particularly important in patients with chronic obstructive pulmonary disease (COPD) and chronic hypercapnia. For example, high-intensity NPPV (HI-NPPV), using higher IPAP levels and a controlled type of NPPV, has been found to be superior to assisted NPPV with lower levels of IPAP for controlling nocturnal hypoventilation as well as improving lung function parameters and health-related quality of life [6, 10].

Intelligent volume-assured pressure support (iVAPS), a new hybrid mode of NPPV, has a variable backup rate intended to maximize the patient's opportunity to spontaneously trigger the ventilator. This is in contrast to the technique of HI-NPPV, which aims to achieve a controlled type of NPPV [10–12]. Despite these differences, iVAPS has been shown to be as effective as conventional pressure support ventilation for stable hypercapnic COPD patients with respect to daytime blood gases and mean nocturnal oxygen saturation [13]. However, the impact of iVAPS on the sleep quality of COPD patients has not yet been determined. This study compared the sleep quality of COPD patients with chronic hypercapnia during periods of ventilation with iVAPS and HI-NPPV.

Materials and Methods

Subjects

We enrolled patients receiving NPPV to treat chronic hypercapnic respiratory failure secondary to COPD, diagnosed according to the GOLD criteria [14]. Patients were familiar with NPPV and had received treatment at home for at least 2 months prior to the study. Obesity per se was not an exclusion criterion. Patients with acute respiratory failure (pH <7.35) were not included in the study.

The study protocol was approved by the ethics committee at the Albert Ludwig University, Freiburg, Germany (approval Nos. 277/10 and 353/10), and the study was performed in accordance with good clinical practice and the ethical standards as laid down by the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to the study.

Measurements

Lung function parameters (Masterlab-Compact® Labor, Jaeger, Hochberg, Germany) were assessed in accordance with international guidelines [15]. Capillary blood gas measurements were taken from the arterialized earlobe with supplemental oxygen. In hospital, the AVL Omni® (Roche Diagnostics GmbH, Graz, Austria) was used, and the ABL 80 Basic® (Radiometer, Copenhagen, Denmark) was used for patients at home. The Tosca 500® (Radiometer) was used for transcutaneous partial pressure of CO₂ (PtcCO₂) measurements. Pneumotachographic measurements (RSS 100 Research PneumoSeries, Hans Rudolph, Inc., Shawnee, Kans., USA) using a flow sensor connected between the ventilatory mask and the exhalation port (Silentflow 2®, Weinmann, Hamburg, Germany) assessed expiratory minute ventilation (MV) during HI-NPPV. MV was defined as the product of tidal volume and respiratory rate (RR). Full polysomnography (PSG; SOMNOscreen™ plus, Somnomedics GmbH, Randersacker, Germany) was used to objectively assess sleep quality as described previously [12]. Subjective sleep quality and comfort with NPPV were assessed using 100-mm visual analog scales (VAS) as follows. (1) How restful was your sleep? 0 = very restless and 100 = very restful. (2) How refreshed did you feel this morning? 0 = exhausted and 100 = very refreshed. (3) How much discomfort did you get from the pressure? 0 = severe discomfort and 100 = no discomfort. (4) How well did your mask fit? 0 = very badly and 100 = very well. Higher VAS scores were indicative of a more positive response [16]. Compliance with NPPV was assessed from the counter reading on the ventilator.

Study Design

The primary outcome of the study was the difference between HI-NPPV and iVAPS in the time spent in N3/4 sleep. The study was of a randomized, open-label, two-treatment, two-period, crossover design (fig. 1). Demographic data, lung function parameters, ventilator settings, blood gas analysis during spontaneous breathing and MV during HI-NPPV were assessed at baseline in hospital. Patients were randomized to receive HI-NPPV followed by iVAPS or iVAPS followed by HI-NPPV (fig. 1) [17]. All patients were monitored in hospital for 2 consecutive nights while using HI-NPPV and iVAPS in the order determined by the randomization process. Full PSG and PtcCO₂ monitoring were performed at night, and blood gas analysis during NPPV was taken at 5.00 a.m. Patients were asked to answer questions 1–4 on the VAS every morning in hospital.

