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ABSENCE OF AIRWAY SECRETION ACCUMULATION PREDICTS TOLERANCE TO NONINVASIVE VENTILATION IN ALS.

Nadia Vandenberghe[1], Anne-Evelyne Vallet[2], Thierry Petitjean[3], Pierre Le Cam[3], Stéphane Peysson[2], Claude Guerin[3], Frédéric Dailler[4], Sylvie Jay[5], Vincent Cadiergue[5], Françoise Bouhour[6], Isabelle Court-Fortune[7], Jean-Philippe Camdessanche[8], Jean-Christophe Antoine[8], François Philit[3], Pascal Beuret[9], Sylvie Bin-Dorel[10], Christophe Vial[6], Emmanuel Broussolle[2].

[1]Hospices Civils de Lyon, Centre SLA de Lyon (Service d'Electroneuromyographie et Service de Neurologie C), Hôpital Neurologique Pierre Wertheimer, Lyon, France

[2]Université Lyon 1, Faculté de Médecine Lyon Sud, Hospices Civils de Lyon, Service de Neurologie C, Hôpital Neurologique Pierre Wertheimer and CNRS UMR 5229, Lyon, France

[3]Hospices Civils de Lyon, Service de réanimation Médicale et d'Assistance Respiratoire, Hôpital de la Croix Rousse, Lyon, France

[4]Hospices Civils de Lyon, Service de Réanimation Neurologique, Hôpital Neurologique Pierre Wertheimer, Lyon, France

[5]Réanimation Polyvalente Adulte, Centre Hospitalier d'Annonay, Annonay, France

[6]Hospices Civils de Lyon, Service d'Electroneuromyographie et des pathologies musculaires, Hôpital Neurologique Pierre Wertheimer, Lyon, France

[7]Service de Pneumologie B, Hôpital Nord, St Etienne, France

[8]Service de Neurologie, Centre SLA, Hôpital Nord, St Etienne, France

[9]Service de réanimation, Centre Hospitalier Général de Roanne, Roanne, France

[10]Hospices Civils de Lyon, Pôle Information Médicale Evaluation Recherche, Unité de recherche clinique ; Université de Lyon, RECIF, EA Santé Individu Société 4129 ; Université Lyon 1, Lyon, France

Correspondence to

Dr Nadia Vandenberghe ; Hospices Civils de Lyon ; Centre SLA de Lyon (Service d'Electroneuromyographie et Service de Neurologie C) ; Hôpital Neurologique Pierre Wertheimer ; 59 Boulevard Pinel ; 69677 Lyon-Bron Cedex ; France

The studywasperformedin Centre SLA de Lyon (Service d'Electroneuromyographie et Service de Neurologie C), Hôpital Neurologique Pierre Wertheimer, Lyonand Service de Neurologie, Centre SLA, Hôpital Nord, St Etienne, France.

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ABSTRACT

BACKGROUND: This study aimed to assess factors which predict good tolerance of noninvasive ventilation (NIV), in order to improve survival and quality of life in amyotrophic lateral sclerosis (ALS) patients.

METHODS: We conducted a prospective study on ALS patients requiring NIV. The study's primary endpoint was NIV tolerance at one month. Patients, several of whom failed to complete the study, were classified as 'tolerant' or 'poorly tolerant' according to the number of hours of NIV use (more or less than 4 hours per night, respectively).

RESULTS: 81 patients, 73 of whom also attended the one-month follow-up visit, participated over 34 months. NIV tolerance after the first day of utilisation predicted tolerance at 1 month (77.6 % and 75.3 % of patients, respectively). Multivariate analysis disclosed three factors predicting good NIV tolerance: 1° absence of airway secretion accumulation prior to NIV onset (odds ratio, OR=11.5); 2° normal bulbar function at initiation of NIV (OR=8.5) and 3° older age (weakly significant, OR=1.1).

CONCLUSION: Our study reveals three factors which are predictive of good NIV tolerance, in particular the absence of airway secretion accumulation, which should prompt NIV initiation before its appearance.

Keywords: prognosis, cohort studies, amyotrophic lateral sclerosis, noninvasive ventilation tolerance, airway secretion accumulation, mechanically assisted coughing.

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Abbreviation list

ALS: amyotrophic lateral sclerosis

EPAP: expiratory positive airway pressure

IPAP: inspiratory positive airway pressure

OR: odds ratio

MAC: mechanically assisted coughing

NIV: noninvasive ventilation

PCEF: peak cough expiratory flow

PNO: percutaneous nocturnal oximetry

SVC: slow vital capacity

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Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating disease affecting respiratory muscles causing breathlessness, morning headaches, unrefreshing sleep, daytime sleepiness, fatigue, impaired concentration and poor appetite.[1] Respiratory failure is the most common cause of death.[2, 3] Noninvasive ventilation (NIV) improves survival and quality of life in ALS patients.[4-6] Tolerance is known to correlate with increased survival and improved quality of life. Previous studies on NIV tolerance in ALS patients have yielded controversial results regarding age (most of the studies concluded that younger patients are more likely to benefit from NIV or did not retain this criterion as specific)[7], whereas the majority demonstrated less tolerance in patients with bulbar involvement at NIV initiation.[4-13] This last population requires careful attention in the clinical management of problems such as excess saliva and in the choice of the interface, choice of the ventilator and the ventilator settings.

