ORIGINAL ARTICLE

Impact of an early respiratory care programme with non-invasive ventilation adaptation in patients with amyotrophic lateral sclerosis

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Keywords:
amyotrophic lateral sclerosis, chronic care, neuromuscular degenerative diseases, non-invasive ventilation

Received 5 September 2017
Accepted 4 December 2017

European Journal of Neurology 2018, **0:** 1–7

doi:10.1111/ene.13547

Background and purpose: Forced vital capacity (FVC) <80% is one of the key indications for starting non-invasive ventilation (NIV) in amyotrophic lateral sclerosis (ALS). It was hypothesized that a very early start of NIV could lengthen the free interval before death compared to later-start NIV; as a secondary outcome, the survival rate of patients on NIV without tracheotomy was also evaluated.

Methods: This retrospective study was conducted on 194 ALS patients, divided into a later group (LG) with FVC <80% at NIV prescription (n = 129) and a very early group (VEG) with FVC ≥80% at NIV prescription (n = 65). Clinical and respiratory functional data and time free to death between groups over a 3-year follow-up were compared.

Result: At 36 months from diagnosis, mortality was 35% for the VEG versus 52.7% for the LG (P = 0.022). Kaplan–Meier survival curves adjusted for tracheotomy showed a lower probability of death (P = 0.001) for the VEG as a whole (P = 0.001) and for the non-bulbar (NB) subgroup (P = 0.007). Very early NIV was protective of survival for all patients [hazard ratio (HR) 0.45; 95% confidence interval (CI) 0.28–0.74; P = 0.001] and for the NB subgroup (HR 0.43; 95% CI 0.23–0.79; P = 0.007), whilst a tracheotomy was protective for all patients (HR 0.27; 95% CI 0.15–0.50; P = 0.000) and both NB (HR 0.26; 95% CI 0.12–0.56; P = 0.001) and bulbar subgroups (HR 0.29; 95% CI 0.11–0.77; P = 0.013). Survival in VEG patients on NIV without tracheotomy was three times that for the LG (43.1% vs. 14.7%).

Conclusion: Very early NIV prescription prolongs the free time from diagnosis to death in NB ALS patients whilst tracheotomy reduces the mortality risk in all patients.

Introduction

In patients with amyotrophic lateral sclerosis (ALS), acute respiratory failure usually leads to death within 5 years from symptom onset [1]. The prescription of non-invasive mechanical ventilation (NIV) in ALS patients can improve survival [2–11]. The most recent European Federation of Neuroscience guidelines [12] proposed sitting forced vital capacity (FVC) as the main parameter for starting NIV, and suggested elevating its level from <50% (as in previous guidelines) to <80% of FVC% predicted. The potential disadvantages of early NIV in Duchenne muscular dystrophy have been shown in a study in which the use of NIV was disapproved for preventive purposes [13]. For this reason, our purpose was to verify in ALS that a very early adaptation to NIV can in fact improve survival, quality of life and adherence to NIV and decrease respiratory

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EUROPEAN JOURNAL OF NEUROLOGY

functional derangements. To this end, it was assessed whether, within 3 years from diagnosis, a very early adaptation to NIV (i.e. NIV prescription in patients with FVC% predicted ≥80%) can lengthen the free interval to death compared to a later NIV prescription. As a secondary aim, the survival rate of patients on NIV without tracheotomy was measured at 3 years.

