Short-Term Effects of Pressure Controlled Versus Volume Controlled Noninvasive Ventilation in Subjects With Amyotrophic Lateral Sclerosis

Grazia Crescimanno, Francesca Greco, Manuela Bertini, Salvo Arrisicato, and Oreste Marrone

BACKGROUND: Comparison of the effects of pressure controlled and volume controlled noninvasive ventilations (NIV) has usually been limited to the degree of improvement in blood gases. We compared sleep quality, abnormal respiratory events, and patient-ventilator asynchronies during administration of pressure controlled continuous mandatory ventilation (PC-CMV) and volume controlled continuous mandatory ventilation (VC-CMV) in subjects with amyotrophic lateral sclerosis naive to NIV after titration aimed at maximally improving nocturnal arterial blood gases. METHODS: A crossover evaluation of PC-CMV and VC-CMV was performed in 27 subjects with amyotrophic lateral sclerosis. After baseline polysomnography, ventilators were set in random order so as to warrant similar and satisfactory oxygen saturation and transcutaneous P_{CO_2} in both NIV modalities during day and night. Soon after titration, polysomnography was repeated during administration of each type of NIV. RESULTS: With respect to the baseline night, non-rapid eye movement 3, and rapid eye movement sleep stages increased, and the arousal index decreased during PC-CMV ($P = .005$, $P = .02$, and $P = .01$, PC-CMV vs VC-CMV, respectively) but not during VC-CMV. The arousal index during NIV was correlated to the peak pressure delivered by the ventilators ($\rho = 0.47$, $P < .001$). Few abnormal respiratory events were observed in both NIV modes. Patient-ventilator asynchronies were more frequent during VC-CMV (median [IQR] 20.8 [0.0 – 22.0] vs 31.8 [30.1 – 34.0] no./h, PC-CMV vs VC-CMV; $P = .002$). Twenty-one subjects declared that they preferred PC-CMV therapy. CONCLUSIONS: In the short term, PC-CMV may be a preferred NIV modality to VC-CMV for patients with amyotrophic lateral sclerosis, even when both NIV modes are similarly effective in the correction of hypoventilation. Evaluation of the effectiveness of NIV should not be limited to the assessment of blood gas correction. *Key words: Pressure control continuous mandatory ventilation; Volume control continuous mandatory ventilation; amyotrophic lateral sclerosis; hypoventilation; abnormal respiratory events; patient-ventilator asynchrony.* [Respir Care 2021;66(10):1593–1600. © 2021 Daedalus Enterprises]

Introduction

Noninvasive ventilation (NIV) is standard care in patients with amyotrophic lateral sclerosis (ALS). However, an increase in survival with NIV in ALS rarely exceeds 1 year.[1,2] Adaptation may be more challenging in patients with ALS than in other patients with neuromuscular diseases.[3] Short-term acceptance may influence long-term adherence and, in turn, clinical deterioration and survival.[4,5] This implies that much research is still needed, with the aim of more substantial success. The effectiveness and acceptance of NIV may differ, depending on mode and setting of ventilators. Generally, in the classification of NIV modes, pressure controlled ventilation and volume controlled ventilation are distinguished. Today, the NIV mode is usually chosen in relation to each center's experience.[6,7] Most comparative analyses of NIV modes addressed just blood gas values. However, it would be important to consider other aspects, which may or may not be associated with adequate correction of hypoventilation. Indeed, improvement of ventilation during sleep is not sufficient to warrant an improvement of sleep quality and is not always associated with acceptance of NIV.