After the second night, patients were discharged, and then used HI-NPPV and iVAPS at home for 6 weeks each (as per the order at randomization). They were asked to answer question 1 every morning at home. They were telephoned weekly and asked questions 1–4. At the end of each 6-week treatment period, they were visited at home for assessment of blood gases and treatment compliance, and to change the NPPV mode.

Noninvasive Positive Pressure Ventilation

All patients were established on effective ventilation prior to the study using HI-NPPV. The aim of HI-NPPV is to maximally decrease arterial CO₂ pressure (PaCO₂) by stepwise increases in IPAP and RR beyond the spontaneous breathing frequency, in order to achieve controlled ventilation. The assist or control mode was chosen. The technique has been described previously in detail [11]. Ventilators and ventilator settings were not changed during

Fig. 1. Study protocol. ABG = Arterial blood gas analysis.

the study. For iVAPS, the Stellar 150 (ResMed Inc., Sydney, Australia) was used. iVAPS combines pressure support ventilation with a target volume, aiming to guarantee a set alveolar ventilation by adjusting the level of pressure support within predefined pressure ranges [13, 18, 19]. Alveolar ventilation is defined as MV minus anatomical dead-space ventilation. The anatomical dead space is approximated by the patient's height $[120 \times (\text{height}/175)^{2.363}]$ [20]. iVAPS has a variable backup rate, which is intended to maximize the patient's opportunity to spontaneously trigger the ventilator. When spontaneous triggering ceases, the set RR is adopted. It will adjust quickest (within 4–5 breaths) typically when the ventilation is below the target ventilation. During spontaneously triggered ventilation, the device will reduce the backup rate at two thirds of the set RR. A more detailed description of iVAPS can be found elsewhere [21]. The MV needed for the calculation of the alveolar target volume was assessed during daytime ventilation using unchanged ventilator settings. Expiratory positive airway pressure (EPAP) and RR during iVAPS remained unchanged when compared with HI-NPPV, but the range of inspiratory pressure support was set between -5 and $+5$ from the original pressure support (IPAP minus EPAP). In patients receiving an EPAP >5 mbar, the maximum pressure support was 35 mbar minus EPAP because maximal IPAP using the Stellar 150 device was limited to 35 mbar. Commercially available, nonvented nasal or nasal-mouth masks with an exhalation port (Silentflow 2) were used for all patients.

Statistical Analysis

Statistical analysis was performed using Sigma-Plot® (Version 12.1, Systat Software, Inc., Point Richmond, Calif., USA). Data are presented as mean $\pm$ standard deviation (SD) after testing for normal distribution (Kolmogorov-Smirnov test). For nonnormally distributed data, median and interquartile range values are shown. The primary outcome parameter, the difference in time spent in

N3/4 sleep, was used to determine the minimum sample size required to ensure adequate power to detect an effect of the interventions. Assuming a power (β) of 90% with an α of 0.05 to detect a 10% change in N3/4 sleep (with an SD of 10%) according to previous findings, at least 13 patients were needed for the analysis [3, 12]. The paired t test was used for the comparison of iVAPS and HI-NPPV. The Wilcoxon signed-rank test was used for data with a nonnormal distribution. One-way repeated-measures ANOVA on ranks was used to compare sleep quality at different time points (in hospital, and then after 1 and 6 weeks of home mechanical ventilation). For normally distributed data, 95% confidence intervals (CIs) were given if appropriate. Statistical significance was set at a p value of <0.05 .

Results

Study Population

Fourteen patients were consecutively enrolled from January to November 2011. Demographic data are shown in table 1. One patient dropped out during the first 6-week period at home after being diagnosed with abdominal cancer. Ventilator settings during HI-NPPV and iVAPS are shown in table 2. The patients had received HI-NPPV for a mean 32.9 ± 37.4 months prior to the study. Over this period, PaCO₂ was reduced from 58.6 ± 6.9 to 42.9 ± 6.5 mm Hg (95% CI for the difference -20.4 to -9.2 , $p < 0.001$) and bicarbonate (HCO₃⁻) decreased from 31.8 ± 2.9 to 27.5 ± 3.0 mmol/l (95% CI for the difference -5.9 to -2.1 , $p < 0.001$).