Methods

This was a retrospective, real-life, observational, pilot, cohort study conducted on an institutional database derived from medical charts of ALS patients admitted to three Italian facilities, ICS Maugeri Lumezzane (Brescia), Don Gnocchi Foundation IRCCS – Onlus (Milano) and NEMO Clinical Centre (Milano), in the period 2008–2013. The study was approved by the local Scientific and Technical Committee (CTS 24/01/2017). During the 36-month study, patients received usual multidisciplinary care at all facilities (nursing, respiratory physical therapy, speech and swallowing assistance, nutritional guidance, neurological, respiratory and psychological second opinion). NIV prescription was based on guideline recommendations [12,14] and the physician's own clinical judgement regarding the FVC% impairment (regardless of the starting value) and the patient's feeling of respiratory fatigability. NIV initiation was performed with pressure-support ventilators in spontaneous/timed mode with a preset tidal volume (5 ml/kg) and a fixed back-up respiratory rate (12 breaths/min). NIV trials included choice of the best fitting mask (nasal/oronasal), setting of pressures to maximal patient comfort, and advice to use nocturnal NIV as much as possible. If necessary, the ventilator setting could be further adjusted to optimize nocturnal oximetry/polysomnography, partial pressure of CO_2 ($paCO_2$) normalization and NIV adherence (at least 4 h/night or 120 h/month of NIV use) [15]. Our time period of analysis started from time of diagnosis. Patients without spirometry data at the time of NIV prescription, not undergoing NIV due to their refusal, or with dementia confirmed by Mini-Mental State Examination score <20 were excluded [16]. Patients were arbitrarily divided into two groups according to the sitting FVC% predicted at the time of NIV prescription: a later group (LG) with FVC <80% and a very early group (VEG) with FVC ≥80%.

For all patients the following data were collected: anthropometric data, riluzole use, spirometry sitting measures [FVC%, forced expiratory volume at 1 s (FEV_1%), FEV_1/FVC] [17] and, when available, respiratory muscle strength [maximal inspiratory (MIP%) and expiratory (MEP%) pressures] obtained with a mouthpiece (or full-face mask for better compliance and spirometry tracing reliability in people with bulbar or facial muscle weakness). Spirometry measurements [18] and MIP/MEP [17] were expressed as a percentage of predicted. Also data were collected on blood gases, the Amyotrophic Lateral Sclerosis Functional Rating Scale revised score, site of onset [bulbar (B) versus non-bulbar (NB)], time elapsed (months) between symptom onset and ALS diagnosis, months elapsed from diagnosis to NIV prescription, prescribed modality of NIV, and NIV setting. The primary outcome was all-cause death from ALS diagnosis to the end of the 3-year follow-up.

Statistical analysis

Statistical analysis was performed using STATA 11.2 (Stata; StataCorp LLC, College Station, TX, USA). Cumulative data were described as mean ± standard deviation for continuous variables and as percentage for binary or categorical variables. Differences between groups were analysed by the unpaired *t* test for continuous variables and by the chi-squared test for categorical and binary variables. Survival was analysed using Kaplan–Meier survival curves adjusted for tracheotomy presence; the effect of early NIV was assessed using the log-rank test. Finally, the effect of early NIV and of tracheotomy on survival was evaluated using a multivariate proportional hazards regression analysis (Cox model). $P < 0.05$ was considered significant for all analyses.

Results

A total of 228 patients were screened for inclusion, of whom 34 were excluded due to lack of spirometry data ($n = 11$), NIV refusal ($n = 3$), dementia ($n = 1$) or follow-up <36 months from diagnosis ($n = 19$). Of the remaining 194 patients, 65 were in the VEG and 129 in the LG. Patients' demographic, clinical, functional characteristics and follow-up care plan are reported in Tables 1 and 2, respectively. During the 36 months of follow-up, all patients received scheduled (every 2–6 months) in-hospital visits by the multidisciplinary team. All patients and caregivers were instructed about air-stacking and thoracic-abdominal thrust techniques. During follow-up, 11.6% of the VEG and 10.7% of the LG patients (difference not significant) changed NIV settings.