In addition, normal blood gas values do not exclude irregular breathing patterns, such as abnormal respiratory events or patient-ventilator asynchronies.[8,9] Of note, even patients with ALS who present with these events and no desaturation may have poor survival.[10] Patient-ventilator

asynchronies may be an index of imperfect titration of the ventilator or of poor adaptation to NIV, but they are rarely completely eliminated. An association between patient-ventilator asynchronies and arousals in subjects with neuromuscular disease has been described.[11,12] However, in ALS, the relevance of patient-ventilator asynchronies as factors that disturb sleep is uncertain.[13,14] We performed a prospective crossover study of pressure controlled ventilation and volume controlled ventilation after careful NIV titration aimed at maximally improving nocturnal arterial blood gases. Our aim was to make a comprehensive comparison of these therapy modalities in subjects with ALS who were naive to NIV, based on assessment of polysomnographic (PSG) recordings and on short-term subjective acceptability.

Methods

Study Protocol

Consecutive patients with ALS who underwent scheduled clinical control at our ALS clinic were evaluated. The degree of functional impairment was assessed with the revised Amyotrophic Lateral Sclerosis Functional Rating Scale. Spirometry, respiratory muscle strength (Vmax22, Sensormedics, Yorba Linda, California), and arterial blood gases (BGE IL, Lexington, Massachusetts) were measured. In addition, a standard PSG (SomnoLab 2 AASM, Weinmann, Hamburg, Germany) with simultaneous transcutaneous monitoring (SenTec AG, Therwil, Switzerland; software version SMB SW-V04.03) was performed. Patients who required NIV according to the European Federation of Neurological Societies criteria[15] or with a peak nocturnal $\geq$ 50 mm Hg were enrolled.[16] Patients already using NIV and with frontotemporal dementia or other mental disorders that precluded their collaboration were excluded.

Drs Crescimanno and Marrone are affiliated with the Italian National Research Council, Institute for Biomedical Research and Innovation, Palermo, Italy. Drs Crescimanno, Bertini, and Arrisicato are affiliated with the Regional Center for Prevention and Treatment of Respiratory Complications of Rare Genetic Neuromuscular Diseases, Villa Sofia-Cervello Hospital, Palermo, Italy. Dr Greco is affiliated with the Italian Union Against Muscular Dystrophy, branch of Palermo, Palermo, Italy.

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Correspondence: Grazia Crescimanno MD, Italian National Research Council, Institute for Biomedical Research and Innovation, Via Ugo La Malfa, 153, 90146 Palermo, Italy. E-mail: grazia.crescimanno@irib.cnr.it.

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QUICK LOOK

Current knowledge

The optimal ventilation mode for noninvasive ventilation (NIV) in subjects affected by amyotrophic lateral sclerosis (ALS) has not yet been identified. The role of residual abnormal respiratory events and patient-ventilator asynchronies in disturbing sleep of patients with ALS should be considered, together with the degree of improvement of blood gas exchange when assessing NIV success. Early acceptance of NIV is associated with long-term tolerance and, in turn, with improved survival.

What this paper contributes to our knowledge

In this prospective randomized controlled intervention study, 27 subjects with ALS naive to NIV were randomized to pressure controlled ventilation or volume controlled ventilation. The ventilator setting was optimized to obtain similar blood gas exchange at night in both NIV modes. Polysomnography (PSG) showed that volume controlled ventilation was associated with worse sleep quality and more patient-ventilatory asynchronies than pressure controlled ventilation despite its similar effectiveness on nocturnal blood gas exchange. A preference was expressed for pressure controlled ventilation by 21 subjects.

The subjects were informed that they would receive NIV with different modalities, whose characteristics were not explained. Thereafter, they underwent NIV titration, in random order for pressure controlled ventilation and volume controlled ventilation by using the same machine (Astral 150, ResMed, San Diego, CA). Each titration process lasted 3 to 7 d. The subjects then were asked to use NIV at night as long as they tolerated it. Once the subjects were adapted to NIV, they were submitted to a new PSG during NIV administration. No supplemental oxygen was administered. Full-night PSGs were performed according to standard procedures.[17] The performance of each type of NIV was evaluated on PSG and on data memorized by the ventilator. Finally, all the subjects were informally asked if they felt more comfortable with the NIV modality used during the first or the second period and, possibly, for what reason. The study was approved by the local ethics committee (Palermo 2, 14, p.a. 325, 2016), and all included subjects gave informed consent.

