Effectiveness of long-term noninvasive ventilation measured by remote monitoring in neuromuscular disease

Jeremy E. Orr [1], Kenneth Chen[1], Florin Vaida [2], Christopher N. Schmickl[1], Chamindra G. Laverty[3], John Ravits[3], Daniel Lesser[4], Rakesh Bhattacharjee[4], Atul Malhotra[1] and Robert L. Owens[1]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, UC San Diego, San Diego, CA, USA. [2]School of Public Health, UC San Diego, San Diego, CA, USA. [3]Department of Neurology, UC San Diego, San Diego, CA, USA. [4]Department of Pediatrics, UC San Diego, San Diego, CA, USA.

Corresponding author: Jeremy E. Orr (j1orr@health.ucsd.edu)

Shareable abstract (@ERSpublications)
NIV is effective at maintaining long-term ventilatory support in neuromuscular disorders. Differences in ventilatory parameters at baseline and over time are found between ALS and non-ALS patients, and in ST *versus* VAPS modes of ventilation. https://bit.ly/44La8Bm

Cite this article as: Orr JE, Chen K, Vaida F, *et al*. Effectiveness of long-term noninvasive ventilation measured by remote monitoring in neuromuscular disease. *ERJ Open Res* 2023; 9: 00163-2023 [DOI: 10.1183/23120541.00163-2023].

Received: 22 March 2023
Accepted: 14 July 2023

Abstract

Background and objective Patients with neuromuscular disease are often treated with home noninvasive ventilation (NIV) with devices capable of remote patient monitoring. We sought to determine whether long-term NIV data could provide insight into the effectiveness of ventilation over time.

Methods We abstracted available longitudinal data for adults with neuromuscular disease in monthly increments from first available to most recent. Generalised linear mixed-effects modelling with subject-level random effects was used to evaluate trajectories over time.

Results 1799 months of data across 85 individuals (median age 61, interquartile range (IQR) 46–71 years; 44% female; 49% amyotrophic lateral sclerosis (ALS)) were analysed, with a median (IQR) of 17 (8–35) months per individual. Over time, tidal volume increased and respiratory rate decreased. Dynamic respiratory system compliance decreased, accompanied by increased pressure support. Compared to volume-assured mode, fixed-pressure modes were associated with lower initial tidal volume, higher respiratory rate and lower pressures, which did not fully equalise with volume-assured mode over time. Compared with non-ALS patients, those with ALS had lower initial pressure support, but faster increases in pressure support over time, and ALS was associated wtih a more robust increase in respiratory rate in response to low tidal volume. Nonsurvivors did not differ from survivors in ventilatory trajectories over time, but did exhibit decreasing NIV use prior to death, in contrast with stable use in survivors.

Conclusion NIV keeps breathing patterns stable over time, but support needs are dynamic and influenced by diagnosis and ventilation mode. Mortality is preceded by decreased NIV use rather than inadequate support during use.

Introduction

Patients with systemic neuromuscular diseases often develop respiratory muscle weakness, which drives morbidity and mortality. Absent appropriate treatment, resulting hypoventilation and chronic respiratory failure contribute to symptoms such as dyspnoea, sleep disturbances and early morning headaches, and have been linked with a high risk of hospitalisation and death [1–4].

Ventilatory support can help to assist weak breathing muscles and stabilise gas exchange [5]. Historically, long-term ventilation was provided *via* a tracheostomy, but more recently has been provided *via* home noninvasive ventilation (NIV) [6–9]. NIV has convincingly been shown to improve survival and quality of life in neuromuscular disease [9–14] and may slow disease progression [15]. Overall, NIV is a mainstay of treatment in this population, often being used for years or even decades [16], although not all eligible patients are treated with NIV [17]. Substantial uncertainty remains regarding individualising therapies with

respect to underlying disease processes, which can have different manifestations and rates of progression (*e.g.* ALS *versus* non-ALS). Similarly, there are different modes of ventilation (*i.e.* set pressure *versus* volume) with different parameters and physiological effects.

Recent technological advances have allowed for devices to record and remotely transmit data on a near-continuous basis, including observed usage, respiratory rates, tidal volume, pressures, *etc*. [18]. These "remote patient monitoring" (RPM) data are stored on manufacturer servers and can be accessed by clinicians *via* secure web applications. RPM data may be utilised during NIV initiation and titration [19]. However, there are scant data examining NIV data from RPM over time.

The goals of this study were to 1) explore the long-term trends in parameters obtained from RPM in patients with neuromuscular disease, 2) compare trajectories across individuals, disease states and ventilator modes and 3) determine whether trajectories associate with patient outcomes. Such novel information might ultimately be used to guide further research into the optimal NIV management of such patients.

Methods

We performed a retrospective study of patients using home NIV for neuromuscular disorders. The study was approved by the University of California San Diego Human Research Protections Program with a waiver of consent (institutional review board identifier 182136). All patients with remote patient monitoring data available in the ResMed Airview platform followed by the UC San Diego Pulmonary Neuromuscular and Assisted Ventilation Program since 2015 were screened for inclusion. We included patients with the following diagnoses: amyotrophic lateral sclerosis (ALS), muscular dystrophy, spinal muscular atrophy, congenital myopathy, myositis, phrenic paralysis and kyphoscoliosis. Owing to substantial differences in physiology, patients with a primary diagnosis of chronic lung disease, cerebral palsy or myotonic dystrophy were excluded, along with those using invasive ventilation.

