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Alveolar Ventilation-Targeted vs. Spontaneous/Timed Mode for Home Non-Invasive Ventilation in Amyotrophic Lateral Sclerosis

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AUTHOR CONTRIBUTIONS

PP: literature search, data analysis and interpretation, manuscript writing.

MK: study design and supervision, data interpretation, manuscript review

JK: data interpretation, manuscript review

VA: study design, data collection, manuscript review

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

All participants gave a written informed consent and Research Ethics Board at MUHC had approved the study protocol.

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Abstract

Introduction: Home noninvasive ventilation (NIV) is increasingly used in ALS to improve symptoms and survival. Our primary objective was to compare iVAPS vs. ST modes regarding time to first change in ventilator parameters and the number of interventions over 6 months in subjects with ALS in a respiratory therapist (RT)-led program.

Methods: In this study, 30 subjects with ALS meeting criteria for NIV initiation were randomized to iVAPS or ST. NIV was initiated using standardized protocols targeting optimal tidal volume and comfort in a daytime session. "Download" data was recorded at 1 week, 1 and 6 months. Any changes in ventilator parameters were recorded.

Results: Of the 30 subjects, 56.7% had bulbar onset ALS, 8 died and 11 in each group completed the study. Median time to first parameter change was 33.5 (IQR:7.7-96) vs. 41 (IQR: 12.5-216.5) days for iVAPS vs. ST groups, respectively (P = 0.48). The average number of RT interventions was similar between groups (1.1±1.1 vs 0.9±0.9 at 1 month, P = 0.72; 2.4±2.1 vs 2.4±2.3 at 6 months, P = 0.95; for iVAPS vs ST respectively). Adherence was significantly lower with iVAPS than ST at 1 week, but not at 1 or 6 months. Download parameters were similar between groups at 1 week and 6 months, except for higher residual apnea-hypopnea index (AHI) and less spontaneously triggered breaths with iVAPS at 6 months.

Conclusions: The time to first change of parameters and the number of interventions at 6 months from NIV initiation were similar for the iVAPS and ST modes in subjects with ALS. With iVAPS, adherence was lower transiently at NIV initiation, and the residual AHI was higher at 6 months. Alveolar ventilation-targeted NIV may require a longer adaptation period and result in greater upper airway instability in predominantly bulbar ALS subjects.

Keywords: noninvasive ventilation (NIV); intelligent volume-assured pressure support (iVAPS); bilevel spontaneous timed ventilation; amyotrophic lateral sclerosis (ALS); respiratory therapist interventions; apnea hypopnea index

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that is incurable and leads to progressive respiratory muscle weakness.[1] A recent systematic review and meta-analysis demonstrated that the overall worldwide ALS prevalence and incidence were 4.42 (95% CI 3.92–4.96) per 100,000 population and 1.59 (95% CI 1.39–1.81) per 100,000 person-years, respectively.[2] The most common causes of death in ALS patients are chronic hypercapnic respiratory failure, airway obstruction by secretions due to ineffective cough, and aspiration pneumonia.[3,4] Home noninvasive ventilation (NIV) is increasingly used in ALS patients for improving respiratory function, health-related quality of life, and survival.[5-18] The randomized controlled trial (RCT) by Bourke and colleagues showed that NIV improves survival and quality of life in ALS patients with orthopnea, maximum inspiratory pressure(MIP) < 60% of predicted or symptomatic hypercapnia, but without severe bulbar dysfunction.[10] No new RCT in subjects with ALS addressing survival and quality of life with NIV has been published.[19] However, the recent well-designed retrospective study by Ackrivo and colleagues demonstrated that NIV was associated with a 26% reduction in mortality, particularly in the limb-onset ALS subtype and with NIV use ≥4 hours/ day.[18] Limb-onset ALS patients were more likely to tolerate NIV, compared to bulbar-onset ALS patients (odds ratio 6.25, 95% CI: 1.09–33.33).[6,20] Recently, a prospective study reported that NIV conferred a significant survival advantage even in those with severe bulbar impairment with median survival of 13 months, compared with 3 months in those not using NIV (P <0.01). However, bulbar impairment was a cause of NIV failure in 49% of cases, and a major prognostic factor[21]

Recently, the Canadian Thoracic Society (CTS) published guidelines for long-term NIV in ALS patients.[22] They suggested earlier initiation of NIV in ALS compared with previous guidelines, based on studies suggesting that earlier initiation of NIV in ALS patients results in improved rate of decline in respiratory function, survival, and quality of life.[10,23-24] Data remain limited regarding optimal ventilation modes and parameters, and no recommendation could be made regarding volume assured pressure support (VAPS) modes of NIV. The Intelligent Volume-Assured Pressure Support (iVAPS) is an adaptive ventilation mode that uses an algorithm to adjust pressure support to target a specified alveolar ventilation.[25] It has a learning mode that uses the baseline awake ventilation to determine the settings for ventilation.

