How to increase noninvasive ventilation effectiveness in bulbar amyotrophic lateral sclerosis patients

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In ALS patients, bulbar dysfunction has a negative impact on NIV tolerance and effectiveness. Optimal ventilatory parameters, adequate interface selection, effective respiratory secretion management and control of bulbar symptoms are required. https://bit.ly/3HKOGEi

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease in which the respiratory muscles are also affected, leading to respiratory failure. Bulbar impairment develops in almost all cases during the course of the disease, becoming severe in the late stages of disease. Noninvasive ventilation (NIV) has been shown to increase survival in ALS; however, severe bulbar dysfunction has a negative impact on NIV tolerance and effectiveness. Therefore, certain steps should be taken to improve NIV outcomes in these patients including optimal ventilatory parameters, adequate interface selection, effective respiratory secretion management and control of bulbar symptoms.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that causes loss of both upper and lower motor neuron functions, resulting in muscle weakness [1]. The respiratory muscles are also affected, leading to respiratory failure and an ineffective cough effort. Respiratory problems secondary to respiratory muscle impairment are the main cause of hospitalisation and death in ALS patients [2]. Although there is no treatment for this disorder, respiratory muscle aids (both noninvasive ventilation (NIV) and assisted coughing techniques) have been shown to increase survival, avoid hospitalisations, relieve symptoms and increase quality of life (QoL) in ALS [3, 4].

Irrespective of the clinical syndrome at disease onset (spinal, bulbar or respiratory), bulbar impairment develops in almost all cases along the course of the disease, becoming severe in the late stages of the disease [5]. Bulbar dysfunction is one of the most serious clinical problems in ALS, involving both communication and swallowing, and may interfere with the effectiveness of respiratory muscle aids [5, 6].

Bulbar dysfunction in ALS

Bulbar dysfunction in ALS patients is a group of symptoms produced by progressive degeneration of motor neurons at the medulla oblongata and cortico-bulbar tracts, affecting the facial nerve (cranial nerve (CN) VII), glossopharyngeal nerve (CN IX), vagus nerve (CN X), accessory nerve (CN XI) and hypoglossal nerve (CN XII) [6]. These nerves control the reflex activity of the pharynx, larynx and tongue, and are involved in many functions such as coughing, swallowing, sneezing, salivation, sucking and speaking.

Secondary to weakness or spasticity of the bulbar-innervated muscles, ALS patients suffer a progressive loss of swallowing function. Reduced motility, strength and coordination of the orofacial and lingual muscles hampers food preparation, mastication and transport of food. This results in oropharyngeal food or secretion residue in valleculae, pyriform sinuses and the postcricoid region, a risk of pulmonary aspiration

with recurrent bronchial infections, and malnutrition with weight loss [7]. Moreover, bulbar muscle weakness decreases saliva clearance, resulting in sialorrhoea and drooling caused by drooping lips [8].

Dysarthria is another symptom of bulbar dysfunction, caused by flaccid or spastic paresis of the oropharynx and larynx muscles. This paresis results in weak speech production and impaired articulation, and patients ultimately develop anarthria. In predominantly lower motor neuron impairment at bulbar level, characterised mainly by weakness and hypotonia, the voice is soft, weak, low-pitched and monotonous [9]. In contrast, when the impairment occurs in the upper motor neuron at the bulbar level, characterised by weakness, spasticity and hyperreflexia, the voice sounds harsh and strained [9].

Another characteristic symptom in patients with upper motor neuron bulbar involvement is episodes of choking, defined as a feeling of suffocation or blockage of breathing [10]. This phenomenon could be triggered by inefficient pharyngeal clearance, causing pooling of saliva or detritus in valleculae or pyriform sinus [10].

Due to inspiratory and expiratory muscle weakness, ALS patients exhibit decreased cough effectiveness, which can be exacerbated by an inability to close the glottis due to bulbar dysfunction, affecting the compressive phase of the cough [11].

Finally, spastic or flaccid weakness of orofacial muscles causes failure of lip closure, and the resulting airflow through the mouth leads to thickened oral secretions [6].

Bulbar dysfunction and NIV in ALS

Despite the benefits NIV confers in terms of survival and respiratory symptoms in ALS patients, the effectiveness of this technique is hampered by the deleterious effects of bulbar dysfunction [12]. Different studies have found that severity of bulbar dysfunction at NIV initiation is a prognostic factor for NIV effectiveness [12–15]. Muscle weakness at bulbar level interferes with NIV outcomes in different ways.