Clinical care was performed by two physicians specialising in pulmonary neuromuscular disease. NIV was initiated according to recommendations from professional societies [20–23], along with clinical assessment. The mode of ventilation was chosen based on device capabilities and any pre-existing settings; no systematic preference was given to one mode over another. Patients were seen in clinic every 3–6 months according to need. During these visits, NIV data were routinely assessed and adjustments were made according to data along with patient symptoms. In general, NIV was initiated and titrated on an outpatient basis; in-laboratory titration sleep studies were rarely performed.

Demographic data were obtained from the electronic medical record *via* manual review (through April 2022). All available RPM data were obtained *via* download from the ResMed AirView platform. To be included, patients needed to have ⩾30 days of available data. Reports were downloaded in sequential 30-day (*i.e.* monthly) intervals (as per common clinical practice) starting from first available, and the reported median values for all parameters were taken directly from the report. Additionally, we calculated two ventilatory parameters from the monthly reports: 1) NIV-assisted rapid shallow breathing index (aRSBI), defined as median observed respiratory rate over median observed tidal volume (in litres), and 2) dynamic compliance (C_{dyn}), defined as the median observed tidal volume divided by median observed pressure support (*i.e.* inspiratory pressure minus expiratory pressure in centimetres water pressure (cwp)) [24]. aRSBI reflects work of breathing [25], and predicts nocturnal hypercapnia and need for NIV [2, 26]. C_{dyn} reflects global respiratory system mechanics with contributions from patient effort, chest wall and lung compliance, and airways resistance [27]. Data abstracted did not necessarily include the NIV initiation, since many patients had been using NIV for years prior to RPM availability. Similarly, the last available data did not necessarily coincide with the end of use (*e.g.* death or discontinuation), as care for many patients remains ongoing. Final vital status was determined from chart review; individuals were classified as "deceased at study end" if known to have died within 90 days of the last available data, otherwise they were classified as "alive at study end". In the case of missing data between first and last available time points, no data were imputed.

Analysis was performed in RStudio (version 2022.07.2) running R (version 4.2.1). Generalised linear-mixed effects modelling was used (packages: nlme and lme4) to examine observed parameters from the monthly reports. Gaussian distributions were assumed for data except percentage of nights with ⩾4 h use (%⩾4 h) which was assumed to be binomial. Subject-level random effects were included with random intercept and slope over time. Parameters were examined at baseline and over time using a saturated model with fixed effects of time, diagnosis group dichotomised into ALS *versus* non-ALS (based on substantial differences in disease progression rate) and ventilation mode. A separate mixed-effects model excluding

time was used to examine differences in breathing pattern (*i.e.* relationship between observed respiratory rate and tidal volume) in ALS *versus* non-ALS patients. Lastly, to explore whether trajectories in ventilatory parameters were associated with vital status, we constructed a separate saturated mixed effects model including time and alive *versus* deceased vital status. Model responses are presented as least-squares means with associated 95% confidence intervals (packages: emmeans, ggeffects). A p-value of <0.05 was defined as statistically significant. The sample size was based on available data; no formal power analysis was performed.

Results

269 records of patients using NIV were available, of whom 85 subjects met inclusion/exclusion criteria and were included in the analysis, with characteristics summarised in table 1. 1799 months of data were available for analysis, with a median (interquartile range (IQR)) of 17 (8–35) months of data for each individual. Settings and usage data from the reports are summarised in table 2. Five subjects changed modes during the study: two who started on bilevel spontaneous timed (ST) mode, and three who started on volume-assured pressure support (VAPS). Gaps in available data were present for a total 147 months, with a median of 0 (0–2) months of missing data per subject. Thus, the total timeframe spanned 1946 months across the 85 subjects. Individual-level data for observed parameters, along with model-fitted values are shown in supplementary figures S1–S7.

Ventilatory parameters

Across all subjects, baseline mean tidal volume was 417 (384–450) mL (p<0.001) with an increase of 3 (1–5) mL per month (p=0.001). Baseline mean respiratory rate was 17 (16–18) breaths·min^{-1} (p<0.001) with a decrease of −0.1 (−1–0) breaths·min^{-1} per month (p=0.03). Baseline aRSBI was 45 (40–50) breaths·min^{-1}·L^{-1} (p<0.001) with no change over time (0 (−1–0) breaths·min^{-1}·L^{-1} per month; p=0.45). Baseline C_{dyn} was 63 (55–71) mL·cwp^{-1} (p<0.001) with a decrease of −0.5 (−0.9–−0.2) mL·cwp^{-1} per month (p=0.005). Baseline mean pressure support was 7 (7–8) cwp (p<0.001) with an increase of 0.1 (0.1–0.2) cwp per month (p<0.001). Baseline spontaneously triggered breaths was 61% (50–72%) (p<0.001) with no change over time (0% (−1–0%) per month; p=0.34).

TABLE 1 Characteristics of patients included in the study

	ALS	Non-ALS
Patients	42	43
Age (years)	69 (60–72) (44–87)	47 (28–66) (17–89)
Sex		
Female	17 (40)	20 (47)
Male	25 (60)	23 (53)
BMI (kg·m^{-2})	24 (22–28) (16–42)	26 (20–30) (15–38)
Seated FVC (% pred)	51 (38–65) (16–96)	42 (34–57) (13–93)
Diagnosis		
ALS	42 (100)	0 (0)
Duchenne/Becker muscular dystrophy	0 (0)	5 (12)
Collagen VI-related disease	0 (0)	5 (6)
Other muscular dystrophy	0 (0)	5 (6)
Spinal muscular atrophy	0 (0)	4 (5)
Inclusion body myositis	0 (0)	4 (5)
Congenital myopathy	0 (0)	6 (7)
Neurodegenerative	0 (0)	3 (4)
Kyphoscoliosis	0 (0)	6 (7)
Phrenic paralysis	0 (0)	3 (4)
Post-polio	0 (0)	1 (1)
Myasthenia gravis	0 (0)	1 (1)
Months of data per subject	10 (5–19) (1–42)	32 (16–44) (2–73)
Months missing per subject	0 (0–1) (0–9)	0 (0–2) (0–25)
Initial mode bilevel ST	7 (17)	13 (30)
Alive at study end	22 (52)	40 (93)
NIV started >1 year prior to available data	5 (12)	19 (45)

Data are presented as n, median (interquartile range) (range) or n (%). ALS: amyotrophic lateral sclerosis; BMI: body mass index; FVC: forced vital capacity; % pred: % predicted; ST: spontaneous timed mode; NIV: noninvasive ventilation.