Several RCTs showed similar efficacy of iVAPS compared to standard pressure support ventilation (PSV) on improving gas exchange, pulmonary function, sleep disturbances and adherence, in individuals with obstructive or restrictive lung disease with chronic hypoventilation.[26-32] Interestingly, one RCT showed that the adherence to iVAPS over 1 month was better than standard PSV in a mixed population (5.4 vs.4.2 hours/night for iVAPS vs. PSV; P <0.01). iVAPS delivered a lower median pressure support compared with standard PSV.[32] The principle of iVAPS is theoretically well-suited for ALS due to its adaptive response that obviates the need for overnight NIV titration and its ability to react to progressively deteriorating spontaneous respiratory function over time. Progression of ventilatory failure may result in recurrent periods of inadequate ventilation if parameter adjustments cannot be made, with reduced quality of life and more stress-related to respiratory or sleep-related symptoms.[33-35] Hence a device that can be titrated in a daytime trial and would “self-adjust” automatically over time as respiratory muscle weakness progresses could be beneficial for patient-related

outcomes and could be more cost-effective. On the other hand, ALS patients may have difficulty tolerating NIV and may require an adaptation period with progressive increase in NIV support. [32] A recent retrospective study comparing iVAPS to standard PSV in ALS patients showed that iVAPS provided more reliable target tidal volume than PSV and was associated with decreased rapid shallow breathing index (f/V_T) as an indicator of work of breathing.[36] However, whether iVAPS results in fewer respiratory therapist interventions related to NIV than standard pressure modes has not been studied. Therefore, the primary aim of this study was to compare iVAPS and Spontaneous Timed (ST) modes in subjects with ALS with respect to time to first change in ventilator parameters and the number of interventions over 6 months, following daytime NIV initiation in the context of a respiratory therapist (RT)-led home ventilation program.

Methods

We performed a pilot RCT with recruitment from February 2014 to September 2018 of patients referred for home NIV to the National Program for Home Ventilatory Assistance (NPHVA or Programme National d'Assistance Ventilatoire á Domicile, PNAVD) of the McGill University Health Centre (MUHC). Consecutive subjects with ALS meeting criteria for NIV initiation were approached. Criteria for NIV were: the presence of hypoventilation symptoms and at least one criterion such as daytime hypercapnia (P_{aCO2} > 45 mmHg), orthopnea, nocturnal hypoventilation (P_{CO2} during sleep increase > 10 mmHg compared with awake P_{CO2} or nocturnal oxygen desaturation <88% for a period of at least 5 consecutive minutes), FVC < 50% of predicted, SNIP <-40 cmH_2O or MIP <-40 cmH_2O. Subjects were excluded if they had other

major neurological disorders or active cancer; were referred from hospital and were already on a mechanical ventilator; or could not provide informed consent. This study has been registered on clinicaltrials.gov (NCT01746381). The MUHC Research Ethics Board approved the study protocol. All subjects gave written informed consent.

Subjects with ALS were randomized 1:1 to iVAPS or ST mode, both with a ResMed Stellar 150 ventilator. Randomization was performed using numbered sealed opaque envelopes based on a random sequence generator. NIV was initiated by an experienced RT using standardized protocols targeting optimal tidal volume and comfort in a daytime session in an outpatient day hospital setting lasting approximately 3 hours. Patients were encouraged to sleep while titration was ongoing, if possible. For subjects randomized to ST mode, expiratory positive airway pressure (EPAP) was set at 5 cmH2, pressure support was adjusted to achieve optimal tidal volume (8 ml/ideal body weight) if tolerated, and the back-up rate was set just below the subject's spontaneous respiratory rate aiming to maximize the subject's comfort. For those randomized to iVAPS, the learning mode was used to determine the target alveolar ventilation as per the ResMed protocol.[25] The RT selected the five-minute window where the subject's ventilation and respiratory rate looked stable to set up target alveolar ventilation and back-up rate (as per the "intelligent backup rate" algorithm). Parameters were then tested and adjusted if needed by increasing the minimum level of pressure support to target tidal volumes of 8 ml/ideal body weight and for the subject's comfort. The RT also adjusted inspiratory time (Ti), rise time, fall time, trigger sensitivity, and cycle sensitivity for each subject's comfort in both iVAPS and ST groups. If a subject fell asleep during the trial and obstructive events were noted, EPAP was raised manually for both ST and iVAPS modes. For all subjects, the RT recorded vital

signs, oxygen saturation (S_{pO2}), capillary blood gases before the trial of ventilation. All subjects underwent spirometry[37] and a SNIP test[38-39], including $SNIP_{open}$ and $SNIP_{closed}$[40] at baseline.

The RT visited all subjects at home at 1 week, at 1 and 6 months after NIV initiation. Download parameters such as compliance data (hours of daily usage), air leak, ventilator pressures used, minute ventilation, and respiratory events were recorded. Adjustments to ventilator settings were made if deemed necessary to optimize ventilation, minimize the apnea-hypopnea index (AHI), and maximize comfort, and subject symptoms for both iVAPS and ST groups. Adjustments could be initiated by the RT with pulmonologist approval or by the supervising pulmonologist, based on downloaded data. Any changes were recorded. In addition, daytime S_pO2 and end-tidal CO_2($EtCO_2$) were measured at baseline, 1 month, and 6 months. Overnight oximetry also was assessed at 1 month and 6 months using the Rad-8, Masimo SET®**.** Health-related quality of life was assessed at baseline and 3 months using the Severe Respiratory Insufficiency (SRI) questionnaires (scores range from 0 to 100, with higher scores indicating a better quality of life).[41] Participant's sleep-related symptoms and ventilator satisfaction were assessed at baseline and 6 months using our own questionnaire (Supplementary document).