Procedures

Ventilator Setting. For each subject, one suitable nonvented oronasal mask was chosen. A double-limb configuration that incorporated an expiratory spirometer was

always used. Pressure controlled continuous mandatory ventilation (PC-CMV) and volume controlled continuous mandatory ventilation (VC-CMV) modes were used. The titration procedure was started during the day. Parameters of ventilation were slowly increased based on subjects' tolerance, until reaching an inspiratory pressure ≤ 18 cm H_2O during PC-CMV, and a tidal volume ≤ 10 mL/kg of ideal body weight during VC-CMV. In both modes of NIV, the inspiratory time (T_I) was set between 1.0 and 1.5 s, backup breathing frequency was set at 2 breaths beneath the spontaneous awake frequency, and a PEEP between 0 and 5 cm H_2O was established, depending on the presence of obstructive events in the baseline PSG. To complete the titration procedure, a cardiorespiratory polygraphy during NIV application with the setting established during the day was performed. Ventilator settings were modified if one of the following occurred: high patient-ventilator asynchronies recurrence, volumes recorded by the ventilator (ReScan ResMed software) not adequately matching the values that had been set, lowest oxygen saturation (S_{pO_2}) < 88%, percentage of time with S_{pO_2} < 90% (T90) > 5 min, peak transcutaneous P_{CO_2} (P_{tcCO_2}) ≥ 50 mm Hg.[15]

Analysis. Data stored by the ventilator during PSG were downloaded and analyzed. Median and 95th percentile values of minute ventilation, T_I, expiratory time (T_E), air leaks, pressures, and volumes were compared between the NIV modalities. On PSGs, sleep and arousals were scored according to the American Academy of Sleep Medicine 2007 criteria.[18] Total sleep time, sleep efficiency (total sleep time/total recording time × 100), sleep onset latency (the time between lights off and the first non-rapid eye movement (NREM) stage 1 (N1) epoch), duration of sleep stages as a percentage of the total sleep time, and wake after sleep onset were measured. The arousal index was calculated as the number of arousals/total sleep time (h). Arousals after abnormal respiratory events or patient-ventilator asynchronies were scored as respiratory arousals.

Nocturnal blood gas exchanges were monitored by S_{pO_2} and P_{tcCO_2}. The P_{tcCO_2} device was calibrated before and at the end of each recording to automatically correct drift when necessary. The mean S_{pO_2}, lowest S_{pO_2}, T90, oxygen desaturation index (the number of S_{pO_2} falls ≥ 3%/h of total sleep time), and mean and peak P_{tcCO_2} were measured. Abnormal respiratory events classification included events with partial or total upper-airway obstruction with and without a decrease of central drive.[8] Patient-ventilator asynchronies were scored as recently described.[9] The abnormal respiratory events index and patient-ventilator asynchronies index were calculated as the number of events / total sleep time (h). In addition, the percentage of total sleep time with patient-ventilator asynchronies was measured.