TABLE 2 Settings and observed use from monthly data reports across all patients, by mode of ventilation

	Bilevel ST	VAPS
Patients	588	1211
ALS	70 (12)	443 (37)
Non-ALS	518 (88)	768 (63)
Mode		
VAPS	NA	1079 (88)
VAPS auto-EPAP	NA	132 (11)
Spontaneous timed	588 (100)	NA
Device		
Respiratory assist device	558 (93)	839 (69)
Ventilator	30 (6)	372 (31)
Set EPAP (cwp)	5 (4–6) (3–12)	5 (4–6) (3–10)
Set respiratory rate (breaths·min^{-1})	14 (12–15) (8–22)	14 (14–15) (8–18)
Set V'_A (L·min^{-1})	NA	4.9 (4.0–5.9) (1.6–9.1)
Set IPAP (cwp)	15 (12–17) (8–21)	NA
Nights ⩾4 h use (%)	100 (87–100) (0–100)	100 (90–100) (0–100)

Data are presented as n, n (%) or median (interquartile range) (range). ST: spontaneous timed mode; VAPS: volume-assured pressure support; ALS: amyotrophic lateral sclerosis; EPAP: expiratory positive airway pressure; cwp: centimetres water pressure; V'_A: alveolar ventilation; IPAP: inspiratory positive airway pressure; NA: not applicable.

Comparisons between trajectories in ventilatory parameters between ALS and non-ALS (independent of mode) and ST *versus* VAPS (independent of diagnosis) are shown in table 3. Differences between ST and VAPS mode in ventilatory parameters over time in ALS and non-ALS groups are shown in figure 1 and supplementary figures S8–S9. Interactions between trajectory in ventilatory parameters between groups and modes were not statistically significant (p>0.15 for all).

Device usage

Baseline probability of device use for ⩾4 h averaged 92% (p<0.001) and use significantly increased over time (p<0.001 for trend). Baseline use was lower for ALS *versus* non-ALS patients (p<0.001), but increased

TABLE 3 Baseline values and change over time in observed ventilatory parameters

	Group comparison		Mode comparison	
	ALS	Non-ALS	ST	VAPS
Tidal volume				
Baseline (mL)	434 (384–483)	399 (356–443)	**383 (332–433)****	**450 (418–483)**
Change (mL per month)	**6 (3–10)**$^{\#}$	**0 (−2–2)**	**5 (2–8)***	**1 (0–3)**
Respiratory rate				
Baseline (breaths·min^{-1})	17 (16–19)	17 (15–18)	**18 (17–20)**$^{\#}$	**16 (15–17)**
Change (breaths·min^{-1} per month)	−0.1 (−0.2–0.0)	0.0 (−0.1–0.0)	−0.1 (−0.2–0.0)	0.0 (−0.1–0.0)
aRSBI				
Baseline (breaths·min^{-1}·L^{-1})	43 (35–51)	47 (41–53)	**51 (43–59)***	**39 (34–44)**
Change (breaths·min^{-1}·L^{-1} per month)	0 (−1–0)	0 (0–1)	0 (−1–0)	0 (0–0)
C_{dyn}				
Baseline (mL·cwp^{-1})	**72 (60–84)**$^{\#}$	**54 (43–66)**	60 (49–71)	66 (58–74)
Change (mL·cwp^{-1} per month)	−0.8 (−1.4–−0.1)	−0.3 (−0.6–0.1)	−0.6 (−1.2–0.1)	−0.5 (−0.8–−0.2)
Pressure support				
Baseline (cwp)	**6 (5–8)****	**9 (8–10)**	**7 (5–8)***	**8 (7–9)**
Change (cwp per month)	0.2 (0.0–0.3)	0.1 (0.0–0.1)	0.1 (0.0–0.2)	0.1 (0.1–0.2)
Spontaneously triggered breaths				
Baseline (%)	67 (47–87)	56 (44–65)	62 (47–78)	59 (46–72)
Change (% per month)	−0.1 (−1.0–0.8)	−0.3 (−0.6–−0.1)	−0.5 (−1.3–0.4)	0.0 (−0.3–0.4)

Data are presented as mean (95% CI). Bold type represents statistical significance. Analysis includes trend comparison between amyotrophic lateral sclerosis (ALS) *versus* non-ALS (model adjusted to be independent of mode) and bilevel spontaneous timed (ST) mode *versus* volume-assured pressure support (VAPS) (model adjusted to be independent of diagnosis). aRSBI: assisted rapid shallow breathing index; C_{dyn}: dynamic compliance; cwp: centimetres water pressure. *: p<0.05 for ALS *versus* non-ALS, or ST *versus* VAPS; **: p<0.01 for ALS *versus* non-ALS, or ST *versus* VAPS; $^{\#}$: p<0.005 for ALS *versus* non-ALS, or ST *versus* VAPS.