Statistical Analysis

The sample size for this pilot study was calculated based on the expected number of ventilator changes over 6 months. We assumed a difference of 2 interventions between the study arms and a standard deviation (SD) of 1.5. We would then need 10 subjects per group to detect this difference with alpha 0.05 and power 80%. To account for withdrawal from the study or premature death, the total planned sample size was 30 subjects. Descriptive statistics

were provided for each group. Continuous variables were reported as mean and SD. Binary and categorical variables were summarized using frequency counts and percentages. Comparisons of continuous variables were performed using the T-test and of categorical variables with the chi-squared test. Pearson's correlation was used to determine variables associated with adherence to NIV. Time to first ventilator change was analyzed using survival analysis and Kaplan-Meyer plots with a log-rank test. A p-value of < 0.05 was considered statistically significant. All analyses were carried out using SPSS software, version 27 (IBM Corp., Armonk, NY).[42]

Results

Five hundred fifty-five subjects with ALS were referred to the NPHVA between February 2014 to September 2018. Of these, 289 subjects were ineligible on the basis of not meeting criteria for NIV initiation and 236 subjects declined to participate in the study. Thirty subjects were randomized to iVAPS or ST mode. One subject crossed over from iVAPS to ST due to intolerance at NIV initiation. At 6 months, a total of 3 and 5 patients died in the iVAPS and ST groups, respectively. There remained 11 subjects in each group who completed follow-up at 6 months (Figure 1). Participants' mean age was 62.8±9.5 years and 53.3% were male (Table 1). Most subjects were non-obese. Over half (56.7%) of the subjects had bulbar onset ALS. A minority (13.3%) of subjects had feeding tubes. Most subjects had daytime normocapnia (P_{aCO2} = 42.5±3.8 mm Hg) and normal oxygen saturation (S_{pO2} =95.9±2.4%) at NIV initiation. On average, the subjects had moderately severe restrictive lung disease based on FVC (55.4±17.8 % of predicted at enrolment). At baseline, no significant differences in demographics, health-related quality of life (SRI), gas exchange, and pulmonary function were observed between

iVAPS and ST groups except for higher proportions of wheelchair users and pregabalin users in the ST group and higher daytime P_{aCO2} in the iVAPS group (Table 1).

Table 2 shows the ventilator settings in iVAPS and ST groups at 1 week, 1 month, and 6 months. At 1 week, the back-up rate was significantly higher in the iVAPS group at 15.4 vs. 11.4 breaths per minute(bpm) for iVAPS vs. ST groups, respectively (*P*=<0.01). Adherence to NIV was significantly lower with iVAPS than ST at 1 week (Table 3). At 1 week, 13.2% of participants in the iVAPS group were using NIV ≥ 4 hours/night, compared with 45.4% using ST (*P* =0.03). The average hours of NIV use at 1 week was 2.2 and 4.6 hours/night for iVAPS vs.ST groups, respectively (*P*=0.03). However, there were no significant differences in NIV adherence between groups at 1 and 6 months. (Table 3). Download parameters were similar between groups at 1 week, 1 month, and 6 months (Table 3) except for significantly higher residual AHI and hypopnea index with iVAPS at all timepoints and less spontaneously triggered breaths with iVAPS at 6 months, possibly related to differences in trigger sensitivity. To assess if the AHI is related to variability in ventilation, we calculated Pearson correlation coefficients between the residual AHI and the difference between 95th percentile and median IPAP (delta IPAP) for the iVAPS group. Then we found no significant relationship between the residual AHI and the delta IPAP for the iVAPS group at any timepoint: r=0.494, p=0.09 at 1 week, r=0.176, p=0.57 at 1 month, and r=0.089, p= 0.81 at 6 months (Figure S1). However, we found significant correlations between the residual AHI and the difference between 95th percentile and median tidal volume (delta tidal volume) for the iVAPS group at 1 and 6 months (r=0.480, p=0.08 at 1 week, r=0.683, p<0.01 at 1 month, and r=0.706, p=0.01 at 6 months) (Figure S1). In exploratory analyses, we divided subjects into bulbar and non-bulbar onset ALS. We observed a significantly

higher residual AHI with iVAPS only at 1 month in bulbar-onset ALS subjects (Table S1 and S2), though non-significant differences occurred in both groups at other time points. We used the rapid shallow breathing index (f/V_t) to evaluate the work of breathing in subjects on NIV. We found no significant difference in f/V_t during NIV use between groups over 6 months (Table 3). In this cohort, mask leak did not differ significantly between iVAPS and ST (Table 3). We also found no significant relationships between average hours of NIV use and demographics, gas exchange parameters, download parameters, mask changes, or lung function parameters except for an inverse relationship with $SNIP_{open}$ (r = -0.55, P = 0.02) (Table 4).

As shown in Figure 2, the median time to first ventilator parameters change was 33.5 (IQR:7.7-96) vs. 41 (IQR: 12.5-216.5) days for iVAPS vs. ST groups, respectively (P = 0.48 by log-rank test). The average number of RT interventions was similar between iVAPS and ST groups at 1 month and 6 months (1.1±1.1 vs. 0.9±0.9 at 1 month, P = 0.72; 2.4±2.1 vs. 2.4±2.3 at 6 months, P = 0.95; for iVAPS vs. ST, respectively). The characteristics of interventions were similar in both groups except for more increases in trigger sensitivity with ST (Table 5). No significant difference in interventions to optimize mask fit between iVAPS and ST groups was observed. At 6 months, 3 and 5 patients died in the iVAPS and ST groups, respectively (Chi^2 P=0.54), all from respiratory failure.