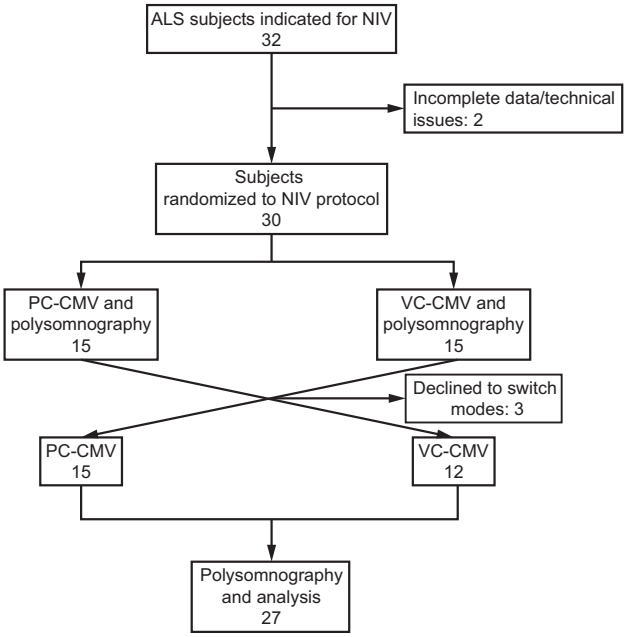

Fig. 1. Flow chart of the study. ALS - amyotrophic lateral sclerosis; NIV = noninvasive ventilation; PC-CMV = pressure controlled continuous mandatory ventilation; VC-CMV = volume controlled continuous mandatory ventilation.

Statistical Analysis

A total of 25 subjects were required to have an 80% power to detect a difference in the arousal index of 20% as significant when assuming an SD of ±6.5.[19] The Kolmogorov-Smirnov test was used to assess data distribution. Normally distributed data were expressed as mean ± SD, and non-normally distributed data were expressed as median (interquartile range [IQR]). Between-groups comparisons were performed by using the unpaired *t* test or the Mann-Whitney U test. Intra-individual comparisons between settings were performed by using the paired Student *t* test or the Wilcoxon test, as appropriate. Multiple comparisons were performed by using repeated measures analysis of variance or the Friedman test, followed by the post hoc Bonferroni test or the Conover test for pairwise comparisons. The chi-square test was used to compare paired proportions. Correlation analyses were performed by using the Spearman rank test. A 2-tailed $P < .05$ indicated statistical significance. Statistical analysis was performed by using IBM SPSS Statistics (version 22, IBM, Armonk, New York) and MedCalc (version 19.2.6, MedCalc Software, Ostend, Belgium).

Results

Between January 2017 and June 2019, 35 patients with ALS started using NIV. Thirty-two subjects were included in the study. None of the subjects had cough or an abnormal increase of bronchial secretions at the time of this protocol.

Table 1. Demographic Data, Characteristics of the Disease, and Baseline Respiratory Function in the Studied Subjects

Parameter	Results
Age, y	65.2 ± 11.4
Men/women, *n*	13/14
BMI, kg/m^2	23.6 ± 5.4
ALSFRS-R score	23.3 ± 8.5
ΔFS	0.5 ± 0.2
Duration of disease, months	50.7 ± 21.5
FVC, %	53.2 ± 22.2
P_{Imax}, cm H_2O	25.5 ± 17.0
SNIP, cm H_2O	27.2 ± 13.6
P_{Emax}, cm H_2O	26.0 ± 18.0
CPF, L/min	226.2 ± 94.6
P_{aO_2}, mm Hg	79.4 ± 10.1
P_{aCO_2}, mm Hg	45.3 ± 6.8
pH	7.42 ± 0.04
HCO_3, mmol/L	29.3 ± 3.3
BE, mmol/L	4.7 ± 3.0

Data are mean ± SD, unless otherwise noted.
BMI = body mass index
ALSFRS-R = Revised ALS Functional Rating Scale
ΔFS = progression rate
P_{Imax} = maximum inspiratory pressure
SNIP = sniff nasal inspiratory pressure
P_{Emax} = maximum expiratory pressure
CPF = cough peak flow
BE = base excess

Table 2. Ventilator Setting in Each Mode of Noninvasive Ventilation

Ventilator Setting	PC-CMV	VC-CMV
Inspiratory pressure, cm H_2O	13.9 ± 3.1	ND
Tidal volume, mL	ND	603.3 ± 89.7
PEEP*	4.1 ± 1.2	4.1 ± 1.2
Frequency, breaths/min	14.0 ± 1.6	14.0 ± 1.6
Inspiratory time, s	1.16 ± .11	1.16 ± .11

Data are mean ± SD.
*18 subjects.
PC-CMV = pressure controlled continuous mandatory ventilation
VC-CMV = volume controlled continuous mandatory ventilation
ND = no data

All the subjects were trained to the use of a cough-assist device. Seven had excessive saliva production and were treated with anticholinergic drugs. Two subjects were excluded because of incomplete data or PSG artifacts. Three subjects randomized to start with PC-CMV declined to switch to VC-CMV. Twenty-seven subjects completed the study (Fig. 1). Among them, 11 subjects had moderate-to-severe bulbar involvement. The remaining subjects were classified as non-bulbar. Demographic and functional data at baseline are shown in Table 1. The median (IQR) baseline apnea-hypopnea index was 4.5 (2.4 – 15.6).