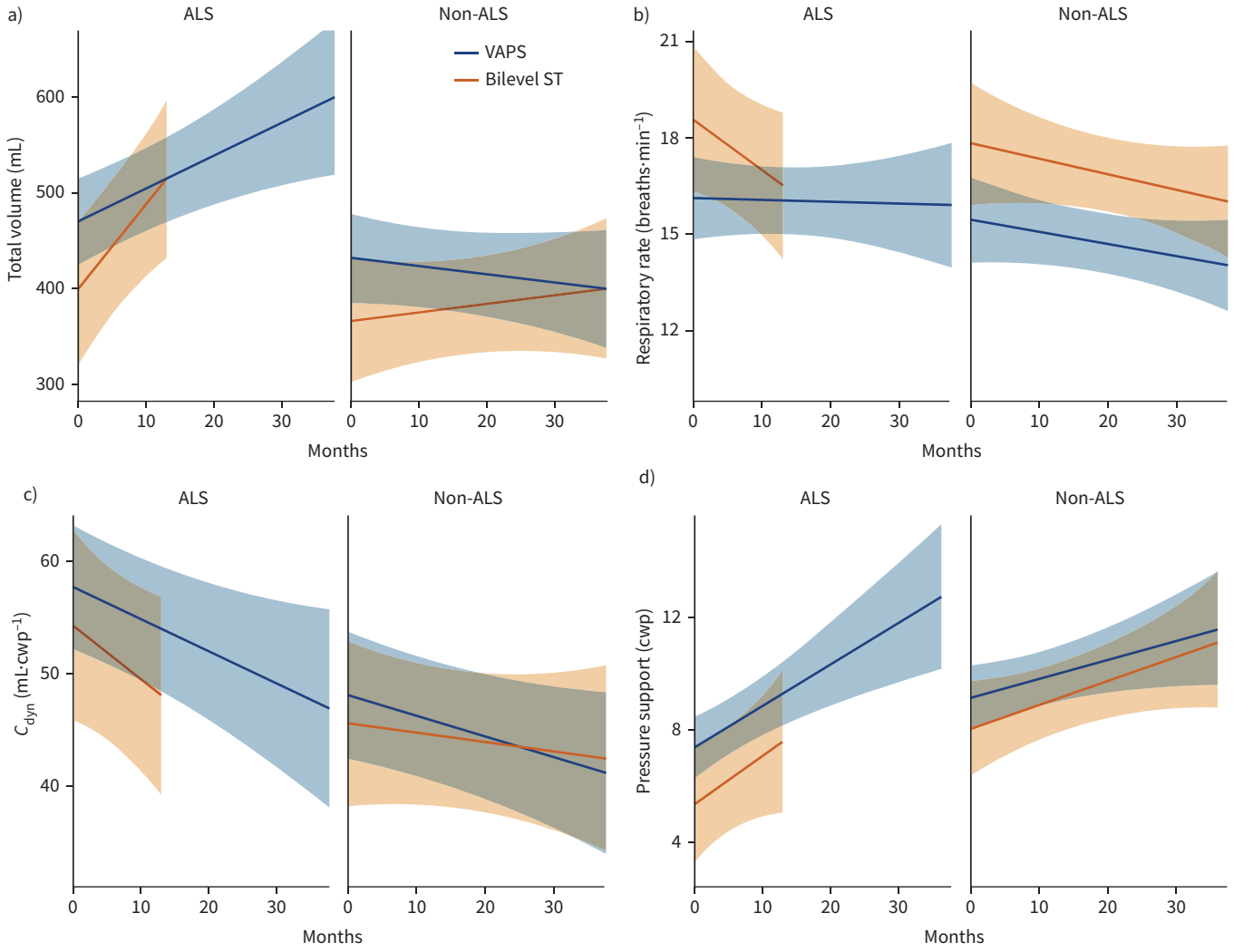

FIGURE 1 Changes in ventilatory parameters over time (up to 36 months, or last available data), by diagnosis. Lines and shaded 95% confidence intervals represent trajectory over time, by mode. a) Tidal volume over time. For those with amyotrophic lateral sclerosis (ALS), bilevel spontaneous timed mode (ST) had a nonsignificantly lower tidal volume at baseline than volume-assured pressure support (VAPS) (difference: 71 (−7–150) mL; p=0.08) and a steeper trajectory over time (difference: 5 (−1–12) mL per month; p=0.10). For those with non-ALS diagnoses, ST had a nonsignificantly lower tidal volume at baseline than VAPS (difference: 65 (−6–135) mL; p=0.07), and a similar trajectory over time (2 (−1–5) mL per month; p=0.26). b) Respiratory rate over time. For those with ALS, ST had a higher respiratory rate at baseline than VAPS (difference: 2 (0–5) breaths·min^{-1}; p=0.042), and a similar trajectory over time (difference: −0.2 (−0.3–0) breaths·min^{-1} per month; p=0.13). For those with non-ALS diagnoses, ST had a higher baseline respiratory rate than VAPS (difference: 2 (0–5) breaths·min^{-1}; p=0.039), and a similar trajectory over time (difference: 0 (−0.1–0.1) per month; p=0.83). c) Dynamic compliance (C_{dyn}) over time. For those with ALS, ST was associated with a similar baseline C_{dyn} as VAPS (difference: −7 (−23–10); p=0.43), and a similar trajectory over time (difference: −0.4 (−1.6–0.8) mL·cwp^{-1} per month; p=0.52). For those with non-ALS diagnoses, ST had a similar C_{dyn} at baseline as VAPS (difference: −5 (−20–10) mL·cwp^{-1}; p=0.51), and a similar change over time (difference: 0.2 (−0.4–0.8) mL·cwp^{-1} per month; p=0.51). d) Pressure support over time. For those with ALS, ST was associated with nonsignificantly lower pressures at baseline than VAPS (difference: −2 (−4–0) cwp; p=0.08), but a similar trajectory over time (difference: 0.0 (−0.2–0.3) cwp per month; p=0.83). For those with non-ALS diagnoses, ST had similar pressures at baseline as VAPS (difference: −1 (−3–1) cwp; p=0.31), and a similar trajectory over time (difference: 0.0 (−0.1–0.1) cwp per month; p=0.76). cwp: centimetres water pressure.

faster in ALS *versus* non-ALS patients (p<0.001). Baseline use was lower in ST *versus* VAPS mode (p<0.001), but increased faster in ST *versus* VAPS (p<0.001). Significant differences between modes in the change in use over time were noted between groups (p<0.001 for interaction; supplementary figure S10).

