NIV in amyotrophic lateral sclerosis: The 'when' and 'how' of the matter

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NIV series: NIV in amyotrophic lateral sclerosis – the "when" and "how" of the matter

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Abstract (175 words)

Noninvasive ventilation (NIV) has become an essential part of the treatment of amyotrophic lateral sclerosis since 2006. NIV very significantly improves survival, quality of life and cognitive performances. The initial NIV settings are simple, but progression of the disease, ventilator dependence, and upper airway involvement sometimes make long-term adjustment of NIV more difficult, with a major impact on survival. Unique data concerning the long-term adjustment of NIV in ALS show that correction of leaks, management of obstructive apnoea, and adaptation to the patient's degree of ventilator dependence improve the prognosis. Non-ventilatory factors also impact on the efficacy of NIV and various solutions have been described and must be applied, including cough assist techniques, control of excess salivation, and renutrition. NIV in ALS has been considerably improved as a result of application of all of these measures, avoiding the need for tracheostomy in the very great majority of cases. More advanced use of NIV also requires pulmonologists to master the associated end-of-life palliative care, as well as the modalities of discontinuing ventilation when it becomes unreasonable.

Key-words : Amyotrophic Lateral Sclerosis ; non invasive ventilation; Palliative Care ; drainage, postural ; Sleep Apnea, Obstructive

Short title: non invasive ventilation in amyotrophic lateral sclerosis

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative motoneuron disease that induces rapidly progressive paralysis of the limbs, bulbar muscles (controlling speech, mastication and swallowing) and respiratory muscles. Onset of the disease is usually observed during the sixth decade. The prevalence of the disease varies slightly from one country to another, for example from 3 to 5 cases per 100,000 inhabitants in Europe and the USA, respectively, with an annual incidence of 1 to 2 new cases per 100,000 inhabitants(1). Although about 5 to 10% of patients report a family history of the disease(2), ALS appears to occur sporadically in the majority of cases. Multiple pathophysiological processes that have not yet been fully elucidated are involved in ALS. It is generally accepted that ALS has a multifactorial origin resulting from the interaction of genetic and environmental factors, and the pathophysiology of ALS could involve a multistep process(3). Since 1999, it has been confirmed that, in the great majority of cases, ALS is complicated by respiratory failure secondary to diaphragmatic dysfunction, responsible for dyspnoea and impaired sleep, causing severe suffering. ALS also impairs cough function, resulting in frequent episodes of bronchial congestion and infection. The characteristic feature of ALS is its rapid and severe course: the median survival is 3 years from onset of the first symptoms and 6 months after onset of diaphragmatic dysfunction, in the absence of treatment(4). Respiratory involvement of ALS is the leading cause of death. The impact on the patient's family is devastating, as a result of the combined motor deficit and respiratory failure and the rapid course of the disease, for which no curative treatment is available. Two molecules, riluzole and edaravone, have been shown to be effective in the treatment of ALS. Riluzole, which inhibits presynaptic glutamate release(5), prolongs median survival by 3 months (6).

Edaravone, which has antioxidant properties, also slows the functional impairment related to the disease, although its effect remains limited and is only observed in some patients(7, 8). Since 2006, a consensus has been reached among pulmonologists and neurologists that ventilatory assistance relieves dyspnoea, improves sleep, improves quality of life and prolongs survival(9). Cough assistance(10), especially by means of mechanical devices, improves patient comfort and limits infectious episodes.

However, management of ALS patients by pulmonologists is not limited to prescription of mechanical ventilation. From 2006 to the present time, not only has it been demonstrated that NIV is difficult to adjust in this setting, but also that NIV must be integrated into multidisciplinary management, taking into account progression of the disease and the patient's living conditions outside of hospital. The ALS patient's family plays a predominant role in supportive care and everyday management of treatment, including end-of-life palliative care.