Table 1. Demographic data, lung function parameters and daytime blood gases during spontaneous breathing with supplemental oxygen

	Patients (n = 14)
Male/female	11/3
BMI, kg/m ²	31.1 ± 10.1
Age, years	64.3 ± 7.5
Height, m	1.74 ± 0.09
Smoking history, pack-years	23.7 ± 22.7
FVC, % predicted	54.3 ± 16.7
FEV ₁ , % predicted	34.7 ± 17.1
FEV ₁ /FVC, %	46.4 ± 17.0
TLC, % predicted	98.6 ± 34.9
HMV, months	32.9 ± 37.4
PaO ₂ , mm Hg	71.1 ± 13.8
PaCO ₂ , mm Hg	42.9 ± 6.5
pH	7.42 ± 0.05
HCO ₃ ⁻ , mmol/l	27.4 ± 3.0
Supplemental O ₂ , l/min	1.3 ± 1.1

Data are presented as number or mean ± SD. FEV₁ = Forced expiratory volume in 1 s; FVC = forced vital capacity; HCO₃⁻ = bicarbonate; HMV = home mechanical ventilation; HI-NPPV = high intensity noninvasive positive pressure ventilation; iVAPS = intelligent volume-assured pressure support; TLC = total lung capacity.

Table 2. Ventilator settings for HI-NPPV and iVAPS

	Patients (n = 14)
HI-NPPV	
IPAP, mbar	25.5 ± 3.8
EPAP, mbar	5.8 ± 2.1
RR, per min	17.2 ± 2.6
Inspiratory time, s	1.0 ± 0.2
iVAPS	
Alveolar target volume, l/min	11.5 ± 3.1
Minimum PS, mbar	14.7 ± 4.1
Maximum PS, mbar	24.7 ± 4.1

Data are presented as mean ± SD. PS = Pressure support.

Sleep Quality

There was no difference between HI-NPPV and iVAPS in objective sleep quality, including the primary end point (time spent in N3/4 sleep; table 3). Apart from pressure discomfort, which was higher during iVAPS than with HI-NPPV ($p = 0.04$), no other significant differences were found with regard to subjective sleep quality and comfort with NPPV in hospital (table 3). There was also no differ-

Fig. 2. Subjective sleep quality (restfulness of sleep on 100-mm VAS) during nighttime NPPV in hospital and at home after 1 and 6 weeks of HI-NPPV or iVAPS (n = 13). Data are presented as median values. n.s. = Not Significant. Repeated-measures ANOVA on ranks was used.

ence in the apnea-hypopnea index and desaturation index between the two modes of NPPV (table 3). At home, patients reported more restful sleep during iVAPS than with HI-NPPV ($p = 0.04$), but other subjective sleep quality and comfort parameters were not significantly different (table 3). Subjective sleep quality in hospital was not different from that assessed at home after 1 and 6 weeks of HI-NPPV [71.0 (60.0–90.0) vs. 77.0 (66.0–90.5) vs. 75.0 (70.0–88.5), respectively, $p = 0.81$], whereas subjective sleep quality during iVAPS improved over time [68.0 (50.0–80.0) vs. 80.0 (60.0–90.3) vs. 90.0 (73.8–90.3), in hospital and after 1 and 6 weeks at home, respectively, $p = 0.032$; fig. 2].

Blood Gases

Blood gases during in-hospital NPPV with HI-NPPV and iVAPS are shown in table 4. Supplemental oxygen during NPPV was used for 11 patients, with no change during the study. There were no significant differences in arterial blood gases after 6 weeks of HI-NPPV versus iVAPS: PaO₂ 67.6 ± 7.7 versus 68.0 ± 8.0 mm Hg (95% CI for the difference –3.0 to 5.0, $p = 0.58$), PaCO₂ 43.6 ± 9.7 versus 42.8 ± 7.4 mm Hg (95% CI for the difference –4.6 to 1.9, $p = 0.37$), pH 7.43 ± 0.04 versus 7.43 ± 0.03 (95% CI for the difference –0.02 to 0.02, $p = 0.84$) and HCO₃⁻ 27.5 ± 3.2 versus 27.5 ± 3.4 mmol/l (95% CI for the difference –0.9 to 1.4, $p = 0.61$).