Overall mean survival from diagnosis to death was 28.79 ± 9.72 months (31.33 ± 7.55 for VEG vs. 27.51 ± 10.44 for LG, $P = 0.0094$) whilst the crude death rate was 23/65 for VEG (35%) vs. 68/129 for LG (52.7%) ($P = 0.022$). Reasons for death were advanced bulbar symptoms (45.5%), sudden death

Table 1 Demographic characteristics of the study patients at diagnosis

	Total	LG (FVC% < 80)	VEG (FVC% ≥ 80)	*P*
Patients, *n*	194	129	65	
ALS care centre				
ICS Maugeri, *n* (%)	72	52	20	
Don Gnocchi, *n* (%)	37	31	6	
NEMO, *n* (%)	85	46	39	
Male, *n* (%)	57.73%	51.94%	69.23%	0.0214
Bulbar onset, *n* (%)	29.53%	28.91%	30.77%	0.7886

ALS, amyotrophic lateral sclerosis; FVC, forced vital capacity; LG, late group; VEG, very early group.

(21.1%) and death under full palliative medical care (11.3%). The crude death rate for the NB subgroup ($n = 136$) was 15/45 in the VEG (33.3%) and 43/91 in the LG (47.2%) ($P = 0.123$), whereas for the B subgroup ($n = 58$) it was 8/20 in the VEG (40%) and 24/37 in the LG (64.9%) ($P = 0.071$).

Figure 1 shows the Kaplan–Meier survival curves adjusted for tracheotomy: the VEG had a lower overall probability of death ($P = 0.001$), which was significant in the NB subgroup ($P = 0.007$) (Fig. 2, top), whilst no difference was found in B patients ($P = 0.115$) (Fig. 2, bottom).

The effect of very early NIV on survival adjusted for tracheotomy remained significant on multivariate

Table 2 Demographic and functional characteristics of the patients included in the study at the time of NIV prescription

	Total	LG FVC% < 80	VEG FVC% ≥ 80	*P* (between LG and VEG)
Patients, *n*	194	129	65	
Mean time from diagnosis to NIV, months	10.78 ± 8.45	11.36 ± 8.91	9.65 ± 7.4	0.1840
Age, years	63.98 ± 11.34	64.66 ± 11.33	62.62 ± 11.34	0.2393
BMI, kg/m^2	23.89 ± 5.17	23.22 ± 4.72	25.29 ± 5.81	0.0205
ALSFRS-R score	27.69 ± 10.22	25.04 ± 10.32	33.26 ± 7.44	0.0000
Riluzole users, %	93.41	93.33	93.54	0.9558
pH	7.44 ± 0.04	7.44 ± 0.04	7.45 ± 0.03	0.1228
paO_2, mmHg	80.09 ± 13.58	80.41 ± 14.85	79.47 ± 10.78	0.6658
$paCO_2$, mmHg	42.11 ± 7.29	42.38 ± 7.04	41.61 ± 7.76	0.5878
$SaTO_2$, %	94.66 ± 2.74	94.59 ± 2.89	94.92 ± 2.10	0.7841
FEV_1/FVC	86.60 ± 14.92	88.35 ± 15.55	81.52 ± 11.79	0.0701
FVC% predicted	64.57 ± 27.58	49.02 ± 18.87	95.45 ± 11.20	0.0000
FEV_1% predicted	62.14 ± 27.28	49.59 ± 20.75	86.10 ± 21.68	0.0000
MIP% predicted[a]	38.18 ± 22.09	32.98 ± 20.35	54.8 ± 19.41	0.0001
MEP% predicted[a]	32.51 ± 20.92	28 ± 17.75	46.48 ± 24.09	0.0003
Modality of NIV, %				
ST	21.13	21.7	20	
ST-AVAPS	17.01	17.83	15.38	
Bi-level	38.14	36.43	41.53	
Volumetric	1.03	0.77	1.53	
APCV	6.70	9.03	1.53	
IPAP, cmH_2O	15.33 ± 3.62	15.5 ± 3.67	14.94 ± 3.53	0.3109
Delta IPAP, cmH_2O[b]	9.58 ± 5.74	10.63 ± 5.29	7.6 ± 6.31	0.0005
EPAP, cmH_2O	5.34 ± 1.77	5.22 ± 1.71	5.58 ± 1.8	0.1755
Back up RR, acts/min	12.67 ± 1.46	12.75 ± 1.51	12.52 ± 1.36	0.3022
Mandatory tidal volume[b,c], ml/kg	7.06 ± 1.47	7.21 ± 1.53	6.48 ± 1.12	0.000
Follow-up care plan, %				
Respiratory function	45.63	35.9	76	0.0005
Telemedicine	39.45	34.94	53.85	0.0852
Gastrostomy	60.19	62.02	54.16	0.4909
Motor rehabilitation	75.49	76.62	72	0.6405
Motor devices	90.29	88.46	96	0.2679
Cough devices	45.10	46.75	40	0.5555
Psychological care	77.54	74.80	82.81	0.2127