2. Pathophysiology of respiratory involvement and indication for NIV

Progressive degeneration of phrenic motoneurons results in diaphragmatic muscle impairment(11, 12). In the early 2000s, the role of diaphragmatic weakness as the major cause of poor sleep and impaired quality of life in ALS patients was confirmed, (4, 13), although this effect was first described in 1979(14). Diaphragmatic dysfunction initially affects REM sleep, when accessory respiratory muscles are impaired, then extends to involve all phases of sleep, and with subsequent progression of the disease. Arnulf *et al.* reported that some patients are able to use their accessory muscles during REM sleep, as a result of an as yet unexplained phenotypic change(4). These authors also demonstrated a dramatic reduction of survival due to diaphragmatic involvement (217 days versus 620 days), providing a major physiological argument in favour of the use of NIV in

ALS(4), confirming the results of earlier trials(15–18). Following these studies, the diaphragmatic involvement of ALS and the benefit provided by NIV have been the subject of numerous publications and considerable improvements in therapy that will be reviewed in this article.

3. Beneficial effects of NIV

From the first non-controlled studies published in 1993(15), to the randomized controlled trial published in 2006(19), many studies have shown NIV significantly improves survival, quality of life and cognitive performances in ALS despite progression of the disease(13, 15–18, 20, 21). The survival gain as a result of NIV has been estimated to be 7 months(19). Ten years later, with improvement of the quality of NIV and multidisciplinary management, NIV now provides an improvement of median survival of more than 13 months(22). This improvement is even observed in patients with bulbar muscle involvement (muscles controlling speech, mastication and swallowing), considered to be poor candidates for NIV in 2006(19). Bulbar patients derive greater benefit from NIV (survival gain of 19 months) than non-bulbar patients(22). Progressive improvement of survival of ALS patients over the years has been clearly shown to be due to the introduction of NIV after 2006(23) (Figure 1)

Recent physiological studies have further refined our knowledge of the benefit of NIV in ALS. By resting accessory muscles, NIV allows a dramatic reduction of energy expenditure (-7% of daily resting energy expenditure)(24), as well as “cortical resting” via decreased premotor cortex activity(25).

4. Criteria for initiation of NIV

All studies published since 1993 have proposed NIV in patients with daytime or nocturnal hypoventilation. As discussed below, only a few studies have proposed so-called “early” ventilation prior to onset of hypoventilation.

From a database comprising more than 600 patients, Georges *et al.(26)* showed that, in more than 80% of cases, NIV was initiated at a stage of daytime hypoventilation with a median $PaCO_2$ of 48 mmHg. However, all guidelines (27) recommend that the indication for NIV be based on pulmonary function parameters, nocturnal oximetry, or even plasma bicarbonate, but these recommendations are not contradictory. As shown in Table 1, all of these examinations, at the proposed cut-offs, can raise the suspicion of hypoventilation with varying degrees of sensitivity. More recently diaphragm ultrasound has been shown to detect those at high risk of hypoventilation(28, 29). In view of the nature and rapid progression of ALS, three-monthly assessments are necessary to determine the appropriate time to initiate NIV., but three-monthly assessment of PCO_2 are not practical due to the painful and invasive nature of arterial blood gases, and/or the cost of percutaneous measurements. The examinations shown in Table 1 are minimally invasive, inexpensive and can be performed on an outpatient basis by non-pulmonology teams after a short learning phase. The best examination at the present time to detect hypoventilation is the sniff test(30) with a sensitivity of 97% for a sniff < 40 cmH20. Thi is much better than that of vital capacity (VC), which has a sensitivity of only 58% for a value < 50%. More reliable measurements are obtained with a mask rather than a mouthpiece, especially for patients with bulbar disease(31). Measurement of the fall in VC between sitting and supine positions increases the sensitivity of the test to 90%(32). Two studies have recently confirmed the value of diaphragm ultrasound, with a good correlation between diaphragm thickening fraction with vital capacity and $PaCO_2$,

measurement although no cut-off value has yet been defined to suspect hypoventilation(28, 29). This technique would be an attractive for pre-NIV follow-up, but diaphragm ultrasound is rarely available outside of highly specialized centres.