Identification of factors which predict good NIV tolerance is a major issue. Implementation of medical support is required as soon as respiratory failure becomes significant, to enable patients to obtain maximum benefit from treatment.[4-12, 14, 15] Most clinicians caring for ALS patients face the dilemma of either premature or belated introduction of NIV. The former can result in the failure and subsequent refusal of the treatment because of the discomfort involved. The latter may increase the risk of respiratory failure and admission to intensive care.

In a previous retrospective study, we assessed factors predicting survival following NIV.[14] Advanced age and airway mucus accumulation (i.e. airway secretion accumulation) were both factors of poorer prognosis. These results prompted us to conduct a prospective study to determine whether clinical and pulmonary parameters at initiation play a role in NIV tolerance.

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Methods

This is a descriptive study of a cohort of ALS patients followed by two French ALS centers (Lyon and St Etienne). This observational work entailed no additional visits or examinations for patients. The study was approved by the Institutional Ethical Committee and all subjects gave written informed consent.

Patients

We included patients with probable or definite ALS [16], treated by riluzole and referred to us between 2006 and 2009, requiring NIV initiation. Patients benefited from quarterly monitoring as recommended [17,18] and most were prescribed NIV by bilevel positive airway pressure (Bipap) in the S/T mode. A few patients were treated by the volumetric NIV method following immediate intolerance to the Bipap mode after a 4 –hour trial. NIV was proposed when at least one clinical respiratory symptom was present (orthopnea of under 3 months onset; dyssomnia due to respiratory sleep disorders, with insomnia or suffocating wake-ups; nightmares; headaches, non-restorative sleep; paradoxical breathing), in association with at least one abnormal functional pulmonary respiratory exam score (slow vital capacity (SVC) lower than 50% of predicted value; percutaneous nocturnal oximetry (PNO) of under 90% of SaO2 for more than 5% of recording time; daytime (10am-6pm) PaCO2 > 6 kPa (45 mmHg).(16,17) Duration of NIV use (hours per night and per 24h) was obtained by interrogation of patients' machines. Once NIV was scheduled, it commenced within the following month. When the need for NIV was deemed urgent or semi-urgent, treatment commenced within 1 to 10 days. Exclusion criteria for the study were: associated chronic respiratory insufficiency such as COPD, other rapidly progressing diseases with a survival

expectancy of less than 1 month, tracheotomy, and behavioral or psychiatric disorders which might compromise NIV observance.

The study's primary endpoint was NIV tolerance at one month. Good tolerance was defined as NIV use for more than 4 consecutive hours each night. Poor NIV tolerance was defined as NIV use of 4 consecutive hours or less per night.[11] Several patients failed to complete the study, and were released, either before commencing NIV, or in the period between NIV initiation and the one month visit. These patients were included in the group of patients with poor NIV tolerance.

Clinical data

The following data were collected prospectively: gender, age at ALS onset and at NIV initiation, nutritional status and body mass index, active smoking, past smoking history, smoking exposure in pack-years, place of residence, delay between first clinical signs and ALS diagnosis, revised El Escorial criteria classification of ALS, bulbar function at initiation of NIV, ALSFRS-R, Norris bulbar scale and Epworth daytime sleepiness scale. Patients were classified as having ALS with bulbar involvement when the ALSFRS-R score component pertaining to speech or swallowing impairment was ≤ 7/8. When the subscore was equal to 8/8, the patient was classified as non-bulbar ALS or pure spinal form at NIV initiation. [15,19,20] We also used the saliva subcomponent of ALSFRS-R (with a total score on 12) and decided arbitrarily and a priori that the score of ≤ 9/12 corresponded to bulbar form at NIV initiation. Respiratory status was assessed from the following: dyssomnia and paradoxical breathing, and pulmonary function test results The SVC was obtained with a SpiroAir Spirometry from Medisoft®. Testing was done in seated position. Measuring the CV supine was not performed because too difficult to achieve in the laboratory of functional exploration in patients with severe disabilities. PaCO2 was obtained on arterial blood gases during daytime (10am-6pm).

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Blood sample was analysed with ABL825 Radiometer® machines. PNO was done with Konica Minolta® Pulsox – 300i oximeters. Pulmonary function and PNO tests were performed in two laboratories at the same time. PNO was measured continuously during sleep, by a fingertip infrared pulse-oximeter and a multisite finger-clip probe. Most of the time patients were propped up at 45°during sleep, and adjusted their sleeping position in order to minimize any dyspnea present. We recorded the proportion of time during which SaO2 was less than 90%.