Most subjects had normal daytime oxygen saturation and end-tidal CO_2 at baseline, 1 month, and 6 months. We found that daytime oxygen saturation and end-tidal CO_2 in iVAPS were similar to the ST group from NIV initiation to 1 month and 6 months follow-up (Table S3). Six participants underwent overnight oximetry at 1 month and 6 months in iVAPS and ST groups. We found no difference in the mean or nadir S_{pO2} during sleep, 4% oxygen desaturation

index (4% ODI), and % time with oxygen saturation < 90% (T90%) from 1 month to 6 months between iVAPS and ST groups (Table S3). We also observed no significant difference in participant's sleep-related symptoms between iVAPS and ST groups from NIV initiation to 6 months follow-up (Table S4). According to the SRI questionnaires, there was no significant difference in health-related quality of life between iVAPS and ST group in change from baseline to 3 months, except that the Respiratory complaint component deteriorated significantly in the ST group but not in the iVAPS group (Table S5). In addition, no significant difference in participant-reported ventilator comfort and satisfaction was observed between iVAPS and ST groups at 1 and 6 months (Table S6).

Discussion

In this study, we found that time to first ventilator parameter change and number and type of RT interventions over 6 months were similar in subjects with ALS using iVAPS and ST modes of NIV. This study demonstrated that the iVAPS mode did not require fewer interventions than the ST mode over 6 months from NIV initiation. The iVAPS mode was as effective as standard ST pressure ventilation, when initiated by a highly skilled respiratory therapist in a home ventilation program with respect to physiologic and patient-related outcomes. We also found ventilator download parameters, daytime gas exchange, ventilator comfort, and respiratory symptoms to be similar between groups, except for higher residual AHI on iVAPS. These findings support the previous studies comparing VAPS with standard PSV in subjects with neuromuscular disease.[28,43]

Interestingly, we found that adherence was significantly lower with iVAPS than ST at 1 week, but not at 1 or 6 months. Jaye and colleagues had found no significant difference in adherence between auto-titrating and standard PSV in neuromuscular disease.[28] On the other hand, this finding is contrary to the previous RCT by Kelly and colleagues, which suggested that the adherence to iVAPS over 1 month was better than standard PSV and lower median pressure support with iVAPS in a mixed population.[32] Although we demonstrated that alveolar ventilation-targeted NIV may require a longer adaptation period, there was no significant difference in adherence or survival between iVAPS and ST at 6 months among our subjects with ALS. We hypothesize that a longer adaptation period may be needed in ALS subjects with bulbar impairment to the iVAPS mode which is inherently less stable than the ST mode. Patients with bulbar symptoms may be more prone to reflex laryngospasm[44-46], glottic closure or discoordination with more variable pressure but we have not assessed this systematically. An important element associated with adherence to NIV is adequate mask fit. While there were more mask changes in the ST group in our study, the difference was not statistically significant, and similar proportions of patients used facial vs. nasal masks in each group. We found no significant relationship between NIV adherence and mask changes (Table 4). Irrespective of NIV mode, adherence was related to lower SNIP (Table 4), which suggests that greater diaphragm weakness is the main factor driving ALS patients to use NIV.

Nicholson and colleagues[36] found that adequate tidal volumes were more reliably attained for iVAPS compared with PSV in subjects with ALS. However, we found no significant difference in median tidal volume between iVAPS and ST modes over 6 months. They also reported a significantly lower rapid shallow breathing index with iVAPS compared to PSV,

whereas we found no difference. This may be due to differences in the study populations (more bulbar symptoms and higher FVC in our study population) and in the effectiveness of the parameters set for the ST mode. In our study, participants in the ST group achieved higher tidal volumes and a lower rapid shallow breathing index than the ST group in the Nicholson study. The learning mode in iVAPS uses the patient's respiratory pattern to set the ventilation parameters. In ALS patients, it is prone to "learning" the patient's dysfunctional rapid shallow breathing pattern which results from respiratory muscle weakness. It would then apply inadequate NIV settings with underestimated pressure support. Both the Nicholson and our study protocols have ensured the minimum pressure support setting is manually corrected if needed to provide sufficient tidal volumes.

Previous studies reported that subjects with limb-onset ALS were more likely to tolerate NIV compared with bulbar-onset ALS subjects.[10-11,20] We found no significant relationships between average hours of NIV use and type of onset of ALS. That is, adherence was no different for bulbar vs. non-bulbar subjects. Several studies showed bulbar onset ALS had a greater risk for upper airway obstruction during sleep.[34,47-48] We found significantly higher residual AHI in subjects using iVAPS, primarily but not exclusively in bulbar-onset subjects. We hypothesize that the iVAPS mode, with fluctuating levels of pressure support, might result in greater upper airway instability in predominantly bulbar ALS subjects. Moreover, the iVAPS mode may have resulted in transient intermittent over-ventilation and hypocapnia which resulted in central or obstructive hypopneas, despite relatively low levels of pressure support. This hypothesis is supported by our finding of significant correlations between the residual AHI and Delta tidal

volume for the iVAPS group. Larger studies, ideally with polysomnographic confirmation, will be needed to confirm this hypothesis.