The cut-off value for CO2 adopted to define hypoventilation in ALS is PCO_2 > 45 mmHg on arterial blood gases during spontaneous breathing, while resting in a seated position for at least 15 minutes. There is no recommendation, at the present time, concerning the best time of day to perform arterial blood gases (on waking, in the morning or in the evening at bedtime?)(33)

The value of nocturnal transcutaneous carbon dioxide ($PtcCO_2$) in ALS has also been recently emphasized(34), but particular attention must be paid to the technical difficulties of $PtcCO_2$ and its reliability in certain circumstances (drift, aberrant values). Concomitant analysis of the SpO_2 signal allows detection of aberrant values. The $PtcCO_2$ cut-off to propose NIV has not been unequivocally defined at the present time, but a 10 mmHg increase of $PtcCO_2$ above 50 mmHg for more than 10 minutes is classically used to define nocturnal hypoventilation(33).

A currently unresolved question concerns the value of NIV before hypoventilation occurs, co called, “early” NIV. This approach was initially proposed in Duchenne’s myopathy in 1994, before being ceased following demonstration of excess mortality in the “early NIV” group(35). However, several arguments suggest that early ventilation could slow respiratory decline in ALS and decrease respiratory work(24). A large retrospective study(36) and 3 small series demonstrated an improvement of survival in patients initiating NIV with vital capacity > 80% predicted(37–39), although this effect was not confirmed when sham NIV was used in the control group(39). In practice, patients with only minimal respiratory symptoms, essentially presenting features of

motor disability, are unlikely to continue NIV long-term if therapy is initiated prior to exhibiting hypoventilation. Jacobs *et al.* reported an adherence of about 3 hours per day with true both sham early NIV(39). A large randomized controlled trial on this subject

(40) was terminated due to insufficient recruitment. One of the hypotheses proposed of the excess mortality observed in the 1994 Duchenne study was under-use of NIV in the "early NIV" group when patients had reached the stage of hypoventilation. Recent data showing poor adherence to early NIV would tend to support these results(39, 40)

5) How should ALS patients be ventilated?

5.1 Site of initiation of NIV

NIV can be initiated in any setting experienced in NIV. No site of NIV initiation has been demonstrated to be superior to another, with home(41), ambulatory care unit(42, 43), and even telemonitoring(44) all reporting successful establishment of NIV. The current trend, especially in view of the major motor disability of these patients, is to avoid hospitalization and all outpatient approaches are highly appreciated by patients and are associated with health cost savings(41). Sheers *et al.* showed that outpatient initiation of NIV can save time and consequently improve patient survival(43).

5.2 Presentation of NIV

Mechanical ventilation is an important step in the life of ALS patients. It can be a feared and traumatic step for the patient and their family, with many associating ventilation with tracheostomy and end of life.. Patients must be clearly informed about this treatment modality. Mitsumoto and Rabkin(45) proposed advice to accompany the patient and announce this new treatment: "*Many assistive devices can greatly help your breathing, which left unassisted may decrease your energy levels and impede your sleep at night.*

One such device is a noninvasive positive pressure ventilator. It includes an easy-to-use mask that fits on your face. It should increase energy and provide better sleep". It could be added that "*this treatment will also relieve your breathlessness, while you are using ventilatory assistance, but probably also when you are breathing on your own*" (24).

5.3 Choice of equipment and settings

No particular mode of ventilation has been demonstrated to be superior. No difference in terms of efficacy has been demonstrated between volume assist-control ventilation, in which the patient receives a predefined volume of gas, and pressure assist-control ventilation, in which partial pressure assistance is provided(46).

The disadvantage of volume assist-control ventilation is the rigid feeling of ventilation and the absence of compensation for leaks. The 2 main theoretical advantage are that it allows the patient to perform air stacking to assist airway clearance and it will be able to overcome an obstacle, such as obstruction. This is the preferred mode in invasive ventilation. Some highly experienced teams effectively use this mode for NIV(46), probably with good efficacy on obstructive events (see below). The main advantages of pressure assist-control ventilation are that it is more comfortable for the patient, but, more importantly, it compensates for leaks. Pressure assist-control ventilation is the preferred mode for NIV, even in ventilator-dependent patients.