We had the following NIV titration protocol for the patients: We started with choosing mask model following clinical signs and adjusting the interface in function of discomfort (air leaks, face/nose pain, nasal congestion, aerophagia)Initial pressures were low with inspiratory pressure (IPAP) between 8 to 10 cm H_2O, expiratory pressure (EPAP) at 4 cm H_2O and back-up respiratory rate at 14 breaths/minute. These parameters were readjusted in function of compliance, tolerance, percutaneous nocturnal oximetry and arterial blood gases results. NIV characterization was based on the following variables at onset: patient's age, ALS duration, time elapsed between indication and actual start, presence of gastrostomy, NIV tolerance after first day of use, NIV settings in BiPAP mode (levels of both inspiratory and expiratory positive airway pressure, back-up respiratory rate), kind of interface used (commercially or individually customized masks). Airway secretion accumulation in the lower airways was assessed by auscultation in the subglottic area. A physiotherapist specialized in respiratory diseases also evaluated patients. This assessment included drainage maneuvers, clinical examination, and thoracic mobilisation. A small nasopharyngeal aspiration was performed in some cases of doubt about the exact location of the secretion accumulation. If the patient was improved by this aspiration, the secretion accumulation was considered above the glottis. If discomfort persisted, combined to elements obtained by the physiotherapy assessment, secretion accumulation was considered subglottic. Mechanically

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assisted coughing (MAC) was administered to all patients presenting lower airway secretion accumulation and when PCEF was lower than 270 L/min. We used the following protocol with the Alpha 200 device: we use a face mask or end piece with oral intake, the patient is in half-sitting or lying position, maximal inspiratory pressures ranging between -30 and -40 cm H2O, repeated 5 to 10 cycles depending on tolerance and efficiency to removing secretions. We had the following protocol with the Cough Assist® machine: we use a face mask, the patient is in a sitting position, the maximal inspiratory/expiratory pressures are ranging between -30/+35 and -40/+40 cm H2O, the inspiratory time to expiratory time ratio is 2/1, repeated 5 to 10 cycles depending on tolerance and efficiency to removing secretions.

Any pooling of saliva was treated either by suction, medical treatment, botulinum toxin, or by a combination of all three before NIV initiation. Patients who were eligible for NIV, but who were not included in the protocol (exclusion criteria or refusal to participate), also benefitted from its implementation and the usual monitoring. Patients were discharged from hospital on average 2 to 3 days. Home visits were performed systematically in routine when patients went back home, the day of back home, at 15 days and 48 hours before the evaluation at 1 months by the nurse and technician of the home performing who delivers material. In case of problem, the ALS centre is warned in the following 24 hours.

Statistical Analysis

Variables were expressed as means, standard deviations, minimum and maximum values when quantitative, and as counts (percentages) when qualitative. The sample size was computed to detect Odds-Ratios (OR) of 0.25 [confidence interval 95% 0.07 – 0.90] on the basis of the primary objective at first order of risk of 5% according to the Miettinens method.[21] We therefore determined that the inclusion of 80 patients would fulfill this requirement.

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Univariate comparisons between tolerant and intolerant NIV patients were performed using a nonparametric Mann-Whitney test for quantitative variables, and a chi square test for categorical variables when conditions permitted (otherwise, we used Fischer's exact test). In the univariate analysis, variables significant at 20% (p value output of 0.20) between the two NIV tolerance groups were introduced into a multivariate logistic regression model with stepwise selection of variables. When a strong relationship was shown between several variables, we used only the variable with the highest correlation. Variables with more than 10% of values missing were not entered into the model, and no replacement method was used (since missing values for one variable do not affect other variables). We used the SAS proc logistic stepwise method, which enabled us to combine backward and forward methods, and the Homes and Lemeshow Goodness of Fit test, which showed no evidence of lack of fit. The analysis was performed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA).

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Results

Baseline clinical characteristics

81 ALS patients who fulfilled selection criteria were recruited (see flow chart in figure 1). Of the 73 patients undergoing complete assessment at one month, 55 were tolerant, and 18 were poorly tolerant. The poorly tolerant group included 15 patients who used NIV for 4 hours or less, one patient who refused NIV immediately after the first attempt at using the NIV machine, and 2 patients who did not attend the one-month visit because NIV was discontinued after one day due to personal intolerance.

Evaluation at NIV initiation

Comparisons of the clinical and demographic baseline characteristics of NIV tolerant versus poorly tolerant patients who completed the study are displayed in table 1.

We investigated the effect of smoking (active smoking, past history of smoking or smoking in pack-years). No effect of these variables on NIV tolerance was shown (table 1). The respiratory status of tolerant and poorly tolerant patients on initiation of NIV is presented in table 2. 4/73 patients had volumetric, and 69/73 had barometric NIV machines. We describe only the parameters of barometric NIV machines. No statistical differences were observed in the functional pulmonary values (PNO, SVC) at time of inclusion, circumstances at start of NIV, or mean elapsed times between NIV indication and NIV initiation, of the tolerant and poorly tolerant groups (table 2).