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale revised; APCV, assisted pressure controlled ventilation; AVAPS, average volume assured pressure support; BMI, body mass index; EPAP, expiratory positive airway pressure; FEV_1, forced expiratory volume at 1 s; FVC, forced volume capacity; IPAP, inspiratory positive airway pressure; LG, late group; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; NIV, non-invasive ventilation; $paCO_2$, arterial partial pressure of carbon dioxide; paO_2, arterial partial pressure of oxygen; RR, respiratory rate; $SaTO_2$, arterial oxygen saturation; ST, spontaneous timed; VC, vital capacity; VEG, very early group. [a]Available for 84 patients; [b]for AVAPS; [c]for volumetric.

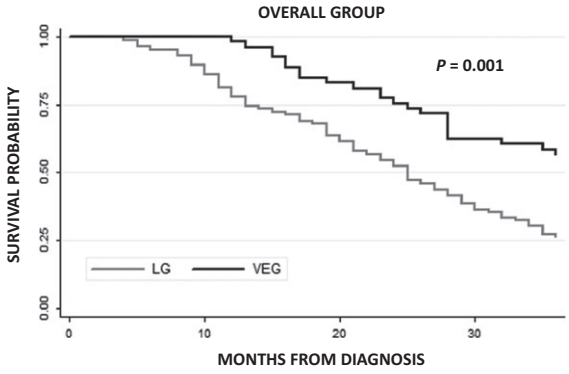

Figure 1 Time from ALS diagnosis to death (in months) for all patients. LG, late group; VEG, very early group.

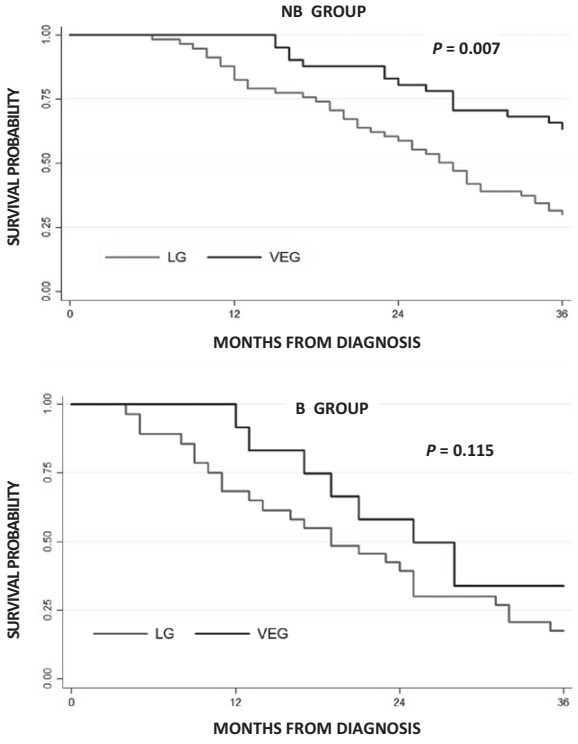

Figure 2 Time from ALS diagnosis in non-bulbar (NB) (top) and bulbar (B) patients (bottom). LG, late group; VEG, very early group.