Predominant among these is the presence of obstructive events at the upper airway during NIV, which are one of main reasons this treatment fails in ALS (figure 1). After correction for air leaks, in 67% of ALS patients with ineffective NIV the cause is the presence of obstructive events [16]. This results in decreased survival, mainly in those who present with oxygen desaturations but even more so in those patients with no oxygen desaturation [16]. These obstructive episodes are related to bulbar dysfunction and are associated with a reduction in ventilatory drive [16, 17]. Several mechanisms have been proposed in order to explain this upper airway obstruction in ALS during NIV [16]. They include decreased strength of the tongue and pharynx predisposing to upper airway collapsibility; decreased ventilatory drive due to a reduction in arterial carbon dioxide tension induced by NIV, promoting glottic closure; and decrease in ventilatory drive related to NIV-based changes in thoracic afferents. These obstructive events have recently been linked to bulbar upper motor neuron dysfunction and instability in breathing control, triggering central apnoea with glottic closure [17].

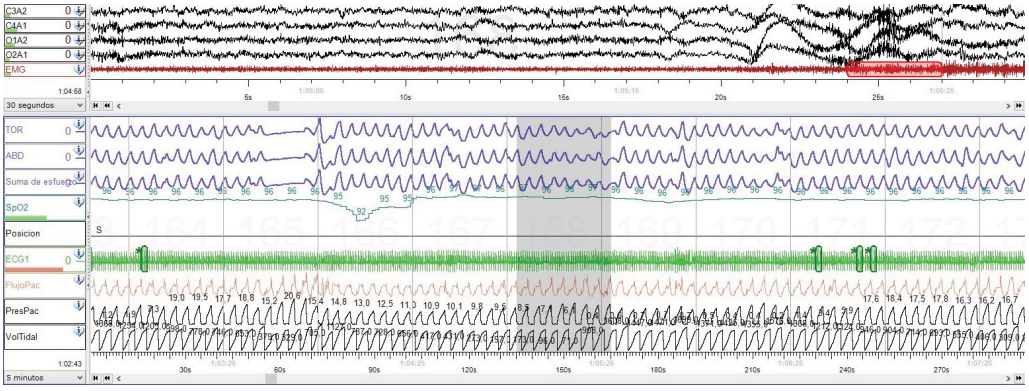

FIGURE 1 Polysomnography recording of an obstructive event in the upper airway with decreased central drive in a patient with amyotrophic lateral sclerosis under noninvasive ventilation in volume assisted/control mode (increase in peak inspiratory pressure, abolition of thoraco-abdominal movements, oxygen desaturation).

ALS causes progressive respiratory muscle weakness, so although NIV is used initially during sleep hours, the number of required hours of NIV use increases as the disease progresses [3]. In the case of continuous NIV, use of a comfortable mask such as a nasal mask or a mouthpiece during the day is recommended. Nonetheless, failure of lip closure caused by poor bulbar function generates excessive air leaks through the mouth and an inability to retain the mouthpiece, making NIV ineffective with these interfaces [18].

Finally, another major complication derived from bulbar dysfunction concerns secretion management. Adequate respiratory secretions management is crucial to achieve effective NIV [19]. Bulbar impairment generates sialorrhoea and interferes with the efficacy of assisted coughing techniques, exerting a negative impact on tolerance and effectiveness of NIV in ALS [20].

Many studies have analysed the different ways bulbar impairment interferes with NIV in ALS patients. The results of different studies show that survival is lower in patients with severe bulbar impairment at NIV initiation than in those with normal or moderate bulbar impairment. The only randomised controlled trial designed to evaluate the effect of NIV on survival in ALS corroborated these results; moreover, in patients with severe bulbar dysfunction, no survival benefit was found with NIV compared with patients who received standard care (median survival 222 *versus* 261 days, respectively, p=0.92) [4]. Nonetheless, two aspects of the study should be highlighted: mean NIV use in the severe bulbar dysfunction group was very low (3.8 h per day), and most patients had no access to a mechanical in-exsufflation device for assisted coughing [21]. A further study comparing ALS patients with NIV and patients who refused this treatment option showed enhanced survival in patients with severe bulbar dysfunction and NIV compared with those without NIV (mean survival with NIV 13.00 months *versus* 3.00 months without NIV, p=0.001) [12]. In this study, respiratory secretions were managed in a uniform way according to a standardised protocol.

Studies focused on NIV tolerance in ALS report levels ranging from 46% to 90% [13, 15, 19, 22, 23]. NIV tolerance is found to be lower in patients with mild or severe bulbar dysfunction. In fact, severe bulbar dysfunction at NIV initiation has been identified as a prognostic factor for poor NIV tolerance. Furthermore, studies have found that NIV intolerance is related to bulbar dysfunction-associated symptoms such as sialorrhoea [20], accumulated airway secretions [19] and presence of oxygen desaturations, despite the presence of upper airway obstructive events. Regarding QoL, severe bulbar dysfunction is associated with less improvement in QoL, which could be related to lower NIV compliance [22].