There was, however, a statistical difference between the 2 groups at NIV onset, with lower rates of paradoxical breathing (P=.03) and lower rates of airway secretion accumulation (P=.05) in the tolerant group than in the poorly tolerant group. Of the 77 patients who started

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NIV, 59 (75.6%) were tolerant on the first day, and 17 (22.4%) were not. NIV parameters of 8 of the 69 patients treated with barometric mode were modified in the first month.

Evaluation at 1 month

55/73 patients (75.3%) were tolerant to NIV at one month (Figure 1). One month after NIV onset, tolerant patients had used it for a mean duration of 8.3 hours (SD 2.9) per 24 hours, and 7.8 hours (SD 1.5) per night. In the poorly tolerant group, mean NIV utilisation was 4.6 hours (SD 2.8) per 24 hours, and 2.3 hours (SD 1.4) per night. The interface of two patients was changed from a nasal mask to a naso-oral industrial model. No patient changed from barometric to volumetric mode or vice versa. When looking the airway secretion accumulation and tolerance, we observe the following data:

- tolerant patients (55/73): this includes 50/73 patients without airway secretion accumulation before NIV start, 2/73 patients with airway secretion accumulation and succesfull intervention on it and 1/73 patients with persistent airway secretion accumulation despite intervention.

- poorly tolerant patients (18/73): this includes 12/18 patients without airway secretion accumulation, 3/18 patients with airway secretion accumulation and succesfull intervention on it and 1/18 patient with airway secretion accumulation with failure of intervention on it.

Importantly, immediate tolerance on the first day predicted NIV tolerance at one month. 82.1% of patients who were tolerant initially remained so at one month (P=.04).

We found that tolerance to NIV at 1 month was significantly better in patients with no bulbar involvement (pure spinal form) than in those with bulbar involvement at NIV initiation (P=.02). This was further confirmed in the univariate analysis of bulbar impairment subscores on the ALSFRS-R scale and bulbar Norris scale (table 2). Multivariate analysis also predicted

better tolerance in patients with no bulbar involvement (table 4). Further multivariate analysis using ALSFRS-R subscores and Norris bulbar scale total scores was less sensitive and revealed no significant findings (data not shown). When using either the saliva subcomponent of ALSFRS-R (with a total score on 12) and arbitrarily and a priori deciding that the score of ≤ 9/12 correspond to bulbar form at NIV initiation, we obtain the following data (*P=.03*):21/80patients present with bulbar form at NIV initiation (26.25%) from who 11/55 (20%) are toerant at 1 mont and 9/18 (50%) are poorly tolerant.

This subscore does not change the classification of the patients clinical form at NIV initiation as bulbar or non bulbar (pure spinal) ALS in our study.

When using the ALSFRS-R subscore on 12 to classify the patients clinical form at initiation, in the multivariate model, we still found this independently prognosis factor (p value of the model *P=.0015*): non Bulbar form (pure spinal form) OR=6.0 (confidence interval 1.3-27.2), airway secretion accumulation OR=10.9 (confidence interval 1.6-76.3).

The presence of gastrostomy, related to the bulbar ALS form at NIV initiation, influenced NIV tolerance negatively (*P*=.02). There was no correlation between age and number of hours of NIV use per day (R = 0.14 (Spearman) with *P=.3*). Patients without pooling of secretions used NIV for a mean of 6.7 hours per day at 1 month (SD=2.7), whereas patients with pooling of secretions used it for a mean of 5.15 hours per day (SD=3.1) with *P= .15*.

Five patients died before the one-month evaluation. Four of them presented with progressive hypercapnic coma despite adaptation of NIV settings and /or interface, and one patient presented with acute respiratory distress. Death did not result from NIV discontinuation. Prior to death, all 5 patients had used NIV for between 3 and 12 hours per day. The 4 patients who developed progressive hypercapnia while on NIV had used it for 3 to 17 days before death.

The multivariate analysis disclosed three predictive factors of good NIV tolerance (table 3). The most important and significant predictive factors were absence of airway secretion

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accumulation prior to the establishment of NIV, and having non bulbar ALS rather than bulbar ALS at initiation. The association between older age and NIV tolerance was weakly significant.

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Discussion

The aim of the present study was to determine predictive factors of good NIV tolerance at one month, since these may be associated with increased survival and better quality of life.[4-6]

We will discuss firstly methodological issues and comparisons with current literature, then the results of the multivariate analysis. The new finding brought by the present study was that the absence of airway secretion accumulation was an independent predictor of good tolerance to NIV in ALS patients.