Table 3. Objective and subjective sleep quality, respiratory analysis and comfort during nighttime HI-NPPV versus iVAPS, in hospital and at home

	HI-NPPV	iVAPS	95% CI for between-group difference	p value
PSG (n = 14)				
Total sleep time, min	280.9±46.1	244.9±81.9	−80.1 to 8.3	0.10
Sleep efficiency, %	71.1±15.9	65.9±19.8	−13.9 to 3.4	0.22
N1 sleep, %	28.9±22.0	34.0±17.5	−5.4 to 15.5	0.32
N2 sleep, %	43.0 (37.0–50.0)	44.5 (33.0–53.0)		0.74
N3/4 sleep, %	17.4±15.6	15.3±12.3	−6.3 to 2.1	0.31
REM sleep, %	12.3±8.0	8.9±8.2	−7.1 to 0.3	0.07
Arousal index, /h	11.9±7.2	12.4±10.8	−4.6 to 5.5	0.85
Apnea-hypopnea index, /h	0.3±0.8	0.5±0.9	−1.0 to 0.6	0.56
Desaturation index, /h	5.0±2.0	4.6±1.5	−4.2 to 3.5	0.84
In-hospital VAS score (n = 14)				
Restfulness of sleep	70.5 (60.0–90.0)	64.0 (50.0–80.0)		0.68
Morning freshness	75.0 (50.0–90.0)	67.5 (50.0–80.0)		0.21
Pressure-induced discomfort	83.5 (70.0–90.0)	75.0 (40.0–80.0)		0.04
Mask fit	85.0 (80.0–90.0)	80.0 (80.0–90.0)		0.65
At-home VAS score (n = 13)				
Restfulness of sleep, daily	77.0 (65.8–87.0)	81.0 (75.0–89.5)		0.04
Restfulness of sleep	77.0 (66.5–89.3)	81.7 (74.1–91.0)		0.02
Morning freshness	80.0 (64.7–90.1)	82.5 (74.3–90.2)		0.19
Pressure-induced discomfort	80.0 (73.8–88.7)	81.0 (73.0–90.0)		0.84
Mask fit	81.0 (68.8–90.0)	81.0 (73.0–90.0)		1.00

Data are presented as mean ± SD or median (interquartile range). On the VAS, higher scores indicate a better outcome.

Compliance with NPPV

Compliance with HI-NPPV (mean daily usage 6.2 ± 1.6 h) and iVAPS (mean daily usage 6.5 ± 1.3 h) was similar (95% CI for the difference −0.2 to 0.7, p = 0.27).

Discussion

This randomized, crossover study compared sleep quality during iVAPS and HI-NPPV in COPD patients with chronic hypercapnia. Sleep quality was assessed objectively using PSG in hospital, and then subjectively in hospital and during the two 6-week periods of ventilation at home. Objective sleep quality was not significantly different during ventilation with iVAPS and HI-NPPV, but sleep was reported to be more restful during the 6 weeks of home NPPV with iVAPS.

Although iVAPS uses a pressure range with variation of IPAP, sleep quality was not adversely affected when compared with HI-NPPV using a fixed level of IPAP. This is in line with previous studies showing no differ-

Table 4. Capillary (5 a.m.) and transcutaneous (mean overnight) blood gas analysis during night-time HI-NPPV versus iVAPS (n = 14)

	HI-NPPV	iVAPS	95% CI for between-group difference	p value
PaO ₂ , mm Hg	76.0±14.0	73.4±15.6	−11.7 to 6.6	0.55
PaCO ₂ , mm Hg	43.6±7.1	40.6±7.6	−5.7 to −0.2	0.04
pH	7.42±0.04	7.45±0.04	0.006 to 0.05	0.02
HCO ₃ [−] , mmol/l	27.5±3.1	27.2±3.6	−1.2 to 0.7	0.60
PtcCO ₂ , mm Hg	43.2±6.7	37.8±5.5	−6.6 to −1.8	0.003

Data are presented as mean ± SD.