Breathing patterns: tidal volume versus *respiratory rate*

There was a statistically significant reciprocal relationship between tidal volume and respiratory rate; higher respiratory rates were observed with lower tidal volume (p=0.001). When comparing by diagnosis, ALS

demonstrated a substantially increased respiratory rate response to low tidal volume compared to non-ALS patients (p=0.003 for interaction; figure 2).

Parameters associated with survival during NIV

23 subjects died within 90 days of the last available NIV data; all others were known to be alive within 90 days of the last available NIV data. Those who died were significantly older (median 69 (IQR 61–72) years *versus* 53 (32–71) years), more likely to have ALS (87% *versus* 35%) and had fewer months of data (13 (5–22) months *versus* 22 (11–42) months). Comparing those who did *versus* did not survive, baseline probability of use of ⩾4 h was similar (OR 1.4, 95% CI 0.4–5.4; p=0.63), but nonsurvivors had a decrease in use over time relative to survivors (OR 0.91, 95% CI 0.83–0.99; p=0.03; figure 3). Between survivors and nonsurvivors, there was no significant difference in tidal volume at baseline (p=0.84) or trajectory over time (p=0.59). There was no difference in respiratory rate at baseline (p=0.50) or over time (p=0.12), aRSBI at baseline (p=0.81) or over time (p=0.70), C_{dyn} at baseline (p=0.32) or over time (p=0.64), pressure support at baseline (p=0.53) or over time (p=0.33) or SB at baseline (p=0.31) or over time (p=0.44).

Discussion

The major findings of this study were that in patients with pulmonary complications of neuromuscular disease 1) NIV prevents worsening ventilation (as measured by tidal volume and respiratory rate) over time, but pressure support increases are generally needed in order to maintain stability; 2) ALS patients have clear differences from non-ALS patients, including more rapid changes in ventilatory needs over time and differences in breathing patterns; 3) VAPS mode appears to provide increased ventilation sustained over time compared to ST mode; and 4) death despite NIV support was not attributable to any long-term worsening ventilation parameters, but was associated with decreasing proportion of use.

An overall goal of home NIV in neuromuscular disease is to provide adequate support for weakened respiratory muscles. While treatment of symptoms relating to weakness such as orthopnoea or poor sleep is of clear importance, other potential targets for long-term titration strategy are not well established. Maintenance of normal blood gas measures is a reasonable marker of adequate support, but pulse oximetry may not fully capture ineffective ventilation, and carbon dioxide monitoring is not widely available. Other

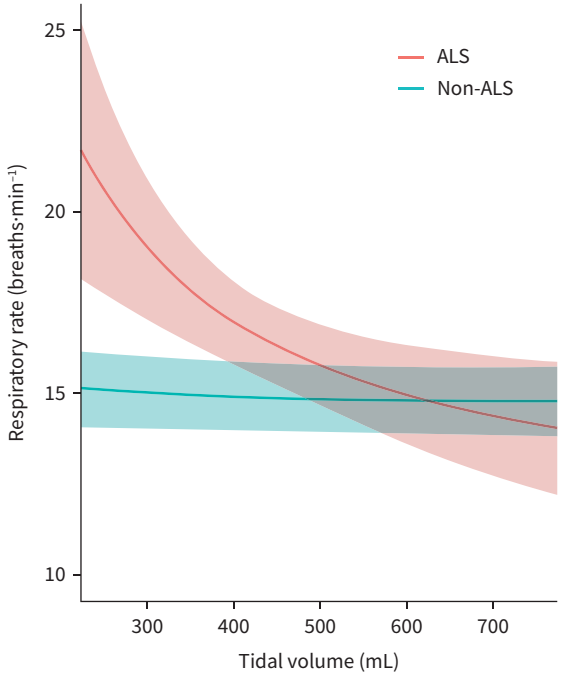

FIGURE 2 Observed respiratory rate as a function of observed tidal volume, comparing amyotrophic lateral sclerosis (ALS) to non-ALS. Lines indicate predicted respiratory rate based on mixed-effects model including subject-level effects, with 95% confidence intervals shaded. Across all subjects, there is an increase in respiratory rate with decreasing tidal volume (p=0.001 for trend). There is a significantly higher slope in ALS *versus* non-ALS patients (p=0.003 for interaction).