Methodological issues and comparisons with literature

The clinical profiles of our ALS patients were comparable to those commonly reported in the literature. We retained only definite and probable ALS El Escorial categories in order to strengthen the final diagnosis. NIV was prescribed in our patients mainly in cases of overt paradoxical breathing and dyssomnia associated with PNO anomalies.[22] Although SVC reduction is still the most widely used indicator of restrictive respiratory defect, it is susceptible to variation.[23,24] Death can occur in patients with SVCs above the critical threshold of 50% recommended for NIV establishment.[25] Recent UK guidelines on NIV indicate that while clinicians rely on VC, the threshold for initiating NIV is VC < 50% regardless of symptoms or VC = 50- 80% in the presence of symptoms. [26] Elevated daytime PaCO2 (> 6 kPa) is another primary criterion for starting NIV, but reflects a more severe degree of alveolar hypoventilation. It therefore exposes the patient to acute respiratory failure and death in the event of exacerbation or intolerance to NIV.[7, 27] When NIV is initiated following early changes such as those recorded with PNO, and associated to clinical respiratory symptoms, longer survival rates have been described, compared to patients who started NIV when FVC had declined to 50% or less.[28]. Nevertheless, the converse may be true in patients with bulbar involvement.[9] A too early NIV introduction can also result in the

failure and subsequent refusal. A multicentre French national randomised study in ALS patients tried to evaluate the benefits on survival and quality of life from early NIV initiation, comparing 2 groups. One group had an early nasal NIV (no clinical signs, only respiratory functional test anomalies). The second group comprised patients requiring urgent NIV (clinical signs compatibles with respiratory insufficiency associated with functional test anomalies). The study was prematurely stopped for failure and refusal by the early nasal NIV group to continue NIV because of the generated discomfort.[29]

In the present study, NIV tolerance, assessed as use > 4 hours per night, was achieved in 75% of patients both immediately in the first session, and at one month. This finding is coherent with previous studies.[7, 10, 30] In our study, 55% of the patients with bulbar involvement at NIV initiation, were tolerant. Every effort should, therefore, be made to improve patients' tolerance.[4, 7, 8, 28, 30] One study reported tolerance in 100% of patients on discharge following initial hospitalization for NIV initiation. This may be related to a longer duration of hospital stay (on average 12 days). However, in this study, the NIV implementation method differed from our daily practice, and from that of most centres. Pressure support and valves with naso-oral masks were administered to all patients.[31] In our study, length of hospital stay for the initiation of NIV was 2.7 (SD 1.1) days. We believe that thorough information about NIV, describing its advantages and disadvantages, and the positive attitude of multidisciplinary teams involved in both ALS medical treatment and NIV initiation in an experienced unit, should reduce patients' refusal of the procedure and improve tolerance over time, especially in patients with severe bulbar impairment. When using either the saliva subcomponent of ALSFRS-R (with a total score on 12) and arbitrarily and a priori deciding that the score of ≤ 9/12 correspond to bulbar form at NIV initiation, this subscore did not change the classification of the patients clinical form at NIV initiation as bulbar or non bulbar (pure spinal) ALS in our study.

Some study limitations have to be acknowledged. When realising diurnal PaCO2 measurement (10am-6pm), we could have missed a lot of patients with nocturnal hypoventilation that could benefit from NIV. That is why, in our study, we associated this parameter with PNO. Polysomnography would have been better suited for evaluation of nocturnal abnormalities during sleep. However, the ability of the sleep laboratory to provide with quick appointments on demand was a limitation for its use, making PNO easier to perform. It should be noted that polysomnography is not mentioned as mandatory in the proceeding of the Consensus Conference on Amyotrophic Lateral Sclerosis in France[17], for the same reason.

Multivariate analysis

Absence of airway secretion accumulation was the best predictor of NIV tolerance in our series. Contrary to our expectations, it was more frequent in non-bulbar ALS at NIV initiation (15%) than in bulbar ALS (5%). Airway secretion accumulation probably results from salivary stasis in the oro-pharyngeal region and from respiratory failure. Cough efficiency can be impaired when peak cough expiratory flow (PCEF) is lower than 270 L/min, which probably favours airway secretion accumulation. An effective cough is dependent on inspiratory, expiratory and bulbar muscle function. In some patients, the expiratory muscle weakness, may run parallel with, or even precede, that of the inspiratory muscles.[30-32] Mufta *et al*.[33] reported a positive correlation between inspiratory and expiratory muscle strength and PCEF in non-bulbar ALS patients, demonstrating the importance of both muscle groups. Accordingly, MAC has been shown to improve recruitment of nonventilated pulmonary areas, preventing atelectasis and removing mucous debris.[27, 34] This should enhance the effect of NIV in improving lung compliance by re-expanding microatelectastic lung areas.[11] Statistically, all MAC techniques are better than manual techniques for ALS patients, and