ences in sleep quality between pressure support ventilation with and without target volume (average volume assured pressure support) in patients with obesity hypoventilation syndrome [8, 9]. Furthermore, Jaye et al. [18] reported no difference between iVAPS and pressure sup-

port ventilation in restrictive patients. However, all of these studies focused only on sleep quality measured in hospital via PSG [7, 8, 18], and it is widely accepted that sleep quality at home is different from that in hospital [22]. Data about how NPPV using target volumes influences sleep quality at home and whether there might be an improvement in sleep quality over time are lacking; we assessed these in this study. Our results show that subjective sleep quality in hospital was not different with HI-NPPV and iVAPS. Therefore, it could theoretically be argued that iVAPS did not provide additional benefit with regard to sleep quality in COPD patients already treated with NPPV. This is supported by previous studies showing no improvements in sleep quality measured in hospital when using NPPV with target volumes compared to conventional NPPV [7, 8, 18]. In contrast, we reported sleep at home as more restful when patients were being treated with iVAPS than with HI-NPPV, despite no statistical significant differences between the devices with respect to sleep quality being detected during in-hospital PSG assessments. There were trends towards poorer sleep quality with iVAPS in hospital but this improved continuously over time. This might be explained by the fact that patients were naïve to iVAPS at the beginning of the study and some time was required to become familiar with this treatment strategy. Sleep quality did not change over time during HI-NPPV, which had been the standard therapy for all patients prior to enrollment. So one finding is that measuring subjective sleep quality in hospital does not adequately reflect sleep quality at home, particularly if a familiarization process with new equipment or ventilation techniques is involved. However, the clinical interpretation of unevaluated VAS data is difficult, and the results of our VAS data should be reflected with care.

There was no difference in daytime blood gases between iVAPS and HI-NPPV after 6 weeks of home mechanical ventilation. These results are in agreement with data from a previous trial comparing 8 weeks of volume- and pressure-preset noninvasive ventilation with iVAPS in COPD patients [13]. In addition to measuring blood gases during spontaneous breathing, this study also assessed blood gases during nighttime NPPV in order to assess the quality of ventilatory support. It was shown that PaCO₂ values were significantly lower during ventilation with iVAPS than with HI-NPPV. This might be caused by the fact that minute ventilation for the calculation of alveolar target volume for iVAPS was assessed during the day.

Our study population represented a specific phenotype of COPD, as the demographic data showed no hyperinflation and the BMI was overweight-to-obese in

most of the patients. Therefore, iVAPS might be an effective, alternative mode of noninvasive ventilation for non-hyperinflated COPD patients with obesity that are not adequately treated with existing therapy.

Our study had some limitations. Firstly, patients were familiar with the technique of HI-NPPV but not with iVAPS. Therefore, the possibility that the sleep quality measured in hospital during the first night with iVAPS was underestimated due to a lack of familiarity and adaptation cannot be excluded with certainty. During the assessments at home over 6 weeks, iVAPS was associated with improvements in self-reported sleep quality compared with HI-NPPV. Deterioration in sleep quality is unlikely during HI-NPPV, so iVAPS is likely to have been responsible for the improvement in sleep quality that we observed. Secondly, the MV needed for the calculation of alveolar target volume for iVAPS was assessed during ventilation with HI-NPPV during the day. So our findings can only be generalized to patients being switched to iVAPS after effective NPPV. Thirdly, the ventilator's software used a fixed formula for the estimation of alveolar ventilation. This formula does not take into account the specifics of COPD regarding hyperinflation and air-trapping. Therefore, the alveolar ventilation might, at least from a physiological point of view, have been underestimated in these patients. In conclusion, sleep quality in chronic hypercapnic COPD patients without hyperinflation measured in hospital via PSG did not differ during therapy with iVAPS and HI-NPPV. However, subjective sleep tended to be more restful in the course of 6 weeks of home mechanical ventilation with iVAPS. Since iVAPS has been used to successfully treat chronic hypercapnia, it would appear to be a good alternative mode of non-invasive ventilation for chronic hypercapnic COPD patients without hyperinflation. Additional studies are needed to address if and how iVAPS can be effectively initiated in this patient group.

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