Survival differences in favour of pressure assist-control ventilation have been observed in large patient cohorts with a follow-up of 10 years (+13 months under pressure controlled(22), versus +10 months under volume controlled(47), although many other factors probably differ between these two centers working in different countries.

All commercially available masks can be used. Nasal ventilation allows better natural humidification, allows speech and induces a lower rate of obstructive apnoea(48) (see

below). Ventilation with a single-limb circuit with intentional leak requires a mask leak during expiration and has the advantage of allowing a wider choice of mask, but also allows the use of simpler circuits(49). Expiratory valve ventilation requires the use of a no-leak mask. A higher error rate (**85% in active circuit vs 30% in passive circuit, *P* < .001)**

with the same efficacy has recently been reported with the use of expiratory valve circuits in ALS patients treated by invasive ventilation (i.e. more advanced disease(49)

Harnesses and masks fitted with security systems can also be useful in motor disabled patients, especially ALS patients, when the mask needs to be removed in an emergency. Adaptation by an occupational therapist should be considered when a suitable mask is not available (Figure 1).

Low-level inspiratory pressure support is generally sufficient when initiating NIV. Semi-controlled pressure modes (spontaneous modes with back-up frequency) are preferred, being more effective in ALS than spontaneous modes(51). Ventilator settings can then be adjusted to ensure inspiratory assistance in order to obtain normal daytime and nocturnal $PaCO_2$. Initial settings are proposed in Table 2 and must be adjusted during the first minutes of ventilation to meet the patient's needs and symptoms. Ventilator settings are then continuously adjusted over the first hours and days of ventilation with 3 to 5 days usually needed to achieve optimal settings. The efficacy of ventilation should be evaluated at 1 month and then reviewed every three months(52). An illustration of the settings usually required to ensure optimal NIV is presented in Table 1. These settings should not constitute an objective *per se* and should be adapted on the basis of good quality monitoring of NIV (see below).

5.4 Adaptation of NIV in ventilator-dependent patients

Although the definition of a ventilator-dependent patient differs from one country to another (patient ventilated for more than 16 hours per day to more than 20 hours per day, depending on the country), and even remains unclear in the ISO standard ISO(53), special measures must be taken.

Pressure assist-control ventilation does not need to be changed to volume assist-control ventilation in ventilator-dependent patients. A semi-controlled mode(51) with back-up rate is sufficient, even in 24-hour-a-day ventilator-dependent patients. The security of ventilation, the presence of alarms and batteries, the dimensions, simplicity (or complexity), and noise are not better, at the present time, with either pressure assist-control or volume assist-control ventilators, but several safety measures must be applied :

-The provision of two so-called life support ventilators(53) is recommended.

-The patient must have several types of masks, for example a nasal mask or a nostril mask, in order to change pressure points and to allow eating or talking for several hours a day.

-A check list of parameters that should be monitored several times a day is very useful to avoid death due to a technical or logistic problem. An example of such a check-list is provided in the online supplement

Other daytime NIV techniques must be considered in highly ventilator-dependent patients in addition to mask ventilation:

- Mouthpiece ventilation (54), has been recently tested in ALS and can be proposed to ventilator-dependent patients who still retain good orofacial muscle control(55). Severe bulbar involvement (ALS functional rating scale (ALSFRS) score between 0 and 3) “contraindicates” the use of this technique(55).

- Hand held ventilators designed for COPD have been recently used in a very preliminary trial in 5 ALS patients, with interesting prospects provided certain technical improvements can be made(56).

- Intermittent abdominal compression ventilation(57) is also available in a few centres, but has never been studied in ALS.

Note that implanted phrenic nerve stimulation, that initially raised great hopes in ALS(58) but has unfortunately been shown to be dangerous, causing deterioration of the disease in two randomized controlled trials(59, 60), even in patients with primarily upper motoneuron disease(61). This technique cannot currently be recommended as an alternative or complement to NIV in ALS.