Taking the above into account, different strategies have been employed aimed at enhancing NIV tolerance and tracheostomy-free survival in ALS patients with mild to severe bulbar dysfunction (table 1) [24, 25]. The first of these is effective NIV adjustment to correct upper airway obstructive events during NIV and to control oxygen desaturations [16]. Second, optimal respiratory secretion management with individualised set parameters is advisable when mechanical assisted coughing is indicated, due to the negative effects of bulbar dysfunction on the efficacy of this technique [26, 27]. The third is adequate management of bulbar-related symptoms (mainly sialorrhoea), and finally, adequate interface selection to avoid the negative effects of bulbar impairment on the usefulness of NIV [18]. The deterioration of bulbar function

TABLE 1 Problems related to bulbar dysfunction during NIV in ALS and proposed solutions from the literature

Problems	Proposed solutions
NIV	Check effectiveness (built-in software, polygraphy, polysomnography) [12, 17]
Obstructive events	Increase EPAP [16, 24, 25] Decrease ventilator support [12, 16, 24, 25] Reduce inspiratory time [12, 16, 24, 25] Switch to volume assist/control mode [12, 16, 24, 25]
Orofacial muscle weakness	Switch from nasal or MPV during day to a nasal mask with chin strap, leap-seal MPV or an oronasal mask [18]
Sialorrhoea	Anticholinergic drugs [30] Botulinum toxin [30] Radiotherapy [30]
Respiratory secretions	Assisted coughing techniques [3, 11, 12, 26, 27, 29]
MI-E	Optimal adjustments and individualised settings (laryngoscopy or waveforms analysis) [26, 27]
Obstruction during insufflation	Decrease insufflation pressure [26, 27]
Obstruction during exsufflation	Decrease exsufflation pressure [26, 27]

NIV: noninvasive ventilation; ALS: amyotrophic lateral sclerosis; EPAP: expiratory positive airway pressure; MI-E: mechanical in-exsufflation; MPV: mouthpiece ventilation.

in ALS is progressive; moreover, bulbar impairment is associated with faster functional decline [28]. Therefore, continued assessment of patients with bulbar dysfunction over time is essential, because an initially successful therapeutic technique may worsen in its effectiveness as bulbar involvement progresses, requiring new adjustments or a new treatment.

Finally, when bulbar dysfunction reaches a critical level, NIV becomes ineffective to support ventilation and it is essential to perform a tracheostomy or apply appropriate palliative care. NIV failure is considered in the presence of one or more of the following criteria despite NIV: dyspnoea, hypoventilation symptoms (orthopnoea, disrupted sleep, diurnal somnolence, headache, altered cognitive status), oxygen desaturation and/or hypercapnia [29].

Conclusions

In ALS patients with bulbar dysfunction, severe impairment has a negative impact on NIV tolerance and effectiveness. Certain steps should therefore be taken to improve NIV outcomes in these patients: optimal ventilatory parameters, adequate interface selection, effective respiratory secretion management and control of bulbar symptoms. Our conclusion is that NIV should not currently be ruled out in these patients, and we recommend undertaking a trial with NIV in ALS patients with mild or severe bulbar dysfunction.

Key points

- Bulbar dysfunction develops in almost all patients with ALS along the course of the disease.
- Severity of bulbar impairment is a prognostic factor for NIV effectiveness in ALS patients.
- NIV intolerance in ALS patients is related to bulbar-associated symptoms.

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References

1 Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. *Neurology* 1998; 50: 66–72.
2 Pisa FE, Logroscino G, Giacomelli Battiston P, *et al.* Hospitalizations due to respiratory failure in patients with amyotrophic lateral sclerosis and their impact on survival: a population-based cohort study. *BMC Pulm Med* 2016; 16: 136.
3 Bach JR. Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory aids. *Chest* 2002; 122: 92–98.
4 Bourke SC, Tomlinson M, Bullock RE, *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.
5 Hadjikoutis S, Wiles CM. Respiratory complications related to bulbar dysfunction in motor neuron disease. *Acta Neurol Scand* 2001; 103: 207–213.
6 Kühnlein P, Gdynia H-J, Sperfeld A-D, *et al.* Diagnosis and treatment of bulbar symptoms in amyotrophic lateral sclerosis. *Nat Clin Pract Neurol* 2008; 4: 366–374.
7 Robison R, DiBiase L, Ashley A, *et al.* Swallowing safety and efficiency impairment profiles in individuals with amyotrophic lateral sclerosis. *Dysphagia* 2022; 37: 644–654.
8 Wang Y, Yang X, Han Q, *et al.* Prevalence of sialorrhea among amyotrophic lateral sclerosis patients: a systematic review and meta-analysis. *J Pain Symptom Manage* 2022; 63: e387–e396.
9 Lévêque N, Slis A, Lancia L, *et al.* Acoustic change over time in spastic and/or flaccid dysarthria in motor neuron diseases. *J Speech Lang Hear Res* 2022; 65: 1767–1783.
10 Hadjikoutis S, Eccles R, Wiles CM. Coughing and choking in motor neuron disease. *J Neurol Neurosurg Psychiatry* 2000; 68: 601–604.
11 Sancho J, Servera E, Diaz J, *et al.* Predictors of ineffective cough during a chest infection in patients with stable amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 2007; 175: 1266–1271.
12 Sancho J, Martinez D, Bures E, *et al.* Bulbar impairment score and survival of stable amyotrophic lateral sclerosis patients after noninvasive ventilation initiation. *ERJ Open Res* 2018; 4: 00159-2017.
13 Aboussouan LS, Khan SU, Meeker DP, *et al.* Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. *Ann Intern Med* 1997; 127: 450–453.
14 Gonzalez-Calzada N, Prats-Soro E, Mateu-Gomez L, *et al.* Factors predicting survival in amyotrophic lateral sclerosis patients on non-invasive ventilation. *Amyotroph Lateral Scler Frontotemporal Degener* 2016; 17: 337–342.