Cough Assist® is considered to be the most effective clearing method.[33, 35] MAC was proposed in our study when PCEF was lower than 270 L/min, irrespective of ALS clinical picture. We observed in some patients with severe bulbar impairment, failure to close the glottis associated or not with a severe dynamic collapse of the upper airways during the exsufflation cycle.[36] We tried to remove airway secretion accumulation with Alpha 200® or Cough Assist® machine. The retained technique was based on tolerance and efficacy. When none of both worked, manual physiotherapy or mechanical insufflation was used. If airway secretion accumulation was not controlled, NIV implementation was nevertheless selected. The limitation of MAC is that it is mostly efficient to clear the upper and middle airways. Intrapulmonary Percussive Ventilation could be much more efficient to clear the lower airways, but in France, it has not been evaluated in patients with ALS. In addition, there is no financial support from social security for using this technique. MAC applied prior to the use of NIV in presence of airway secretion accumulation should facilitate adaptation and tolerance for some patients. Systematic verification for the presence of airway secretion accumulation before commencing NIV is, therefore, worthwhile.

The second positive predictive factor for good NIV compliance was the absence of bulbar involvement at NIV initiation. Many studies have reported greater tolerance in non-bulbar ALS, with a corresponding increased relative risk of death in poorly tolerant patients.[7, 8, 10, 15] In these studies, bulbar involvement at NIV initiation was associated with lower compliance and less improvement in quality of life, but NIV was still clinically useful in bulbar ALS.[4, 22] These patients show less tolerance probably due to problems with handling airway mucus accumulation and saliva. They need intensive and prolonged monitoring at NIV onset[20] so as to maximize NIV compliance.[15] Gastrostomy is usually performed in patients with more severe bulbar weakness, which have a higher risk of being discomforted by airway secretion accumulation. We expected to observe less tolerance for this patient profile like in other

studies.[4] Indeed, bulbar patients reportedly have difficulty distinguishing the choking sensation when lying flat from true orthopnea, and perform poorly on volitional tests of respiratory function. They may therefore be considered for NIV when their true respiratory muscle function appears better than that of patients with good bulbar function.[26] Based on our own experience and that of other groups, bulbar ALS forms are associated with more mouth leaks with nasal interfaces, more pharyngeal obstruction with naso-oral masks and increased likelihood of further airway secretion accumulation due to ventilator asynchronism.[9, 37] We observed that apnoea syndromes were more frequent on polygraph charts in bulbar forms. More systematic performance of polysomnography may be worthwhile to confirm their co-occurence. Even though, several studies indicate no clear relationship between presence of bulbar disease and obstructive sleep apnea. [38-40]

The third positive prognosis factor identified by the multivariate analysis, but which cannot be retained as highly significant, was advanced age (OR=1.1). However, literature mostly reports young age as being a good prognosis factor.[4, 8] Does acceptance of substitute ventilator techniques differ according to age? Good tolerance in the older group is probably due to optimization of NIV initiation in hospital and during home visits for the whole sample of our patients. As for the bulbar function at NIV initiation, our findings provide another argument against restricting NIV proposal to certain age brackets.

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Conclusion

Our study enabled us to determine three predictive factors of good NIV tolerance, in particular absence of airway secretion accumulation prior to NIV establishment, which should prompt its initiation. The present work provides evidence in support of wide access to units delivering NIV, irrespective of the ALS clinical picture. As patients with bulbar involvement at NIV onset have a poorer prognosis than those without, they can be further disadvantaged by more frequent intolerance to NIV. They need intensive and prolonged monitoring at NIV onset to maximize its compliance. Poor tolerance and intolerance to NIV can perhaps be reduced for some additional ALS patients by controlling airway secretion accumulation by MAC but should be confirmed by another study and solving the problems of the mask model.[13]

Further work is ongoing to assess the factors that can increase tolerance of long term home mechanical ventilation, and its impact on quality of life.

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Disclosure of interests

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The paper includes as authors those who made a substantive intellectual contribution to the design or conceptualization of the study (N Vandenberghe, F Philit, S Bin-Dorel), analysis or interpretation of the data (N Vandenberghe, AE Vallet, T Petitjean, P Le Cam, S Peysson, C Guerin, S Bin-Dorel, E Broussolle), drafting or revising the manuscript (N Vandenberghe, AE Vallet, T Petitjean, P Le Cam, S Peysson, C Guerin, F Dailler, S Jay, V Cadiergue, F Bouhour, I Court-Fortune, JP Camdessanche, JC Antoine, F Philit, P Beuret, S Bin-Dorel, C Vial, E Broussolle) or acquisition of data (N Vandenberghe, AE Vallet, T Petitjean, P Le Cam, S Peysson, C Guerin, F Dailler, S Jay, V Cadiergue, F Bouhour, I Court-Fortune, JP Camdessanche, JC Antoine, F Philit, P Beuret, S Bin-Dorel, C Vial, E Broussolle).