The strength of our study is that we studied subjects with ALS for a period of 6 months, though with several deaths during the study period. We assessed a wide range of outcomes, and although this has led to multiple comparisons, results should be seen as exploratory for this pilot study. There were some limitations to our study. First, participants and respiratory therapists were not blinded to the intervention, which may have introduced bias. However, this would have been expected to result in fewer interventions or longer time to interventions in the iVAPS mode, which was not the case. Second, our findings were based on a small sample of subjects because of its pilot nature. Third, we did not evaluate quality of life in our subjects at 6 months because most subjects refused to do the SRI questionnaires at 6 months and some subjects died before 6 months of follow up. Furthermore, unexpectedly, over half of the subjects had bulbar-onset ALS. These results might therefore not be representative of a more typical group of ALS patients with a larger proportion of non-bulbar onset initiating NIV. There were other unbalanced baseline characteristics between groups that may have impacted results such as medication differences and statistically but not clinically significant $PaCO_2$ differences. Additionally, we did not evaluate baseline polysomnography to evaluate the prevalence of sleep-disordered breathing before NIV initiation, nor were sleep-disordered breathing and gas exchange assessed in all patients on NIV at follow-up. A future larger randomized control study comparing iVAPS with standard ST mode with overnight gas exchange monitoring at baseline and follow-up would be useful to better understand differences between the two modes in both bulbar and non-bulbar-onset ALS subjects. Finally, this study was conducted in the context

of a large, well-established home ventilation program staffed by highly trained and experienced respiratory therapists accustomed to dealing with the ALS population. Conceivably, the iVAPS mode could provide advantages for adaptation to therapy over ST in other clinical contexts, although further research would be required to specifically address this question.

Conclusions

The iVAPS mode did not require fewer interventions than the ST mode over 6 months from NIV initiation in subjects with ALS. With iVAPS, adherence was transiently lower at NIV initiation, and the residual AHI was higher at 6 months. Alveolar ventilation-targeted NIV may require a longer adaptation period and result in greater upper airway instability in subjects with ALS.

Quick look

Current knowledge

Home noninvasive ventilation (NIV) is increasingly used in ALS and improves symptoms and survival. The Intelligent Volume-Assured Pressure Support (iVAPS) is an adaptive NIV mode that targets alveolar ventilation and might be well-suited for ALS in the context of progressively deteriorating respiratory function over time. Previous studies demonstrated that the iVAPS mode might enhance comfort and adherence to treatment in neuromuscular patients with hypoventilation.

Contributes To Our Knowledge:

In this pilot trial, the iVAPS mode did not require fewer interventions or parameter adjustments than the ST mode over 6 months from NIV initiation in a group of subjects with ALS, including a large proportion of bulbar-onset individuals. Adherence to the iVAPS mode was transiently

lower suggesting that alveolar ventilation-targeted NIV may require a longer adaptation period in subjects with ALS. Adherence and subject symptoms were similar with both NIV modes.

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Figure legends

Figure 1: Consort Flow Diagram

Figure 2: Kaplan-Meier Curves for Time to First Change in Ventilator Settings According to Ventilator Mode

Figure S1: Correlation plots between apnea-hypopnea index and the difference between 95th percentile and median inspiratory positive airway pressure (delta IPAP) or the difference between 95th percentile and median tidal volume (delta tidal volume) for subjects with iVAPS

Tables

Table 1: Baseline Demographics, Blood gas and Pulmonary Function Parameters for Subjects with ALS using iVAPS versus ST modes

	Total	iVAPS (n=14)	ST (n=16)	*P*
Male, n (%)	16 (53.3%)	8 (57.1%)	8 (50.0%)	0.70
Age, years	62.8±9.5	64.4±9.0	61.4±10.0	0.39
Body mass index, kg/m2	24.6±3.1	24.8±3.7	24.5±2.7	0.78
Time from symptom onset to ALS diagnosis, months	14.8±13.5	16.4±16.3	13.3±10.6	0.56
Time from ALS diagnosis to NIV start, months	12.5±14.2	13.8±17.8	11.2±10.0	0.64
Onset ALS				0.43
Spinal	13(43.3%)	5 (21.4%)	8 (50.0%)	
Bulbar	17(56.7%)	9 (64.3%)	8 (50.0%)	
Feeding tube	4(13.3%)	3 (21.4%)	1 (6.25%)	0.22
Mobility				0.04*
Completely ambulatory	11(36.7%)	7 (50.0%)	4 (25.0%)	
Occasional wheelchair use	10(33.3%)	6 (42.9%)	4 (25.0%)	
Full-time wheel-chair-bound	9(30.0%)	1 (7.1%)	8 (50.0%)	
Smoking status:				
Never smoker	12(40.0%)	7 (50.0%)	5 (31.3%)	0.30
Pack-years	8.7±13.1	12.4±17.1	5.9±7.7	0.23
Alcohol consumption				
Occasional or daily	3(10.0%)	1 (7.1%)	2 (12.5%)	0.61
Comorbidities illness				
Hypertension	8 (26.7%)	6 (42.9%)	2 (12.5%)	0.06
Depression	3 (10.0%)	1 (7.1%)	2 (12.5%)	0.63
Rheumatoid arthritis	1 (3.3%)	0	1 (6.3%)	0.34
Diabetes mellitus	3 (10.0%)	1 (7.1%)	2 (12.5%)	0.63
Asthma	3 (10.0%)	1 (7.1%)	2 (12.5%)	0.63
Valvular heart disease	1 (3.3%)	0	1 (6.3%)	0.34
Hypothyroidism	2 (6.7%)	1 (7.1%)	1 (6.3%)	0.92
On specific ALS medication	22(73.3%)	10(71.4%)	12 (75.0%)	0.82
Other Medications				
Muscle relaxant	8(26.7%)	3(21.4%)	5(31.3%)	0.54
Antidepressant	14(46.7%)	9 (64.3%)	5 (31.3%)	0.07
Opioid	5(16.7%)	2(14.3%)	3 (18.8%)	0.74
Pregabalin	8(26.7%)	0 (0.0%)	8 (50.0%)	<0.01*
Benzodiazepine	10(33.3%)	7 (50.0%)	3 (18.8%)	0.07
Total severe respiratory insufficiency score	50.6±14.2	49.2±17.8	51.5±11.6	0.72
S_{pO2}, %	95.9±2.4	96.2±2.8	95.6±2.0	0.47
Capillary blood gas:				
pH	7.45±0.02	7.45 ±0.02	7.45 ±0.01	0.76
P_{aCO2}, mm Hg	42.5±3.8	44.4 ±4.7	40.8 ±1.3	0.01*
Baseline pulmonary function				
FVC, liters	1.8±0.7	1.8±0.6	1.8±0.7	0.98