5.5 Adjustment of ventilator settings and monitoring of the quality of NIV

In 2011, the difficulty of long-term NIV in ALS was first raised(62). Following the publication of guidelines for NIV quality monitoring based on nocturnal recordings(63), Atkeson et all. applied this approach to ALS patients and observed a high rate of patient/ventilator asynchrony(62).Poor quality of nocturnal NIV is associated with poorer survival(52, 64) (figure 1). Leaks are the leading cause of failure of NIV, in more than half of cases(52) and must be monitored at each follow-up visit. Ventilator software allows very simple verification of leaks, even at home, or by teletransmission. Correction of leaks is now fairly simple as a result of the large range of masks available on the market.

After correcting any leaks, the main problem remains obstructive apnoea, which also impacts negatively on survival when it is not corrected(64). Obstructive apnoea in ALS can be due to various causes, but pharyngolaryngeal muscle impairment obviously predisposes to upper airway collapse. Schellhas *et al.* (48) confirmed the presence of

obstructive apnoea during NIV in ALS patients and suggested the use of an oronasal mask as an additional cause. Corrective measures of these obstructive events have been proposed by various teams(48, 64–66). An increased positive expiratory pressure is clearly the best treatment but is not always effective nor well tolerated by the patient. Various steps of treatment adjustment can be considered(48, 64) and are summarized in Table 3. When all of these corrective measures fail, Sayas *et al.(67)* propose a more detailed analysis of the cause of obstruction by videolaryngoscopy during NIV. Finally, some authors have reported the efficacy of a cervical collar(65, 66) or a mandibular advancement device in addition to ventilation(48, 64). Unfortunately, mandibular advancement may be difficult to apply due to excess salivation and/or the patient's motor disability making insertion of the device more difficult.

Other causes, also common in other disorders, can also be responsible for failure of NIV, including claustrophobia, mask-induced skin lesions, and rhinitis, with solutions the same as used in other diseases.

6) Non-ventilatory causes of failure of NIV in ALS

6.1 Bronchial congestion secondary to impaired cough

Concomitant impairment of the diaphragm, expiratory muscles and airways makes cough very ineffective in ALS. The absence of cough, when left untreated, is associated with marked excess mortality(68). Chatwin *et al.* reviewed all of the currently available airway clearance techniques and essentially recommended three-monthly monitoring of cough peak expiratory flow (CPEF) (69). This very simple measurement can even be

performed with an asthma flowmeter. A mechanical aid is used when CPEF < 270 l/min.

Several methods can be useful, but an insufflator-exsufflator is the most effective method(10), even in bulbar patients(70), although it is obviously more difficult. Setting adjustments, available on modern insufflator-exsufflators, can be proposed in severe bulbar ALS patients:

- Ensure triggering on every insufflation
- Decrease inspiratory flow
- Decrease inspiratory pressure
- Increase inspiratory time

Flexible pharyngolaryngoscopy while using the insufflator-exsufflator device should also be considered in case of failure of setting adjustments(70).

6.2 Congestion due to excess salivation

Excess salivation can be a specific cause of failure of NIV in ALS. Various drugs can be used (atropine, scopolamine, belladonna tincture), but salivary gland radiotherapy has been shown to be very effective and should be proposed to these patients(71), even in patients already treated by NIV(72). Botulinum toxin injection into the salivary glands is difficult to perform and only has a temporary effect.

6.3 Undernutrition secondary to swallowing disorders and the need for gastrostomy

Swallowing disorders, preventing feeding other than by tube feeding, can occur after commencing NIV, which may require feeding gastrostomy. Various solutions have been proposed, including endoscopic gastrostomy with NIV support(73), but they are difficult to perform in patients with severe bulbar lesions who are be unable to control mouth leaks during NIV, or percutaneous endoscopic gastrostomy with NIV support(73–76), which can sometimes be impossible in the presence of very advanced diaphragmatic dysfunction with intrathoracic stomach. Surgical gastrostomy may sometimes need to be performed under brief general anaesthesia with intubation and rapid extubation followed by NIV support.