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Table 1: clinical and demographic profile at inclusion time of tolerant and poorly tolerant patients who were evaluated at one month (n=73). (univariate analysis)

	Tolerant at 1 month (n=55)	Poorly tolerant at 1 month (n=18)	*P*-value
Gender, n (%) • Male • Female	 31/55 (56.4) 24/55 (43.6)	 12/18 (66.7) 6/18 (33.3)	*P*=.4
BMI (kg/m^2), mean (SD)	23.2 (4.12)	23.9 (4.9)	*P*=.5
Active smoking, n (%)	10/55 (18.2)	5/18 (27.8)	*P*=.5
Past history of smoking, n (%)	13/55 (23.6)	8/18 (44.4)	*P*=.09
Smoking exposure in pack-years, mean (SD)	6.1 (13.3)	13.2 (18.4)	*P*=.08
Place of residence, n (%) • Home • Institution	 55/55 (100.0) 0/55 (0.0)	 17/18 (94.4) 1/18 (5.6)	*P*=.3
Age (years) at disease onset, mean (SD)	62.3 (9.0)	57.1 (13.1)	*P*=.2
Delay from onset to diagnosis (months), mean (SD)	13.9 (12.7)	13.8 (18.7)	*P*=.6

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Revised El Escorial criteria, n (%) • Probable • Definite	 34/55 (61.8) 21/55 (38.2)	 10/18 (55.6) 8/18 (44.4)	*P*=.6
ALSFRS-R scale, mean score (SD), (maximal-normal score=48)	29.0 (8.1)	26.4 (8.9)	*P*=.2
Bulbar Norris scale, mean score(SD) (maximal-normal score=39)	30.5 (8.9)	22.3 (12.8)	*P*=.01
Number of patients with gastrostomy, n (%)	3/55 (5.5)	5/18 (27.8)	*P*=.02
Epworth score, mean score (SD) (n=65) (minimal-normal score=0)	8.5 (5.9)	7.5 (4.7)	*P*=.8

n=number, BMI=body mass index

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Table 2: Respiratory profile at inclusion time of tolerant and poorly tolerant patients who were evaluated at one month (n=73). (univariate analysis)

	Tolerant at 1 month (n=55)	Poorly tolerant at 1 month (n=18)	*P*-value
Number of patients with dyssomnia, n (%)	39/55 (70.9)	11/18 (61.1)	*P*=.4
Number of patients with paradoxical breathing, n (%)	13/55 (23.6)	9/18 (50.0)	*P*=.03
Number of patients with PaCO2 > 6 kPa, n (%)	24/55 (43.6)	10/18 (55.6)	*P*=.4
Number of patients with SVC < 50%, n (%)	15/54 (27.8)	7/17 (41.2)	*P*=.3
PNO with SaO2 < 90% for more than 5% total time	46/55 (83.6)	14/18 (77.8)	*P*=.7
Duration of disease before NIV onset (months), mean (SD)	n = 55 28.6 (22.1)	n = 17 28.1 (24.5)	*P*=.8
Age at NIV initiation (years), mean (SD)	64.7 (8.7)	58.8 (12.3)	*P*=.1
Clinical form at NIV initiation, n (%) • Pure spinal form (non-bulbar ALS) • Bulbar involvement	 44/55 (80.0) 11/55 (20.0)	 9/18 (50.0) 9/18 (50.0)	*P*=.02
ALSFRS-R scale: sum of subscores of items 1 and 3 (max. score: 8), n (%)			*P*=.05

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Severe bulbar impairment: [0-2] Moderate bulbar impairment: [3-7] No bulbar impairment: [8]	5/55 (9.1) 35/55 (63.6) 15/55 (27.3)	5/18 (27.8) 12/18 (66.7) 1/18 (5.6)	
Time elapsed between indication and true start of NIV (days), mean (SD)	n = 54 11.6 (15.1)	n = 17 9.6 (15.4)	*P*=.2
SVC (%), mean (SD)	n = 45 59.9 (21.0)	n = 10 46.8 (18.7)	*P*=.1
Arterial blood gas before NIV • pH (mean, SD) • pCO2 (kPa) (mean, SD) • p02 (kPa) (mean, SD)	n = 52 7.41 (0.03) 6.20 (1.18) 10.95 (3.02)	n = 15 7.40 (0.05) 6.41 (1.40) 11.04 (3.05)	 *P*=.3 *P*=.6 *P*=1
Circumstances of NIV start, n (%) • Planned • Urgent/semi urgent	n = 55 38/55 (69.1) 17/55 (30.9)	n = 17 9/17 (52.9) 8/17 (47.1)	*P*=.2
NIV tolerance after first day of use • Total nocturnal utilisation (hours), mean (SD)	n = 54 7.4 (2.1)	n = 17 5.1 (3.2)	 *P*<.01
NIV settings in BiPAP mode; n=69 • IPAP, mean (SD)	n = 52 13.6 (4.1)	n = 17 14.7 (3.4)	 *P*=.2

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• EPAP, mean (SD)	4.6 (1.7)	4.8 (1.4)	*P*=.9
• Back-up respiratory rate, mean (SD)	15.7 (3.5)	14.9 (2.6)	*P*=.6
Interface used BiPAP mode; n=69, n (%)	n = 52	n = 17	*P*=.3
• Commercially	38/52 (73.1)	10/17 (58.8)	
• Individually customized	14/52 (26.9)	7/17 (41.2)	
Airway secretion accumulation, n (%)	n = 53	n = 17	
• Before NIV	3/53 (5.7)	4/17 (23.5)	*P*=.05

n=number

IPAP=inspiratory positive airway pressure, EPAP= expiratory positive airway pressure

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Table 3: multivariate analysis for predictive factors of good tolerance to NIV (global multivariate p value of model: p = 0.024).