FVC, % of predicted	55.4±17.8	58.4±16.4	52.7±19.1	0.39
$FEV_{1,}$ liters	1.5±0.5	1.4±0.4	1.5±0.6	0.46
$FEV_{1,}$ % of predicted	54.3±17.5	55.5±15.6	53.2±19.4	0.73
FEV_1/FVC	81.3±9.8	78.7±10.4	83.6±9.0	0.18
$SNIP_{OP,}$ cm H_2O	24.3±16.0	21.1±16.4	27.1±15.6	0.31
$SNIP_{CL,}$ cm H_2O	30.8±16.1	27.0±7.7	34.1±20.5	0.23

Values are presented in means ± SD or numbers (%).
*P-value < 0.05 for iVAPS versus ST
ALS= amyotrophic lateral sclerosis, NIV= noninvasive ventilation, S_{pO2} = oxygen saturation, P_{aCO2} = arterial partial pressure of carbon dioxide, FVC= Forced vital capacity, FEV_1= Forced expiratory volume in the first seconds, $SNIP_{OP}$= sniff nasal inspiratory pressure with nostril contralateral to the pressure-sensing probe open, $SNIP_{CL}$= sniff nasal inspiratory pressure with nostril contralateral to the pressure-sensing probe closed

Table 2: Noninvasive Ventilation Settings and Type of Mask at 1 week, at 1 month and 6 months

NIV settings at 1 week	**iVAPS (n=14)**	**ST (n=16)**	***P***
Target alveolar ventilation	5.3±2.1	NA	NA
Inspiratory positive airway pressure, cm H_2O	NA	10.4±2.5	NA
PSmin, cm H_2O	3.5±1.8	NA	NA
PSmax, cm H_2O	11.8±5.0	NA	NA
Expiratory positive airway pressure, cm H_2O	5.1±0.6	4.9±0.8	0.61
Timin, ms	1.0±0.2	1.0±0.2	0.58
Timax, ms	1.8±0.2	1.9±0.3	0.21
Back-up rate, bpm	15.4±3.9	11.4±1.9	<0.01*
Rise time, ms	289.3±94.4	353.1±140.8	0.16
Falling time	178.6±42.6	193.7±77.2	0.52
Trigger sensitivity: Medium High	 13 (92.9%) 1 (7.1%)	 9(56.3%) 7 (43.8%)	0.02*
Cycle sensitivity: Medium High	 13 (92.9%) 1 (7.1%)	 14 (87.5%) 2 (12.5%)	0.63
Mask type: Full face mask Nasal mask	 10(71.4%) 4(28.6%)	 11(68.8%) 5(31.2%)	0.63
NIV settings at 1 month	**iVAPS (n=14)**	**ST (n=16)**	***P***
Target alveolar ventilation	5.3±2.1	NA	NA
Inspiratory positive airway pressure, cm H_2O	NA	10.8±2.3	NA
PSmin, cm H_2O	3.8±1.7	NA	NA
PSmax, cm H_2O	11.8±5.1	NA	NA
Expiratory positive airway pressure, cm H_2O	5.0±0.7	5.2±0.9	0.50
Timin, ms	1.0±0.2	1.0±0.2	0.92
Timax, ms	1.8±0.2	1.9±0.2	0.21
Back-up rate, bpm	14.9±3.5	12.6±2.9	0.07
Rising time, ms	283.3±86.2	353.6±99.0	0.07
Falling time	175±45.2	185.7±77.0	0.68
Trigger sensitivity: Medium High	 12(85.7%) 2 (14.3%)	 10(62.5%) 6(37.5%)	0.12
Cycle sensitivity: Medium High	 13 (92.9%) 1 (7.1%)	 13 (81.2%) 3 (18.8%)	0.31
Mask type: Full face mask Nasal mask	 10(71.4%) 4(28.6%)	 14 (87.5%) 2(12.5%)	0.37

NIV settings at 6 months	iVAPS (n=11)	ST (n=11)	*P*
Target alveolar ventilation	4.9±1.2	NA	NA
Inspiratory positive airway pressure, cm H_2O	NA	11.5±1.4	NA
PSmin, cmH_2O	4.2±1.3	NA	NA
PSmax, cmH_2O	11.4±4.6	NA	NA
Expiratory positive airway pressure, cm H_2O	5.4±1.4	6.0±1.1	0.26
Timin, ms	1.1±0.2	1.1±0.2	0.78
Timax, ms	1.8±0.2	2.0±0.2	0.11
Back-up rate, bpm	13.8±2.1	12.1±1.7	0.07
Rising time, ms	323.1±83.2	403.8±170.1	0.14
Falling time	184.6±55.5	200.0±100.0	0.63
Trigger sensitivity: Medium High	 10 (81.8%) 1 (9.1%)	 3(27.3%) 8(72.7%)	0.01*
Cycle sensitivity: Medium High	 10(90.9%) 1 (9.1%)	 9(81.8%) 2(18.2%)	0.48
Mask type: Full face mask Nasal mask	 9(81.8%) 2(18.2%)	 9(81.8%) 2(18.2%)	1.0