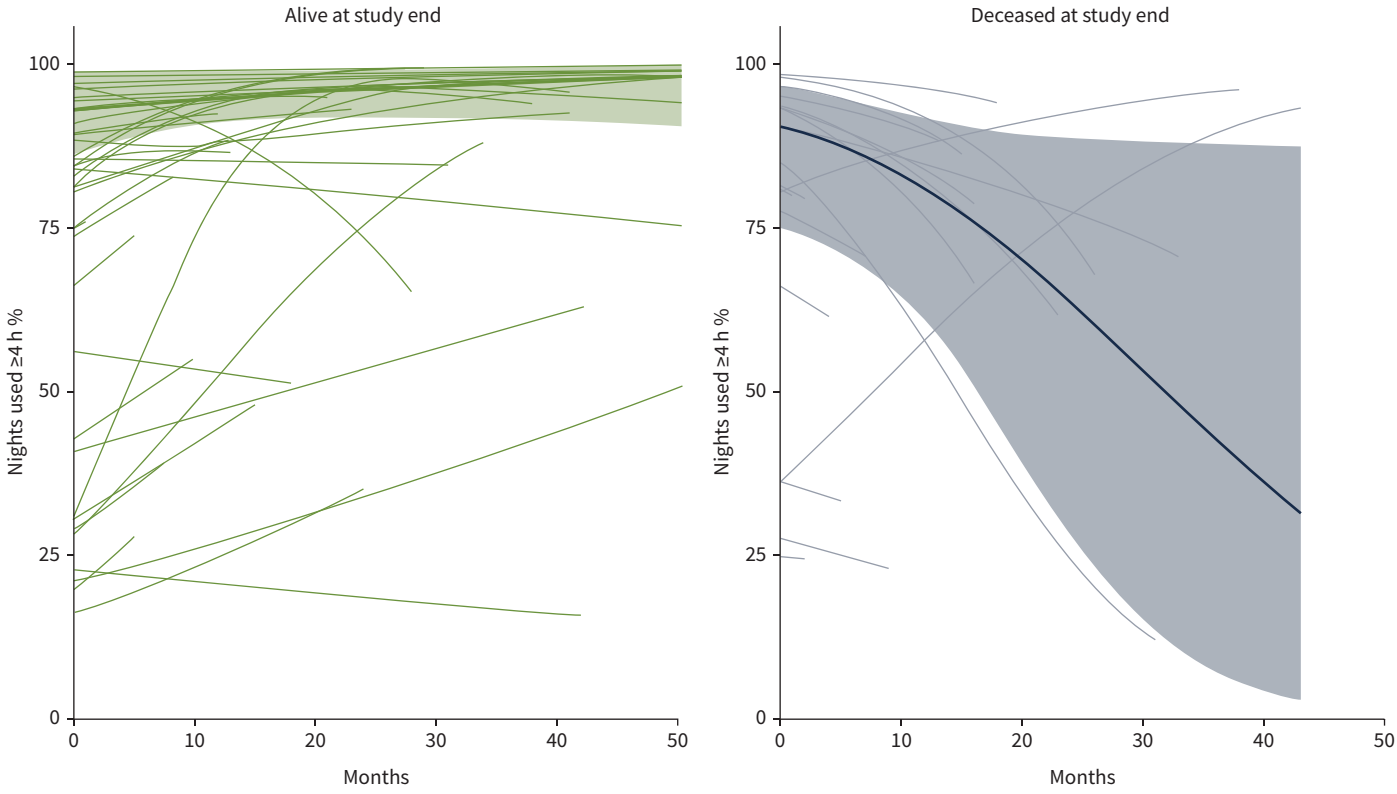

FIGURE 3 Use over time, comparing those who were alive within 90 days of last available data *versus* those deceased within 90 days of last available data. Thick lines denote group estimated marginal means based on mixed-model, with shaded confidence intervals. Thin lines denote individual-level predicted values. There was no difference in baseline use comparing survivors to nonsurvivors (p=0.63). Survivors were noted to have an increase in use over time, while nonsurvivors had a decrease over time (p=0.03 for the interaction).

potential targets include maintaining stable ventilation at a "physiological" level, normalising ventilatory drive to limit excess muscular strain or inactivity [28]. The RSBI is considered a marker of impending respiratory failure that is well established in the intensive care setting [29]. Restoration of a physiological breathing pattern with NIV can be quantified by the NIV-assisted RSBI, which has been validated as a marker of adequate ventilatory support in the setting of acute respiratory failure (less so in chronic respiratory failure) [30–32]. As measured by aRSBI, we observed that long-term NIV maintained an overall stable control of respiratory effort. However, increases in pressure support were required to maintain such stability, and the relationship encapsulated by aRSBI (*i.e.* decreasing tidal volume associating with increasing respiratory rate) varies across individuals and disease states.

With regard to markers of ventilation effectiveness, we did not see any clear differences in ventilation parameters between survivors and nonsurvivors. One might presume that worsening ventilation or progressive respiratory failure physiology would portend poor outcomes in this group, but our observations suggest that NIV support was equally adequate in both survivors and nonsurvivors, at least by available metrics. In contrast, decreased proportion of use was associated with mortality. This seems to align with other data regarding the importance of NIV adherence [33]. Conversely, worsening NIV use over time could be confounded by other factors occurring at end-of-life, such as decreasing overall quality of life, upper airway issues, hospitalisations, *etc*.

Long-term trends underscored differences between ALS and non-ALS patients. ALS patients appeared to have small, but significant, increases in tidal volume over time, contrasting with stable tidal volume in non-ALS patients. While pressure support did also increase in ALS patients over time, the C_{dyn} also decreased suggesting worsening mechanics, which are likely to reflect progression of weakness, but also might include worsening airway resistance and/or lung compliance. The reasons for these findings are unclear, but could reflect increased symptoms of dyspnoea (with resulting adjustments made to increase pressure support and tidal volume). Beyond the differences in rate of progression between ALS and most

other neuromuscular diseases, ALS can also impact upper motor neurons and can have "patchy" muscle group involvement allowing for (temporary) compensatory mechanisms, both of which might influence breathing patterns and symptoms [34, 35].