7) Tracheostomy is not systematically the next step after NIV

Tracheostomy has been shown to markedly improve survival, as recently highlighted by Stephen Hawking's very long-term survival(77), with a quality of life considered to be satisfactory by patients(78, 79), although less so by caregivers(80) (figure 1).

The technical and financial feasibility of this approach may be important determinants of tracheostomy placement in some countries, with assessment of the possibility for the patient of returning to his/her place of residence following the tracheostomy.

For example, tracheostomy with ventilatory assistance is fully reimbursed in Japan, where the tracheostomy rate is 27%, partially reimbursed in France where 5% of patients are tracheotomised, with almost no reimbursement in the USA where the tracheostomy rate is 3%. There is no reimbursement in the United Kingdom.(45).

This lack of reimbursement can lead to problematic and inextricable situations for the families of ALS patients. Some patients and their families nevertheless request

tracheostomy and they must be informed as completely as possible about the consequences of this decision, ideally as early as possible, to avoid performing tracheostomy in an acute setting when the patient and the family have not had time to discuss this option. Mitsumoto and Rabkin(45) have proposed various examples of the way in which tracheostomy can be presented to patients and families.

Improvement of the quality and efficacy of NIV, even in ventilator-dependent patients, and limited discussions regarding provision of ventilation other than with NIV probably explain the very low rate of tracheotomised patients in western countries. The situation appears to be changing in Japan(81), where the almost automatic transition from NIV to tracheostomy has been declining over recent years with patients who have used NIV for more than 6 months being less inclined to request tracheostomy.

8) Palliative care and discontinuation of NIV

8.1 Dyspnoea and end of life

End of life is accompanied by a number of symptoms: dyspnoea, weakness, physical fatigue, decreased activity, psychological fatigue and lack of motivation(82). According to one study, patients may experienced distress and pain during the last month of life and often receive suboptimal treatment(82). Although these studies were published many years ago and comprised a large number of non-ventilated patients, symptomatic treatments for dyspnoea, such as opioids, should be readily available, even fairly early in the course of the disease, if dyspnoea is not fully relieved by NIV. A strong correlation between dyspnoea and pain has been described in patients who are effectively relieved by NIV. Relieving dyspnoea by NIV in patients with ALS having respiratory failure is associated with decreased pressure pain thresholds. (83).

8.2 Discontinuation of NIV

Although ventilatory support can meaningfully extend life, the patient sometimes requests cessation of NIV when allowed by local legislation. However, discontinuation of NIV will inevitably be accompanied by severe symptoms, or even true acute respiratory distress. This type of situation must be anticipated, which necessitates rigorous and carefully appropriate drug treatment.

As in any situation of end-of-life dyspnoea, opioids and benzodiazepines, possibly associated with administration of oxygen, effectively relieve the symptoms induced by discontinuation of ventilatory support. It is only common sense to initiate these treatments before discontinuing ventilatory support, which can be legitimately temporarily resumed if the doses administered are insufficient to relieve the patient's symptoms and promote patient comfort. It is important to ensure the continuous presence of a doctor or a nurse in the patient's room after stopping ventilatory support, to allow a rapid response when the doses need to be increased to reassure the family about the significance of any respiratory pauses or agonal gasps, which, despite their spectacular nature, must not be interpreted as signs of suffering. If death does not occur rapidly, a doctor or nurse should frequently visit the patient's room, or the permanent presence of a doctor or nurse may sometimes be necessary.