Values are presented in means ± SD or numbers (%).
**P*-value < 0.05 for iVAPS versus ST
NIV= non-invasive ventilation, PS= pressure support, Ti = Inspiratory time

Table 3: Download Parameters of Noninvasive Ventilation at 1 week, at 1 month and 6 months

Download parameters at 1 week	**iVAPS (n=14)**	**ST (n=16)**	***P***
Days used ≥ 4 hours, %	13.2±30.1	45.4±40.9	0.03*
Average daily use, hours/night	2.2±2.0	4.6±3.4	0.03*
Median leak, L/min	8.8±17.5	7.5±8.1	0.80
Median inspiratory pressure, cm H_2O	11.9±4.6	10.2±2.4	0.21
95th percentile inspiratory pressure, cm H_2O	14.3±3.7	NA	NA
Delta (95th percentile – median) inspiratory pressure, cm H_2O	2.4±1.3	NA	NA
Expiratory positive airway pressure, cm H_2O	5.1±0.6	4.9±0.8	0.61
Median tidal volume, mL	459.3±104.6	492.5±101.5	0.39
95th percentile tidal volume, ml	653.9±187.2	737.9±161.8	0.20
Delta (95th percentile – median) tidal volume, ml	194.6±90.3	245.4±95.3	0.15
Median respiratory rate, bpm	19.3±5.9	16.2±2.5	0.09
Rapid shallow breathing index, breath/min/L	43.7±16.1	33.9±9.2	0.07
Median inspiratory time, seconds	1.3±0.3	1.2±0.2	0.38
Apnea-hypopnea Index, events/hour	16.5±10.5	9.5±8.1	0.048*
Apnea index, events/hour	0.5±0.8	0.9±1.4	0.37
Hypopnea index, events/hour	16.0±10.1	8.6±6.9	0.02*
Spontaneously patient triggered breaths, %	72.8±30.5	82.7±15.3	0.32
Spontaneously patient cycled breath, %	40.8±29.4	53.3±33.6	0.32
Download parameters at 1 month	**iVAPS (n=14)**	**ST (n=16)**	***P***
Days used ≥ 4 hours, %	47.0±44.6	55.8±42.1	0.61
Average daily use, hours/night	3.9±3.1	5.6±4.3	0.28
Median leak, L/min	2.8±2.9	5.5±6.4	0.18
Median inspiratory pressure, cm H_2O	11.6±2.8	10.8±2.3	0.42
95th percentile inspiratory pressure, cm H_2O	15.8±4.8	NA	NA
Delta (95th percentile – median) inspiratory pressure, cm H_2O	4.2±2.7	NA	NA
Expiratory positive airway pressure, cm H_2O	5.0±0.7	5.2±0.9	0.5
Median tidal volume, mL	460.4±102.1	465.4±108.5	0.90
95th percentile tidal volume, ml	663.1±168.6	651.5±140.8	0.84
Delta (95th percentile – median) tidal volume, ml	202.7±79.0	186.1±64.1	0.53
Median respiratory rate, bpm	17.4±4.1	16.1±2.9	0.35
Rapid shallow breathing index, breath/min/L	39.8±14.2	37.3±13.7	0.65
Median inspiratory time, seconds	1.3±0.3	1.2±0.2	0.38
Apnea-hypopnea Index, events/hour	16.6±9.7	6.6±6.4	<0.01*
Apnea index, events/hour	0.7±1.5	0.9±2.0	0.77
Hypopnea index, events/hour	15.9±9.6	5.7±4.8	<0.01*
Spontaneously patient triggered breaths, %	70.8±24.2	68.8±25.9	0.84
Spontaneously patient cycled breath, %	38.5±24.5	50.9±27.8	0.24
Download parameters at 6 months	**iVAPS (n=11)**	**ST (n=11)**	***P Value***
Days used ≥ 4 hours, %	57.0±40.8	65.2±46.5	0.69
Average daily use, hours/night	6.0±4.1	6.7±4.1	0.74
Median leak, L/min	2.7±3.3	5.2±4.0	0.15

Median inspiratory pressure, cm H_2O	12.1±3.3	11.5±1.4	0.63
95th percentile inspiratory pressure, cm H_2O	14.8±3.7	NA	NA
Delta (95th percentile – median) inspiratory pressure, cm H_2O	2.7±1.8	NA	NA
Expiratory positive airway pressure, cm H_2O	5.4±1.4	6.0±1.1	0.26
Median tidal volume, mL	449.5±95.8	487.5±116.4	0.41
95th percentile tidal volume, ml	672.5±146.1	651.3±166.7	0.75
Delta (95th percentile – median) tidal volume, ml	223.0±89.6	163.8±61.7	0.09
Median respiratory rate, bpm	16.1±3.9	17.9±5.1	0.40
Rapid shallow breathing index, breath/min/L	37.6±14.1	41.1±22.6	0.68
Median inspiratory time, seconds	1.3±0.3	1.2±0.3	0.27
Apnea-hypopnea Index, events/hour	13.9±15.4	3.0±2.1	0.04*
Apnea index, events/hour	0.4±1.1	0.1±0.2	0.49
Hypopnea index, events/hour	13.6±15.0	2.9±2.0	0.04*
Spontaneously patient triggered breaths, %	48.5±31.5	82.4±19.2	0.02*
Spontaneously patient cycled breath, %	23.8±16.3	42.3±33.2	0.13