Ventilator settings are shown in Table 2. The same settings for PEEP, minimum breathing frequency, and T_I were used with both NIV modes. Data downloaded from the ventilators after PSG are shown in Table 3. The differences between NIV modes were observed in breathing frequency, T_E, peak inspiratory pressure, and inspiratory flow. T_I, V_T, and minute ventilation did not differ between modes. S_{pO_2} and P_{tcCO_2} improved similarly with PC-CMV and VC-CMV (Table 4). Data of the sleep architecture are shown in Table 5. During PC-CMV, the NREM stage 3 (N3) and REM stage increased, and the arousal index decreased from baseline. Conversely, during VC-CMV, the N3 duration and the arousal index did not differ from baseline and were significantly different from the PC-CMV at night. In particular, non-respiratory arousals, but not respiratory arousals, differed between PC-CMV and VC-CMV.

Abnormal respiratory events occurred more frequently in PC-CMV, but, on average, they were rare in both NIV modes (median [IQR] 0.5 [0.0 – 4.7] vs 0.0 [0.0–0.4] events/h; $P < .001$). During PC-CMV, the abnormal respiratory events index was > 5 in 7 subjects and >10 in 6 subjects; instead, during VC-CMV, 4 subjects had an abnormal respiratory events index value >5, and only one had a value >10. The types of abnormal respiratory events recorded with each NIV mode in the subjects with abnormal respiratory events index > 5 are shown in Supplementary Table 1 (see the supplementary materials at http://www.rcjournal.com). The majority of abnormal respiratory events were partial airway obstructions with reduction of ventilatory drive. Unlike abnormal respiratory events, patient-ventilator asynchronies were more frequent with VC-CMV (median [IQR] patient-ventilator asynchronies index 20.8 [0.0 – 22.0] vs 31.8 [30.1 – 34.0] for PC-CMV vs VC-CMV; $P = .002$). The most common patient-ventilator asynchronies were ineffective efforts (Supplementary Table 2 [see the supplementary materials at http://www.rcjournal.com]).

Several 95th percentile values of variables elaborated by ventilators' software were significantly correlated with the PSG scores. Peak pressure was correlated with the arousal index ($\rho = 0.47$, $P < .001$) but especially with the rate of non-respiratory arousals ($\rho = 0.50$, $P < .001$). In addition, the peak flow was correlated with the abnormal respiratory events index ($\rho = 0.46$, $P < .001$), air leaks with patient-ventilator asynchronies index ($\rho = 0.36$, $P = .006$), and breathing frequency with percentage of sleep time with patient-ventilator asynchronies ($\rho = 0.47$, $P < .001$). Twenty-one of 27 subjects (77.7%) preferred PC-CMV, whereas 6 of 27 subjects (22.2%) preferred VC-CMV ($P < .001$). The most frequent concern with VC-CMV was related to sudden increases in pressure.