We found potentially important differences between ST and VAPS modes of ventilation. Independent of diagnosis, ST was associated with a lower baseline pressure and tidal volume, with a higher respiratory rate and aRSBI, as has been reported previously [32]. Percentage of spontaneously triggered breaths were similar, probably reflecting differences in backup rate between ST and VAPS (supplementary figures S11–S12). Differences in ventilation may reflect the difficulty in setting an appropriate pressure support in the setting of unknown lung mechanics, *versus* relative ease in setting an appropriate tidal volume for those without parenchymal lung disease. We observed that manual adjustments made to ST settings did result in increases in pressure support over time. However, ST failed to "catch up" with the VAPS mode. Inadequate pressure support might result in excessive strain on respiratory muscles, excessive respiratory drive, and more uncontrolled symptoms. For this reason, it appears that VAPS mode may be more appropriate in neuromuscular patients, particularly those with a need for immediate respiratory assistance, those with more rapidly changing needs over time, or those without close follow-up for ongoing titration. Prior literature has suggested equivalency in modes, but did not examine long-term trends where differences may be apparent [36, 37]. VAPS does have pressure limits that can restrict ventilation, while automatic pressure increases might not be universally tolerated; superiority of one mode cannot be universally concluded. We note that recent COPD guidelines have emphasised the use of ST modes, but our findings suggest a need for NIV treatment strategies specific to neuromuscular disease [38].

Beyond long-term linear trends, we observed substantial variability both across and within subjects that were not accounted for by neither mode of ventilation nor diagnosis. There is substantial interest in developing predictors of impending decompensation for patients using NIV, in whom such events have high morbidity and mortality. The degree of observed variability likely means that a "one-size-fits-all" approach is not likely to be provide sufficient accuracy; rather, adaptive algorithms based on individual data will be needed.

To our knowledge, this is the first study examining long-term objective data from NIV devices in patients with neuromuscular disease. Nonetheless, there are important limitations. First, our dataset is retrospective and lacks detailed information on symptoms and clinical issues (*e.g.* hospitalisations and causes of death). Prospective studies incorporating such data are needed. Second, there may be survivorship bias. For example, since one would expect that higher pressure support would associate with "sicker" patients with greater risk of mortality, our analysis may underestimate changes in pressure support over time despite using robust mixed-effects modelling. Third, our current data include a heterogeneous population in terms of diagnoses, and not all patients have available data. We routinely utilise RPM to manage NIV, but getting patients connected can be a challenge. We chose to restrict our subjects to those using a single platform (ResMed AirView) from which we had the most available data. Fourth, we used summary parameters from NIV devices. Issues such as leak may have variable effects on reported tidal volumes along with the aRSBI [39]. Similarly, median measures (including use in calculations) may not fully reflect breath-by-breath data. While our relatively large sample size and consistent analysis approach should help mitigate issues, biased individual-level data and even parameter estimates are possible. Lastly, we acknowledge that our data are from a single site and observational rather than a randomised trial, and thus comparisons might not be fully generalisable and could include unmeasured confounding. However, we believe these findings at our experienced centre are a reflection of real-world differences.

In conclusion, long-term NIV appears to keep ventilation stable for months to years in patients with neuromuscular disease. Differences in parameters based on mode and underlying diagnosis highlight a need for individualised NIV management and ongoing follow-up.

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors wish to thank the clinical staff and institutional supporters of the UCSD Assisted Ventilation Program.

Author contributions: J.E. Orr is the guarantor for this work. All authors have met authorship criteria.

Conflict of interest: J.E. Orr participates in an advisory board for ResMed. C.N. Schmickl reports income related to consulting for Verily outside of this work. C.G. Laverty is a principal investigator for industry-sponsored studies by

Novartis Gene Therapies, Avidity, Dyne, Biohaven, Italfarmaco, Scholar Rock and Sarepta, medical education grants from NS Pharma, Biogen, Novartis Gene Therapies and Sarepta, and consulting for Avidity. A. Malhotra reports income related to medical education from Livanova, Jazz, Zoll and Eli Lilly. ResMed provided a philanthropic donation to UC San Diego. The other authors report no relevant conflicts of interest.