	Odds Ratio	Confidence Interval
Absence of Airway Secretion Accumulation	11.5	1.3-98.4
Pure spinal form (non-bulbar ALS) versus bulbar form	8.5	1.6-46.2
Age at NIV initiation	1.1	1.03-1.19

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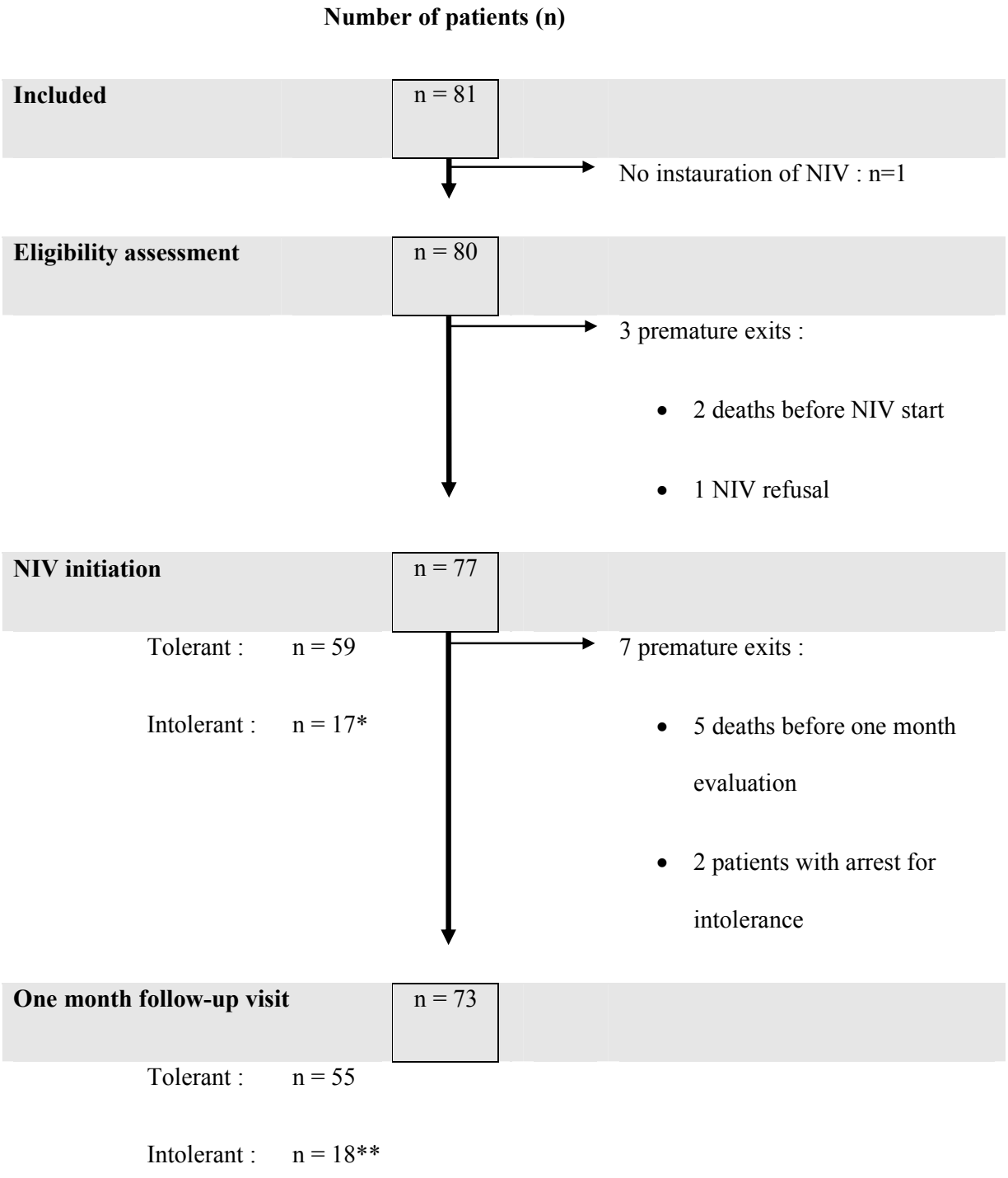
Figure 1: flow chart of the study



*One patient not evaluable

**15 patients and one patient with refusal of NIV and 2 patients with arrest for intolerance