Discussion

Both pressure controlled ventilation and volume controlled ventilation are commonly used in the treatment of respiratory failure in ALS.[2,20,21] The results of this study showed that,

Table 3. Nocturnal Breathing Pattern, Mask Pressure, and Volumes During NIV

Parameter	PC-CMV	VC-CMV	*P*
Median peak inspiratory pressure, cm H_2O	12.8 ± 3.2	10.4 ± 4.0	.006
Peak inspiratory pressure, 95th percentile, cm H_2O	13.6 ± 3.5	16.2 ± 5.7	.02
Median leaks, %	34.8 ± 24.5	38.5 ± 23.7	.31
Leaks, 95th percentile, %	13.4 ± 12.2	14.2 ± 13.4	.78
Median V_T, mL	371.8 ± 175.4	405.4 ± 146.0	.32
V_T, 95th percentile, mL	526.7 ± 91.6	511.6 ± 103.5	.14
Median frequency, breaths/min	16.5 ± 1.9	18.0 ± 2.9	.02
Frequency 95th percentile, breaths/min	21.1 ± 3.5	23.1 ± 3.4	.01
Median T_I, s	1.12 ± .1	1.15 ± .2	.45
T_I, 95th percentile, s	1.10 ± .1	1.10 ± .3	.39
Median T_E, s	2.5 ± .4	2.1 ± .5	.002
T_E, 95th percentile, s	3.0 ± .5	3.0 ± .6	.50
Median V_E, mL/min	5.9 ± 2.3	7.2 ± 1.9	.06
V_E, 95th percentile, mL/min	11.6 ± 3.6	12.3 ± 3.2	.21
Median inspiratory flow, L/min	52.9 ± 16.9	42.4 ± 8.2	.004
Inspiratory maximum flow 95%, L/min	68.8 ± 30.4	55.7 ± 21.5	.01

Data downloaded from the ventilators. Data are mean ± SD.
PC-CMV = pressure controlled continuous mandatory ventilation mode
VC-CMV = volume controlled continuous mandatory ventilation mode
V_T = tidal volume
T_I = inspiratory time
T_E = expiratory time
V_E = minute ventilation

Table 4. Nocturnal Blood Gas Exchanges at Baseline and During Noninvasive Ventilation

Parameter	Baseline	PC-CMV	VC-CMV
Mean S_{pO_2}, mean ± SD, %	92.5 ± 3.4	94.5 ± 1.8*	94.2 ± 1.7*
Lowest S_{pO_2}, mean ± SD %	77.3 ± 8.9	79.5 ± 8.4	78.2 ± 7.1
ODI, median (IQR), events/h	1.3 (0.4 – 4.7)	0.4 (0.0 – 1.4)†	0.5 (0.1 – 1.3)†
T90, median (IQR), min	14 (2.7 – 132.3)	1.0 (0.0 – 12.0)†	3.0 (0.0 – 12.0)†
Mean P_{tcCO_2}, mean ± SD, mm Hg	47.4 ± 6.8	42.7 ± 6.1‡	42.8 ± 5.5‡
Peak P_{tcCO_2}, mean ± SD, mm Hg	52.9 ± 5.6	48.5 ± 5.6‡	47.0 ± 9.6‡

* $P < .01$ vs baseline
† $P < .05$ vs baseline
‡ $P < .001$ vs baseline
PC-CMV = pressure controlled continuous mandatory ventilation mode
VC-CMV = volume controlled continuous mandatory ventilation mode
ODI = oxygen desaturation index (number of oxygen desaturation ≥ 3%/h of sleep)
IQR = interquartile range
T < 90 = time spent with oxygen saturation below 90%;
P_{tcCO_2} = transcutaneous P_{CO_2}

after a titration, which ensured a similar and satisfactory correction of nocturnal hypoventilation with both types of NIV, pressure controlled ventilation, administered in the PC-CMV mode, was associated with better improvement of objective sleep quality and a lower occurrence and duration of patient-ventilator asynchronies than volume controlled ventilation, administered as VC-CMV. Abnormal respiratory events were more frequent with PC-CMV, but, on average, their rate remained low. From the subjects' personal point of view, treatment by using PC-CMV was more acceptable than by VC-CMV. Previous studies compared the efficacy of pressure controlled and volume controlled NIV in subjects with different diseases, including kyphoscoliosis,[22] COPD,[23] heterogeneous neuromuscular diseases,[5] and ALS[6] in terms of correction of blood gas derangements. Generally, no significant differences in alveolar ventilation or respiratory muscle unloading were found,[6,22,23] but one study in subjects with ALS found that pressure controlled ventilation was less effective.[7]