Support statement: J.E. Orr is supported by NIH K23HL151880. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Aboussouan LS. Sleep-disordered breathing in neuromuscular disease. *Am J Respir Crit Care Med* 2015; 191: 979–989.
2 Toussaint M, Steens M, Soudon P. Lung function accurately predicts hypercapnia in patients with Duchenne muscular dystrophy. *Chest* 2007; 131: 368–375.
3 Phillips MF, Quinlivan RC, Edwards RH, *et al.* Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. *Am J Respir Crit Care Med* 2001; 164: 2191–2194.
4 Phillips MF, Smith PE, Carroll N, *et al.* Nocturnal oxygenation and prognosis in Duchenne muscular dystrophy. *Am J Respir Crit Care Med* 1999; 160: 198–202.
5 Toussaint M, Soudon P, Kinnear W. Effect of non-invasive ventilation on respiratory muscle loading and endurance in patients with Duchenne muscular dystrophy. *Thorax* 2008; 63: 430–434.
6 Bach JR, Gonçalves MR, Hon A, *et al.* Changing trends in the management of end-stage neuromuscular respiratory muscle failure: recommendations of an international consensus. *Am J Phys Med Rehabil* 2013; 92: 267–277.
7 Luo F, Annane D, Orlikowski D, *et al.* Invasive *versus* non-invasive ventilation for acute respiratory failure in neuromuscular disease and chest wall disorders. *Cochrane Database Syst Rev* 2017; 12: CD008380.
8 Bach JR, Tran J, Durante S. Cost and physician effort analysis of invasive *vs*. noninvasive respiratory management of Duchenne muscular dystrophy. *Am J Phys Med Rehabil* 2015; 94: 474–482.
9 Ishikawa Y, Miura T, Ishikawa Y, *et al.* Duchenne muscular dystrophy: survival by cardio-respiratory interventions. *Neuromuscul Disord* 2011; 21: 47–51.
10 Simonds AK, Muntoni F, Heather S, *et al.* Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* 1998; 53: 949–952.
11 Eagle M, Baudouin SV, Chandler C, *et al.* Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscul Disord* 2002; 12: 926–929.
12 Bourke SC, Tomlinson M, Williams TL, *et al.* Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol* 2006; 5: 140–147.
13 Radunovic A, Annane D, Rafiq MK, *et al.* Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2017; 10: CD004427.
14 Annane D, Orlikowski D, Chevret S. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database Syst Rev* 2014; 12: CD001941.
15 Brasil Santos D, Vaugier I, Boussaïd G, *et al.* Impact of noninvasive ventilation on lung volumes and maximum respiratory pressures in Duchenne muscular dystrophy. *Respir Care* 2016; 61: 1530–1535.
16 Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. *Chest* 1997; 112: 1024–1028.
17 Andrews JG, Soim A, Pandya S, *et al.* Respiratory care received by individuals with Duchenne muscular dystrophy from 2000 to 2011. *Respir Care* 2016; 61: 1349–1359.
18 Ackrivo J, Elman L, Hansen-Flaschen J. Telemonitoring for home-assisted ventilation: a narrative review. *Ann Am Thorac Soc* 2021; 18: 1761–1772.
19 Duiverman ML, Vonk JM, Bladder G, *et al.* Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. *Thorax* 2020; 75: 244–252.
20 Miller RG, Jackson CE, Kasarskis EJ, *et al.* Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009; 73: 1218–1226.
21 Finkel RS, Mercuri E, Meyer OH, *et al.* Diagnosis and management of spinal muscular atrophy: part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord* 2018; 28: 197–207.
22 Finder JD, Birnkrant D, Carl J, *et al.* Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. *Am J Respir Crit Care Med* 2004; 170: 456–465.
23 Birnkrant DJ, Bushby K, Bann CM, *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol* 2018; 17: 347–361.
24 Tawfik P, Syed MKH, Elmufdi FS, *et al.* Static and dynamic measurements of compliance and driving pressure: a pilot study. *Front Physiol* 2022; 13: 773010.

25 Johannigman JA, Davis K Jr, Campbell RS, *et al.* Use of the rapid/shallow breathing index as an indicator of patient work of breathing during pressure support ventilation. *Surgery* 1997; 122: 737–740.
26 Hamada S, Ishikawa Y, Aoyagi T, *et al.* Indicators for ventilator use in Duchenne muscular dystrophy. *Respir Med* 2011; 105: 625–629.
27 Lucangelo U, Bernabé F, Blanch L. Respiratory mechanics derived from signals in the ventilator circuit. *Respir Care* 2005; 50: 55–65.
28 Hahn A, Duisberg B, Neubauer BA, *et al.* Noninvasive determination of the tension-time index in Duchenne muscular dystrophy. *Am J Phys Med Rehabil* 2009; 88: 322–327.
29 Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991; 324: 1445–1450.
30 Berg KM, Lang GR, Salciccioli JD, *et al.* The rapid shallow breathing index as a predictor of failure of noninvasive ventilation for patients with acute respiratory failure. *Respir Care* 2012; 57: 1548–1554.
31 El-Khatib MF, Zeineldine SM, Jamaleddine GW. Effect of pressure support ventilation and positive end expiratory pressure on the rapid shallow breathing index in intensive care unit patients. *Intensive Care Med* 2008; 34: 505–510.
32 Nicholson TT, Smith SB, Siddique T, *et al.* Respiratory pattern and tidal volumes differ for pressure support and volume-assured pressure support in amyotrophic lateral sclerosis. *Ann Am Thorac Soc* 2017; 14: 1139–1146.
33 Ackrivo J, Hsu JY, Hansen-Flaschen J, *et al.* Noninvasive ventilation use is associated with better survival in amyotrophic lateral sclerosis. *Ann Am Thorac Soc* 2021; 18: 486–494.
34 Nichols NL, Van Dyke J, Nashold L, *et al.* Ventilatory control in ALS. *Respir Physiol Neurobiol* 2013; 189: 429–437.
35 Georges M, Morawiec E, Raux M, *et al.* Cortical drive to breathe in amyotrophic lateral sclerosis: a dyspnoea-worsening defence? *Eur Respir J* 2016; 47: 1818–1828.
36 Kelly JL, Jaye J, Pickersgill RE, *et al.* Randomized trial of 'intelligent' autotitrating ventilation *versus* standard pressure support non-invasive ventilation: impact on adherence and physiological outcomes. *Respirology* 2014; 19: 596–603.
37 Huang XA, Du YP, Li LX, *et al.* Comparing the effects and compliance between volume-assured and pressure support non-invasive ventilation in patients with chronic respiratory failure. *Clin Respir J* 2019; 13: 289–298.
38 Macrea M, Oczkowski S, Rochwerg B, *et al.* Long-term noninvasive ventilation in chronic stable hypercapnic chronic obstructive pulmonary disease. An official American Thoracic Society Clinical Practice guideline. *Am J Respir Crit Care Med* 2020; 202: e74–e87.
39 Contal O, Vignaux L, Combescure C, *et al.* Monitoring of noninvasive ventilation by built-in software of home bilevel ventilators: a bench study. *Chest* 2012; 141: 469–476.