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Table 1: Simple tests suitable for general clinic or bedside use to identify and monitor respiratory muscle weakness and the possibility of hypoventilation in patients with ALS and to introduce NIV. Adapted from (27, 30, 52)

Measurement	**Thresholds and comments**
Vital capacity (VC)	**Threshold : between <80% to <50%** -Simple and readily accessible measurement able to be performed routinely at bedside, in clinics or patient's home -Erect to supine fall in VC>20% indicative of diaphragmatic weakness -Provides sensitive thresholds for predicting survival at 6 months (Sensibilty at 58%) -Is a late predictor of respiratory failure compared to MIP
Maximum Inspiratory Pressure (MIP)	**Threshold : <40cm H2O to <60 cm** -A value >80cmH_2O excludes significant inspiratory muscle weakness -MIP <40cmH_2O widely used to identify those at risk of

	hypoventilation -May be difficult for some patients to perform and is affected by leaks in those with orofacial muscle weakness -Reliant on patient effort -Wide range of normal values. % of the normal would be more pertinent (ie. 40 to 60% predicted)
Sudden Nasal Inspiratory Pressure (SNIP)	**Threshold : <40cm H2O** -Normal values >70cmH2O (males) and 60cmH2O (females) -SNIP<40cmH_2O more sensitive (than VC or MIP in identifying ALS patients at risk of hypoventilation -Both MIP and SNIP assess global inspiratory muscle function rather than specific diaphragm strength -Wide range of normal values. % of the normal would be more pertinent (ie. <40%)
Diaphragmatic ultrasound	**Threshold and conditions of the measurement not standardized**
Nocturnal pulse oxymetry	Threshold : % time spent <90% >5% or 10% -Measurement is not useful where the patient has lung disease or is using supplemental oxygen".

Table 2 : Proposal for setting NIV in ALS patients. RR = respiratory rate; EPAP : expiratory positive airway pressure. Ti = inspiratory time, I/E ration : inspiratory time/expiratory time ratio

Setting	To start	Target
Mode	Pressure mode and assisted-controlled mode	
Pressure support (cmH_20)	4 to 6	10 to 12
EPAP (cmH_20)	Non bulbar patient	
	4	4
	Bulbar patient	
	4	6 to 14 or automatic EPAP
Backup RR (cycles/min)	14	16 to 20
Rise time (msec)	200	Minimal to 400ms
Inspiratory trigger	Medium sensitivity	
Expiratory trigger	Medium sensitivity (50% of the peak flow)	
Inspiratory Time (s)	Timin-Timax 0.8 to 1.6 or	

	fixed Ti : 1.3 to 1.6 (calculated for a I/E ratio to ½ with the backup RR set)

Table 3 : Possible measures to reduce apneas and hypopneas persisting with NIV. Following tolerance and efficacy of waveforms of the ventilator softwares. Adapted from (48, 64–66). EPAP= expiratory positive airway pressure. IPAP :inspiratory positive airway pressure

Steps	Desire effect	Tool
1) FIT MASK	Decrease on facial structures	Switch to nasal mask (without chin strap) in patients without buccal weakness
	Decrease facial pressure and prevent leakage	Switch to nasal mask (with chin strap)
	Prevention of air leakage and drop in the EPAP	Optimization of oronasal mask fitting
2) increase EPAP	Improvement of upper airway patency	Increase fixed EPAP (from 4 to 14)
	Improvement of upper airway patency with better tolerance	Automatic EPAP from 8 to 14*
3) Shorting expiratory time	Reducing time window for end-expiratory upper	-Switch to a mode with Ti max.

	airway collapse	-Decrease Ti max and/or fixed Ti from 1,6 to 1s
4) High Increase of inspiratory pressure	Increasing pressure during inspiration can open closed upper airway	-Volumetric mode -Automatic IPAP devices with short answer*
4)Positional treatment	Reduction of positional apnea	Avoidance of the supine sleep position
5) Mandibular action	Anterior displacement of the jaw	-cervical collar -mandibular advancement device (poorly tolerated)

*The automatic algorithms (for EPAP or pressure support) are very different between the devices. In case of failure of one device, other devices must be tested.

figure legends and figures

Figure 1 : ChinStrap adaptation by the occupational therapist for ALS patients

Figure 2 : Illustration of the different expected survivals depending of the quality of mechanical ventilation. These survivals are only examples, extrapolated from selected lasts publications in ALS patients(22, 52, 64, 79). OA= obstructive apneas