15 Lo Coco D, Marchese S, Pesco MC, *et al.* Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. *Neurology* 2006; 67: 761–765.
16 Georges M, Attali V, Golmard JL, *et al.* Reduced survival in patients with ALS with upper airway obstructive events on non-invasive ventilation. *J Neurol Neurosurg Psychiatry* 2016; 87: 1045–1050.
17 Sancho J, Bures E, Ferrer S, *et al.* Unstable control of breathing can lead to ineffective noninvasive ventilation in amyotrophic lateral sclerosis. *ERJ Open Res* 2019; 5: 00099-2019.
18 Chatwin M, Gonçalves M, Gonzalez-Bermejo J, *et al.* 252nd ENMC international workshop: Developing best practice guidelines for management of mouthpiece ventilation in neuromuscular disorders. March 6th to 8th 2020, Amsterdam, the Netherlands. *Neuromuscul Disord* 2020; 30: 772–781.
19 Peysson S, Vanderberghe N, Philit F, *et al.* Factors predicting survival following noninvasive ventilation in amyotrophic lateral sclerosis. *Eur Neurol* 2008; 59: 164–171.
20 Russo M, Bonanno C, Profazio C, *et al.* Which are the factors influencing NIV adaptation and tolerance in ALS patients? *Neurol Sci* 2021; 42: 1023–1029.
21 Bourke SC, Tomlinson M, Williams TL, *et al.* Non-invasive ventilation in amyotrophic lateral sclerosis – authors' reply. *Lancet Neurol* 2006; 5: 292–293.
22 Bourke SC, Bullock RE, Williams TL, *et al.* Noninvasive ventilation in ALS: indications and effect on quality of life. *Neurology* 2003; 61: 171–177.
23 Volanti P, Cibella F, Sarvà F, *et al.* Predictors of non-invasive ventilation tolerance in amyotrophic lateral sclerosis. *J Neurol Sci* 2001; 303: 114–118.
24 O'Brien D, Stavroulakis T, Baxter S, *et al.* The optimisation of noninvasive ventilation in amyotrophic lateral sclerosis: a systematic review. *Eur Respir J* 2019; 54: 1900261.
25 Morelot-Panzini C, Bruneteau G, Gonzalez-Bermejo J. NIV in amyotrophic lateral sclerosis: The 'when' and 'how' of the matter. *Respirology* 2019; 24: 521–530.
26 Andersen T, Sandnes A, Brekka AK, *et al.* Laryngeal response patterns influence the efficacy of mechanical assisted cough in amyotrophic lateral sclerosis. *Thorax* 2017; 72: 221–229.
27 Sancho J, Ferrer E, Bures E, *et al.* Waveforms analysis in patients with amyotrophic lateral sclerosis for enhanced efficacy of mechanically assisted coughing. *Respir Care* 2022; 67: 1226–1235.
28 Gordon PH, Cheng B, Salachas F, *et al.* Progression in ALS is not linear but is curvilinear. *J Neurol* 2010; 257: 1713–1717.
29 Sancho J, Servera E, Díaz JL, *et al.* Home tracheotomy mechanical ventilation in patients with amyotrophic lateral sclerosis: causes, complications and 1-year survival. *Thorax* 2011; 66: 948–952.
30 James E, Ellis C, Brassington R, *et al.* Treatment for sialorrhea (excessive saliva) in people with motor neuron disease/amyotrophic lateral sclerosis. *Cochrane Database Syst Rev* 2022; 5: CD006981.