Cox regression for all patients and for the NB subgroup (Table 3). The protective effect on survival of tracheotomy was significant in all patients as well as in both the NB and B subgroups (Table 3). At 3-year follow-up, tracheotomy was needed in 23.1% (15/65) of VEG vs. 41.9% (54/129) of LG ($P = 0.009$) patients. For the NB subgroup, the tracheotomy rate was 11.1% (5/45) in VEG vs. 45% (41/91) in LG ($P = 0.000$), whilst for the B subgroup it was 50% (10/20) in VEG vs. 35.1% (13/37) in LG ($P = 0.275$). Reasons for tracheotomy need were urgent endotracheal intubation (21.1%), secretion encumbrance unresponsive to in-exsufflator use (20.2%) and scheduled intervention (24.8%).

As shown in Fig. 3, at 3-year follow-up, VEG patients had a higher survival rate on NIV without tracheotomy, both overall and in the NB and B subgroups.

Discussion

Several studies have reported beneficial effects of NIV [2–11] or its ability to postpone respiratory function decline [3] and respiratory muscle strength decline [9] within 4 months of follow-up. NIV initiation in ALS patients is reported within a range 42% ± 13% to 65% ± 14% of FVC% predicted and 31%–36% of MIP% [7–10,19]. Early diagnosis of respiratory insufficiency and the early use of NIV has been reported to increase patient compliance with NIV [20], reduce the respiratory functional derangements in vital capacity and/or respiratory muscles [21], reduce hypercapnia [21] and improve survival [10,22,23]. The median survival time from onset of ALS symptoms to death is variously reported as 44 months [1,14] or within the range 18–40 months [3,7,24–26].

In our study, overall survival from time of ALS diagnosis (28.79 ± 9.72 months) was similar to that reported by Sanjuán-López *et al.* (28 months) [5]. But survival was significantly longer (31.33 ± 7.55 vs. 27.51 ± 10.44 months) and the crude death rate significantly lower (35% vs. 52.7%) in patients started very early on NIV compared to those started on NIV when FVC% was <80%, as generally recommended by the European guidelines [14]. To our knowledge, this is the first study to demonstrate that very early NIV prescription can prolong the free time from diagnosis to death.

In a randomized study on 41 ALS patients, NIV improved survival and quality of life only in the subgroup without severe bulbar dysfunction [10]. In a retrospective study [22], the median time from ALS diagnosis to death was significantly longer in the early NIV group (FVC ≥ 65% predicted) compared to those who started NIV when their FVC was <65% predicted (2.7 vs. 1.8 years). In a large cohort of 1034 patients with ALS [24], the median survival of patients with baseline FVC <75% was much shorter than that of patients with baseline FVC >75% independently of the medical treatment. NIV significantly decreased the mortality rate of ALS patients with FVC <75%, as well as the median FVC% rate decline, which was much slower compared to the FVC slope of ALS

Table 3 Multivariate Cox regression model (at 3 years from diagnosis)

	Overall group			NB subgroup			B subgroup		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Group (VEG/LG)	0.4596	0.2851–0.7410	0.001	0.4360	0.2391–0.7949	0.007	0.5421	0.2434–1.2078	0.134
Tracheotomy	0.2785	0.1538–0.5044	0.000	0.2635	0.1228–0.5654	0.001	0.2948	0.1128–0.7703	0.013

B, bulbar; CI, confidence interval; HR, hazard ratio; LG, late group; NB, non-bulbar; VEG, very early group.

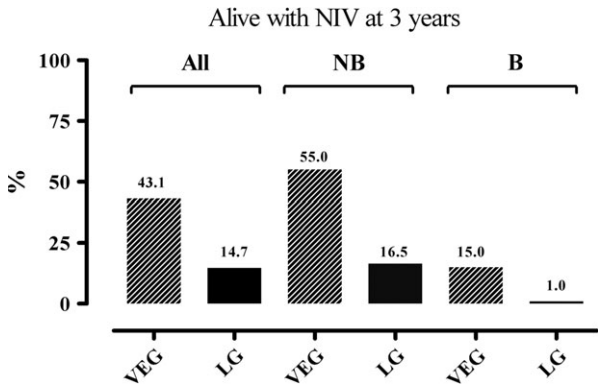

Figure 3 Percentage of patients according to bulbar or non-bulbar subgroups still alive under NIV at 3 years from diagnosis. VEG, very early group; LG, late group; NB, non-bulbar; B, bulbar.

patients with FVC <50% [21]; interestingly, also the control group of ALS patients with FVC >75% and without NIV prescription had a death rate of 15% at 12 months [21] showing that the mortality risk is present also at the beginning of the FVC decline.