Table 5. Sleep Characteristics Recorded Without and During Noninvasive Ventilation

Characteristic	Baseline	PC-CMV	VC-CMV
TST, min	300.9 ± 78.0	332.3 ± 51.6	31.0 ± 63*
SE, % TST	65.8 ± 17.2	74.6 ± 10.0	70.9 ± 12.8
SL, min	37.1 ± 22.4	29.8 ± 19.3†	29.1 ± 14.7†
N1, % TST	35.0 ± 20.3	27.6 ± 19.3	35.0 ± 21.1
N2, % TST	50.2 ± 17.7	44.8 ± 15.8	45.1 ± 15.4
N3, median (IQR), % TST	1.9 (0.0 – 9.3)	11.7 (5.3 – 21.1)‡	3.8 (0.0 – 11.3)§
R, % TST	8.4 ± 6.7	14.5 ± 8.0†	12.5 ± 8.5
Arousal index, no./h	24.3 ± 12.4	17.8 ± 7.9‡	22.4 ± 12.6*
Non-respiratory arousal index, no./h	14.3 ± 9.1	9.9 ± 6.7	18.6 ± 9.2§
Respiratory arousal index, median (IQR), no./h	4.5 (1.9 – 15.6)	3.2 (0.5 – 13.9)	0.9 (0.0 – 5.1)†

Data are mean ± SD unless otherwise noted.
* $P < .05$ vs PC-CMV
† $P < .05$ vs baseline
‡ $P < .01$ vs baseline
§ $P < .01$ vs PC-CMV
PC-CMV = pressure controlled continuous mandatory ventilation mode
VC-CMV = volume controlled continuous mandatory ventilation mode
TST = total sleep time
SE =sleep efficiency
SL = sleep latency
N1 = NREM stage 1
N2 = NREM stage 2
N3 = NREM stage 3
IQR = interquartile range
R = REM stage

Peculiarities of our study were the criteria adopted for ventilator settings. In previous studies, ventilators were set only during wakefulness[6] or did not require a similar correction of nocturnal blood gases with both NIV modes.[7] Indeed, if NIV titration is performed when looking at nocturnal blood gases, it is usually possible to set the ventilator to determine similar effects on nocturnal S_{pO_2} and P_{tcCO_2} with different types of NIV. However, similar effects on blood gases do not exclude notable differences in other respects. When keeping this in mind, our purpose was to compare sleep characteristics, some respiratory events, and subjects' preferences for one type of NIV when different NIV modalities similarly and effectively corrected nocturnal hypoventilation.

Sleep quality, evaluated on electroencephalography, was better with PC-CMV than with VC-CMV. Also, compared with the baseline night, only PC-CMV improved sleep quality. Some characteristics of each type of NIV could be responsible for the better effects of PC-CMV. VC-CMV was associated with lower median but with higher 95th percentile levels of peak inspiratory pressure. Therefore, pressure administered during VC-CMV was more variable than during PC-CMV. This finding could be expected because, during VC-CMV, the ventilator attempts to deliver the set volume, irrespective of the pressure that is required. Pressure requirements may change, for example, due to changes in compliance of the respiratory system after position changes. Sporadic high spikes in pressure occasionally required to reach the set volume could be responsible for disturbing sleep and decreasing acceptability of the VC-CMV. In fact, the 95th percentile values of peak inspiratory pressure were significantly correlated with non-respiratory arousals, and, in most cases, the subjects stated that they found VC-CMV less tolerable due to sudden pressure augmentations. A lower adaptability to this type of NIV is also suggested by the greater occurrence of patient-ventilator asynchronies, which may have contributed to fragmented sleep and to reduced slow-wave sleep. Thus, PC-CMV and VC-CMV are not always interchangeable. A high pressure variability and a frequent occurrence of patient-ventilator asynchronies during VC-CMV may be considered an indication to prefer PC-CMV.