Values are presented in means ± SD.
*P-value < 0.05 for iVAPS versus ST

Table 4: Association between NIV adherence (daily use, all days) and Other Variables at 6 months (n=22)

Variables	**Average all days NIV used, hours** ***r (p-value)***
Age	-0.33(0.18)
Sex	0.23(0.35)
Body mass index	-0.1(0.70)
Time symptom to ALS diagnosis	-0.48(0.06)
Time from ALS diagnosis to NIV	-0.19(0.46)
Bulbar-onset ALS	0.19(0.45)
S_{pO2} at baseline	-0.33(0.19)
P_{aCO2} at baseline	0.18(0.48)
FVC at baseline	-0.43(0.08)
$SNIP_{OP}$ at baseline	-0.55(0.02)*
$SNIP_{CL}$ at baseline	-0.30(0.22)
NIV Mode	-0.08(0.74)
Mean IPAP	0.35(0.17)
Mean EPAP	0.17(0.50)
Trigger sensitivity	0.37(0.12)
Cycle sensitivity	0.16(0.53)
Median respiratory rate	-0.13(0.61)
Median Tidal Volume	-0.34(0.17)
Rapid shallow breathing index on NIV	0.08(0.75)
Spontaneously patient triggered breath	-0.14(0.58)
Spontaneously patient cycled breath	0.29(0.25)
Apnea-hypopnea index	-0.38(0.12)
Median leak	0.04(0.87)
Mask changes	0.18(0.48)

r = Pearson's correlation coefficient
ALS = amyotrophic lateral sclerosis, NIV= non-invasive ventilation, S_{pO2} = oxygen saturation, P_{aCO2} = arterial partial pressure of carbon dioxide, FVC= Forced vital capacity, $SNIP_{OP}$= sniff nasal inspiratory pressure with nostril contralateral to the pressure-sensing probe open, $SNIP_{CL}$= sniff nasal inspiratory pressure with nostril contralateral to the pressure-sensing probe closed
IPAP = Inspiratory positive airway pressure, EPAP = Expiratory positive airway pressure
Ti = Inspiratory time

Table 5: Characteristics of Respiratory Interventions Over 6-month Follow-up

Respiratory interventions	iVAPS mode (n=14)	ST mode (n=16)
Increased IPAP/Target alveolar ventilation	9(64.3%)	11(68.7%)
Decreased IPAP/Target alveolar ventilation	4(28.6%)	3(18.7%)
Increased EPAP	6(42.8%)	7(43.7%)
Decreased EPAP	4(28.6%)	1(6.2%)
Increased back-up rate	1(7.1%)	5(31.2%)
Decreased back-up rate	2(14.3%)	2(12.5%)
Increased Ti	7(50.0%)	9(56.2%)
Decreased Ti	5(35.7%)	3(18.7%)
Increased rise time	4(28.6%)	6(37.5%)
Decreased rise time	3(21.4%)	3(18.7%)
Increase trigger sensitivity	0 (0.0%)	6(12.5%)
Decrease trigger sensitivity	1(7.1%)	0 (0.0%)
Optimizing mask fit	5(35.7%)	8(50.0%)

Values are presented in number (%).
IPAP = Inspiratory positive airway pressure, EPAP = Expiratory positive airway pressure, Ti = Inspiratory time

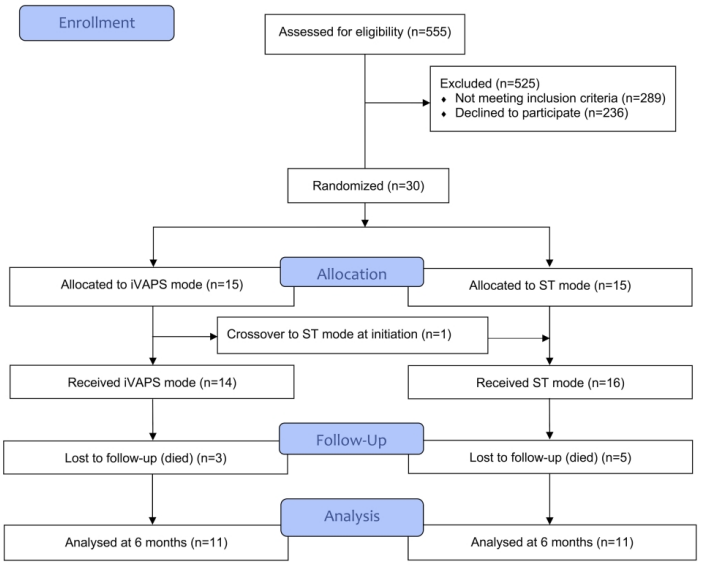
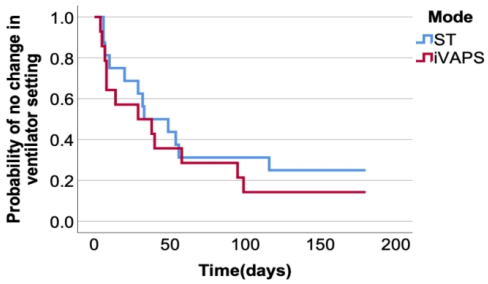


Figure 1: Consort Flow Diagram

215x279mm (600 x 600 DPI)



Number at risk

Time(days)	0	50	100	150	200
iVAPS	14	7	5	4	0
ST	16	5	2	2	0

Figure 2: Kaplan-Meier Curves for Time to First Change in Ventilator Settings According to Ventilator Mode

215x279mm (600 x 600 DPI)