Non-invasive ventilation utility was also compared between NB and B onset. Contrasting findings have been reported, i.e. the sole randomized controlled trial [10] showed a benefit of NIV only in NB patients but another study showed that NIV significantly increased survival in B patients, by 19 months [3]. Our finding agrees with the previous data [10] demonstrating that only NB patients have a survival benefit from NIV.

It is possible that the positive effect demonstrated by a very early prescription of NIV is due to the fact that, starting NIV when neuromuscular junctions are more intact, patients may adhere better to NIV. Supporting this hypothesis, LG patients at NIV start had a worse nutritional status and worse neurological and respiratory function impairment. In our experience, increasing progressively the hours of ventilation during the night and on demand during the day improves patient adherence to NIV by allowing patients a more comfortable adaptation to the technique and giving them more confidence. Another fascinating hypothesis, not demonstrated by our data, is that an early use of NIV could actually decrease the respiratory functional derangements in vital capacity and/or respiratory muscles [22] and reduce hypercapnia (particularly for rapidly declining ALS patients), so avoiding relapses and early atelectasis and improving secretion clearance. Also the synergic effect of early multidisciplinary care of patients regarding all their clinical, social and psychological problems [1] may have positively influenced our results.

Our data showed a high number of patients who underwent tracheotomy (32% of patients overall, 23% for the VEG and 42% for the LG) which in no case was due to personal desire or decision. The percentage of ALS patients in different countries who undergo tracheotomy varies from 0% to 6.6% and from a mean of 2.4% in Europe to 6.6% in the USA [27] demonstrating the current lack of consensus on this topic with significant global variability. As expected, the strong effect of tracheotomy as a protective method to reduce mortality risk was confirmed [26] whilst it was shown (for the first time to our knowledge) that, at 3 years from diagnosis, more than 50% of NB patients on very early NIV adaptation were still alive without tracheotomy whilst fewer than 15% of B patients survived.

Strengths and limitations

It is believed that the strength of this pilot study is the large sample size, the long follow-up of 3 years, the multicentre experience and the robust demonstration of an association between very early respiratory care with NIV prescription and lower risk of NIV failure (death and tracheotomy). A possible bias is that inclusion of patients for NIV was according to the physician's clinical judgement: on the other hand, this provides an important picture of real-life ALS patient care. The results may not be generalizable to all ALS patients as they come from three highly specialized ALS centres. Further, possible confounding conditions, not reported in the study, are the effects of access to a telephone line, the provision of airway clearance techniques, the diversity of local community treatment modes, lack of rigid follow-up of respiratory function and neurological conditions, and lack of knowledge about the causes of death, recorded compliance/adherence to NIV,

associated experimental therapeutic protocols, presence/influence of anxiety and depression, and knowledge of ALS phenotype [28].

In conclusion, a very early NIV prescription prolongs the free time from diagnosis to death in NB ALS patients whilst tracheotomy decreases the mortality risk in all patients. These findings need to be confirmed in robust randomized controlled trials, and the cost-effectiveness of such an approach needs to be evaluated before advocating it in clinical practice.

Acknowledgements

Laura Comini is thanked for critical revision and editing assistance, and Rosemary Allpress for the English revision. The study was approved by our local Scientific and Technical Committee (CTS 24/01/2017). Being a retrospective study based on the hospitals' database report prospective informed consent was not necessary. Patients gave a generic written informed consent for use of their clinical data for scientific purposes (a routine requirement of our research centre) at the moment of hospital admission to be trained to NIV. No funding.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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Appendix

ALS Respiration Lombardia (RESPILOM) Study Group members

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