Residual abnormal respiratory events were few with both NIV modes, but, during PC-CMV, more subjects showed abnormal respiratory events. Because abnormal respiratory events have been pointed out as possible negative prognostic factors, even when they are not associated with hypoxemia, this finding may be of relevance.[10] Therefore, it may be important to identify and, if possible, to correct these events. Predictive criteria of abnormal respiratory events should be researched. We found that peak flow was higher with PC-CMV and was correlated to the abnormal respiratory events index. High peak flows may have negatively influenced laryngeal muscle activity, which generated airway narrowing or closure and a higher number of abnormal respiratory events. In healthy individuals, the mode of ventilation influences glottis response.

Parreira et al[24] found that the influence of pressure controlled ventilation on the glottis was less predictable and

more variable in comparison with the volume controlled mode. Patients with ALS may be more prone to develop glottic events under NIV than healthy individuals. Such events have been reported, especially in subjects with pseudobulbar dysfunction,[25] or in subjects with spinal onset disease with early involvement of the vagus nerve.[26] Glottic events have been attributed to laryngeal dysfunction and altered upper-airway reflex regulation, and are exaggerated by high pressure or flow.[27] In subjects with ALS, when using pressure controlled ventilation, Georges et al[10] reported a remarkably high prevalence of abnormal respiratory events (45%). However, Sancho et al,[25] during volume ventilation, reported a low prevalence of these events (10%). These data were consistent with our results, which showed fewer abnormal respiratory events under VC-CMV. A switch from pressure to volume ventilation may be considered if a high number of these events is observed in the pressure mode.

Finally, we found that patient-ventilator asynchronies were more common during VC-CMV. Ineffective efforts and underassistance were the predominant types of patient-ventilator asynchronies, which is in agreement with previous studies on patients with ALS under pressure NIV.[13,14] One study compared patient-ventilator asynchronies during invasive pressure and volume invasive ventilation, and, similar to our study, showed that the incidence of patient-ventilator asynchronies was higher in volume ventilation.[28] Generally, ineffective efforts are associated with leaks or auto-PEEP, which may be aggravated by a high breathing frequency. Accordingly, in our study, ineffective efforts not only correlated with leaks but also with breathing frequency. In turn, breathing frequency differences were mainly accounted for by T_E. We hypothesize that short T_E durations influenced the occurrence of ineffective efforts. Unlike in studies in young subjects with neuromuscular diseases,[11,12] but similarly to one study in subjects with ALS,[14] in our sample patient-ventilator asynchronies were not correlated with the arousal index or with other electroencephalographic sleep characteristics. In fact, the clinical importance of patient-ventilator asynchronies in ALS is still uncertain.[29] Nevertheless, better patient-ventilator synchrony during PC-CMV versus VC-CMV suggests that patients with ALS may adapt better to the former NIV modality.

Strengths of this study were the inclusion of a relatively large sample of subjects and the crossover design. One more strength was that it explored effects of NIV from an original point of view, which demonstrated that improvement of blood gases may be an insufficient criterion to evaluate NIV therapy. A limitation was that it explored only short-term effects of NIV. Furthermore, because the incidence of abnormal respiratory events reflects a center's practice and expertise in ventilator settings, it might not be possible to extrapolate our results to other centers.

Conclusions

In the short term, PC-CMV may be a better NIV modality than VC-CMV for patients with ALS, even when both NIV modes are similarly effective in the correction of hypoventilation. The better performance of PC-CMV was due to greater improvement in sleep quality, lower occurrence of patient-ventilator asynchronies, and higher subjective acceptability. Efficacy of NIV therapy would be better assessed if improvement of blood gases were not the only evaluation criterion. In the long term, the differences that we observed may result in a different compliance to NIV therapy and in a different efficacy of the two NIV modalities. Further studies are necessary to verify if our results can be reproduced in the long term.

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